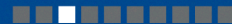




An Oral History Of Neuropsychopharmacology

The First Fifty Years
Peer Interviews

SERIES EDITED BY: Thomas A. Ban



Volume Three:
NEUROPHARMACOLOGY

EDITED BY: Fridolin Sulser

American College of Neuropsychopharmacology

**AN ORAL HISTORY OF
NEUROPSYCHOPHARMACOLOGY
THE FIRST FIFTY YEARS**

Peer Interviews

Volume Three: Neuropharmacology

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Thomas A. Ban (series editor)
AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY

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VOLUME 3: NEUROPHARMACOLOGY

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THE FIRST FIFTY YEARS
Peer Interviews

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Thomas A. Ban

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VOLUME 3

NEUROPHARMACOLOGY

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VOLUME 3

Fridolin Sulser

NEUROPHARMACOLOGY

The Neurotransmitter Era in Neuropsychopharmacology

Preface

Thomas A. Ban

Dedicated to the Memory of Bernard B. Brodie, President ACNP, 1965

PREFACE

Thomas A. Ban

In 1957 Ralph Gerard coined the term “psychotropic drugs” for chemicals which can control or induce mental pathology.¹ Neuropharmacology studies the molecular substrate involved in the mode of action of these drugs.

Interviewees, in the first two volumes of this series, reflected on their contributions to the delineation of the effects of psychotropic drugs on behavioral measures (Volume 1) and neurophysiologic parameters (Volume 2). In Volume 3 the emphasis shifts and interviewees reflect on their contributions to the development of neuropharmacological research. Since neuropharmacological research may provide information on the biochemical underpinning of mental pathology, neuropharmacology has been the moving force of psychotropic drug development during the fifty years covered in Volume 3.

Development of neuropharmacology was triggered in the 1950s by the serendipitous discovery of the first set of effective psychotropic drugs; chlorpromazine, reserpine, meprobamate, iproniazid and imipramine in the treatment of mental pathology.² The commercial success of these drugs, and especially of chlorpromazine and meprobamate, stimulated the pharmaceutical industry to develop substances with similar effects. By the end of the 1950s there were twelve effective drugs for the treatment of psychoses, seven for the treatment of depression, and two for the treatment of anxiety.* In 1967 an “expert committee” of the World Health Organization (WHO) classified psychotropic drugs into five categories: neuroleptics (major tranquilizers, antipsychotics), anxiolytic sedatives (minor tranquilizers), antidepressants, psychostimulants, and psychodysleptics (psychomimetics).³ By the end of the 20th century two further categories were added: mood stabilizers and cognitive enhancers. Each of these categories was broad, and within each category there were substances with different pharmacological actions. The WHO classification has had a major impact on neuropharmacology and on psychotropic drug development.

* Drugs for the treatment of psychoses at the end of the 1950's: chlorpromazine, chlorprothixene, haloperidol, methotrimeprazine (levomepromazine), perphenazine, prochlorperazine, reserpine, thiopropazate, thioroperazine, thioridazine, trifluoperazine, and triflupromazine. Drugs for the treatment of depression by the end of the 1950's: amitriptyline, imipramine iproniazid, isocarboxazid, nialamide, phenelzine, and tranylcypromine. Drugs for the treatment of anxiety by the end of the 1950s: hydroxyzine and meprobamate

Neurotransmitters

The initial targets of neuropharmacological research were *neurotransmitters*. By the end of the 1950s there were six neurotransmitters identified: acetylcholine, norepinephrine (noradrenalin), serotonin, dopamine, γ -aminobutyric acid, and substance P.

Acetylcholine (ACh) was first detected at parasympathetic nerve endings in 1914 by Henry Dale.⁴ The effect of the substance on adjacent cells to the nerve endings was first noted by Otto Loewi in 1921.⁵ In 1937 ACh was isolated from brain homogenates by Juda Quastel and his associates,⁶ and Stedman and Stedman.⁷ The effect of ACh on neuronal transmission in the spinal cord was demonstrated by Eccles and his associates in 1954.⁸

Sympathin was first detected at sympathetic nerve endings in 1904 by R.T. Elliott.^{9, 10} The substance was identified as *noradrenaline (NA)/norepinephrine (NE)*¹¹ and separated from adrenaline/epinephrine by Ulf Von Euler in 1946.¹² In 1954, Marthe Vogt reported on the concentration of NE in different parts of the brain in normal conditions and after the administration of drugs.¹³

In 1884 Stevens and Lee described a vasoconstrictor substance in the blood.¹⁴ The substance was crystallized from ox serum by Rapport, Green and Page, and identified as *5-hydroxytryptamine (5HT)*, referred to as *serotonin*, in 1948.¹⁵ In 1937 Vittorio Erspamer extracted a substance from the enterochromaffin cells of the intestinal mucosa of rabbits, he referred to as enteramine.¹⁶ In 1952 he recognized that enteramine was a structurally identical indoleamine with serotonin.¹⁷ In 1953 Twarog and Page demonstrated the presence,¹⁸ and in 1954 Amin, Crawford and Gaddum described the distribution of 5HT in the brain.¹⁹

Dopamine (DA) an intermediary in the synthesis of NE from tyrosine was detected in the brain in 1957 by Kathleen Montagu.²⁰ The same substance was identified in 1958 by Arvid Carlsson and his associates.²¹ In 1959 Carlsson described the distribution of dopamine in the central nervous system. He also demonstrated that DA was not just an inactive intermediary, a precursor of NE, but an active neurotransmitter in the brain.²² The distribution of dopamine was further elaborated by Bertler and Rosengren,²³ and Sano and his associates²⁴ in the same year (1959).

The presence of *γ -aminobutyric acid (GABA)* in plants and bacteria has been known since the late 19th century. In 1950 Awapara and his associates,²⁵ and Roberts and Frankel²⁶ detected the presence of GABA in the brain. Seven years later, in 1957, Purpura and his associates,²⁷ and Curtis and his associates²⁸ demonstrated its marked depressant action on nerve terminals and identified GABA as an inhibitory neurotransmitter.

Substance P (SP) was detected in the intestine and in the brain in 1931 by Von Euler and Gaddum.²⁹ In 1952 Zetler had shown the presence of the substance in high concentration in the human cerebral cortex,³⁰ and in 1959 he demonstrated that SP is a centrally acting transmitter of inhibitory neurons.³¹

The Aminco Bowman *spectrophotofluorimeter* (SPEC) was introduced in 1955³² and employed in the same year by Bernard Brodie and his associates for measuring the concentration of neurotransmitter monoamines, such as NE, 5-HT and DA and their metabolites in the brain. (See, Overview, Volume1.) SPEC complemented *paper, gas and high-speed liquid chromatography* and was instrumental in opening up research in neuropharmacology.

The enzyme monoamineoxidase (MAO), involved in the oxidative deamination of monoamines,³³ was first detected in the liver by Blaschko and his associates in 1937.³⁴ The same year MAO was also detected in the brain by Pugh and Quastel.³⁵ In 1938, MAO oxidase was separated from diamine oxidase by Zeller.³⁶

Psychotropic Drugs

Psychotropic drug development has been closely linked to neuropharmacological research and for about thirty years it was dominated by studies on the effect of drugs on neurotransmitter mediated signal transduction in the brain.

Developments in the neuropharmacology of *neuroleptics* (*antipsychotics*) began in the mid 1950s with the demonstration of a linear relationship between the sedative and the anti-5HT effect of chlorpromazine (CPZ) and its congeners.³⁷ In the late 1950s, neuroleptics were divided into “sedative” or CPZ-type, and “incisive” or prochlorperazine-type drugs.³⁸ There was no difference in therapeutic efficacy between the two groups, but “incisive” neuroleptics were more potent on a mg per kg basis and produced more frequent and severe extrapyramidal symptoms/signs (EPS).³⁹ In the early 1960s DA receptor blockade was implicated in the mode of action of neuroleptics,⁴⁰ and amphetamine antagonism was introduced as a pharmacological screen for the detection of potential antipsychotic drugs.⁴¹ By the mid-1960s, “incisive” neuroleptics dominated the treatment of schizophrenia. During the 1970s their dominance was perpetuated by the demonstration that they block dopamine-D₂ receptors^{42,43}; by the finding of an inverse relationship between DA receptor blocking potency and dose requirements⁴⁴; and by the formulation of the DA-hypothesis of schizophrenia.⁴⁵ In the late 1970s, the steadily growing number of patients with tardive dyskinesia turned interest to thioridazine, a piperidyl side chain containing sedative neuroleptic. Treatment with thioridazine induced considerably less frequent and severe EPS than treatment

with incisive neuroleptics, but thioridazine produced cardiac conductance changes.^{46,47} (See, Gottschalk, Volumes 1 & 9; Ban, Volumes 4 & 9; Gallant, Volume 4.) In the early 1970s, clozapine, a substance with an even lesser propensity to induce EPS than thioridazine, was introduced in Europe.⁴⁸ (See, Hippius, Volume 1; Ackenheil, Volume 8.) In the mid-1970s, clozapine was withdrawn from clinical use (in most countries) because of eighteen cases of agranulocytosis, including eight fatal cases, encountered in Finland.⁴⁹ In the mid-1980s, clozapine was re-introduced, and became the prototype of a series of so-called “atypical neuroleptics.” (See, Kane, Volume 4.) Atypical neuroleptics differ from “typical neuroleptics,” like haloperidol, by their lesser propensity to induce EPS and higher affinity to serotonin 5HT_{2A} receptors than to dopamine-D₂ receptors. (See, Meltzer, Volumes 5 & 9.) They also have a broader receptor profile than “typical neuroleptics.” Thus, “atypical neuroleptics” are similar to CPZ-type of “sedative neuroleptics,” drugs with a broad receptor profile and higher affinity to serotonin-5HT₂ receptors than to dopamine-D₂ receptors.⁵⁰

Developments in the neuropharmacology of *iproniazid-like antidepressants* began in the mid-1950s with the findings that iproniazid, a MAO inhibitor (MAOI), increased 5HT and NE in the brain and produced euphoria in some patients treated for tuberculosis.⁵¹ In the late 1950s several MAOIs were introduced in the treatment of depression. By the early 1960s hepatotoxicity⁵² and hypertensive crises⁵³ were encountered with some of these drugs. Deprenyl (selegiline) the first selective inhibitor of the Type B iso-enzyme of MAO was developed in the mid-1960s,⁵⁴ and moclobemide, a selective inhibitor of the Type A iso-enzyme, in the mid-1970s.^{55, 56}

Developments in the neuropharmacology of *imipramine-like antidepressants* began in the late 1950's with the demonstration that imipramine, a tricyclic substance, has antihistaminic, anticholinergic, noradrenergic, and serotonergic properties.⁵⁷ It reversed reserpine-induced sedation, hypothermia, ptosis and diarrhea.^{58, 59} In the early 1960s reserpine reversal was introduced as a pharmacological screen for the identification of imipramine-like antidepressants. About the same time, both imipramine and amitriptyline, the two available tricyclic antidepressants, were found to block NE reuptake into neurons.⁶⁰ Since reserpine-reversal with desipramine (DMI), the demethylated metabolite of imipramine, a selective NE re-uptake blocker, was more potent than with imipramine, and imipramine's reserpine reversal was suspended by the administration of α -methyl-metatyrosine, a substance that blocked the formation of NE, the possibility was raised that NE and not 5HT is the neurotransmitter involved in the antidepressant effect of these drugs.⁶¹ In the mid-1960's, the catecholamine hypothesis of affective disorders was formulated,⁶² and several NE re-uptake inhibitor antidepressants (NARIs),

including DMI⁶³ and maprotiline,⁶⁴ were introduced. (See, Bunney, Volume 5; John Davis, Volume 5; Schildkraut, Volume 5.) Then, in the 1970's it was recognized that NE re-uptake inhibitors convert into 5HT reuptake inhibitors by halogenation.⁶⁵ It was also shown that an intact 5HT system was a prerequisite for β -adrenergic receptor down regulation, a common characteristic of DMI-type of antidepressants.⁶⁶ Simultaneously with this development the pharmacological concept of depression was extended by the introduction of the "behavioral despair - learned helplessness, swimming survival - test" in the screening for antidepressants. (See, Ackenheil, Volume 8.) The new test was based on a "stress model", instead of the reserpine-model of depression. In 1980, a correspondence was shown between imipramine binding sites and 5HT binding sites in the human platelet⁶⁷ and in the hypothalamus of the rat.⁶⁸ Introduction of a series of selective 5HT re-uptake inhibitors (SSRIs) followed, and by the 1990s SSRIs became the main stream in the treatment of depression.^{69*} By the end of the 20th century with the introduction of venlafaxine, a non-selective, but prevalingly 5HT re-uptake inhibitor, a full complement of monoamine re-uptake inhibitors was completed.⁷⁰ With the introduction of reboxetine,⁷¹ a selective NE reuptake inhibitor, the circle opened in the early 1960s with the introduction of DMI was reopened.

The development of *anxiolytic sedatives* began in 1950 with the synthesis of meprobamate,⁷² a propanediol preparation that depressed multineuronal reflexes by accelerating acetylcholine breakdown at the synaptic cleft.⁷³ The substance was introduced in 1955, and became the first "blockbuster drug."⁷⁴ In the 1960's chlordiazepoxide, diazepam and several other benzodiazepine preparations were introduced and within a few years virtually replaced meprobamate in the treatment of anxiety.⁷⁵ In the late 1970's benzodiazepine receptors were identified⁷⁶ and it was shown that benzodiazepines acted on the GABA neurotransmitter system.⁷⁷ During the 1990s, SSRIs replaced benzodiazepines as the primary treatment of anxiety disorders.

The development of *mood stabilizers* began in the late 1940's with the re-introduction of lithium into psychiatry by John Cade,⁷⁸ and the demonstration in the mid-1960s that lithium has mood stabilizing effects.⁷⁹ In the mid 1970s, based on clinical observations, it was suggested that the anticonvulsants, carbamazepine⁸⁰ and sodium valproate,⁸¹ could also stabilize mood. In the late 1970s it was discovered that carbamazepine controlled amygdala

* Drugs used in the treatment of depression at the end of the 20th century: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline); NARIs (amoxapine, lofepramine, maprotiline, nortriptyline, reboxetine, viloxazine); double, 5HT and NE, re-uptake inhibitors (SNRIs) (amitriptyline, dibenzepine, dosulepine/dothiepin, doxepin, duloxetine, imipramine, melitracen, milnacipran, protriptyline); serotonin modulators (SMAs) (trazodone and nefazodone); noradrenergic and selective serotonergic drugs (NaSSAs) (mianserin and mirtazepine); a DA receptor antagonist (trimepramine); a dopamine and NE re-uptake inhibitor (DNRI) (bupropion); and a glutaminergic modulator (GM) (tianeptin.)

kindled seizures (see, Post, Volume 5), and in 1980 it was demonstrated that in the action of sodium valproate the GABA system was involved.⁸² In the 1990s several more drugs were introduced as mood stabilizers, including the anticonvulsant lamotrigine,⁸³ as well as some atypical neuroleptics,⁸⁴ like quetiapine⁸⁵ and risperidone.⁸⁶

The development of *cognitive enhancers* began in the mid 1950's with the discovery that tetrahydroaminoacridane (THA), a cholinesterase inhibitor, controlled aberrant-behavior induced by atropine, an anticholinergic drug. (See, Gershon, Volume 1.) Interest in THA was revived in the 1970's with William Summers report on the effect of THA in Alzheimer's disease (AD),⁸⁷ and with the demonstration that physostigmine, a short acting cholinesterase inhibitor, enhanced cognition in Stanford students. (See, Kenneth Davis, Volume 8.) In the 1990s several cholinesterase inhibitors, including galantamine,⁸⁸ rivastigmine,⁸⁹ and donepezil were introduced in the treatment of AD.⁹⁰

Interviewees & Interviewers

The preceding information provides the necessary orientation for identifying the place of the contributions of the thirty-three interviewees whose transcripts in this volume record the development of neuropharmacology. All transcripts are based on videotaped interviews.

From the thirty-three interviewees five (Carlsson, Dahlström, Jarvik, Knoll and Pletscher) have an MD and PhD; fourteen (Agranoff, Barchas, Barondes, Berger, Fuxe, Garattini, Kandel, Kopin, Langer, Paul, Sandler, Snyder, Sulser and Wurtman) are MDs; and fourteen, (Akil, Axelrod, Dingell, Enna, Fibiger, Frazer, Greengard, Iversen, Karczmar, Lal, Pert, Sanberg, Sanders-Bush, and Spector) are PhDs. All, but two interviewees (Dahlström and Knoll) are ACNP members. Four interviewees (Axelrod, Greengard, Jarvik and Karczmar) are founders, and four other interviewees (Akil, Kopin, Paul and Sulser) are past-presidents.

All interviews were conducted from 1995 to 2008, and with the exception of five, at annual meetings of the College. Three (Dingell, Spector and Sulser) of the five interviews done between annual meetings were conducted in Nashville, Tennessee, one (Pletscher) in Riehen, Switzerland, and one (Knoll) in Budapest, Hungary.

The thirty-three interviews were conducted by sixteen interviewers. Eleven interviewers (Akil, Braslow, Cook, Costa, Koslow, Meador-Woodruff, Nestler, Sulser, Tone, Watson and Wayner) conducted one interview; three (Bromley, W. Bunney and Healy) conducted two; one (Hollister) six, and another one

(Ban) nine. One interviewee (Barondes) was interviewed by two interviewers (Tone and Ban.)

By the time the editing of Volume 3 was completed, four of the interviewees (Axelrod, Berger, Jarvik and Pletscher), and one of the interviewers (Hollister) passed away.

Contributions of Interviewees

The 33 interviewees were involved in ten different broadly defined areas of research related to neuropharmacology. Most of the interviewees contributed to several areas.

The research of one interviewee, *Alexander Karczmar*, was focused entirely on the **cholinergic system**. In the 1950's, Karczmar, in collaboration with Koketsu, Nishi and Dun, identified three ganglionic receptor sites of ACh: nicotinic, muscarinic (metabotropic) and peptidergic.⁹¹ Also in the 1950's, in collaboration with Lang, he demonstrated the structural similarity between peripheral and central muscarinic acetylcholine receptors.⁹²

The research of three interviewees (Pletscher, Sandler and Knoll) involved **monoamine oxidase and its inhibitors**. *Alfred Pletscher* was first to demonstrate that administration of iproniazid, a MAOI, increased brain 5HT levels.⁹³ Pletscher was a member of Brodie's team which revealed that reserpine released 5HT from its vesicular storages in pre-synaptic 5HT neurons.⁹⁴ (See, Pletscher also in Volume 9.)

Merton Sandler's research was focused on MAO, the enzyme itself. In the mid 1960's, *Merton Sandler*, in collaboration with Moussa Youdim, provided electrophoretic evidence that MAO was present in the brain in multiple forms.⁹⁵ In the early 1970's, in collaboration with Vivette Glover, he demonstrated that DA was metabolized by the type-B isoenzyme of MAO.⁹⁶

The first MAO-B inhibitor, deprenyl (selegiline,) was synthesized and developed during the 1960's by *Joseph Knoll* and his team.⁹⁷ Knoll's discovery was based on his recognition that deprenyl differs from other MAOIs by inhibiting, instead of potentiating, the blood pressure increasing effect of amphetamine and tyramine.⁹⁸ Knoll had also shown that deprenyl increased longevity and sexual activity in rats.⁹⁹

Three interviewees (Axelrod, Kopin, and Spector) contributed to the elucidation of **catecholamine metabolism**. In the 1950s, *Julius Axelrod*, one of the Nobel Laureates (1970) of Brodie's school identified, two enzymes, catechol-O-methyl transferase (COMT) and phenylethanolamine-N-methyl transferase (PNMT), involved in catecholamine metabolism.¹⁰⁰ In 1961, in collaboration with Whitby and Hertting, he discovered that the action of NE was terminated by reuptake into pre-synaptic noradrenergic neurons.¹⁰¹ The

demonstration by Axelrod and his team that cocaine and imipramine blocked the reuptake of NE¹⁰² was instrumental to the development of the neuropharmacology of tricyclic antidepressants.

Irwin Kopin was a member of Axelrod's team which established that neuronal reuptake was important in the inactivation of NE.¹⁰³ Kopin's findings that NE metabolizes into dihydroxyphenylglycol (DHPG), and DHPG converts through 3-methoxy-4-hydroxy-phenyl glycol (MHPG) into 3-methoxy-4-hydroxymandelic acid (vanilmandelic acid-VMA),¹⁰⁴ filled a gap in catecholamine metabolism.

Sydney Spector, another Brodie disciple, identified tyrosine hydroxylation as the rate limiting step in the formation of catecholamines. He demonstrated, in the mid-1960's, that blocking the activity of tyrosine hydroxylase by α -methyltyrosine depleted NE in the brain.¹⁰⁵ Spector, with the employment of radioimmunoassay, developed antibodies to psychotropic drugs which could distinguish between the isomers of a substance.¹⁰⁶ With the use of antibodies he isolated, in the mid-1970s, an endogenous morphine-like substance in the brain^{107, 108}

Six interviewees (Carlsson, Snyder, Langer, Greengard, Fibiger, and Sanberg) contributed to the neuropharmacology of **dopamine (DA)**. *Arvid Carlsson*, another Nobel Laureate (2000) from Brodie's school had shown in the late 1950s that the reserpine-induced depletion of monoamines was not restricted to 5HT but included NE.¹⁰⁹ He had also shown that reserpine-induced akinesia was reversed by the administration of 3, 4-dihydroxyphenylalanine (DOPA), the precursor of DA and NE¹¹⁰ In 1959 Carlsson demonstrated the neurotransmitter function of DA, and in 1963, in collaboration with Lindqvist he revealed that administration of chlorpromazine and haloperidol increased the metabolites of NE and DA in the mouse brain.¹¹¹ Carlsson's recognition that dopamine receptor blockade was possibly the crucial step in the mode of action of these (antipsychotic) drugs was instrumental to the development of the neuropharmacology of neuroleptics. It also triggered research which led to the formulation of the dopamine hypothesis of schizophrenia.¹¹² In the development of zimelidine in the 1970s, the first SSRI antidepressant introduced for clinical use (in the early 1980s), Carlsson played a pivotal role.¹¹³

Solomon Snyder, a student of Joel Elkes, (see, Elkes, Volumes 1 and 10,) and a disciple of Julius Axelrod, was among the first to demonstrate DA receptor blockade with neuroleptics.¹¹⁴ He was also among the first in the 1970s to isolate endorphins in the mammalian brain and to elucidate their structure.¹¹⁵ In the 1990's Snyder recognized nitric oxide (NO) as a new class of gaseous neurotransmitter¹¹⁶ and as a physiologic mediator of penile erection.¹¹⁷

Salomon Langer was first to describe pre-synaptic autoreceptors for DA, 5HT, ACh, GABA and glutamate.^{118,119} He was also among the first in the 1970s to demonstrate co-transmission,¹²⁰ the release of several types of neurotransmitters from one nerve terminal. Langer played a pivotal role in developing the atypical antipsychotic, aripiprazole.¹²¹

Paul Greengard, another Nobel Laureate included in this volume, was first to show that interaction between DA and its receptors leads to the activation of specific cAMP (cyclic adenosine monophosphate) dependent protein kinases which, through phosphorylation, activate some proteins in the neuron.¹²² His discovery of the presence of neurotransmitter sensitive adenylyl cyclases on the cell membrane opened the path to study the second messenger system in signal-transduction.¹²³ In the 1980's, Greengard identified DARP-32 (dopamine and cyclic adenosine monophosphate response element binding protein), in striatal cells.^{124, 125} DARP-32 is regulated by dopaminergic and glutamatergic stimulation in the opposite direction; its identification has stimulated interest in molecular genetic research in schizophrenia. (See, Bunney, Volume 5.)

Hans Christian Fibiger and his associates were first to demonstrate that destruction of DA terminals in the nucleus accumbens stopped animals self-administering cocaine.¹²⁶ They also showed DA release in the nucleus accumbens during various stages of sexual behavior in male rats.¹²⁷ The findings of Fibiger and his associates indicate that DA and not NE, is the biochemical substrate of self-perpetuating reward, pleasure seeking, behavior. (See, Stein, Volume 1.) In the 1980s Fibiger contributed to the mapping of muscarinic (cholinergic) neurons;^{128,129} and, in the 1990s, he was instrumental in introducing early gene (cFos) expression in screening for psychotropic drugs.¹³⁰

Paul Sanberg found that nicotine enhanced the cataleptogenic effect of haloperidol, a dopamine antagonist in rats.¹³¹ He also demonstrated that transdermal nicotine could reduce by about 50% the dose of haloperidol in treatment of Tourette's syndrome.^{132,133}

Four interviewees (Garattini, Dingell, Sulser, and Frazer) contributed to the **neuropharmacology of antidepressants**. In the late 1950's, *Silvio Garattini*, in collaboration with Costa and Valzelli, found that imipramine reversed reserpine induced hypothermia and ptosis. (See, Costa, Volume 7.) In the early 1960's reserpine reversal was introduced in the screening for potential antidepressants.¹³⁴ In the late 1960's Garattini showed that oxazepam was a pharmacologically active metabolite of diazepam.¹³⁵

In the early 1960's *James Dingell*, a second generation disciple of Brodie, and a pupil of Gillette, isolated desmethylinipramine (desipramine, DMI), a secondary amine metabolite of imipramine.¹³⁶ In collaboration with Sulser and Gillette, Dingell demonstrated that DMI has a longer half-life than its

parent substance.¹³⁷ He had also shown that chronic administration of imipramine to rats led to accumulation of DMI (and not of imipramine) in tissues, including the brain.¹³⁸

Fridolin Sulser, another Brodie disciple was first in the early 1960's to recognize that reserpine reversal was dependent on the availability of NE.¹³⁹ He found that DMI no longer reversed the effects of reserpine after depleting brain NE by α -methyltyrosine.¹⁴⁰ In the mid-1970s, in collaboration with Jerzy Vetulani, Sulser discovered that chronic treatment with tricyclic and MAOI antidepressants (as well as with ECT) decreased the number of β -adrenoreceptors, and reduced the responsiveness of the β -adrenoreceptor-coupled adenylate cyclase system to NE in limbic and cortical structures in the rat brain.¹⁴¹ Pursuing this line of research further, with a shift in emphasis from pre-synaptic to post-synaptic mechanisms, he found in collaboration with Sanders-Bush, that both NE, through the activation of the cyclic AMP - protein kinase A pathway, and 5HT, through the activation of the diacylglycerol (DAG) - protein kinase C pathway, caused phosphorylation of nuclear CREB (cyclic adenosine monophosphate regulated element binding protein).¹⁴² Furthermore, in collaboration with Manier and Shelton, he also revealed that chronic treatment with noradrenergic antidepressants produced a highly significant reduction (down-regulation) of CREB - P, the biologically active form of the transcription factor.¹⁴³

The finding of β -receptor down regulation in chronic treatment with noradrenergic antidepressants was further refined by *Alan Frazer* who had shown, with the employment of quantitative-autoradiography, that desipramine preferentially down-regulated β - adrenoreceptors.¹⁴⁴ Frazer was first to demonstrate that chronic treatment with SSRIs down-regulated SERT (serotonin transporter)¹⁴⁵ and that the ovarian hormones, estradiol and progesterone could inhibit the ability of SSRIs to slow the clearance of 5HT.¹⁴⁶ Screening for potential antidepressants with the forced swimming test, Frazer and his associates found a dose dependent improvement of "behavioral despair" with leptin, a hormone with receptors in limbic structures, secreted by adipose tissues.¹⁴⁷

Two interviewees (Wurtman and Sanders-Bush) contributed to the neuropharmacology of **serotonin**. In the early 1970's *Richard Wurtman*, in collaboration with John Fernstrom demonstrated that administration of tryptophan increased brain 5HT.¹⁴⁸ They, had also shown increase in brain serotonin following ingestion of a carbohydrate diet.¹⁴⁹ Wurtman, a disciple of Axelrod, discovered in the mid-1960's that melatonin is synthesized in the pineal gland and the synthesis of melatonin is controlled by light.^{150,151} He also revealed that the NE content of the pineal gland changes during the 24 hour diurnal rhythm.¹⁵²

Elaine Sanders-Bush, a disciple of Sulser, was one of the first to demonstrate that there are multiple serotonin receptors; she also described their regional distribution.¹⁵³ In the mid-1980s, Sanders-Bush discovered that calcium was a second messenger of the 5HT-2 family of 5HT receptors.¹⁵⁴

Two interviewees (Berger and Lal) contributed to the neuropharmacology of **anxiolytics**. In the mid 1940's, *Frank Berger* found that mephenesin produced reversible flaccid paralysis in mice.¹⁵⁵ He also noted that animals became quiet and "tranquilized" after small doses of the drug.¹⁵⁶ Berger was instrumental in synthesizing, developing, and introducing meprobamate,¹⁵⁷ a substance with a similar pharmacological profile to mephenesin but with a longer duration of action.¹⁵⁸

Harbans Lal developed a pentylenetetrazol-induced model of anxiety for studying the anxiolytic effect of drugs.^{159,160} Lal was first to show that centrally acting antimuscarinic drugs antagonized the effect of neuroleptics on apomorphine induced aggression but not of the effect of morphine.¹⁶¹

Three interviewees (Iversen, Paul and Enna) contributed to the neuropharmacology of **γ -aminobutyric acid**. *Leslie Iversen*, a disciple of Axelrod¹⁶² was first, in the 1960s, to demonstrate a calcium dependent release of GABA in crustaceans in response to stimulation of an inhibitory nerve.^{163,164} He was also first to demonstrate GABA uptake mechanisms in the mammalian brain.¹⁶⁵ In the 1970's Iversen found that naloxone, an opiate antagonist, blocked morphine's suppressant effect on the release of Substance P from the sensory nuclei of the brain and spinal cord.^{166,167}

In the late 1970s, *Steven Paul* and his associates demonstrated the action of benzodiazepines, ethyl alcohol and barbiturates on the GABA receptor system.¹⁶⁸ Paul was first to show the binding of imipramine to the 5HT transporter in man.¹⁶⁹ In the late 1980s he had discovered neuroactive progesterone metabolites in the brain and showed that these metabolites interacted with the GABA receptor system.^{170,171}

Salvatore Enna, contributed to the delineation of the biochemical properties of the GABA receptor system and to the demonstration of correspondence between GABA receptors and benzodiazepine recognition sites.¹⁷² In collaboration with Sands and Reisman, Enna was first to demonstrate the effect of antidepressants on GABA function.¹⁷³

Two interviewees, Fuxe and Dahlström, both students of Nils-Åke Hillarp, mapped the major **DA, NE and 5HT pathways** in the brain with the use of fluorescence histochemistry, a technique developed by Falck and Hillarp.^{174,175,176} In the late-1960s, *Kjell Fuxe*, in collaboration with Anden, Corrodi and Hökfelt had shown that hallucinogenic drugs of the indolealkylamine types, such as LSD, activated post-synaptic 5HT receptors in the brain.¹⁷⁷ In the mid-1970's, in collaboration with Luigi Agnati, he demonstrated that bromocriptine

was a dopamine agonist. In the early 1980s, Fuxe and Agnati introduced the concept of intra-membrane, receptor-receptor interactions;¹⁷⁸ and in the mid-1980s, they demonstrated a slow, “volume transmission,” in the brain¹⁷⁹ that involves the diffusion and “convection” of transmitters and modulators in the extra-cellular and cerebrospinal fluid.^{180, 181}

Annica Birgitta Dahlström and Kjell Fuxe were first in the mid-1960’s to demonstrate the presence of monoamines in the cell bodies of brain stem neurons.¹⁸² They were also first to show experimentally-induced changes in the intraneuronal amine levels of bulbospinal neurone systems.¹⁸³ In the late 1960’s Dahlström discovered axonal transport mechanisms¹⁸⁴ and identified two groups of adenosinetriphosphatase molecules, one involved in the fast transport from the cell body to the nerve endings, and the other in “retrograde transport.”¹⁸⁵

Three interviewees (Pert, Akil and Barchas) contributed to the neuropharmacology of **neuropeptides \ endorphins**. In 1973, *Candace Pert*, a student of Solomon Snyder, was one of the first to discover the opiate receptor.¹⁸⁶ She also localized in the rat brain the receptor with the employment of autoradiography.¹⁸⁷ In 1986, Pert identified T (thymus) peptide that blocks HIV (human immunodeficiency virus) infection.¹⁸⁸

Huda Akil, in the mid-1970s found that analgesia induced in rats by electrical stimulation of the brain, was blocked by the administration of naloxone, a morphine antagonist.¹⁸⁹ She was the first to demonstrate that stress increased endorphin levels.¹⁹⁰ Akil, in collaboration with Stanley Watson, mapped the distribution of different endorphins in the brain.¹⁹¹

Jack D. Barchas was member of the team which demonstrated the presence of dynorphin 1-8 in hypothalamic magnocellular neurons in the 1980s.¹⁹² He was also member of the team which isolated metorphamide, an amidated octopeptide from bovine brain.¹⁹³ Focusing on neuropeptides, Barchas and his associates had shown the release of BAM 18, a product of peptide E, in response to stimulation.¹⁹⁴ They had also shown that dynorphin 1-8, and α -endorphin, are localized in the same cerebral systems.¹⁹⁵

Three interviewees (Agranoff, Barondes, and Jarvik) contributed to the elucidation of the **biochemistry of memory**. *Bernard Agranoff*, in the 1950s, discovered cytidine diphospho-diacylglycerol, a substance important as an intermediate in the phosphoinositide cycle and in signal transduction.¹⁹⁶ He also demonstrated a competition between dietary choline and inositol in growing chicks.¹⁹⁷ In the mid-1960s Agranoff had shown that administration of actinomycin D, a substance that blocks RNA synthesis, impaired retention.¹⁹⁸ He had also shown that administration of puromycin, a substance that blocks protein synthesis, produced retrograde amnesia in goldfish.^{199,200}

The relationship between protein synthesis and memory storage was further substantiated by *Samuel Barondes* demonstration that cycloheximide produced impairment of long-term memory in mice.^{201,202,203,204} During the 1970s and 1980s Barondes discovered sugar binding proteins, called lectins, in slime molds, and suggested that lectins play a role in cellular connections and interactions.²⁰⁵ He also identified a family of animal β -galactoside-binding lectins, he referred to as galactins, in chicken, mouse, frog, and human tissues, including the brain.²⁰⁶

Murray E. Jarvik collaborated with Barondes in studying the effect of actinomycin D on brain RNA synthesis and memory.²⁰⁷ He corroborated evidence for the negative effect of protein synthesis inhibition on memory.²⁰⁸ In the 1980s Jarvik's research shifted from memory to smoking and in the 1990's he introduced, a "nicotine patch" that released nicotine through the skin.²⁰⁹ Jarvik was first to show that bromocriptine, a dopamine agonist, decreased smoking.²¹⁰

Interviewees included in Volume 3 entered the field at different stages in the development of neuropsychopharmacology. Hence, the transcripts cover fifty years of history, from the introduction of the spectrophotofluorometer to the introduction of molecular genetic techniques. During these fifty years research in neuropharmacology extended from synaptic events, measured by neurotransmitter metabolism, to intracellular events, measured by protein synthesis and breakdown, and from the first to the third messenger systems in defining the action of psychotropic drugs.

Fridolin Sulser, the editor of this volume, was one of the leaders in the field during the neurotransmitter era. His research has been a moving force in the elucidation of the mode of action, and in the development of antidepressants. His Introduction and Dramatis Personae complement the information covered in the interviews.

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ABBREVIATIONS

A	adenosine
AB	Arts' Bachelor
ACE	acetylcholine esterase; angiotensin converting enzyme
Acetyl Co	acetyl coenzyme A
ACh	acetylcholine
ACNP	American College of Neuropsychopharmacology
ACTH	adrenocorticotrophic hormone
AF64A	acethylcholine mustard aziridinium
AD	Alzheimer's disease
ADD	attention deficit disorder
AIDS	acquired immune deficiency syndrome
AMP	adenosine monophosphate
ANU	Australian National University
APN	aminopeptidase N
APP	amyloid precursor protein
ASN	American Society for Neurochemistry
ASPET	American Society of Pharmacology and Experimental Therapeutics
ATP	adenosinetriphosphate
ATPases	adenosinetriphosphatases
BAM-18	opioid peptide that antagonizes morphine analgesia
BBC	British Broadcasting Corporation
BCCM	beta carboline carboxylic acid
BDNF	brain derived neutrotrophic factor
BPAP	benzofuramylaminopentane
BRS	broadband radio service
BS	Bachelor of Science
BSc	Bachelor of Science
C	cytosine
CA	California; catecholamines
cAMP	cyclic adenosine monophosphate
CANMB	cholinergic alert non-mobile behavior
CAR	conditioned avoidance reflex
CAT	choline acetyl transferase
CC	chemokinine
CCK	cholecystokinin
CCNY	City College New York
CCR	chemokine receptor

cDNA	complementary DNA
CDP	cytidinediphospho
CEO	chief executive officer
CFY	specialty bred rats with a larger striatum
cFos	immediate early gene belonging to the Fos family
CGPT	calcitonin gene related peptide
CINP	Collegium Internationale Neuro Psychopharmacologicum
CNS	central nervous system
COMT	catechol-O-methyltransferase
COX	cyclooxygenase
CPZ	chlorpromazine, Largactil
CRC	clinical research center
CRE	cyclic AMP response element
CREB	cyclic AMP response element binding protein
CREB-P	phosphorylated CREB
CS	conditioned stimulus
CSF	cerebrospinal fluid
CT	Connecticut
CTP	cytidine 5-triphosphate
D2	dopamine-D2 receptor
DA	dopamine
DAG	diacylglycerol
DARPP-32	dopamine and cyclic AMP regulated phosphoprotein MW=32 kDa
Dapson	diamino diphenyl sulfone
DATATOP	deprenyl and tocopherol antioxidative therapy of Parkinsonism
DC	District of Columbia
DHPG	dihydroxyphenylethylene-glycol
DMI	desmethylinipramine, desipramine
DNA	deoxyribonucleic acid
DNRI	dopamine and norepinephrine reuptake inhibitor
DoD	Department of Defense
DOPA	3, 4-dihydroxyphenylalanine
DPN	diphosphopyridine nucleotide
DSc	Doctor of Science
ECR	extinguishable conditioned reflex
ECT	electroconvulsive therapy; electroshock
EEG	electroencephalography
EPS	extrapyramidal signs (symptoms)
ER	enhancer receptor

ES	enhancer substance
FASEB	Federation of American Societies of Experimental Biology
FBI	Federal Bureau of Investigation
FDA	Food and Drug Administration
FG 7142	N-methyl-9H-pyrido [5, 4] indole-3 carboxamide
FK 506	fujimycin
FL	Florida
fMRI	functional magnetic resonance imaging
FTC	Federal Trade Commission
G	guanine
GABA	γ -aminobutyric acid
GABAB	γ -aminobutyric acid type B receptors
GDNF	glial cell-derived neurotrophic factor
GI bill	Serviceman's Re-adjustment Act
GLC	gas liquid chromatography
GM	glutamatergic
GMP	guanosine monophosphate
Gp	glycoprotein
6-HDA	6-hydroxydopamine
5-HIAA	5-hydroxyindoleacetic acid
HIV	human immunodeficiency virus
HMPG	4-hydroxy-5-methylphenylglycol
HP	highest performing
HPLC	high pressure liquid chromatography
5-HT (5HT)	5-hydroxytryptamine, serotonin
5-HTP	5-hydroxytryptophan
IBRO	International Brain Research Organization
ICR	inextinguishable conditioned reflex
IIT	Illinois Institute of Technology
IL	Illinois
IN	Indiana
IP3	inositoltriphosphate
IUPHAR	International Union of Pharmacology
IUPS	International Union of Physiological Sciences
ISCM	International Symposia of Cholinergic Mechanisms
ISN	International Society for Neurochemistry
IV	intravenous
JAMA	Journal of the American Medical Association
JBC	Journal of Biological Chemistry
KD	konstant dissociation
LCS	Laboratory of Clinical Science

L-DOPA	levodopa
LH	luteinizing hormone
LP	lowest performing
LR	latency relaxation
LSD	lysergic acid diethylamide
LU	Loyola University
LUMC	Loyola University Medical Center
M	molar
MA	Massachusetts
MAO	monoamine oxidase
MAO B	monoamine oxidase B
MAOI	monoamine oxidase inhibitor
MAP	microtubule associated protein
MCI	mild cognitive impairment
Md	Maryland
MD	medical doctor
MGH	Massachusetts General Hospital
mGluR	metabotropic glutamate receptor
MHPG	3-hydroxy-4-hydroxyphenylglycol
MHRI	Mental Health Research Institute
MIT	Massachusetts Institute of Technology
MPTP	1-methy-4-phenyl-1,2,3,6-tertahydropyridine
MRC	Medical Research Council
MRI	magnetic resonance imaging
mRNA	messenger RNA
MRC	Medical Research Council
MS	Master of Science
NA	noradrenaline
NADP	nicotinamide adenine dinucleotide phosphate
NaF	sodium fluoride
NARI	selective noradrenaline reuptake inhibitors
NAS	National Academy of Sciences
NaSSA	noradrenergic and selective serotonergic drugs
NE	norepinephrine
NIAID	National Institute of Allergy and Infectious Diseases
NIC	National Institute of Cancer
NGF	nerve growth factor
NIDA	National Institute of Drug Abuse
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health

NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Diseases and Stroke
NJ	New Jersey
NK	neurokinin
NMDA	N-methyl-D-aspartate
NO	nitric oxide
NPR	neuropharmacological research
NSF	National Science Foundation
NY	New York
NYU	New York University
OCD	obsessive compulsive disorder
OP	organophosphorus
OR	operating room
PAG	periaqueductal grey region
PA	Pennsylvania
PD	Parkinson's disease
PEA	phenylethylamine
PET	positron emission tomography
PhD	doctor of philosophy
PKA	proteinkinase A
PMS	premenstrual syndrome
PNAS	Proceedings of the National Academy of Sciences
PMA	phorbol-12-myristate-13-acetate
PNMT	phenyl-N-methyltransferase
PPAP	1-phenyl-2-propylaminopentane
3PPP	preclamol
PR	public relations
PTT	pentylenetetrazol
PTZ	pentetrazole
QNB	quinuclidnyl benzilate
Rf	retention factor
RNA	ribonucleic acid
RO1	research project grant
Ro 4-1284	2-Ethyl-1,3,4,6,7,11b hexahydro-3-isobutyl-9-10-dimethoxy-2H-benzo[a]quinoxiline-2-ol hydrochloride
Ro 5-0690	chlordiazepoxide
RS ligands	Reed-Sternberg ligands
SAMe	S-adenosylmethionine
SAR	structure activity relationship
SDS	sodium dodecyl sulfate
SERT	serotonin transporter

SKF-525A	β -diethylaminoethyl diphenylpropylacetate hydrochloride
SMA	serotonin modulators
SNRI	serotonin and norepinephrine reuptake inhibitors
SP	substance P
SPEC	spectrophotofluorimeter
SS	Schutzstaffel
SSRI	selective serotonin reuptake inhibitors
T	thymine
THC	tetrahydrocannabinol
TN	Tennessee
TNI	Tennessee Neuropsychiatric Institute
TLSh	technical life span
TPA	tissue plasminogen activator
TPN	triphosphopyridine nucleotide
TPNH	reduced triphosphopyridine nucleotide
TRH	thyrotropin releasing hormone
U	uracil
UBC	University of British Columbia
UC	University of California; University of Chicago
UCLA	University of California Los Angeles
UCSF	University of California San Francisco
UCSD	University of California San Diego
UK	United Kingdom
UNT	University of North Texas
US	unconditioned stimulus
USA	United States of America
UTP	uridine triphosphate
VA	Veterans Administration
VMA	vanillylmandelic acid
VT	volume transmission
Washington U	Washington University
WHO	World Health Organization
WT	wiring transmission
YMCA	Young Men's Christian Association

INTRODUCTION & DRAMATIS PERSONAE

Fridolin Sulser

This volume contains autobiographical sketches and insight into scientific contributions to Neuropsychopharmacology by some of the founders of our field as it developed from classical neuropharmacology to molecular neurobiology. Historically, the most pertinent scientific catalyst with worldwide influence was the “Brodie School” with its first and second generation pupils, representing about half of the contributors to volume 3. The “Brodie School” launched the Neurotransmitter Era in Neuropharmacology (e.g., Axelrod, Carlsson, Greengard, Pletscher, Kopin, Snyder, Spector, Sulser). Four contributors – Axelrod, Carlsson, Greengard and Kandel – received the Nobel Prize for their pioneering contributions to our field. The contributions to this volume are also testimony to the importance of the role of new methodology in advancing science. It is these new methodologies that catalyzed the birth of the Neurotransmitter Era in Neuropharmacology. Thus, the invention of spectrofluorometric methodology in the early 1950’s made it possible to analyze quantitatively minute amounts of biogenic amines in brain. Using this new methodology, Pletscher, Shore and Brodie demonstrated in 1956 that reserpine’s tranquilizing action is associated with a dose – dependent depletion of brain serotonin. This was a historic finding as it catalyzed worldwide research on the neurobiology of serotonin, dopamine and norepinephrine. As, pointed out by Edward Shorter in his introduction to volume 1, “This made it possible to link specific pharmacologic agents and neurochemicals to given behavioral changes”. Another powerful technique, fluorescence histochemistry developed by Falck and Hillarp made it possible for Carlsson, Fuxe and Dahlström to study the putative neurotransmitters and their regulation at the cellular level. The Swedish group, represented in this volume, discovered the nigro-striatal dopamine system, the mesolimbic and the tubero-infundibular dopamine system. They mapped the major ascending and descending brainstem norepinephrine systems from the pons, mainly the locus coeruleus, and the brainstem serotonin systems from the caudal and rostral raphe nuclei. As pointed out by Kjell Fuxe in his interview with Tom Ban, “It was the dawn of chemical neuroanatomy.” A third revolutionary advance was the availability of radioactive isotopes. Using tritiated NE, Axelrod discusses in this volume the important discovery of the presynaptic reuptake of biogenic amines in peripheral and central monoaminergic neurons as a means to terminate the biological responses of NE. This discovery was followed by the finding that tricyclic antidepressants enhanced noradrenergic activity by blocking the

neuronal reuptake of NE in peripheral and central noradrenergic neurons. Then, Carlsson demonstrated that tricyclic antidepressants also inhibited the reuptake of serotonin into central serotonergic neurons with tertiary amines of tricyclics being more potent in blocking the reuptake of 5HT than the corresponding secondary amines and secondary amines being more potent in inhibiting the reuptake of NE. Besides providing simple screening techniques for the discovery of new antidepressants, these findings contributed further to the clinically relevant monoamine hypotheses of depression. The sophisticated use of radiolabeled agonists and antagonists and the rapid filtration technique of Cuatrecasas led to the discovery of the opiate receptor by Pert and Snyder, the discovery of subtypes of 5HT and DA receptors and also catalyzed studies on the function of β -adrenoceptors. James V. Dingell's research demonstrates the power of solvent extraction procedures and quantitative fluorometric analysis of drugs and their metabolites in brain and other tissues. The studies by Irv Kopin contributed significantly to the understanding of catecholamine metabolism and the role of false transmitters while Wurtman and Axelrod elucidated the function of melatonin and the diurnal rhythm of pineal gland function. Inspired by studies carried out by Earl Sutherland on cyclic AMP, synaptic transmission was carried beyond the receptors to second messenger mediated cascades. Greengard discusses eloquently in this volume the neurobiology of neurotransmitter mediated signaling and the importance of second messenger mediated protein kinase activation. His studies on DA sensitive adenylate cyclase and the phosphorylation by cyclic AMP stimulated protein kinase A of substrates such as DARPP-32, as a bi-functional molecule, are classics in the molecular neurobiology of signal transduction. He establishes that protein phosphorylation is the major molecular event causing changes in signal transduction in brain. Besides the DA sensitive adenylate cyclase mediated by the D1 subclass of DA receptors, there are now several neurotransmitter sensitive adenylate cyclases known. The discovery of the coupling of various receptors via G-proteins to adenylate cyclase or guanylate cyclase, forming the second messenger cyclic AMP or GMP respectively, was a major advance in the elucidation of the principles of slow synaptic transmission. It now seems very likely that all of the biogenic amines and peptide neurotransmitters exert their effects on their target cells through slow synaptic transmission.

With regards to the action of psychotropic drugs on noradrenergic "post-receptor" events, Sulser and his colleagues demonstrated that antidepressant treatments (including ECT), if applied on a clinically relevant time basis, caused a net deamplification of the NE signal. Conceptually, these studies switched the emphasis in understanding the mode of action of antidepressants and the pathophysiology of affective disorders from acute presynaptic

to delayed postsynaptic second messenger mediated events. They opened the gateway for subsequent studies of events beyond the receptors including changes in programs of gene expression. Eric Kandel beautifully analyzed the molecular biology of memory storage using his classical aplysia preparation.

The Neurotransmitter Era in Neuropharmacology has also witnessed the arrival of new drugs; imipramine by Roland Kuhn,, meprobamate by Frank Berger, iproniazid and synthetic benzoquinolizines by Alfred Pletscher, the MAO-B inhibitor deprenyl by Joseph Knoll, aripiprazole, sumatripan and zolpidem by Salomon Langer, and clozapine by Hanns Hippus. (See, Hippus, Volume 1.) The arrival of efficacious pharmacological treatments for psychiatric disorders is expertly discussed by Thomas Ban in his Preface to Volume 1.

Collectively, the interviewees in this volume have been responsible for the epochal changes in neuropharmacology and neuroscience in general. And yet, as pointed out by Samuel Barondes, despite all the sophisticated new methodologies and the advances in our understanding of synaptic transmission, the scientific advances have not translated into equal improvements in the pharmacotherapy of mental illness. But as future research in the Neurotransmitter Era is shifting its emphasis to the functional relevance of changes in programs of gene transcription (as modified, via neurotransmitter-receptor-second messenger transduction cascades,) new targets for psychotropic drugs will emerge, targets for drugs which promise to treat the disease rather than the symptoms of the disease. I am optimistic!

Dramatis Personae

The following pages introduce the dramatis personae of Volume Three and provide a framework to understand their achievements.

Bernard W. Agranoff received his MD in 1950 from the Wayne State School of Medicine in Detroit, Michigan. Following an internship at the Guthrie Clinic, he was awarded a postdoctoral fellowship by the National Foundation for Infantile Paralysis to train under the guidance of F.O. Schmidt in the Biology Department of MIT. In 1952, the navy recalled him as a medical officer to run the clinical chemistry facility at the US Naval Medical Center in Bethesda, Md. He then joined Roscoe O. Brady in the Section of Lipid Chemistry, Laboratory of Neurochemistry, at the National Institute of Neurological Diseases and Blindness. There, in 1957, he discovered a novel compound, cytidinediphosphodiacylglycerol that reacted with free inositol to form phosphatidylinositol. After a sabattical year with Feodor Lynen at the Max Planck Institute of Biochemistry in Munich, working on cholesterol synthesis, he accepted a joint appointment as a Research Biochemist in the MHRI and Associate Professor at the University of Michigan, Ann Arbor. There, his pioneering studies on

biochemical mechanisms on learning and memory were initiated, with the protein doubled p68/70 emerging as a promising marker for biochemical studies on learning and memory. More recently, he has extended his interests to functional imaging of the brain in both animals and man. Agranoff's career is characterized by the integration of biochemistry with the function of the nervous system. From 1985 to 1995, he was Director of the MHRI and served on the editorial boards of a large number of scientific journals. He also served as President of the ASN and as Chairman of the ISN. His achievements have been recognized by a number of honors and awards. He is a member of the Institute of Medicine of the NAS, was selected for the Michigan Scientist of the Year Award, the Distinguished Faculty Achievement Award, the NIH Fogarty Scholar-in-Residence Award, just to mention a few.

Huda Akil received her PhD degree in Psychobiology in 1972 from the University of California, Los Angeles, CA. After postdoctoral studies in the Department of Psychiatry at Stanford University, she moved to the University of Michigan where she occupied a number of academic positions: Assistant and Associate Professor of Psychiatry, and then Professor of Psychiatry and Director of Research in Psychiatry. Since 1995, she is Co-Director of the MHRI of the University of Michigan. Huda Akil's early work focused on the physiology and pharmacology of two models of analgesia, analgesia produced by electrical brain stimulation and by stress. Together with her husband, Stan Watson, she employed, in a series of elegant studies, immunohistochemistry to map the anatomy of the endorphin system and of dynorphin in brain. They then mapped the localization of pro-opiomelanocortin derived peptides in brain. The regulation of the biosynthesis of beta endorphin in brain represents one of their other fascinating studies. Coming from psychology, it is amazing how she became proficient in using pharmacological, electrophysiological, behavioral, biochemical and molecular tools to get answers on the anatomy, regulation and function of neuropeptides in brain. It is the integrative approach that characterizes Huda Akil's research on endogenous opiate peptides. She serves on numerous Editorial Boards of journals in the neuropeptide area and on many national and international committees dealing with neuropeptide research. She is the recipient of the Penrose Award, the NIDA Pacesetter Award, and the co-recipient with Stan Watson of the Robert J. and Claire Pasarow Foundation Award. She was elected a Member of the Institute of Medicine of the National Academy of Sciences.

Julius Axelrod is one of the most celebrated and beloved pupils of the Brodie School. His early work with Brodie at the Goldwater Memorial Hospital in New York included studies on drug metabolism and the development of methods to analyze the parent drug and/or its metabolites. When Brodie moved to the newly created NIH, he joined his old boss in the Laboratory

of Chemical Pharmacology. What followed was a series of brilliant studies that included the discovery of microsomal enzymes (P450 enzymes) responsible for the metabolism of drugs by methylation and deamination. While working towards his PhD degree at George Washington University, he was asked to teach a course in drug metabolism. At age 43, in 1955, he received his PhD degree from George Washington University and joined the NIMH when Seymour Kety was director of the intramural program. There, his work on drug metabolism continued with the demonstration that glucuronide conjugation was a major mechanism for detoxifying drugs. In 1955, he became Chief of the Section on Pharmacology in the Laboratory of Clinical Science. The discoveries in drug metabolism were followed by the discovery of enzymes important in the synthesis and metabolism of catecholamines; COMT and PNMT. Equally imaginative were his studies with Sol Snyder and Dick Wurtman on the formation and metabolism of melatonin and the clinical rhythm of pineal gland function. In brilliantly designed experiments with tritiated NE, Axelrod and George Hertting discovered the high affinity re-uptake mechanism into presynaptic noradrenergic neurons as a means to terminate the action of NE. It was followed by the discovery that cocaine and tricyclic antidepressants such as DMI enhanced the action of NE by blocking this high affinity uptake into noradrenergic neurons. Julie Axelrod was a member of many national and international societies including the National Academy of Sciences, the ACNP, the CINP, the ASPET, the Society for Neuroscience, and the International Society for Neurochemistry. He was also foreign corresponding member of the Royal Society (London) and the Deutsche Akademie der Naturforscher (Berlin). He served on numerous national and international editorial boards, too many to mention. He received at least 12 honorary degrees in the USA and abroad. He was an inspiring mentor of a large group of talented young "second generation Brodie pupils" from the USA and abroad, including Irv Kopin (USA), Sol Snyder (USA), Richard Wurtman (USA), George Hertting (Austria), Jaques Glowinski (France), Hans Thoenen (Switzerland), Leslie Iversen (UK), Ross Baldessarini (USA), Joseph Schildkraut (USA), Saul Schanberg (USA), George Breese (USA), Tom Chase (USA), and Goran Sedvall (Sweden). In 1970, Julie Axelrod received the Nobel Prize in Physiology and Medicine.

Jack D. Barchas received his MD in 1961 from the Yale University School of Medicine. After one year as a Medical Intern at the University of Chicago and two years as a Research Associate at NIH, working with Sidney Udenfriend, Herbert Weissbach and Sidney Spector, he completed his Psychiatry residency at Stanford in 1967 where he moved through the academic ranks from Instructor to Professor of Psychiatry. He was also Director of the Nancy Pritzker Laboratory of Behavioral Neurochemistry and Associate Chairman of

Psychiatry and Behavioral Sciences. In 1990, he moved to UCLA where he was Associate Dean for Neuroscience and then Dean of Research Development and Neuroscience. At present, he is the Barklie Mc Kee Henry Professor and Chairman of the Department of Psychiatry at Cornell University Medical College and Psychiatrist-in-Chief at the New York Presbyterian Hospital. Jack Barchas's scholarly activities have centered on the study of compounds which function as neurotransmitters or modulators of neuronal activity. The program of what became the Nancy Pritzker Laboratory of Behavioral Neurochemistry had a five-prong research effort; molecular regulation, behavioral neuroanatomy, analytical neurochemistry, behavioral neurochemistry and clinical biochemistry and pharmacology. He is best known for his studies on endorphins, their localization in brain and their role in behavioral manifestations such as learned helplessness and certain types of conditioned learning. His group discovered BAM-18, a peptide that antagonizes morphine analgesia. Together with Phil Berger, Glen Elliott and Roland Ciaranello, he published a very popular textbook of psychopharmacology. His more recent scholarly activities deal with biochemical science policy. He is a member of many professional societies including the ACNP, the American Society for Neurochemistry, the ASPET, the Society for Neuroscience, and the Association for Research of Nervous and Mental Diseases. Among his honors, Jack Barchas counts the A.E. Bennet Award of the American Society of Biological Psychiatry, the Daniel Efron Award of ACNP, and membership in the Institute of Medicine of the National Academy of Sciences (USA.).

Samuel H. Barondes received his AB summa cum laude in 1954 and his MD in 1958 from Columbia University, New York. Determined to become an endocrinologist, he went in 1959 to the Peter Bent Brigham Hospital for internship and residency in medicine. In order to avoid the draft, he joined the US Public Health Service at the NIH as a Clinical Associate and Postdoctoral Fellow. It is there he developed his love for Molecular Biology, interacting with Marshall Nirenberg, Gordon Tomkins, Heinrich Mathaei and Julius Axelrod. From 1966 to 1969, he was Assistant then Associate Professor of Psychiatry and Molecular Biology at Albert Einstein College of Medicine, Bronx, New York. In 1969, he accepted the position of Professor of Psychiatry at the University of California, San Diego. In 1986, he moved to San Francisco to become Chair of the Department of Psychiatry and Director of the Langley Porter Psychiatric Institute. After stepping down from the chairmanship, he founded the Center for Neurobiology and Psychiatry. The goal of his research has been bringing molecular biology to psychiatry. He studied the role of protein and RNA synthesis in learning and memory and of sugar binding proteins as a way of studying cell-cell connections. He discovered a number of lectins that play a role in cell interactions, first in slime molds and then in

mammalian cells. Sam Barondes served on numerous committees of national and international organizations, among them The McKnight Foundation is of particular interest. For 20 years, he was on the Board of their Endowment Fund for Neuroscience; for 10 years as its president. The Foundation provides funds to excellent young basic scientists to help them start working on clinically relevant problems, a theme close to Sam Barondes's heart. He has written three books, all on molecular research as it relates to psychiatry; *Molecules of Mental Illness*, *Mood Genes* and *Better than Prozac*. For his contributions to psychiatry, Sam Barondes received the J.Elliott Roger Award and the Stillmark Memorial Medal from Estonia, commemorating the 100th anniversary of the discovery of lectins.

Frank M. Berger received his MD in 1937 from the University of Prague. When Hitler occupied Czechoslovakia in 1939, he left the country for Great Britain. He spent 2 years as a general physician in a refugee camp and then as a microbiologist at British Drug Houses. In 1947, he moved to the USA and accepted a position as Assistant Professor in Pediatrics at the University of Rochester Medical School. In 1949, he joined Wallace Laboratories, Division of Carter-Wallace, and his illustrious career as both a researcher and executive began. He became Director of Research of Wallace Laboratories and President from 1958 to 1973. Frank Berger is best known as the developer of meprobamate, the first minor tranquilizer. After his retirement from the pharmaceutical industry in 1974, he moved to the University of Louisville, Kentucky where he became a Clinical Professor of Psychiatry. He is best known for organizing the International Symposia of Psychopharmacology at the University of Louisville where he brought together basic and clinical researchers for synergistic interaction and state of the art reviews. Frank Berger is a member of numerous professional and scientific societies including the ACNP, the CINP, the ASPET, the Society of Biological Psychiatry, and the British Pharmacological Society, just to mention a few. He is an Honorary Doctor of Science of the Philadelphia College of Pharmacy and Science, and recipient of the Czechoslovak National Prize for Scientific Research in 1938 and of the Taylor Manor Hospital Psychiatric Award.

Arvid Carlsson received both his MD and PhD degrees in 1951 from the University of Lund, Sweden, where he served subsequently as Assistant and Associate Professor. In 1959, he was appointed Professor of Pharmacology and Chairman of the department at the University of Gothenburg. From 1955 to 1956, he was a Visiting Scientist with Brodie at the Laboratory of Chemical Pharmacology, NIH, in Bethesda, Md. This visit changed his research interests from studies on calcium metabolism to neuropsychopharmacology, particularly the effect of drugs on the storage of biogenic amines. When Arvid returned to Sweden, he teamed up with Nils-Åke Hillarp, to study the action

of reserpine on catecholamines in brain and the reversal of the pharmacological action of reserpine by L-DOPA, which was closely associated with the formation and accumulation of DA in brain. They demonstrated that NE and DA were located in nerves and not in glia, findings that triggered the concept of chemical transmission in the central nervous system. Based on the distribution of NE and DA in striatal tissue, Carlsson and his collaborators proposed that DA is a neurotransmitter in its own right and not just a precursor of NE. He also demonstrated that antipsychotic drugs such as chlorpromazine and haloperidol affected the metabolism of NE and DA leading to the proposal that these antipsychotic drugs block DA receptors. The DA hypothesis of schizophrenia was born. Together with results obtained by Hornykiewicz and others, Carlsson's data contributed to our understanding of the role of striatal DA in Parkinson's disease and paved the way for treatment of Parkinson's disease with L-DOPA. In collaboration with Corrodi at Astra, Carlsson developed the first selective 5HT reuptake inhibitor, zimelidine, as an antidepressant. For his many pioneering contributions to neuropharmacology and biological psychiatry, Arvid Carlsson received numerous honors and awards; the Anna-Monika Award, the Wolf Foundation Prize, the Gairdner Foundation International Award, the Paul Hoch Distinguished Service Award of the ACNP, the Japan Prize for outstanding achievement in science and technology, the Lieber Prize for Schizophrenia Research and in 2000, the Nobel Prize for Physiology and Medicine.

Annica Birgitta Dahlström received her PhD degree in 1966 from the Karolinska Institute, Stockholm, Sweden and her MD in 1973 from the University of Gotheborg. From 1983 to 2008, she was Professor of Histology at the Institute of Neurobiology, University of Gotheborg and from 1992 to 1995 she served as Vice Chancellor of Gotheborg University. Dahlström is best known for her elegant studies in collaboration with Kjell Fuxe on the detailed mapping of catecholaminergic and serotonergic pathways in the brain, using the histofluorescence technique developed by her teacher Nils-Ake Hillarp. As Kjell Fuxe said, "it was the dawn of chemical neuroanatomy." She also did pioneering work on axonal transport and the role of ATPases as motors driving fast transport. Her publications, individual research papers and monographs, are classics in neuropsychopharmacology. Annica Dahlström is a member of many committees related to neuroscience. For her scientific achievements, she has received the Fernström Prize of the Fernström Foundation for Swedish and Nordic scientists in medicine, the Retzius Prize from the Karolinska Institute, and the Parkinson Foundation Medal. She has been elected a Fellow of the Royal Society of Arts and Sciences in Gotheborg and is an Honorary Professor at the Medical University of Shengyang, China.

James V. Dingell received his BS, MS and PhD degrees in chemistry from Georgetown University in Washington, DC. He worked from 1955 to 1962 as a chemist, predominantly with James R. Gillette in Brodie's Laboratory of Chemical Pharmacology. In 1962, he moved to the Department of Pharmacology at Vanderbilt University, in Nashville, TN, where he rose from Instructor to Assistant and Associate Professor of Pharmacology. In 1973, he spent his sabbatical year with R.T. Williams at St. Mary's Hospital Medical School in London, UK. After a number of administrative positions at the NIH in 1990 he became the Director of the Division of Basic Research at NIDA. His research focused on various aspects of drug metabolism; the dealkylation of N – alkylamines by model systems, the metabolism of tetrahydrocortisone by uridine diphosphate glucuronyltransferase, the metabolism and distribution of Delta 9 – tetrahydro – cannabinol, and the conjugation of 4 – hydroxy-amphetamine. Jim Dingell is best known for his extensive and systematic studies on the metabolism of imipramine, conducted at NIH and continued at Vanderbilt. In collaboration with James Gillette and Fridolin Sulser, he isolated from rat brain a metabolic product of imipramine, desmethyylimipramine (DMI) and worked out details of species differences in the metabolism of iminodibenzyl derivatives. While at Vanderbilt, he continued his collaboration with Fridolin Sulser on adrenergic mechanisms in the central action of tricyclic antidepressants and substituted phenothiazines, and the effect of chronic treatment with tricyclics and other antidepressants on the NE sensitive adenylate cyclase. At Vanderbilt, James Dingell also played a major role in the development of the Tennessee Neuropsychiatric Institute (TNI).

Salvatore J. Enna received his PhD in Pharmacology in 1970 from the University of Missouri. Following postdoctoral studies in pharmacology at the University of Texas, Southwestern Medical School, he worked at Hoffmann – La Roche in Basel with Alfred Pletscher. After further time in the Department of Pharmacology and Experimental Therapeutics at Johns Hopkins University Medical School, he moved to the University of Texas Medical School in Houston, where he served as Assistant, Associate and Full Professor of Pharmacology and Neurobiology. In 1986, he left academia for the Nova Pharmaceutical Corporation in Baltimore where he served as Scientific Director and Vice President. In 1992, he switched back to academia at the University of Kansas Medical School, Kansas City, Kansas where he assumed the Chair of the Department of Pharmacology, Toxicology and Therapeutics. Sam Enna's primary research activities focus on the function of GABA receptors and their role in the action of benzodiazepines. Importantly, Sam has always stressed the functional aspects of biochemical and molecular studies and put them into a clinically meaningful context. His research contributions were recognized by the Abel Award in Pharmacology from ASPET and the

Efron Award from the ACNP. He has been President of ASPET and is Editor in Chief of the Journal of Pharmacology and Experimental Therapeutics.

Hans Christian Fibiger received his PhD degree in 1970 from Princeton University, Princeton, N.J. In 1970, he moved to the University of British Columbia, Canada, where he became Assistant Professor in the Division of Neurological Sciences in the Department of Psychiatry. Subsequently, he became Associate and then Full Professor and Acting Head of the Department of Psychiatry. After 26 years at UBC, in 1998, he accepted an offer from Eli Lilly to become Vice President of Neuroscience. Subsequently, he joined Amgen, a biotech company, to head up a new neuroscience department. His research interests include studies on axonal transport, microanalysis of neurotransmitter release and the use of immediate early gene expression to study and map the activity of central neurons. At Lilly, he used gene expression to identify new targets for the treatment of psychiatric disorders. Hans Fibiger serves on numerous professional committees and the editorial boards of many journals. He has received many honors, among them the Heinz Lehmann Award of the Canadian College of Neuropsychopharmacology, and the Killam Research Prize from the National Research Council of Canada.

Alan Frazer received his BSc in chemistry in 1964 from the Philadelphia College of Pharmacy and Science and his PhD in pharmacology in 1969 from the University of Pennsylvania. He joined the Department of Psychiatry at the University of Pennsylvania, School of Medicine where he rose through the academic ranks from Instructor to Assistant Professor to Professor of Pharmacology in Psychiatry and Professor of Pharmacology. Parallel to his appointment at the university, he was Chief of the Neuropsychopharmacology Unit of the Veterans Administration Medical Center in Philadelphia, PA. In 1993, he moved to the University of Texas, Health Science Center in San Antonio, assuming the chairmanship of the Department of Pharmacology and as Career Scientist at the Veterans Administration Hospital. Alan Frazer's research is characterized by the careful design of preclinical studies that are therapeutically relevant. He was one of the first preclinical investigators who used chronic treatment of laboratory animals with antidepressant drugs. He was also one of the first investigators to show that acute and chronic treatment with antidepressants affected the noradrenergic cyclic AMP system in brain differently; chronic but not acute administration caused a down-regulation of the β -adrenergic cyclic AMP system. He also showed that chronic but not acute administration of either MAO inhibitors or 5HT agonists decreased tritiated serotonin binding in rat brain. Alan and his associates are among the first investigators to use the technique of in vivo voltammetry to look at transporter function in vivo. Alan Frazer is a member of many editorial boards and currently Editor-in-Chief of the International Journal of

Neuropsychopharmacology. He succeeded Oakley Ray as Secretary of the ACNP.

Kjell Fuxe received his MD degree in 1965 from the Karolinska Institute in Stockholm, Sweden. He became an Associate and then Full Professor of Histology at the Karolinska Institutet. Kjell Fuxe is a pupil of Nils-Ake Hillarp. He used Hillarp's technique of fluorescence histochemistry to map, in collaboration with Annica Dahlström, the major DA, NE and 5HT pathways in brain; the nigro-striatal, mesolimbic and tubero- infundibular DA systems, the major descending and ascending brain stem NE systems, and the brain stem 5HT systems. These were very significant contributions, at "the dawn of chemical neuroanatomy". In collaboration with Arvid Carlsson he eloquently demonstrated the preferential uptake blockade by antidepressants, of either 5HT or NE in the surface membrane of central 5HT or NE neurons. Together with Luigi Agnati, Fuxe developed the new concept of intramembrane receptor – receptor interactions and the concept of volume transmission. Kjell Fuxe's many significant contributions to our understanding of the functional anatomy of the brain and their impact on neuropsychopharmacology were honored by a large number of awards, e.g., the Italian Prize, the Hilda and Alfred Erikssons Prize of the Swedish Royal Academy, the German Humboldt Prize Award, and four Honorary Doctor degrees. Kjell Fuxe is also a prolific writer: He has published about 1233 papers, over 620 abstracts and edited 21 books!

Silvio Garattini received his MD. in 1954 from Torino University in Italy. After a short tenure as Assistant Professor in the Department of Pharmacology at the University of Milano, he established, under the will of Mario Negri in 1960, the Mario Negri Institute of Pharmacological Research and was named its first Director. Silvio Garattini and Erminio Costa were the first to show that chronic treatment with imipramine antagonized some of the behavioral effects elicited by reserpine. The "reserpine reversal test" became a popular test for screening antidepressants. Garattini and his associates also studied the metabolism of many psychotropic drugs. The Mario Negri Institute with its three research domains; cancer, cardiovascular diseases and psychopharmacology is the major achievement of Silvio Garattini. It has achieved a large international reputation as a center for advanced pharmacological research. Silvio Garattini is a member of numerous editorial boards and counts among his awards the Honor of the French Republic, and "Commendatore" of the Italian Republic. He is Doctor Honoris Causa of the Universities of Barcelona (Spain) and Bialystok (Poland).

Paul Greengard received his PhD in 1953 from the Johns Hopkins University, Baltimore, Md. After extensive postdoctoral training at the Institute of Psychiatry, University of London, at the National Institute for

Medical Research, London and the Laboratory of Clinical Biochemistry, NIH, Bethesda, he accepted, in 1959, the position of Director of the Department of Biochemistry of the Geigy Research Laboratories in Ardsley, NY. In 1968, he switched to academia as Professor of Pharmacology and Psychiatry at the Yale University School of Medicine, New Haven, CT. In 1983, he assumed his present position as Vincent Astor Professor and Head of the Laboratory of Molecular and Cellular Neuroscience at the Rockefeller University, New York. Paul Greengard's major contributions are in the area of neurotransmitter sensitive adenylate cyclases in the central nervous system and second messenger activation of protein kinases that mediate actions of neurotransmitters. He has demonstrated that protein kinase mediated phosphorylation is the major molecular event in signal transduction in brain. He has isolated and characterized a number of important protein substrates for the protein kinases; synapsin 1 and synapsin 2, involved in controlling the efficiency of neurotransmitter release and synaptogenesis, and DARPP 32 which plays an important role in mediating the actions of DA. In elegant studies, Greengard demonstrated that DARPP 32 is a bifunctional molecule that, dependent on the site of phosphorylation, can be either a protein phosphatase inhibitor or a protein kinase inhibitor. Paul Greengard serves on numerous editorial boards and is a member of the National Academy of Sciences. His pivotal contributions to understanding of slow synaptic transmission have earned him many honors and awards; the Dickson Prize and Medal in Medicine, the Pfizer Biomedical Research Award, the Academy of Sciences Award in Neurosciences, the Goodman and Gilman Award, the Ralph W. Gerard Prize in Neuroscience, and an Honorary Doctor of Medicine from the Karolinska Institutet. In 2000, he received the Nobel Prize in Physiology and Medicine.

Leslie Lars Iversen received his PhD in Biochemistry and Pharmacology in 1964 from Trinity College, Cambridge, UK. He spent a postdoctoral year with Julius Axelrod at the NIH and with S. Kuffler at the Harvard Medical School. From 1978 to 1983, he served as Director of the Neurochemical Pharmacology Unit of the UK Medical Research Council in Cambridge. In 1983, he joined the Neuroscience Research Center of Merck Sharp & Dohme Research Laboratories in Harlow, Essex, as Executive Director and in 1987 became Vice President of the Center. Leslie Iversen's research activities include the uptake, metabolism and turnover of tritiated NE, the inhibition by antipsychotic drugs of the DA sensitive adenylate cyclase in brain, and the pharmacology of substance P. At Merck, he was involved in studies of NMDA receptors, subunit selective GABA-A pharmacology, and the regulation of neuropeptide release. More recently, Iversen's research interests shifted to Cannabis and studies on Alzheimer's disease. He has written two books; *The Uptake and Storage of Noradrenaline in Sympathetic Nerves* and, together

with his wife S.D. Iversen, *Biochemical Pharmacology*. He is a member of numerous prestigious societies, a Fellow of the Royal Society, a Foreign Honorary Member of the American Academy of Arts and Sciences, and a Foreign Associate Member of the National Academy of Sciences, USA.

Murray Elias Jarvik received his MD in 1951 from the University of California, San Francisco and his PhD in Psychology in 1952 from the University of California, Berkeley. After being a Psychiatry Fellow at Mt. Sinai Hospital, he pursued his career at Albert Einstein College of Medicine as Assistant Professor, Associate Professor and Professor of Pharmacology and Psychiatry. In 1972, he moved to the University of California, Los Angeles where he was a Professor of Pharmacology and Psychiatry and Chief of the Psychopharmacology Unit at the Veterans Administration. Murray Jarvik's research deals predominantly with the effect of psychotropic drugs, protein and RNA synthesis inhibitors on performance, learning and memory. He also studied the effect of smoking on behavior in man and the role of nicotine in helping people to stop smoking. He invented and patented the Nicotine Skin Patch and demonstrated that the effect of nicotine is due to DA release. He is also credited with introducing the One Trial Learning procedure in mice. He received the Alton Ochsner Award and the 25 Years Service Award from the Department of Veterans Affairs.

Eric Richard Kandel received his MD degree in 1956 from the New York University School of Medicine, New York. After residency in Psychiatry at the Massachusetts Mental Health Center, Harvard Medical School, he was an Associate Professor and then Professor in the Department of Physiology and Psychiatry, New York University School of Medicine. In 1974, he assumed his position as Professor, Department of Physiology and Psychiatry at Columbia University. He was also a Professor in the Department of Biochemistry and Molecular Biophysics at Columbia. He served from 1974 to 1983 as Director of the Center for Neurobiology and Behavior at Columbia. Since 1984, he has been a Senior Investigator at the Howard Hughes Medical Institute at Columbia University. Eric Kandel realized very early that learning and memory were central to behavior and thus to psychopathology and psychotherapy. He explored biochemical and molecular mechanisms involved in learning in *Aplysia*, demonstrating that the gill withdrawal reflex can undergo second order conditioning. In a series of elegant experiments, Eric Kandel identified serotonin as a critical transmitter that produced cyclic AMP which, when injected into sensory neurons, produced facilitation. In collaboration with Paul Greengard, they injected a purified catalytic subunit of protein kinase A into presynaptic sensory neurons and found it simulated the actions of serotonin or cyclic AMP. These studies provided the first molecular insight into the process of learning. Turning to the hippocampus in genetically modified mice,

Eric and his associates found that, as in Aplysia, the cyclic AMP, PKA and CREB switch was required for long term synaptic plasticity. Eric Kandel's imaginative studies on learning and memory earned him many honors and awards. He has received honorary degrees from nine universities. His awards are numerous and include the Karl Spencer Lashley Prize in Neurobiology, the Albert Lasker Basic Medical Research Award, the Gairdner Foundation International Award for outstanding achievements in science and technology, the Harvey Prize from Technion in Haifa (Israel), the Ralph W. Gerard Prize from the Society of Neurosciences, the Charles A. Dana Award, the Wolf Foundation Prize in medicine, and, in 2000, the Nobel Prize in Physiology and Medicine.

Alexander G. Karczmar earned his PhD in Biophysics in 1946 from Columbia University, New York. His main research interests focused on cholinergic physiology and pharmacology, first at Columbia with David Nachmanson, then at Georgetown University in the Department of Pharmacology. After a short tenure at the Sterling Winthrop Research Institute where he demonstrated that muscarinic CNS receptors are structurally identical with autonomic peripheral muscarinic receptors, he became, in 1956, the Chair of Pharmacology at Loyola University Medical Center, Maywood, IL. There, he formed the Institute for Mind, Drugs and Behavior. He studied cholinergic ontogeny and the ontogenetic and morphogenetic effects of cholinergic agents and anticholinesterases. He showed that anticholinesterases cause a shift in the ontogeny of cholinesterase isoenzymes. Alexander Karczmar is the organizer and participant in several International Cholinergic Meetings.

Joseph Knoll received his MD in 1951, his PhD in Pharmacology in 1955 and his DSc in 1961 from Semmelweis University, Budapest, Hungary. He is an Emeritus Professor in the Department of Pharmacology, Semmelweis University. In the early 1960s, he developed deprenyl, a selective MAO B inhibitor that is devoid of the "cheese" effect since tyramine is not a substrate of MAO B. He also demonstrated that the enhanced dopaminergic activity following the administration of deprenyl is unrelated to MAO B inhibition. Using first rats and then humans, he demonstrated that deprenyl treated rats lived significantly longer and maintained their sexual potency and learning ability for a significantly longer duration than saline treated peers. These findings let him to propose enhancer regulation in the brain. Joseph Knoll received many honors for his research: He is a member of the Leopoldina Academy of Natural Sciences, and an Honorary Doctor of the Medical Academy of Magdeburg and of Bologna University. He was elected an Honorary Fellow of the Royal Society of Medicine and is a Foreign Member of the Polish Academy of Art and Science. He also is an Honorary Member of the Pharmacology Societies of Poland, Czechoslovakia and Bulgaria. He was honored with the Award for

Distinguished Service from the European Society of Clinical Pharmacology, and the Award for Outstanding Contributions to Anti Ageing Medicine from the World Anti-Aging Academy of Medicine.

Irwin J. Kopin received his MD in 1955 from McGill University, Montreal. Following his internship and residency in Internal Medicine at Boston City Hospital, he became a Research Associate in the Laboratory of Clinical Science, NIMH, in Bethesda, Md. From 1963 to 1983 he was Chief, Section of Medicine and from 1969 to 1983, Chief of the Laboratory of Clinical Science. In 1983, he assumed the position of Director of the National Institute of Neurological Disorders and Stroke of the NIH. Irv Kopin's main research interests focused on the metabolic disposition of catecholamines taking advantage of tritiated epinephrine and norepinephrine. He was part of the group that discovered, with Julius Axelrod and George Hertting, that neuronal reuptake is important for the inactivation of a neurotransmitter. Kopin and his collaborators were able to show that conversion of tyrosine to DOPA is the rate limiting step in the synthesis of NE and this conversion was enhanced by nerve stimulation. They subsequently found that DHPG is the major initial metabolite of NE and is converted by O-methylation to MHPG which in turn is converted to VMA. Irv Kopin, Julie Axelrod and Seymour Kety can also be credited with mentoring outstanding young investigators who are the pride of the second generation of the "Brodie School". Irwin Kopin received twice the Anna- Monika Prize from the Anna Monica Foundation. He serves on numerous Editorial and Scientific Advisory Boards and is a Past President of the ACNP (1992).

Harbans Lal received his PhD in Pharmacology in 1962 from the University of Chicago. He was Research Associate in Neurology and Psychiatry at Northwestern University Medical School, then Associate Professor of Pharmacology at the University of Kansas and Associate Professor and Professor of Pharmacology and Toxicology at the University of Rhode Island, before assuming his present position as Professor and Chairman of the Department of Pharmacology at the University of North Texas Health Science Center at Fort Worth, Texas. He studied drugs of abuse and developed objective methods for measuring aggression and anxiogenic internal cues in animals. In collaboration with clinicians, he developed drug withdrawal rating scales for humans, and tested drugs for efficacy in blocking the withdrawal syndrome. He was a master in designing and using drug discrimination methodology. He also studied developmental aspects of the blood brain barrier. Harbans Lal is a member of many prestigious societies including ACNP, CINP, ASPET, Society of Neuroscience, and the Society of Biological Psychiatry.

Salomon Z. Langer received his MD in 1960 from Buenos Aires University. With a Rockefeller Foundation Fellowship he joined the Department of

Pharmacology at Harvard University, working on the mechanism of denervation supersensitivity. From 1967 to 1969, he worked at the Institute of Animal Physiology in Cambridge, UK where he studied the metabolism of NE released by nerve stimulation. In 1969, Salomon Langer was appointed Director of the Institute of Pharmacological Research in Buenos Aires. There, he characterized the pharmacological differences between presynaptic alpha-2 and postsynaptic alpha-1 adrenoceptors. After 1976, Salomon Langer held various positions in the pharmaceutical industry; Head of the Department of Pharmacology at the Wellcome Research Laboratories in Beckenham, UK; Director and Vice President at Synthelabo in Paris; Senior Vice President at Compugen, Tel Aviv and Vice President Research of Alpha - 2 Pharmaceutica. In 2007, he founded the drug discovery company Euthymic in Tel Aviv, Israel. These years in industry were very productive, during which he made many important discoveries, including the high affinity binding site for tritiated imipramine in brain and platelets in various species and the association between these high affinity binding sites and the 5HT transporter. He also discovered and developed a number of drugs for hypertension, allergic diseases, schizophrenia, depression and insomnia. Langer is editor of several books and a member of the editorial boards of several scientific journals. He received many Awards including the Anna-Monika Award, the Otto Kraye Award by ASPET, the Ciba Award in Hypertension, the Eli Lilly Award, and the Lieber Prize for Schizophrenia Research.

Steven Marc Paul received his MD in 1975 from Tulane University in New Orleans. After being a Research Associate and Clinical Associate in the Laboratory of Clinical Science, he occupied various senior positions at the NIMH; Chief of the Unit on Preclinical Pharmacology, Clinical Psychobiology Branch, Chief of the Section on Preclinical Studies of the Section on Molecular Pharmacology of the Clinical Neuroscience Branch, Acting Director and then Director of the Intramural Research Program. In 1993, he moved to Eli Lilly in Indianapolis, to assume the position of Vice President of the Lilly Research Laboratories. At present he is Executive Vice President, Science and Technology and President, Lilly Research Laboratories. Since 1993, Steven Paul is also Professor of Pharmacology and Psychiatry at the Indiana University School of Medicine in Indianapolis. While at the NIMH, Steven Paul's research interests focused on the mechanism of action of benzodiazepines on GABA-A receptors and the intriguing role of neurosteroids which interact with the GABA-A receptor and not the cytoplasmic steroid receptors. He also studied the 5HT transporter and binding of SSRIs to it. At Lilly, the main emphasis of his research shifted to Alzheimer's disease, particularly on genes that facilitate amyloid deposition in brain such as apolipoprotein E. His group at Lilly is also involved in discovering drugs that interact with

a particular type or subtype of receptors in a cell line such as subtypes of 5HT, glutamate and dopamine receptors. Steven Paul is a member of several Advisory and Editorial Boards. He served as President of ACNP in 1999. He is the recipient of several awards, including the A.E. Bennett Award of the Society of Biological Psychiatry, the Morton Prince Award from the Society of Clinical and Experimental Hypnosis, the Arthur S. Fleming Award for outstanding US Government employees, the Daniel H. Efron Award of the ACNP, the Edward J. Sacher Award of Columbia University, and the Max Hamilton Award of CINP.

Candice Pert received her PhD in Pharmacology in 1974 from the Johns Hopkins University School of Medicine, in Baltimore. After a Postdoctoral Fellowship at the Department of Pharmacology at Johns Hopkins she joined, in 1975, the Section on Biochemistry and Pharmacology of the Biological Psychiatry Branch at NIMH. In 1982 she became Chief of the Section on Brain Biochemistry, Clinical Neuroscience Branch. In 1987, Pert assumed the position of Scientific Director, Peptide Design L.P., and Chairman of the Board, Integra Institute, Bethesda, Md. She also conducted basic research as an Adjunct Professor in the Department of Physiology and Biophysics at the School of Medicine, Georgetown University in Washington, DC. Her major fields of interest are brain peptides and their receptors, the role of neuropeptides in the immune system and the pathogenesis of AIDS and neurological diseases. Using Pedro Cuatrecasas's receptor isolation technique, she discovered, as a Graduate Student in Sol Snyder's Laboratory, the Opiate receptor! Other highlights in Candace Pert's career include the discovery of peptide T that blocks virus binding, protects and even reverses some of the pathologies of AIDS. In elegantly designed studies, she has shown that peptide T binds to CCR and blocks HIV entry. Candace Pert serves on a large number of editorial boards and has received many awards, including the Arthur S. Fleming Award for outstanding US Government employees, and the Kilby Award from the Kilby International Awards Foundation.

Alfred Pletscher received both his MD degree in 1942 and his PhD in Chemistry in 1948 from the University of Zurich, Switzerland. After a year as Visiting Scientist with Brodie at the NIH, he returned in 1955 to Switzerland and assumed the position as Director of Research at Hoffmann-La Roche in Basel. In 1987, he left industry and became Chairman of the Department of Research at the University Clinics of Basel. Alfred Pletscher's scientific contributions had an enormous impact on the development of biochemical neuropsychopharmacology worldwide. In 1955, Alfred Pletscher demonstrated in Brodie's Laboratory at the NIH that reserpine's tranquilizing action is associated with a dose-dependent depletion of brain 5HT by utilizing the new spectrophotofluorimeter designed by Bowman and Udenfriend.

This opened up worldwide research on the neurobiology of monoamines and led to the monoamine hypotheses of affective disorders. Pletscher was first to demonstrate that iproniazid not only attenuated the reserpine induced decrease in brain 5HT but was associated with producing behavioral stimulation by reserpine instead of tranquilization. This discovery provided the scientific rationale for the introduction of MAO inhibitors in the treatment of depression. When Pletscher returned from the NIH to Switzerland, he developed synthetic benzoquinolizines, peripheral decarboxylase inhibitors and a combination of peripheral decarboxylase inhibitor with levodopa, for the treatment of Parkinson's disease. Then, he was involved with benzodiazepines, Librium (chlordiazepoxide) and Valium (diazepam.). Alfred Pletscher received many honors, including four Honorary Doctor degrees, the prestigious Marcel Benoist Prize, the Science Prize of the City of Basel and the CINP Pioneer in Psychopharmacology Award. He was elected President of the Swiss Academy of Medical Sciences and catalyzed creation of the prestigious Biocenter of the University of Basel.

Paul Ronald Sanberg received his PhD in Behavioral Biology in 1981 from the Australian National University, Canberra. After postdoctoral training in Australia and the USA, he assumed the position of Assistant Professor in the Department of Psychology and Behavioral Sciences at Ohio University, Athens, Ohio. Then, he moved to Cincinnati as Associate Professor of Psychiatry, Psychology & Biophysics, in the Department of Psychiatry at the University of Cincinnati, College of Medicine. In 1992, he assumed his present position as Director of Research and Professor in the Departments of Surgery, Neurology, Psychiatry, Pharmacology and Therapeutics at the University of South Florida, College of Medicine in Tampa. Sanberg's main research interests deal with quantitative measurements of animal behavior, using an automated computerized multi-variable approach to locomotor behavior. He was also involved in cell transplantation, using fetal tissue transplants for Huntington's disease and Sertoli cells which release various trophic factors. His ongoing research using gene therapy is promising. Being able to put cells in the body and engineer them to release various substances seems to have great therapeutic potential. Paul Sanberg is a member of many editorial boards and the recipient of the Maurice Klugman Memorial Award and the Ciba-Geigy Research Award.

Elaine Sanders-Bush received her PhD in Pharmacology in 1967 from the Vanderbilt University School of Medicine, Nashville, TN. where She moved through the academic ranks from Instructor to Professor of Pharmacology. Her secondary appointment is Professor of Psychiatry. She is the Director of the Cellular and Molecular Neuroscience Training Program and the Director of Vanderbilt's Brain Institute. Elaine Sanders-Bush's major research

contributions are in the field of the pharmacology and neurobiology of serotonergic receptor systems in the CNS. Her laboratory was one of the first suggesting that multiple 5HT receptors exist. She then showed that calcium was a second messenger for the 5HT₂ family of receptors in brain which activated phospholipase C to produce two second messengers, diacylglycerol that activated protein kinase C, and IP3 which mobilized calcium. More recently, Elaine Sanders-Bush is exploring methods to manipulate intracellular signaling, gene transfer, retroviral transfer strategies and RNA editing of the 5HT_{2C} receptor. Importantly she has always stressed the importance of linking biochemical and molecular changes to changes in behavior function. She serves on numerous national committees, is a member of many editorial boards and scientific societies, including the ACNP, the Society for Neuroscience and ASPET.

Merton Sandler received his M.D. in 1962 from the Manchester University School of Medicine in the UK. From 1973 to 1991, he was Professor of Chemical Pathology at the Royal Postgraduate Medical School, University of London. Since 1991, he has been Emeritus Professor of Chemical Pathology, University of London. Merton Sandler's research over the past 40 years has been in the area of monoamine metabolism and the role of monoamines in neuropsychiatric disorders. He also studied trace amine metabolism extensively in psychiatric illness. He found selective decreases in tyramine and octopamine production in depression and noted an overproduction of phenylethylamine in aggressive psychopaths. Merton Sandler and his colleagues demonstrated multiple forms of MAO for the first time. They assessed the role of these in vivo and the activity of selective MAO inhibitors. They also demonstrated the therapeutic value of the MAO B inhibitor deprenyl in Parkinson's disease. Merton Sandler is a member of numerous editorial boards and learned societies. For his scholarly contributions to neuropsychopharmacology, he received the Anna-Monika Prize, the Franz Burke International Prize for Research in Parkinson's disease, the Arnold Friedman Research Award and the CINP Pioneer in Psychopharmacology Award.

Solomon H. Snyder received his MD in 1962 from Georgetown University Medical School, in Washington, DC. After two years as a Research Associate with Julius Axelrod at the NIMH, he moved in 1966 to the Johns Hopkins University School of Medicine in Baltimore, where he moved up on the academic ladder from Assistant to Full Professor of Pharmacology and Experimental Therapeutics and Professor of Psychiatry. In 1980, he became a Distinguished Service Professor of Neuroscience, Pharmacology and Psychiatry and Director of the Department of Neuroscience. Sol Snyder made history when he and Candice Pert discovered the opiate receptor, using Cuatrecasas's rapid filtration technology. Snyder also identified the

dopamine-D₂ receptor and showed a close correlation between antipsychotic potencies and blockade of that receptor. Then Snyder with his associates identified two subtypes, 5HT₁ and 5HT₂ of the serotonin receptor. The receptor work in Sol Snyder's laboratory provided the pharmaceutical industry with simple and rapid screening tools for the discovery of receptor-specific drugs. The technique also allowed screening for neurotransmitter specific uptake inhibitors. Then came his amazing discovery of nitric oxide in brain that changed all the rules about neurotransmission. Clearly, Sol Snyder's laboratory has been one of the most productive and creative laboratories in our field. It is not surprising that Sol Snyder has received a large number of prestigious awards, including the John Abel Award of ASPET, the Stanley Dean Research Award, the A.E. Bennet Award of the Society of Biological Psychiatry, the Daniel Efron Award of the ACNP, the Anna-Monika Prize, the Albert Lasker Basic Medical Research Award, the Goodman and Gilman Award in Receptor Pharmacology, the Wolf International Research Award, the Dickson Prize in Medicine from the University of Pittsburgh, and the Edward Sacher Memorial Award from Columbia University. He has Honorary Degrees from Northwestern and Georgetown Universities in the United States, and from the Ben Gurion University in Israel. Sol Snyder is a Fellow of both the National Academy of Sciences and the American Philosophical Society.

Sidney Spector received his PhD in Pharmacology in 1957 from Jefferson Medical College, Philadelphia, PA. After spending 5 years as a Pharmacologist in Brodie's Laboratory of Chemical Pharmacology at the NIH, he became, in 1961, Head of the Section on Pharmacology, Experimental Therapeutics Branch at the National Heart Institute of NIH. In 1968, he moved to the Roche Institute of Molecular Biology in Nutley, N.J. where he was first Section Chief and then Department Head of the Department of Physiological Chemistry and Pharmacology, and finally, Laboratory Head in the Department of Neurosciences. After his retirement from the Roche Institute in 1990, he moved to Vanderbilt University in Nashville, as Professor of Pharmacology and Psychiatry. Sidney Spector's research career started at the NIH by studying the synthesis and metabolism of catecholamines. He demonstrated the rate limiting step in the biosynthesis of NE is tyrosine hydroxylase mediated hydroxylation of tyrosine and that this could be inhibited by alpha-methyl-tyrosine, a substance that was to become an important research tool. At the Roche Institute, Sidney Spector moved into a new area of research, immunopharmacology. He started to produce antibodies to various drugs, including barbiturates, reserpine, morphine, tricyclic antidepressants, chlorpromazine and haloperidol. To follow their kinetics radioimmunoassays offered specificity and great sensitivity. One of the most exciting findings was the discovery of endogenous morphine in brain. Sidney thinks that endogenous

morphine is playing a number of roles as an endocoid. Sidney Spector has trained many postdoctoral fellows who occupy worldwide leadership positions in government, universities and industry. He serves on a number of editorial boards and was President of ASPET in 1979. Spector received the Roche Research Award and Development Prize, the Paul K. Smith Award, the ASPET Award for Experimental Therapeutics and the Julius Axelrod Award in Pharmacology.

Fridolin Sulser received his MD degree in 1955 from the University of Basel, Switzerland. From 1956 to 1958, he was an Assistant Professor of Pharmacology at the University of Bern, Switzerland. In October 1958, he moved to the Laboratory of Chemical Pharmacology at the National Heart Institute, NIH, in Bethesda as an International Postdoctoral Research Fellow and became a Visiting Scientist from 1961 to 1963. After a short tenure as Head of the Department of Pharmacology at the Wellcome Research Laboratories, in Tuckahoe, NY, he moved back to academia in 1965 as Professor of Pharmacology and Psychiatry at Vanderbilt University School of Medicine, in Nashville and then Director of the Tennessee Neuropsychiatric Institute. In 1986, he spent his Sabbatical year as a Visiting Scientist at the Roche Institute of Molecular Biology in Nutley, NJ. In 2000, he became an Emeritus Professor of Pharmacology and Psychiatry. In Switzerland Sulser's research was focused on experimental hypertension, particularly the role of the renin-angiotensin system and its modification by adrenal corticoids and the action of digitalis on ion transport. As a postdoctoral Fellow with Brodie, he switched his research interests to neuropsychopharmacology. He has made many contributions to the field, among them the discovery of the first clinically efficacious secondary amine of noradrenergic tricyclics, desmethylinipramine (DMI,) formed in vivo by oxidative N-demethylation of imipramine. DMI turned out to be the first selective inhibitor of high affinity uptake of NE. During the early 1970s, Sulser and Jerzy Vetulani discovered that antidepressant treatments, if administered chronically, reduced selectively the responsiveness of beta adrenoceptor coupled adenylate cyclase in brain. His later studies on the phosphorylation of the transcription factor, CREB, by protein kinase A supported the notion of a net deamplification of the NE signal. Fridolin Sulser and his colleagues provided the first provocative evidence that tricyclic antidepressants can regulate steady state glucocorticoid mRNA levels in vivo by a mechanism that is independent of effects on synaptic NE. He then demonstrated an impairment of the activation of protein kinase A via the β adrenoceptor /cyclic AMP cascade in subcultured fibroblasts of patients with major depression. A number of his "pre-retirement" studies led to the heuristic view that dysregulation of molecular communication between the three integrative systems; nervous, endocrine and

immune, is the cause of or creates predisposition to, psychiatric illnesses such as depression. Fridolin Sulser belongs to numerous prestigious societies, including the ACNP, CINP, ASPET, IBRO, Society of Neuroscience, the Society of Biological Psychiatry and was president of ACNP in 1979. He is recipient of the Anna Monika Award, the Gold Medal Award of the Society of Biological Psychiatry, a Ten Year Merit Award of the NIMH and the CINP Pioneer in Psychopharmacology Award. He is also an Honorary Fellow of the American College of Psychiatrists.

Richard J. Wurtman received his MD degree in 1960 from the Harvard Medical School. After being a Research Associate and Medical Research Officer in the Laboratory of Clinical Science, NIMH, he joined MIT in 1967 as Associate Professor of Endocrinology & Metabolism, then as Professor of Neuroendocrine Regulation. At present, he is Professor of Neuropharmacology at the Whitaker College of Health Sciences and Professor of Neuroscience and Director of the Clinical Research Center at MIT. In 1994, Wurtman became the Cecil H. Green Distinguished Professor at MIT. While a Research Associate with Julius Axelrod, he showed that melatonin is a hormone, the synthesis of which is controlled by light and darkness, as well as by the sympathetic nervous system. Richard Wurtman has been mainly involved in translational research; taking discovery out of the laboratory by developing products useful for people. He discovered the therapeutic potential of tryptophan and melatonin for insomnia, dexphenfluramine for obesity and citicoline for stroke. He is a member of many advisory and editorial boards. His research activities were honored by the Jacob Abel Award of ASPET, the Ernst Oppenheimer Award of the Endocrine Society, the Osborne and Mendel Award of the American Institute of Nutrition, the Ciba-Geigy Award in Biomedical Research, and the International Prize for Modern Nutrition.

INTERVIEWEES & INTERVIEWERS

BERNARD W. AGRANOFF*

**Interviewed by Leonard Cook
San Juan, Puerto Rico, December 14, 1995**

LC: It really is a pleasure, Bernie, to have the opportunity to chat with you. As you just reminded me, we go back 30 years to an ACNP meeting here in Puerto Rico. What brought you to that meeting?

BA: I was invited to participate in a symposium on learning and memory. You were working on ribonucleic acid (RNA) and memory at the time.

LC: Of course. One of the things everybody would be interested in is where you are from originally and your academic background.

BA: I was born in Detroit. I had strong interests in art as well as in science. Like several boys in my neighborhood, I had a basement chemistry lab and kept busy glassblowing and making explosives. I remember an older fellow, Eugene Roberts across the street who had a basement laboratory, and I was interested in what he might want to get rid of. I met Eugene Roberts in later years as a fellow neurochemist, and we have remained good friends. I went to Cass Technical High School, originally as an art major, but from the start I included science courses in my studies. My change of direction came about in a math course designed for art majors. On the first day of the course, our instructor, pointing at the blackboard, said, "These two triangles are similar because they have two angles and a side in common." When I fearfully raised my hand and asked for proof, she said, "You feel it in your bones." That day I switched to the science curriculum math course. I needed proof.

LC: What kind of scientific background do you have?

BA: By the time I graduated from high school in 1944, I had quite a bit of chemistry and math behind me. I was fortunate to be selected for the Navy V-12 officer-training program and was stationed 30 miles from home at the University of Michigan. In 1946, I moved back to Detroit as a civilian and medical student at Wayne State University Medical School. At that time, I was intrigued by histochemistry and made tentative plans to drop out of med school at the end of my second year to pursue scientific training, but the professor of medicine talked me out of it. I completed my medical training and internship and then went to the Massachusetts Institute of Technology (MIT) as a postdoctoral student with F. O. Schmitt in the Department of Biology. There I was immersed more in biophysics than biochemistry. The Navy called me back as a

* Bernard W. Agranoff was born in Detroit, Michigan in 1926.

doctor during the Korean conflict and I spent 1952 to 1954 at the Naval Hospital in Bethesda, teaching and running a clinical chemistry laboratory, looking enviously at NIH across the road. Roscoe Brady offered me a position at the National Institutes of Health (NIH), and rather than completing a PhD at MIT, I went straight to my new NIH lab to begin a career as a lipid chemist. I have maintained a dual career as card-carrying lipid biochemist and/neuroscientist. At NIH I worked on phosphatidylinositol synthesis and discovered CDP-diacylglycerol, which turned out to be more important than anyone guessed as an intermediate in the phosphoinositide cycle, and signal transduction. The atmosphere at NIH was unbelievably stimulating. Seymour Kety was head of the combined laboratories of the Neurological and Mental Health Institutes. It was there I met friends and colleagues, some of whom I still maintain close contact with, notably Louis Sokoloff, Seymour Kaufman and Guilio Cantoni. I spent a total of six years at NIH, one year of which was in Germany, working with Feodor Lynen on cholesterol synthesis. A developing interest germane to psychopharmacology occurred during this period. A new psychoactive drug, meprobamate, otherwise known as Miltown, took the country by storm. Its structure was simple and lipid-like. I went to the library and discovered nothing was known about its metabolism. Today you wouldn't have any drug on the market, let alone a major one, that hadn't been thoroughly studied metabolically. So I went to see a fellow down the hall who seemed to be an expert on drug metabolism named Julius Axelrod.

LC: I've heard of him!

BA: When I asked him what he thought about meprobamate's metabolism, he said, "Why don't you find out? It's easy." So we sat down and talked about the probability it was hydroxylated, conjugated to its glucuronide, and then excreted in urine. From clinical lab experience in the Navy, I was confident that after extracting meprobamate or its derivative from urine with ether or some other lipid solvent and heating with sulfuric acid, we would get a measurable chromogen. So I went home, took four Miltowns, and slept well, collected my urine for three days, got the data, and we published the results in *Proceedings of the Society for Experimental Biology*, a journal nicknamed "Blue Bits." The connection of this story with my research in learning and memory is through a symposium to which I was invited at the New York Academy of Sciences on various aspects of Miltown, in 1956. There I met Eckhard Hess, a psychologist from the University of Chicago who reported that the imprinting period of newly hatched ducklings could be prolonged by treatment with meprobamate. At that time, the Willsbach technique for tritiating

organic substances had just come out, and I was tritiating everything in sight including meprobamate. I had the simplistic idea of using radiola-beled meprobamate to localize it in the brain. That turned out to be not very fruitful. However, in the meantime I had imprinted some ducklings I obtained from Hess and kept them in my lab at the NIH. I still get kidded about having those imprinted ducks following me down the halls of Building 10. This was the beginning of being hooked on learning and memory.

When I moved to the University of Michigan in 1960, Ralph Gerard was Director of Laboratories at the University's Mental Health Research Institute. He was himself interested in learning and memory and very supportive. Also, there was a somewhat flamboyant psychology professor named Jim McConnell, who studied behavior in flatworms and published a very popular semi-scientific periodical, *The Worm Runners Digest*. He claimed he could condition flatworms (*Planaria*) to respond to a light-coupled-to-shock paradigm. Once trained, they could be cut in half and after the halves regenerated, both demonstrated the learned behavior. While I was intrigued, I found the behavioral assay excessively subjective but I hired a student for the summer to pursue this line of research. The first thing we did was to attempt to semi-automate the behavioral assay. We constructed a bank of 10 mini-shuttleboxes. The compartment walls were made out of "egg-crate" plastic used for diffusion of overhead lights. I still have it. We alternately lighted one side of the compartments and then the other by means of an overhead photo-projector, using a Lionel train track switcher. High tech! The worms wouldn't learn. After two months of frustration, I told the student to go to the dime store and buy some guppies. They are the same size as *Planaria*, but have eyeballs and spinal cords. The guppies immediately learned the task, and I was soon in the fish business, specifically goldfish. Our major discovery was that by inhibiting protein synthesis with various antimetabolites, we could demonstrate in goldfish that learning to avoid light by swimming over a hurdle to avoid electrical shock was not blocked, but the formation of permanent memory was dramatically blocked. So I evolved the hypothesis that acquisition of short-term memory involved post-translational mechanisms with very short time constants, but that the formation of long-term memory took place later and required time for protein synthesis to occur. It supported the argument there is a biochemical basis to higher brain function, which today would be taken as a given.

LC: Yes, as a given.

BA: Historically, vitalism died very hard and for the nervous system only in the last couple of decades. I think that's my main contribution.

- LC: If your career could go another 40 years what would you like to do? Where do you think the action is going to be and how would you fit into it?
- BA: If you look at a complex behavioral phenomenon such as memory formation, ways to approach it are either interventional or correlative. By interventional, I mean you interfere with a physiological process, such as to block protein synthesis produced by puromycin. Some of our very sophisticated molecular biological tools, such as over-expression or knockouts, are really interventional, they suffer the same kinds of problems pharmacological agents do; you may not be blocking a single process. In the case of knockouts, you may not be blocking the targeted metabolic step, since there may be multiple genes, giving rise to isozymes. So, it's not perfect. Biochemical approaches are usually correlative. The ultimate correlative science is probably astronomy. All astronomers can do is look. So, historically, when we saw protein synthesis was required, we knew the next step would be very daunting, and it still is. To identify a common protein in certain brain cells necessary for memory formation, but where do you go from there? If you homogenize the brain, you've lost every hope of finding what's going on. Basically, my goal was, and still is, to find biochemical correlates that are causal rather than epiphenomena in memory formation.
- LC: My career goes back 45 years in the field of drugs and behavior, historically from the antipsychotics to stimulants, anxiolytics and antidepressants. This was designed to intervene and selectively suppress certain substrate systems and behaviors for therapeutic gain, but for the last 10-15 years, we have been looking for drugs that enhance behaviors and physiological functions, such as memory and learning. Many people think it is okay to suppress abnormal behaviors, yet feel uncomfortable conceiving of pharmacological agents to enhance brain functions like memory or learning. They feel by doing that "you're messing around with the hand of God." How do you feel about a drug that some day might facilitate or enhance intellectual processes or memory and learning?
- BA: I'm much more positive than when I first got into this field. If I may backtrack a minute, in telling you what I was going to do in the next 40 years, I only got into about six months of that. When we got into the fish brain and wanted to know what was going on, we realized what a difficult problem it was. So we decided to use a simpler model of neuroplasticity, the regeneration of the goldfish optic nerve. We believe that in regeneration, as in memory formation, new synaptic growth occurs within the scaffolding of an adult brain. This seems much simpler than what occurs

during brain development, which involves in addition mitosis, differentiation and cell migration. For me regeneration appeared a more suitable mode to look for biochemical “handles” that could then be investigated in learning and memory formation. We found several potential “handles.” One in particular is made in the retinal ganglion cells, when the optic nerve is regenerating. We think such handles could be turned on in the brain during learning. So what I plan to do in the remaining 39 and 1/2 years is return to learning and memory in the fish, to localize regeneration-linked biochemical handles and find whether they are turned on by behavioral inputs, and then localize them by means of in situ hybridization and other modern tools. We have cloned one protein candidate from our regeneration studies. This will be like a five-year project, maybe that’s a more reasonable time frame. I’m very excited about that; there is a novel experimental species, the zebrafish, for which there are available mutants. Many labs are going into it in a big way.

Now, about the argument whether it’s the hand of God; as you know the nervous system is the most exquisitely tuned part of the human body. Is it possible we can improve on natural selection? Aren’t we already, as a species, operating at our maximum? That’s one argument. On the other hand, I like to use the example of digitalis. The human heart is a wonderful organ, and yet we have a drug that can optimize its function beyond what one would have thought possible. I think there could be a digitalis for the brain, and particularly in people slowed by age. Lots of what we consider memory problems in the aging are retrieval problems. If you speeded up retrieval there would be a tremendous improvement in quality of living. So I think it’s reasonable.

LC: I realize the field is focused on improving a decayed learning memory process, trying to prevent degeneration and facilitate whatever residual function is left, which some of today’s compounds do. But in a normal young adult, who seems to be doing well in his intellectual processes, what are your thoughts? Is it possible to improve his memory and learning process and what is your philosophy about that?

BA: There have been a million science fiction stories about improving the species genetically and the horrible things that could result. I have the same fears any other science fiction reader would have of tampering with genetics in that sort of a way. I have no problem using gene therapy for the amelioration of disease, but . . .

LC: Not making Superman?

BA: If we think about improving the species, I don’t believe we could all agree what the improvement should be, and the great danger is we might wipe out the human race by losing the essential wild genes.

- LC: This has been a very provocative point for 10 to 15 years because of my involvement in the development of drugs to enhance learning and memory. I defend this approach because a pharmacological agent can't do anything more than modulate what's there. And if you can facilitate function, I think it is fine because we do all kinds of things to facilitate whatever else we have. But not many people agree with me.
- BA: I'll turn the tables on you. Obviously, we are not talking about genes but drugs. How do you feel about athletes taking amphetamines or steroids? Do you have any problem with that?
- LC: As long as it doesn't produce untoward side effects, I see nothing wrong. Of course, it gives them an advantage over others, but that's another issue. To pharmacologically enhance a given physiological system you already have; I have no problem. This always comes up in discussion.
- BA: I haven't spent a lot of time thinking about that. I keep thinking about correcting effects of disease or degeneration, bringing things back up to normal, rather than exceeding what is considered normal performance. In terms of the morality, you didn't ask me that. You asked what I think of the possibility. If you dissect what we call performance into various components like cognition, reaction time, and memory, I can see there might be drugs to affect reaction time for sure and probably retrieval time and memory. So, cognition has to be broken down into its subcomponents, but I can't quite fathom a drug that would improve overall cognitive skill.
- LC: One of the things you have been doing, is to intervene with the degenerative process or perhaps enhance regeneration, which to me would be a fascinating hope for the future, particularly in the fields we are both working in, memory, learning, Alzheimer's, senility. What do you think of the feasibility there?
- BA: You have been in the pharmaceutical industry for years, and I think you will agree a major problem in drug discovery is developing the screens you need. We don't have very good animal models here. We usually try to impair the animals and then restore them, but those aren't very good model systems. But maybe there are ways of doing human testing that are relatively safe. I think that an impetus for all of this is going to come from human brain imaging. For example, fMRI is minimally harmful, if at all, and my prediction is we are going to find some drugs that have unexpected actions or some substance that will affect the regional distribution of brain metabolism or blood flow. Then investigators will go back and perform the relevant neuropsychological testing. It's going to come out of that collaboration, not neuropsychology alone.

- LC: Isn't that interesting? Getting back to the future what are some of your grad students working on?
- BA: I mentioned we were looking for handles; with collaborators at Michigan we have cloned a protein that is turned on in regeneration. We had a paper in the Proceedings of the National Academy of Sciences (PNAS) a few weeks ago, and are busy finding out if our finding is a correlate of regeneration or an epiphenomenon. What is it this particular protein does? What is its role in regeneration? At the same time, I have a technician working on a Pavlovian classical conditioning paradigm.
- LC: In what animal?
- BA: In the zebrafish. And that ain't easy but I think its working. They are very tiny. Eventually, it will all come together. As we were discussing before this interview, I recently stepped down from being director of the institute for 12 years, so I have more time to do all this.
- LC: You've been at Michigan for 35 years?
- BA: Yes. I've also been interested in noninvasive imaging, and some of my former students are now doing that.
- LC: For this critical and important research, what is the probability of financial support? Is there concern for the future?
- BA: This is December of 1995, and everybody is worried about federal funding; whether the government is going to close down tomorrow.
- LC: Literally....
- BA: So we have to use every means to keep funding going. The growth in numbers of scientists, particularly neuroscientists, has been so phenomenal that, like with any growth curve, it has to flatten somewhat. But to do this in an excessively disruptive way will throw science back many, many years. One regrettable aspect is so many people are spending time writing grants rather than doing experiments. Also, the grants they write are excessively defensive. The so-called "bulletproof" grant is not as imaginative as it could be.
- LC: Let me switch to another topic. In everybody's career there are people who play a very critical role. You have made reference to this, but probably you could mention some others who had an effect on your career.
- BA: That's a good question. I mentioned working with Feodor Lynen in Munich, who was a wonderful biochemist and a very stimulating man, because he was a chemist as well as a biologist, and had tremendous insight. I gained a lot from being in that laboratory. I also gained an enormous amount from my experience at the NIH. I mentioned some of the people involved. Seymour Kety was inspirational in terms of his insight, his personality, his humility, and also his students, especially Lou Sokoloff, who has been a very close friend all these years.

LC: Seymour Kety has been one of my heroes also.

BA: In a very different way, Ralph Gerard was influential. He was involved in my coming to Michigan, and we had useful chats about memory. He was very witty. One thing he said stuck with me. He classified scientists as either dogs or cats; in other words, collaborators or loners. I walk around our laboratory and say to myself, “he’s a cat, he’s a dog”. I have two kids. One’s a cat and one’s a dog. I love them both, but they are different. It’s a wonderful game you can play when you think about the personalities of creative people. Gerard had the conviction that memory has a physical basis, the engram. He was a fantastic person and a walking history of neuroscience, a term it is said he coined. He had met Ivan Petrovich Pavlov and Sigmund Freud, and had worked in A. V. Hill’s and Otto Meyerhoff’s labs. He was a very, very bright man and, for me, influential.

When I made a decision I was going into neurochemistry in the 1950’s, I wasn’t sure it was even a field, so I looked for a wise man to consult. I went to see Efraim Racker, a famous biochemist, who at the time was at the Public Health facility laboratories in New York. I asked whether he thought neurochemistry was a promising field. He did, so that was encouraging. And I asked the same question of Dewitt “Hans” Stetten at NIH.

LC: One of the questions we have been asked in these interviews is, are you happy about the way things have turned out career-wise?

BA: Yes, I think so. There are some who have said if I had stuck with lipid chemistry I would have gone further professionally. But I am constitutionally unable to narrow down as much as would be professionally advantageous. I’ve had this wonderful opportunity that may never repeat itself for others of being able to do what I wanted in the lab. That’s less and less true.

LC: You have a lot of young people working for you so, if you had words of advice for people starting their careers, what gems would you tell them that reflect your own experiences?

BA: What we were talking about; to find an area in which you can be an expert and stay focused. To my students I often said, “Do as I say, not as I do,” because I think my way is no longer possible, and probably not the way to attempt. I very often had students consult me over the years who tried to make the decision between going into medicine, into biochemistry or a joint MD, PhD degree, and my advice varied, depending on the times. I cautioned them, “Don’t go for the MD if you can’t imagine yourself treating patients.” Don’t go for the MD just to have the degree behind you, because you won’t be happy in medical school if

you can't really relate to patients. Some of my former PhD students are now going for medical degrees, and as bad as medical practice looks at the moment, combining a professional and scientific career is becoming more difficult.

LC: Yes, the biological sciences are going through a tough time in terms of support, and I don't know what the future is. But there are so many questions to be answered and such a fascinating set of careers and opportunities ahead that I wonder how tough young people today are going to have it.

BA: This is both worrisome and heartening, to see young graduate students, wide-eyed and bushy-tailed, who you tell about funding problems, and they see their mentors are not getting grants and are unhappy, but they also know what they want to do and what they want to be.

LC: It's been delightful Bernie, to reminisce this way. We can't finish without a few extra words of wisdom.

BA: I'm amazed how quickly our time has gone. You've heard the saying; people who talk about others are gossips; people who talk about themselves are bores. And people who talk about you are brilliant conversationalists. So I think you've been a brilliant conversationalist!

LC: That's great, Bernie. It's been a pleasure.

BA: Thank you.

HUDA AKIL

**Interviewed by James H. Meador-Woodruff
Boca Raton, Florida, December 11, 2007**

JM: I'm Jim Meador-Woodruff, Professor and Chairman of the Department of Psychiatry at the University of Alabama in Birmingham and it's my pleasure to be interviewing Dr. Huda Akil,* Professor and Co-Director of the Molecular and Behavioral Neuroscience Institute at the University of Michigan, and my former mentor. Thank you for doing this. We'll start with your early educational experiences, if you would.

HA: I grew up in Damascus, Syria in a family that believed in education, even for women, in a place where education was not valued for women. I went to a French Catholic school from pre-school through high school, even though I'm neither French nor Catholic and received a really good education. One of the turning moments of my life was the day I went to the library and one of the French nuns handed me a book about Marie Curie. I did not know anything about her until I read about this young Polish girl who grew up far away from the centers of knowledge but became a great physicist, a Nobel Prize winner. I became extremely excited reading her story and it made me realize it was possible for a woman to be a scientist, even if she was not from Great Britain, France or the United States, where I thought most science was concentrated. So, that was a turning point in my life. It led me to decide to take a Bachelor of Science, even if everyone else in my class took a Bachelor of Arts. I had a terrific Polish nun who taught me Math and Science. That was the beginning of my dream to become a scientist.

JM: Where did you go to college?

HA: I went to the American University of Beirut, which was an interesting mismatch, because I had learned English from an Irish nun. So my English was spotty and the American University of Beirut is a standard American University. I entered as a sophomore, skipping my freshman year which made it all the harder. But my French education was solid enough so I could manage the studies. I went to University on a Rockefeller scholarship that required that I get straight A's to maintain it. So, I had to work really hard. My father is a psychologist, and I got interested in Psychology, in the psychology of language. I thought it was the highest function of the mind so that's what I wanted to understand. I got interested in finding out how people think in different languages and my first research project was studying whether one functioned differently in Arabic and English.

* Huda Akil was born in Damascus, Syria in 1945.

JM: Did you have a mentor for that study?

HA: He was a British professor at the University of Iowa before he migrated to the American University of Beirut. He and another American professor encouraged me to pursue further education in the United States and suggested I apply to the University of Iowa. So, I spent my first year in the United States there.

JM: What did you do?

HA: Before transferring from the American University of Beirut to Iowa, I took a course in physiological psychology and, after reading the work of Jim Lutz, I became fascinated by the idea one could elicit pleasurable behavior by electrically stimulating certain sites in the brain. So, I started to think whether I should shift into a more experimental area. Then, in Iowa, I took a course with John Harvey about the basics of neuroscience and pharmacology, and I thought it was amazing. So, I did a rotation in the electrophysiological lab involved in research on learning. I worked with Steve Fox who was trying to condition evoked responses to see how behavior changes in the course of conditioning rather than the other way around. But there was a lot of political tension in Iowa between Steve Fox and the behaviorists. In the meantime I was accepted at UCLA, but without financial support. Steve Fox called his friend and former student, John Liebeskind, who was studying pain there, told him I was a great student who would fit into his program, and could he find funding for me. So I got a teaching assistantship at UCLA!

JM: Tell us about UCLA

HA: In 1970 I joined John Liebeskind, who was a young assistant professor interested in the neurobiology of pain. He focused on the neural circuitry of phantom pain that was not totally physical but had a psychological aspect. He wanted to know whether there were parts of the brain we could electrically stimulate to elicit the pain experience. We implanted electrodes in areas of the central gray matter in the cortex reported to be associated with an escape response to see whether electrical stimulation would potentiate pain experience. Instead it became apparent electrical stimulation diminished rather than enhanced pain experience. That had never been reported before. The observation was made by Tom Wolfly, while wrapping up his PhD thesis. He left, but David Meyer and I, two graduate students, decided to follow up his observation. In our first experiments we put a rod in a bucket of ice to make sure it was so cold it would be uncomfortable. Then, after we stuck the rod in the brain of the rat, we turned on the electrical current. While the electrical current was on, the rats were sitting and eating their Purina chow, but when the current was switched off they jumped and moved

away. We described what we saw as “stimulation produced analgesia.” It became the topic of my PhD dissertation. By that time I had met Stan Watson, who was to become my husband. Stan had a good friend in Los Angeles, who had been a student of the same Jim Lutz who influenced me in moving into biological-experimental research. This friend had a party for Jim at his house and invited me to dinner with Jim and Nick Lutz. It was just the four of us. Before I went, John Liebeskind, who was also a student of Lutz, told me I should tell Lutz what we were doing. So when Jim Lutz asked me and I told him what I was doing he told me it was bunk. He said, you’re jamming up the pain signal; that’s why there’s no pain, it doesn’t mean anything. I went home somewhat disheartened but determined to prove him wrong. I spoke to Liebeskind and told him there had to be a way to show this was an active and not a passive process. John, who used to call me sweetheart, said, “Okay, sweetheart, you go figure out how to do that.” It happened that David Meyer was comparing stimulation produced analgesia in terms of potency to morphine and found it was as potent as morphine. After I learned about David’s findings I had an opportunity to attend a meeting where they talked a lot about morphine and addiction, and where I met Eddy Way, a very well known pharmacologist, who was the head of the department of pharmacology at UCSF. I told him about our findings and also that I found nalorphine, a morphine antagonist, sometimes did and sometimes did not block the morphine-like effect of electrical brain stimulation. He said, “Nalorphine is a dirty drug; it can be an agonist or an antagonist, use naloxone which is a much cleaner antagonist and does nothing on its own; if it works for you it will be amazing.” So, I went home, ran a naloxone dose response study and within two evenings had a significant blockade of the morphine-like response produced by electrical stimulation. It was our first indication there was something biochemical or pharmacological and not just “jamming up the works”. It was also one of the very first findings which suggested that naloxone was doing something on its own, that there might be something for naloxone to block in the brain.

JM: After that, you went to Stanford?

HA: Not quite yet, because it was interesting what happened after that. When it became apparent there was something for naloxone to block, David Meyer showed if you make animals tolerant to morphine you cause cross tolerance to brain stimulation. Then I showed there were a slew of monoaminergic mechanisms necessary for stimulation analgesia to work, along with opiate like mechanisms. Meyer and I wrote an article saying there must be a natural system for pain inhibition we were

activating electrically which morphine activates pharmacologically; that's what analgesia was about in those pathways. So, at the transition between finishing graduate school and going to Stanford for a post doc, I attended an International Pharmacology Meeting in San Francisco in 1972 where I presented this work in a ten minute presentation. People were very suspicious of the findings. They doubted naloxone would do anything. But, then a man in the front row said that my naloxone findings provided evidence for the first time there is a natural system for analgesia in the brain. He also asked if we were looking for the chemicals involved. I said I had no idea how one would go about finding chemicals for anything. That man turned out to be Hans Kosterlitz, who had been convinced, on the basis of pharmacological evidence, there was a morphine like substance in the brain. So he was pleased we could turn on the system by electrical stimulation, and then block it with naloxone. He and John Hughes were searching at the time for a morphine-like substance in the brain. It was this intersection of behavioral, pharmacological and biochemical work that led to the endorphins.

JM: Tell us about your post doc research.

HA: My post doc had to be coordinated with Stan's residency but finally we ended at Stanford in Jack Barchas's lab. Prior to that we spent some time in Boston where Stan was finishing up medical school and I was writing proposals to fund myself. While in Boston, in May 1972, I attended a neuroscience meeting on pain organized by Steve Matiasy and Sol Snyder. It was at this meeting I heard for the first time the word peptide, and about the existence of two peptides called enkephalins. The meeting was immediately before the June date when Stan was to start his residency and I was to start my post doc in Jack Barchas' lab. When I walked into Jack's office I told him it was now known there are morphine-like chemicals in the brain and there was a race to isolating them with Hughes, Kosterlitz, Snyder, Terenius and Simon involved. I said, "I know this is not what I told you I wanted to do, but now I do." Jack said, "Terrific! You should do it." Then I said, "I don't know what to do." And he replied, "That's your problem; figure it out." He was the second person to tell me, "Go and figure it out." So, I decided I had to figure out how to set up receptor binding assays. This was 1973, after Pert and Snyder published on opiate binding assays. I knew Snyder's group was using these to find and characterize the endogenous ligands and felt somebody would figure out what they were. What I wanted was to go back to the electrical stimulation studies and behavioral paradigms and show what it took to turn the system on. The two models we thought to use were the electrical stimulation model we initially worked

on, and another model to do with stress, after a student in Jack's lab noted that highly stressed animals became analgesic. It makes sense that if you're in a dangerous situation you need to block pain so you can survive. To make a long story short we established the model of stress-induced analgesia. While getting the two models working I found others had also thought of stress induced analgesia but the paradigms were different from one laboratory to another. Ours was naloxone responsive, whereas David Meyer's in Virginia was not. John Liebeskind, as a good mentor, figured out we were both right. We also had something unique; I didn't tell you while my husband was still in medical school, I spent a year at Tulane.

JW: What did you do there?

HA: I worked with a neurosurgeon, Don Richardson, on deep electric brain stimulation in humans. That was in 1972. Richardson was a wild and crazy guy, but a wonderful man. He told me: "if it works in rats, it should work in humans and these people are in a lot of pain." Don would collect cerebral spinal fluid and so, by the time I got to Jack Barchas' lab, we had two animal models and a human model as well as cerebrospinal fluid to look at whether endogenous opiates were altered. At the same time, we were listening to developments in the endorphin field; to all the controversies about whether there were one, two or more chemicals, whether some things were real and others not, whether these are pituitary hormones or neurotransmitters, how many receptors there are, and so on. It was an incredibly rich period of discoveries; tensions and drama. That whole melodrama played out between 1973 and 1976 or 1977. It was an extremely busy time and we raised antibodies. Stan was very interested in the anatomy, to get a sense of where these systems are, how they are laid out in the brain and pituitary, and how they modulate pain.

JM: Was there anything else at Stanford before the Michigan years?

HA: One interesting thing I have not talked about at Stanford related to the ACNP. We are talking about what happened almost thirty years ago. At the time we already had quite a few findings about endorphins; we had antibodies to β -endorphin, β -lipotrophin and enkephalin while Stan had started to use immuno histochemistry to map them. We had shown by lesions of the pro-opiomelanocortin system in the brain that we could abrogate a lot of the stimulation produced analgesia. Also, I was pregnant with my son Brandon. Stan was supposed to come to the ACNP as a young investigator and present all that data while I was supposed to have had the baby. But the baby was two weeks overdue and didn't arrive until December 21st. so Stan could not attend the meeting. In a fit

of youthful naivety we decided Floyd Bloom was going to talk about the same topic so we asked him to present our data. We sent a set of slides to Floyd and Floyd liked them enough to present them over his own showing the anatomy of the endorphin system. While I was in the hospital delivering, all kinds of people sent notes and letters telling us how great and exciting our findings were. It was the first time, through the ACNP, I felt we were making important contributions. That was exciting!

JM: It sounds that way.

HA: On to Michigan. Two of us finding positions was an interesting adventure in its own right. We were very lucky that at the University of Michigan the Mental Health Research Institute was searching for both a basic scientist and a biological psychiatrist. It happened we fit that bill. I think Stan's competition was one person, Joe Coyle, who decided to go to Hopkins. I had maybe a hundred people to compete with, so I thought I would ruin the whole thing, but luckily they hired both of us. We continued our interests in the endorphin field but each wanted to have a separate laboratory until we would get tenure. But we collaborated very closely. In the center of our interest was the observation that beta endorphin was encoded together with ACTH in a common precursor with pro-opiomelanocortin. This appeared to be true in the pituitary through the work of Roberts as well as Herbert and Mann. It was also evident in the mapping studies in our, and Floyd Bloom's lab. The idea of one precursor encoding two and maybe more active substances was fascinating and I started to give talks about how cells don't speak in words, but in sentences; that neural transmission is complicated by post translational processing. Our interest in stress and in humans made it natural for us to interact with Barney Carroll, who was at Michigan at the time. He was very interested in depression and the role of the limbic-hypothalamic-pituitary-adrenal axis. We were studying the pituitary gland because it contained pro-opiomelanocortin; it was a very convenient model system for activating and the changes which resulted were easier to follow than changes in the brain.

JM: What did you do after that? Many papers were published on peptides and depression.

HA: The fine points of signaling in the peptidergic system have got a bit lost. Soon after we moved to Michigan Stan and I started to go to various courses and meetings about molecular biology and started to learn about regulation at the level of DNA and RNA translation and transcription. I was completely ignorant, coming from a background in psychology, so I had to learn it from scratch but it was great fun. Stan hooked up with Jimmy Roberts at Columbia and they began to establish in

situ hybridization as a methodology for neuroscience and published the first paper on in *Nature*. Then, we did a lot of mapping of critical neurotransmitter systems, opiate receptors and ligands after they were cloned. So we had pharmacological, behavioral and electrophysiological tools, and, in addition, we now had biochemical and molecular tools.

JM: What do you think you will be remembered for?

HA: I have not focused on any one thing specifically; so it might be hard to remember me for anything. I liked the freedom of doing everything from working on opiate receptors, structure function analyses, behavioral studies, the neurobiology of severe psychiatric disorders, post mortem brains and molecular genetic research. It has always been about trying to understand the circuits of emotions. I have always been interested in how the process of responding to the world changes the brain and how, in turn, the brain changes an animals environment and perceptions of the world. I love all of it. I can draw a picture of this system, talk about where the gaps are, how far we've come but how far we still have to go.

JM: Let me ask a non science question. You've been very good about naming the mentors you've had throughout your career. But you and Stan have had hundreds of trainees.

HA: I wish I had time to talk about all the work done by them.

JM: Can you talk in more general terms about how mentorship worked in your life and how you in turn have been a mentor?

HA: There is no formula for it. It is a relationship, and like all relationships, it has certain ingredients. You have to respect each other; to care about the same thing and have to share some common interest. You have to fine tune the relationship so you don't deal with everybody the same way. You don't deal with all your friends the same way so you don't deal with all your mentees or mentors the same way. Everybody has something unique to offer and needs they want from you, so you try to be in tune with that. It is not, by any stretch of the imagination a chore, and if it is a chore, something is wrong. I don't feel anybody owes me anything or I deserve gratitude although, funnily enough, I do feel a huge gratitude towards my own mentors, who gave me huge opportunities and, by giving me freedom and room to move, they allowed me to challenge myself and figure out what I wanted to do. I want to pass that spirit on; I want my students to feel they can be free to disagree, to engage in discussion so they will gain self confidence and an individual style with which they can inspire the next generation.

JM: Do you think your mentees have the same feelings towards you as you have towards your former mentors?

HA: I hope some do; others may hate my guts. I have no idea. If I look back on life there are a few things that make me happy. One is my family; the other is my students and mentees and the third is my publications. These are all my children. And like children, sometimes there are mixed feelings, but most of the time you hope the underlying feeling is very positive.

JM: You've alluded a couple of times to Stan when we talked about you. Is there anything else you'd like to say about how it works to have your husband in the lab next door and as an integral part of your career.

HA: Definitely he is. During the day, we don't interact much. We have different styles of work and styles of thinking; although we share tastes and values we bring different strengths to the relationship and that has been very interesting. For example we take rejection very differently. I am one of those women who take rejection personally. If you are a driven, purposeful person who tries to do her best and somebody sends a paper or a grant back you may ask yourself how did I screw up, what did I miss, why did I fail; you may take it hard. I have become stronger over time, in part because you can't survive in this field without developing Teflon but also by interacting with Stan, who would say he was rejected because "they didn't get it". It's good to have the perspective you are right and it's the other people who don't get it. But then, between ourselves, we come to the conclusion maybe they didn't get it because we need to do a better job of communicating. So, for me, it has been interesting and rewarding being married to another scientist. And I am eternally grateful Stan has been totally non competitive about anything we have done and vice versa. We've always wanted the other to go as far and succeed as much as possible with their own strengths.

JM: You talked about the ACNP meeting thirty years ago when you were pregnant. You were one of very few women neuroscientists at the beginning. What's it been like watching more women join and what's it been like having kids. You have two very successful children and a very productive career.

HA: Those are two separate questions. I never worried much about women's minority issues; I have a funny accent and people don't take me seriously in any case! There could have been lots of things I worried about but I didn't, in part because I came from a country where women are treated differently than in the American system; the original battle was won by the women before I showed up. But over the years, I've noticed women do struggle with their role, their position, how to balance things, and they do need advice. I didn't know any other women scientists when I was young with children, so I did the best I could.

Maybe I would like to see my daughter do it differently. I stayed working all through and never entertained another option; it was probably good for my career, but it was also stressful. I'm lucky because my kids are strong, happy and smart and seem to have done okay, so I don't think I did any serious damage. But I can see how a child who's more vulnerable or emotionally demanding, or has a mate who is not as supportive, might have to modify their career path. I've talked to enough colleagues to know there is no simple answer to this question, but the best parent is a happy parent, and whatever it takes to ensure that, is best for the children.

JM: You've had leadership roles in many organizations, including the ACNP. Can you talk about those organizations, how you see them and your role?

HA: I don't know how I got involved; I'm interested in lots of things. As a basic scientist, I try to understand and bridge the issues both basic scientists and clinicians deal with. The ACNP is an amazing organization, because it sits at the interface between basic neurobiology and psychiatry at a time the two should be coming together. They have come closer but are not sufficiently integrated and I think ACNP has a unique role to play in that transformation. There is a lot of soul searching that we should have more neurosurgeons or neuropathologists. I would be happy to see them involved, but it is okay as it is? It's already a big task to combine the science of the brain and the science of mind and how it goes wrong in psychiatric disorders. It's great to have a society that tries to bring them together. I hope we will get to the point of integrating what we still hear in parallel sessions; one on glutamate, another on serotonin, a third on genetics and so forth.

JM: Where do you think this field is going in the next ten years?

HA: I don't know.

JM: Where would you like to see it go?

HA: I would like to see it address the emergent properties of neural circuits. That is the big elephant in the room we have avoided. We describe on the surface what behavior looks like. We categorize it. We added some science to it. But neural imaging is still rather descriptive. On the other hand, we've moved ahead in molecular biology, cell biology and neural chemistry; even cellular physiology is doing very well. But, there is this big gap about neural circuitry, the functioning unit of behavior. Being bipolar is not because one cell is not working, or a homogenous group of cells is not working, or even that a gene is not working. It's really that a circuit is mistuned. How do you understand the tuning of a circuit; not only in terms how it produces a mood, but how it stabilizes or

destabilizes it? These circuits have a dynamic, time based dimension, we have not begun to understand. To me that is the great challenge. To decipher whether what we see is related to a mood disorder, cognition or memory. It need to link what we know to clinical phenotypes.

JM: What would you consider your most important accomplishment?

HA: I don't know, that's a tough question. I would say not being afraid to follow the questions where they lead me. I am very interested in individual differences between brains and the idea the whole emotional circuitry could be dramatically modified by how it's wired and how it biases responses to the environment, the interpretation of events, the kinds of psychiatric disorders you have and what drugs you respond to. Understanding the neurobiology of temperament and how it modifies interactions with the world and the fine tuning of that interface between the inside and outside. That is the challenge we need to face.

JM: By any stretch of imagination, you've had a brilliant career so far. And you still have many decades to go. Is there anything you would have done differently?

HA: I should have been more focused and systematic about what I was doing. Some people, you read in autobiographies, put all their strength behind one purpose. I haven't done it that way. There are certain themes I recognize as me and others I recognize as not me. When I was young I could have asked "what is the best most important question I have the opportunity to ask, and what can I bring to the equation in answering it," but I never did that and maybe it was stupid. Maybe I have a little attention deficit disorder side to me and I couldn't stick it out. But, I do reflect sometimes on the fact I was too broad ranging and maybe I should have found ways to focus myself more. I don't regret it, because it's been a lot of fun. I've learned a huge amount in the process and what I learned has ranged from behavior to genetics and everything in between. Maybe if you make contributions along the way and have fun, you can't complain.

JM: When you reconstruct your story it sounds really linear to me.

HA: Is that right?

JM: It was a great story

HA: It was; you can trust me on that.

JM: Do you ever think about going back to the topic of your masters' degree and doing psycholinguistics?

HA: What I have become very interested in, is not linguistics so much, but how you can influence attitudes, and how attitudes are altered as a function of culture and language. That was very clear in the study I did. I used something called the authoritarian personality scale, which

was developed in World War II. It has split half reliability so you could take half of it and measure pretty much what the other half does. I took half of it in English and half of it in Arabic, counterbalanced the halves, and had a bunch of bilingual Arabic and English college students at the American University of Beirut respond to the questionnaire. What I found was that every single person was significantly more authoritarian in Arabic than in English. It was the most significant difference I ever encountered. I wish I had the data.

JM: It would be timely.

HA: It would. I'm interested whether people think differently when functioning in a different language. Another interesting question is what modulates social and emotional belief systems, and how neuroscientists, can understand that. What's going on in the world is a clash of beliefs and everybody wants to behave as if beliefs are cognitions. But beliefs are emotions or in the twilight zone between cognition and emotion where they serve certain functions. They are so very important. That's why we protect them at all costs, and it takes a lot to change them.

JM: Is there anything that I didn't ask or you'd like to talk about?

HA: No, you are a great interviewer and one of my prize students.

JM: Thanks. You are the easiest interviewee in the world!

HA: Thank you. It was fun.

JM: That was.

JULIUS AXELROD

**Interviewed by Leo E. Hollister
Washington, D.C., April 14, 1997**

- LH: We are in Washington doing another tape in our series of the history of psychopharmacology. I'm Leo Hollister and our guest is a man who needs no introduction, Julius Axelrod.* Welcome Julius, and thank you for coming.
- JA: It's a pleasure.
- LH: Your life began in New York.
- JA: Yes, on the lower east side of New York. It couldn't be more deeply in New York.
- LH: A typical American saga.
- JA: I suppose so. My parents came from Austrian Poland, at the beginning of the century. They met and married here.
- LH: Were they fleeing a pogrom?
- JA: No. In the Russian part of Poland there were pogroms, but not in the Austrian part. It was a bit more liberal. Franz Joseph was the emperor, and he was more tolerant towards Jews. It was mainly poverty.
- LH: They wanted to get to the land of opportunity.
- JA: Yes, the golden land.
- LH: Unfortunately they didn't find the streets paved with gold.
- JA: No, not at all. But they had talked to people who came from the same area of Poland and informed them what to expect.
- LH: They networked. Were you the only child?
- JA: I have two sisters. I was the oldest, born in 1912.
- LH: You know there's a current idea about birth order.
- JA: Yes.
- LH: David Healy tells me that most of the people he interviewed have been either first born or an only child.
- JA: I don't know whether there is anything to that, but it's interesting.
- LH: So, you have two sisters. Are they both alive?
- JA: No, they both died this year. I'm the only surviving member. We lived in a part of New York that was almost all Jewish because otherwise we were either beaten up or called all kinds of names. But I enjoyed that life. We were very poor.
- LH: That was common, wasn't it?
- JA: It was. We were very poor, but I didn't know any better. That was life. Amongst Jewish people there was an intellectual ferment. There were

* Julius Axelrod was born in New York, New York in 1912. Axelrod died in 2004.

theaters, libraries and a lot of talk and politics. Most of those living in the area were socialists and we had a socialist congressman, Pankin.

LH: I remember him. That was not a bad idea in those days.

JA: No, it wasn't. The Russian revolution occurred around 1917 and people were split on the basis of whether they read the socialist or communist newspaper.

LH: Socialism in a democracy, as in the Scandinavian countries, is pretty benign.

JA: Yes, but the discussions in our area were sometime very emotional.

LH: Political discussions can get pretty emotional.

JA: For me they were very interesting.

LH: You went to the New York public schools?

JA: The first public school I went to was built before the civil war. There was one famous alumnus: Isadore Robbie, a physicist. He graduated long before me. And in high school, I went to Seward Park on Hester Street. I wanted to go to Stuyvesant, a school close by where all the smart kids went, but I couldn't get in. I wasn't that smart.

LH: What a paradox!

JA: I wasn't a bad student, but I wasn't in the top of my class and I enjoyed going to Seward Park. We had a lot of interesting alumni. Most were entertainers: Walter Matthau, Zero Mostel, and Tony Curtis were all graduates of Seward Park, and also the songwriter, Hip Haburg. Over the Rainbow was one of his songs.

LH: A lot of talent came from that area.

JA: Oh, yes.

LH: Where did you go to college?

JA: I went to City College; that was tuition-free, a sort of poor man's Harvard. It was not easy to get in. It was fortunate for me because if it weren't tuition-free, I never would have gone to college, we couldn't afford it. I received a high quality education there and we had some world-class teachers. In philosophy we had Morris Rayfield Cohen.

LH: He wrote a textbook.

JA: Yes, he was a famous philosopher. We had good teachers in chemistry, biology and some other subjects. I wanted to get into medical school and majored in biology and chemistry. When I graduated I applied to several medical schools, but could not get in.

LH: You think that was due to the quota system?

JA: Well, to the quotas they had at the time. The only graduate I know who got into medical school was Arthur Kornberg. He was about three years behind me and a smart kid.

LH: He was an MD, wasn't he?

JA: He got an MD, yes. I graduated from college in 1933.

LH: Ooh, bad time.

JA: It was a bad time to graduate, especially from City College. Fortunately a stroke of luck determined my whole career. I heard of a position to work in a laboratory as a volunteer for \$25 a month and I applied. I could have worked in the post office for more than \$25 a month, but I accepted the position at Harriman Research Laboratory of NYU. Making that choice was crucial to my career. I was a technician in the laboratory of Dr. K.G. Falk, a biochemist. He was fairly well known because he wrote a textbook on the mechanism of enzyme action. He worked on enzymes in malignant tissues, and I got my first taste of research by assisting Dr. Falk.

LH: So that was the door to biochemistry in your career.

JA: Yes. I became very interested but after two years I decided to get married. My wife was a student at Hunter College, and couldn't live on \$25 a month.

LH: That old saying two can live as cheaply as one is not true.

JA: Fortunately, the city of New York opened up a laboratory to test vitamins and food supplements. It was a non-profit laboratory. This was in the 1930s; vitamins were just being developed and became a big thing. They still are to a degree. They added vitamin A and D to milk, and various supplements to bread. My job was to set up assays to measure vitamins in milk, bread and pills. I didn't develop my own methods, but had to modify the existing ones. For this I read the original literature. It was a very good experience because methods are so crucial to research. If you have a hypothesis or an idea, you wouldn't get very far, if you can't develop methods for testing it. So I learned about devising methods, and not only chemical or microbiological methods. They were using a spectrophotometer, and I got a great deal of experience working with it that was very useful. I thought I would stay in that lab for the rest of my life. The salary wasn't bad and the work was fairly interesting. And I kept up with the literature. The laboratory subscribed to *The Journal of Biological Chemistry* that I read, so I had a feel for what was going on, mainly in enzyme research, vitamins and nutrition. I was working there for 11 years. In 1945, the head of this vitamin-testing laboratory was George Wallace, the former chairman of pharmacology at NYU. He was editor of *The Journal of Pharmacology*. One day a group of people from an institute for the study of analgesic drugs, a consortium of manufacturers involved in selling drugs like acetanilide, came to Dr. Wallace with the problem that some people became habituated to bromoseltzer.

LH: That had bromine in it.

JA: Yes. But it also contained acetanilide and many people taking the drug got methemoglobinemia. They were very concerned about this and wanted to find out why people get methemoglobinemia on acetanilide. They came to Dr. Wallace for advice, and Dr. Wallace asked me whether I would like to work on the problem. I said yes, but told him I had no experience in research. So he said I can send you to one of my associates, Dr. Bernard Brodie, at NYU.

LH: Oh.

JA: You probably know him. They called him Steve Brodie.

LH: Your name has been intimately connected with his ever since.

JA: I called Brodie and he asked me to visit him. He was at Goldwater Memorial Hospital, on an island now called Roosevelt Island. It was in 1946, a very fateful day for me. It was Lincoln's Birthday, February 12. Brodie was a magnetic man with a great presence. We talked about the problem I was supposed to address. I was fascinated just talking to somebody like him. He had a way of talking I found stimulating. The first thing he told me was that anytime one takes a chemical or drug, the substance changes in the body, it's metabolized and transformed. He asked me to put the structure of acetanilide on his blackboard. And I did. Then he said, let's see what changes this molecule can undergo. Acetanilide consists of an aminobenzene ring with an acetyl group. One possible change is the removal of the acetyl group that should result in aniline. And I vaguely remembered that aniline could cause methemoglobinemia. So I learned immediately the importance of asking the right questions. The second question to be answered was whether aniline was really formed from acetanilide. In order to answer that one has to develop methods to measure aniline in the blood and urine. Brodie was a great methods man, and we developed a specific and sensitive method to measure aniline in the urine, plasma, and blood. And I took acetanilide and found aniline in my urine. So we knew we were off to a good start.

LH: Self-administration, huh?

JA: Yes. There were patients at Goldwater Memorial Hospital. We gave them acetanilide and found aniline in their urine. I don't remember whether they gave informed consent but we definitely told them that the powder they were given was harmless and used for treating headache. Then I took some aniline myself. I thought I'd turn blue.

LH: And prove it beyond any question?

JA: It was really crazy.

LH: Did they have the methylene blue treatment for it then?

- JA: No. I didn't take that much. I became a little woozy, but found a lot of methemoglobin in my blood. We did show there was a direct relationship between methemoglobinemia and aniline in the blood. So we solved that problem.
- LH: This was the first demonstration that the toxic effect of a drug could be due to the metabolism of the compound.
- JA: One of the first demonstrations.
- LH: Did you do this work at Goldwater?
- JA: Yes. I forgot to tell you Brodie asked me to come and work with him, although the laboratory at NYU paid my salary. We also found that when one took acid anilide, aniline represented only about 4%, a very small amount of the entire drug. So, there was some other pathway for metabolism of the drug. Within three months we identified acetanilide's major metabolic product. It was acetyl-para-aminophenol. Dr. Brodie checked it for analgesic activity and it was just as good an analgesic for headache as acetanilide but had the advantage it wasn't toxic and did not cause methemoglobinemia. We suggested it should be used instead of acetanilide. It was used mainly by pediatricians, because it was soluble. This work led to the publication of my first paper.
- LH: This was phenacetin?
- JA: No. Acetanilide metabolized by hydroxylation to acetyl-para-aminophenol and phenacetin, and phenacetin metabolized by de-ethylation to acetyl-para-aminophenol. I think that Squibb had a concoction that consisted of Aspirin, phenacetin and acetyl-para-aminophenol. They called it acetaminophen because of the acetyl-para-aminophenol it contained. But then the company sold the compound to McNeil. Acetaminophen puttered along until Johnson & Johnson bought McNeil in 1970 and had a very powerful marketing campaign for Tylenol. It was their name for acetaminophen.
- LH: A very successful drug.
- JA: Very successful. All we got was a \$10,000 grant. But I got much more, the beginning of a research career. I was pretty good at research, and I loved it. At the time all I had was a master's degree in chemistry from New York University which I had earned by taking night courses while I worked in the vitamin testing laboratory. So that was the beginning of my career as an investigator.
- LH: So you found that acetanilide metabolized to phenacetin and phenacetin metabolized to acetaminophen?
- JA: Both acetanilide and phenacetin are metabolized to acetyl-para-aminophenol. We didn't call it acetaminophen.

LH: I think that was probably the first time that sequence had ever been used.

JA: Yes, it was. We showed that a drug could be metabolized to a toxic as well as to a nontoxic metabolite. Actually there was a precedent for this when, in the early 1930s, Gerhard Domagk developed prontosil (for which he received the Nobel Prize), a very toxic substance that metabolized to sulfonamide.

LH: Sulfonamide was the first really effective antibacterial drug.

JA: Yes, and it revolutionized medicine. Antibiotics, penicillin came later. People think that drug metabolism is not in the mainstream of science. But it certainly was, at least in these cases. Let me talk to you about Goldwater Memorial Hospital. During World War II malaria was very prevalent in troops fighting in the Pacific and the Japanese cut off the supply of quinine. There was a need for new anti-malarial drugs and Shannon, a renal physiologist, was asked to test clinically some synthetic anti-malarial drugs at Goldwater. This happened before Shannon went to Bethesda to become the founding director of the NIH. Shannon had a good nose for picking people and he had at Goldwater a group of young people who, instead of fighting in the Pacific, worked with him on the clinical testing of anti-malarial drugs. The group included Bob Berliner, Bob Bowman, who was to develop the spectrophotofluorimeter, Sidney Udenfriend, Stu Broad, the cancer man, Tom Kennedy, David Earl Steele, an internist, and several others. It was a stimulating group of people. They had a great influence on my thinking. After working for four years at Goldwater, I knew I didn't have a chance for an academic appointment without a PhD but I had no inclination at the time to obtain one. Then I saw an advertisement in The New York Times that Shannon was appointed director of the NIH. I wrote to him and he hired me. Well, the NIH was not like it is now.

LH: That was 1949?

JA: Yes, that was when congress established the National Institutes of Health. It was not just the Heart Institute but also the Cancer Institute, the Arthritis Institute, and various other institutes. The Mental Health Institute was started with Bob Felix as the director. And Shannon persuaded Steve Brodie, Bob Berliner and Sid Udenfriend to join him. He recruited a remarkable group of people. In Building 3, there were three people who ultimately became Nobel Prize winners, Kornberg, Anderson and myself, and there were 20 people who became members of the National Academy of Sciences. It was a small building of three stories. Well, a secure job meant more than anything else to me, and particularly a job doing research. When I joined NIH, I worked first under

Brodie. He recruited a lot of people and had a very large team and I wasn't happy after awhile working in a large group. I was offered a position by one of the drug companies, and I told Brodie I would like to leave. But he asked me "What would it take for you to stay?" I answered: "If I could be completely independent to do my work I would stay." I didn't have a PhD yet. Still, he said: "Fine." So my first project was to study the fate of caffeine in man. There was no study on that despite the fact caffeine was the most widely used drug.

LH: Still is.

JA: Yes, it is. I did that work myself but got only one senior-authorship in 15 to 20 papers we had written. I became interested in sympathomimetic amines, amphetamine, and ephedrine. They interested me primarily because they affected behavior. They also raised blood pressure and being in the Heart Institute, I thought it would be a good idea to work on the metabolism of sympathomimetic amines. I worked out the metabolism of amphetamine and became very curious about why the body can metabolize thousands of synthetic compounds it never saw before. I thought I would like to tackle that problem. My lab mate, the man who occupied the bench next to mine, was Gordon Tompkins, a post-doc with Brodie.

LH: He died early, didn't he?

JA: Yes. He was a brilliant fellow. I used to have wonderful times with him. He was a great raconteur who also used to play the clarinet in the evenings at a nightclub. Knowing my interest in drug metabolism Gordy asked, "Julie, why don't you find out what enzymes there are?" When I told him I had no experience in enzymology he said all you need is a liver and a razor blade. One used to make slices of the liver in those days to study metabolism. By that time I had a method for measuring amphetamine and learned that amphetamine was not deaminated by monoamine oxidase, because it did not have the right structure, but by another enzyme. I was curious to find out what part of the cell carried out amphetamine's metabolic deamination. Around that time Pauletti described methods to separate sub-cellular fractions, such as the mitochondria in the liver by differential centrifugation in sucrose. I learned these methods and found that, when the various sub-fractions were separated, amphetamine couldn't be metabolized. It was metabolized only when I used cofactors like TPN or APN. At the same time Bert La Du, working in Brodie's laboratory on a similar problem, found that TPN could cause the metabolism of one of the drugs I was working on. I think it was antipyrine or something that required ATP so when I added TPN to the mitochondria, amphetamine was metabolized. But I wasn't

careful and didn't wash the mitochondria. Fortunately Bernard Harke, a very good biochemist, who was working on the pentose phosphate shunt in the laboratory below mine, loaned me the substrates he used, and when I added a substrate like isocitric acid or gluconic acid to the unwashed mitochondria, amphetamine was deaminated. And when I added isocitric acid and TPN to the mitochondria, it generated reduced TPN. So is I washed the mitochondria and added reduced TPN, amphetamine was metabolized. I knew I had something. I was also working on ephedrine and when I added ephedrine to the mitochondria it was demethylated. Here were two different metabolic pathways using common cofactors, reduced TPN and oxygen. One led to the deamination of amphetamine, and the other to the demethylation of ephedrine. We named the enzyme responsible for both pathway the microsome. This discovery led to parting with Brodie; I wrote two abstracts based on my findings for the pharmacology meeting in 1953 and when Brodie saw these he became very upset.

LH: Was he upset about the order of authorship?

JA: No, he wasn't a co-author at all. He didn't do anything. He was upset that I solved the problem because there were other people in the lab trying to solve the same problem. He had put the whole laboratory to work on almost any drug they tried and wouldn't allow me to publish until the rest completed all of their work. And he called us together and said: "Let's publish this in Science with the authorship alphabetically." I realized I would be cursed; they would just put my name first along with everybody else. I knew then I had to leave, I had to get my PhD.

LH: By that time, you had more than enough work for a PhD.

JA: Of course I did. I applied to George Washington University, a local school. I knew the chairman. He told me: "Since you have a master's degree, you will not need take courses, but you will have to pass tough exams in five subjects: physiology, biochemistry, drug metabolism, and some other fields. And as far as your thesis is concerned, you can use the work on the sympathomimetic amines and enzymes." I had already published four papers so I put them together in my thesis. I was also asked to teach a course on drug metabolism while working for my PhD. Although I didn't have to, I decided to take the courses for medical students on the various subjects. Shannon, the director of NIH, was very generous. He said I could take a year off for my PhD and still get my salary.

LH: It seems paradoxical you would take courses on drug metabolism.

JA: I had to take the exams on drug metabolism after I gave the course because it was required. I didn't set the questions, somebody else did.

- LH: When you started work on the sympathomimetic amines, had epinephrine been discovered?
- JA: Epinephrine was discovered way back in 1897 by John Abel. He isolated it from the adrenal gland.
- LH: But it wasn't identified as a transmitter?
- JA: There was a big controversy about the neurotransmitter of the sympathetic nervous system. Walter Cannon thought it was epinephrine and named it sympathin A. But then von Euler isolated the substance and showed it was norepinephrine.
- LH: Was he the one who called it sympathin first?
- JA: No, that was Cannon. It's a pity Cannon didn't get the Nobel Prize, he certainly deserved it.
- LH: He was a giant.
- JA: Yes, he did so much work on stress and behavior and how stress affected various organs. Anyway, I left the Heart Institute and sent my application to the Cancer Institute and the Mental Health Institute. At the time Seymour Kety was the director of the intramural program of the Mental Health Institute. He called me for an interview and seemed to be very pleased with it. He thought I had a good chance for a position at the Institute and sent my application to the heads of several laboratories. One of the people was Ed Evarts.
- LH: He was a physiologist, wasn't he?
- JA: Yes, but he was also a psychiatrist and neurologist working on LSD. He saw my application and asked me if I would join his laboratory. So after my PhD I worked in his lab, developing a method for detection of LSD. LSD at that time was a big thing in psychiatry. They thought it was a good tool to study.
- LH: For model psychoses.
- JA: Actually a nurse can recognize the difference between LSD and amphetamine.
- LH: That's what we found.
- JA: I know, I remember when you did that work. Anyway, I developed a method for the detection of LSD. Bob Bowman was developing a fluorometer, and I asked if I could use it. He gave me one of his experimental models, and I developed a method for detection of LSD. So Ed Evarts and I studied the metabolism and distribution of the substance. We found it went into the brain in incredibly small amounts and must have been very potent. I got my own laboratory and was working alone by 1955. I had no experience in neuroscience and knew very little about the brain. I thought neuroscientists had to be very gifted theoreticians and experimentalists working on this very complicated electronic

apparatus. I was worried Kety would want me to work on schizophrenia or depression but instead he said, "Julie, you can work on anything you want as long as it's important and original." So I started to work on the metabolism of drugs I knew best, on morphine and its conjugation. I collaborated with Jack Strominger, a very good biochemist and immunologist, on glucuronide conjugation as a major mechanism for detoxifying drugs. When Jack and I met at NIH, there was a paper published showing glucuronides were formed by a cofactor, uridine diphosphate glucuronic acid; since I had a good method for measuring glucuronides, Jack suggested we should study glucuronide conjugation. To do our research we required uridine diphosphate glucose we could convert to glucuronic acid either by TPN or DPN. Herman Colcott happened to be at the NIH. He was a very distinguished Danish biochemist who had uridine diphosphate glucose. So we all collaborated and showed that DPN, NADP plus uridine diphosphate glucose, would form morphine glucuronide. At that time I had to leave the laboratory to get my PhD but Strominger purified the enzyme and published it. When I returned to the Mental Health Institute, I noticed a paper by Rudy Schmidt, the former Dean of the San Francisco medical school, who found that bilirubin, was detoxified by forming a glucuronide and if it didn't conjugate one became jaundice. I called and told him I could find the enzyme. We collaborated and found the enzyme that forms bilirubin glucuronide. Then Rudy Schmidt told me about a mutant strain of rats, the Gunn rat, studied by Castle at Harvard that has jaundice. He thought it would be a good idea to see whether they developed jaundice because they couldn't form bilirubin glucuronide. Sure enough, we found a defect in the liver, an inability to form glucuronides. When I told Rudy Schmidt we also found acetaminophen was formed from phenacetin by glucuronidation we got patients with Crigler-Najjar disease, and gave them acetaminophen.

LH: And they couldn't conjugate that either?

JA: Exactly. They could, but very, very weakly. By now, I felt a little guilty not working on the brain. Around 1956, Ed Evarts stepped down from his position of lab chief, because he didn't like to be an administrator, and Seymour Kety stepped down from the Directorship of the Institute, to become the head of the Laboratory of Clinical Science. During Kety's tenure we had seminars every week and on one of these we heard a report from two Canadian psychiatrists who found when they left adrenaline in the air it turned pink.

LH: The famous pink spot!

- JA: That comes later. They claimed they hallucinated when they took the pink adrenaline.
- LH: Adrenochrome. Was this Hoffer and Osmond?
- JA: Yes. They had a great impact on my life. They claimed schizophrenia might be caused by the abnormal metabolism of adrenaline. I was fascinated and looked through the literature, but all I could find was an enzyme, monoamine oxidase, discovered many years before by Blaschko that deaminated adrenaline.
- LH: Would that be the same enzyme you were using for deaminating amphetamine?
- JA: No, that was the microsomal or P450 enzyme, one of the most studied enzymes in the world. Anyway, I thought I might as well work on the metabolism of adrenaline since it is so closely related to amphetamine. First, I looked for the enzyme that converted adrenaline to adrenochrome and spent four frustrating months, but couldn't find it. Then, one day there was an abstract published by McMillan and Marvin Armstrong showing patients with pheochromocytoma excreted a lot of vanillylmandelic acid. It was a methylated compound and, looking at its structure, I knew it must come from adrenaline or noradrenaline. I suspected it was formed first by methylation of adrenaline or noradrenaline and then by deamination of the resulting substance by monoamine oxidase. I thought the methyl donor was adenosylmethionine. I didn't want to ask Cantoni, who discovered the methyl donor was adenosylmethionine, so I added a cofactor that contained adenosylmethionine, magnesium, liver extract, methionine and ATP. When I added all these ingredients, adrenaline disappeared. It was metabolized, so I knew I had an enzyme that transferred the methyl group of adenosylmethionine to one of the hydroxy groups of adrenaline. We called the methylated substance metanephrine.
- LH: To do all this the Bowman spectrophotofluorimeter was indispensable?
- JA: Yes, that's what I used. We didn't have radioactive isotopes but I had a new enzyme. We called it catechol-methyl-transferase. And at the time there were only two neurotransmitters recognized; one was acetylcholine and the other was noradrenaline, discovered by von Euler a few years before. But there were a lot of other putative neurotransmitters such as serotonin and dopamine. Nachmansohn and Leary had discovered acetylcholine was inactivated by choline acetyltransferase so I thought the catecholamines, noradrenaline and adrenaline, would be inactivated by catechol methyltransferase. But just around that time, Zeller discovered an inhibitor of monoamine oxidase.
- LH: Iproniazid.

JA: Yes, but when they injected iproniazid to inhibit the activity of monoamine oxidase, it didn't affect the metabolism of norepinephrine sufficiently to be reflected in blood pressure changes. At the same time we found an inhibitor for catechol methyltransferase, called copaline or something like that. But when Dick Crout, who worked at the Heart Institute, inhibited both monoamine oxidase and catechol methyltransferase, and then injected norepinephrine, its action on blood pressure was still rapidly terminated, in spite of the fact that the functioning of both of the enzymes responsible for the metabolic breakdown of norepinephrine were blocked. So we knew they were not the only enzymes that inactivated norepinephrine.

LH: So you didn't stop at the enzymes?

JA: Then it became an intriguing problem. About the time I was conducting these experiments, Kety ordered some tritium-labeled adrenaline to study the metabolism of adrenaline in schizophrenics to test the adrenochrome hypothesis so I asked him for some. By then Irv Kopin and I had already identified several metabolites of adrenaline and noradrenaline including normetanephrine and MHPG so Kety could study the metabolism of adrenaline in schizophrenics. So we studied the tissue distribution of tritium-labeled adrenaline, and found that it persisted in tissues unchanged, long after the physiological actions of the substance were over. The highest concentrations were found in organs that contained a lot of sympathetic nerves, such as the heart and the spleen. So we suspected it must be sequestered in sympathetic nerves, an important finding.

LH: That was a revolution.

JA: Yes, what it led to was...

LH: The reuptake mechanism!

JA: Exactly! Let me tell you how we did the rest of it. Around that time I was attracting post-docs. One was George Hertting. He was a real classical Viennese pharmacologist, and when I was discussing how we could prove norepinephrine is taken up in sympathetic nerves, he came up with a very brilliant idea. He said what we can do is take out the superior cervical ganglia unilaterally. When we do that, the nerves will degenerate on one side and we will have a unilaterally denervated animal. Then, when he injected radioactive noradrenaline he found the radioactivity was localized on the innervated side and we knew it was going into the nerves. We realized we had something very important and began thinking of other experiments. In one of these we perfused norepinephrine in the spleen, and when we stimulated the nerves to the spleen there was a release of noradrenaline. Then we knew noradrenaline was not only taken up but was also released from the sympathetic nerves in the

spleen. We called this process “reuptake”. In the next experiment we did autoradiography. It was carried out by Lincoln Potter, one of my first post-docs, who worked with Keith Richardson and David Wolf, both autoradiographers. I happened to be working on the pineal which is very rich in sympathetic, noradrenergic nerves. When we injected radioactive noradrenaline to do autoradiography, Wolf told me it should take weeks before to get the films ready. I was very impatient so asked to have it in two days. And we did! All radioactivity was in the sympathetic nerves, localized over dense core granules in little vesicles. We suspected these little vesicles were the storage place for noradrenaline. We also studied the distribution of noradrenaline with Weil-Malherbe, a German biochemist who did a lot of work on the biochemistry of mental illness. He left Germany during the Nazi regime and he developed methods in England for measuring adrenaline. Well, I thought, let's measure the effect of drugs on uptake. We couldn't do it in the brain because noradrenaline didn't cross the blood-brain barrier. The first drug Hertting and I tried was cocaine and found it blocked the uptake of noradrenaline into the tissues of the heart and spleen. Then we tried a whole bunch of drugs. Amphetamine did the same as cocaine. But we wanted to get into the brain. At the time I had another post-doc, Jacques Glowinski, who is now vice-president of the College of France. Most of my young people turned out very well.

LH: You've had so many distinguished graduates.

JA: Glowinski developed a technique for introducing radioactive noradrenaline right into the third ventricle. Then we tried antidepressant drugs, a whole series of tricyclic compounds we got from Geigy. We gave these first and then injected radioactive noradrenaline into the brain and measured the amount in the nerves before and after the drug. We found a reduced level of radioactivity in the nerves only after we gave a clinically effective tricyclic drug. Later on one of my post-docs, Joe Coyle, found not only were the antidepressants blocking reuptake of noradrenaline, but they also blocked the reuptake of dopamine. Then Sol Snyder found the antidepressants blocked reuptake of serotonin as well. Antidepressant development was based on the employment of simple methods of reuptake inhibition. Thousands of synthetic drugs were screened with these simple methods rather than giving them to humans. That's why it was so easy to develop antidepressant drugs.

LH: Those methods are probably still used.

JA: Of course. In fact they call these drugs serotonin reuptake inhibitors.

LH: After you discovered the action of neurotransmitters was terminated by reuptake, did you ever have an idea this was important enough to win a Nobel Prize?

JA: Well, we all think we'll win a Nobel Prize! At the time the catecholamines, norepinephrine and dopamine were a hot-subject and there was von Euler, and there was Carlsson.

LH: Did Carlsson work in your lab?

JA: No, he worked with Brodie. Carlsson, Blaschko, Butterworth and I all worked with Brodie. I thought I might have a chance to get the Nobel Prize, but there were other deserving people.

LH: A crowded field?

JA: Yes. I got it with von Euler and Bernard Katz. There were a lot of other things I did. One was discovering catechol methyltransferase. We also found the enzyme that makes adrenaline, noradrenaline and phenylethylamine. The PNMT story is an interesting one; Dick Wurtman got his MD from Harvard and when he came to my lab as a post-doc, he pointed out that in the adrenal gland of the rabbit, the cortex is separate from the medulla, and the catecholamine in the medulla is noradrenaline exclusively. Since in animals in which the cortex and medulla are not separated, the medulla also contains adrenaline, we suspected the cortex has something to do with the formation of adrenaline from noradrenaline by methylation. Evidently glucocorticoids were affecting the synthesis of adrenaline. To study this further we hypophysectomized rats and found it caused a decrease in the synthesis of cortisol and in the activity of PNMT. But we also found that when we gave dexamethasone to hypophysectomized animals, PNMT activity was increased.

LH: Nature made sense putting the adrenals where they were.

JA: Exactly. We also showed the brain can stimulate tyrosine hydroxylase, the enzyme required to make dopamine and also the rest of the catecholamines, trans-synaptically. We've done a lot of experiments with Hans Thoenen and Bob Muller in this area, but when Dick Wurtman came I was working on the pineal gland. I don't know whether you want to hear that story?

LH: Sure. I had a little adventure with the pineal gland myself.

JA: I know. And I think Altschule thought the pineal gland was involved in schizophrenia. I came across that story in 1958 in an article by Aaron Lerner, a dermatologist and biochemist at Yale, who found when he added an extract of the pineal gland to a tank where tadpoles were swimming, it blanched their skin and affected their melanophores.

LH: Did Lerner use the term melatonin?

JA: That's what he called it. He isolated the active principle responsible for blanching the skin of tadpoles and that was melatonin, a methylated serotonin. When I saw the abstract, I became very interested in how melatonin was made because of the methyl group. Herb Weisbach together with Sid Udenfriend worked out the metabolism of serotonin. Since melatonin was a serotonin analogue, I asked Herb whether he wanted to collaborate with me, finding the enzyme that makes melatonin. We found two enzymes; acetyl transferase that acetylated serotonin, which later became a very important enzyme, and another that methylated acetyl serotonin to melatonin. Dick Wurtman and I found light would affect the synthesis of melatonin; in the dark there was more melatonin synthesized than in light.

I love working with the pineal gland. Usually when I was working with catecholamines, many experiments didn't work and that made me feel a little depressed. But every time I did an experiment on the pineal gland, it worked, and it lifted my spirit. It was a good antidepressant! It was a wonderful gland to work with. Dick and I called the pineal gland the neuroendocrine transducer. It was in 1963 or 1964 and we couldn't measure melatonin directly then. What we could measure was serotonin, its precursor. Then, when Sol Snyder came to work in my lab around that time we developed a very sensitive method to measure serotonin in the pineal gland of the rat; we found in the dark serotonin was very low and in the light it was very high. The reason for the low serotonin and high melatonin in the dark was that in the dark serotonin was acetylated and methylated. We thought that would be a measure of melatonin synthesis. Then Bob Moore came to work on this project. He brilliantly identified the biological clock responsible for formation of melatonin from serotonin at night. It was in the suprachiasmatic nucleus and the pineal gland, which was an arm of that clock.

LH: Did you ever think melatonin would become such a big thing as it is now?

JA: I think it's a lot of hype although it may have something to do with sleep.

LH: I think so.

JA: But cancer, aging and all that; it's a lot of baloney!

LH: It makes some sense; it may be related to sleep and perhaps the fragmentation of sleep in older people.

JA: I know Dick Wurtman uses melatonin for all kinds of indications. They sell it over the counter now because it's a natural compound; it's a big seller.

LH: I didn't think there were many things that would put me sound asleep until I tried melatonin. But melatonin sure could put me to sleep.

JA: I tried it but it didn't help me. Anyway, that's the short history of melatonin. We also found it stimulated the β -adrenergic receptor that in turn stimulated the enzyme acetyl transferase. It was acetylation, as David Klein had shown, that drove the biological clock.

LH: The cycling of melatonin.

JA: We missed that one. Let's see, where am I now?

LH: You must be close to about 1970.

JA: Then I worked on methylation reactions, on histamine methyl transferase, which is the major enzyme for inactivation of histamine. Then we found a curious enzyme that methylated tryptamine in the lung and the brain. It became a big thing. Some people thought it might be one of the compounds that would cause.....

LH: Endogenous psychosis.

JA: I didn't buy that, it was too simple an explanation. Our brain is not that simple. But it was fun working on it, and it gave other people something to work on. You remember the pink spot and the Ackerfeld test?

LH: Yes. Once Ackerfeld and I were on a panel together, and he was reporting on his negative results.

JA: He wrote a very influential article for Science about the kind of sloppy work being done.

JA: They found the reason schizophrenics reacted differently from normals on the Ackerfeld test was they didn't drink orange juice.

LH: There was a wonderful article published back in the 1950s. A biochemist from Illinois wrote *Fact and Artifact in the Biology of Schizophrenia*, and it should be on everybody's wall.

JA: I remember a story that happened at the Mental Health Institute. They were doing studies on paper chromatography in the 1950s and found that schizophrenics always had two spots, which controls didn't. Kety was very skeptical about the finding. He said something must be wrong. When the findings were scrutinized it turned the controls were Mennonites who didn't drink coffee. So you have to be very critical about this sort of thing.

LH: You didn't rest on your laurels after 1970, but have done a hell of a lot of things since.

JA: After I retired officially in 1984 I wasn't even called emeritus, but a guest researcher. I was interested in transduction reactions, and one reaction we were especially interested in was the receptor-mediated activation of phospholipase A2. We found it formed arachidonic acid, a very active carcinoid substance.

LH: So you began to get in the 3rd messenger field.

- JA: 2nd messenger. I didn't get to the 3rd messenger, it got too complicated. But I was involved in research with Carol Gelsma on G proteins that became very important in signal transduction.
- LH: Oh, yes.
- JA: The Nobel Prize went to Marty Rodbell and Al Gilman for that discovery. These G proteins were heterotrimers. It was thought the alpha subunit activates phospholipase C or A, when the first messenger, a transmitter or a hormone, recognizes a receptor. But, later it was shown that it was the β,γ -subunit that activates phospholipase A2. We sent that paper to Nature. They rejected it. And just four months later another paper came out saying that the β,γ - subunit activates one of the potassium channels. The β,γ -subunit became a big thing. Of course, we didn't get much credit for it. If Nature would have accepted our paper, we would have had more recognition. But it was fun working in this area of research. One problem I'm working on now should have importance in neuropharmacology. It is cannabis.
- LH: The cannabinoid receptor.
- JA: It was cloned in my laboratory by Lisa Matsuda and Mike Brownstein.
- LH: You know Raphael Meshulam?
- JA: Of course. Once the cannabinoid receptor was identified we knew there had to be a natural ligand for it. And Bill Devane, who worked in Meshulam's laboratory at Hebrew University, isolated the natural ligand. It is arachidonylethanolamide, which they named anandamide. Bill Devane came to my lab and we found one of the enzymes that make it. It's an important enzyme because its receptor is distributed in very interesting places: the hippocampus, the striatum, the cortex, and the cerebellum. It must be doing important things. I think it has a great future.
- LH: This raises an interesting philosophical question. Why in the world would the body have receptors for drugs it never heard of?
- JA: These receptors were there for the normal ligand. Evidently, they lack specificity but have survival value. I have a feeling the anamide receptor is not there to give you a high. It must be for very important reasons because of its distribution.
- LH: What we need is a theory similar to what the Japanese fellow did with antibodies.
- JA: I think like antibodies, we can recognize and detoxify any compound the chemists can synthesize. Anyway, we have been at this for an hour and a half. You should have a general idea of what I have been doing.

LH: I think it has been a remarkable career. You have had more influence in psychopharmacology than any person I can think of, largely because of the eminence of your graduate students and fellows.

JA: Thank you, you're very kind. But these post-docs were so bright to begin with. And when they came to my lab, I realized most of them were much smarter than I am. I could never have gone to Harvard Medical School, to Hopkins or wherever they went. They picked up things fast. They developed things. The interaction between their good brains and my ability to see connections made a good combination. I tried to pick a problem we were both interested in, and got them enthusiastic enough to succeed initially, so they could go off on their own, as most of them did.

LH: Now it goes into the second generation. There is this wonderful book, called *Apprentice to Genius*, in which you figure very prominently.

JA: I came out very well in that.

LH: You tell me you are going to be 85. It's so true, you know; you and Brodie had a tremendous influence.

JA: Brodie had a tremendous influence. I mentioned in the book that the greatest thing that happened to me in research was working with Brodie. The second greatest thing was leaving Brodie. It's been beyond my wildest dreams to think I would last so long do the things I did. It was very satisfying.

LH: I think the whole story of your life is inspirational.

JA: You know, I wasn't a brilliant student. I was a good student. I will be 85 years old next month, on May 30.

LH: And you still have a laboratory.

JA: Actually, I have a new post-doc. I can't tell you much about what we are doing because it is still in the process of development, but if it does develop it's going to be interesting.

LH: I see you are still publishing.

JA: I publish, but not like I used to. I used to publish 15 to 20 papers a year. Now it is good if I publish one or two a year. I've been lucky; research wasn't always a happy experience. There were lots of disappointments; most of the experiments didn't work out. I had very high expectations, and when experiments didn't work I felt pretty depressed. But once an experiment worked, there was nothing like it.

LH: You certainly have been an inspiration and I want to thank you so much for taking time out and coming here.

JA: It's a pleasure. I don't know whether you want to ask me any more questions.

LH: I just wish you could be around for the next 50 years.

JA: I'll be happy to hang around until the year 2000.

LH: And see all the great developments in the future.

JA: Things are happening so fast; just in the last five years the reuptake molecule has been cloned. We call it a transporter.

LH: It's an exciting period.

JA: I know. I think neuropharmacology has a great future.

LH: Thank you so much. It has been a great pleasure.

JA: Well, thank you.

JACK D. BARCHAS

**Interviewed by Stanley J. Watson
Boca Raton, Florida, December 10, 2007**

SW: Hello and good morning. I am Stanley Watson, professor at the University of Michigan of the Department of Psychiatry and today I am interviewing Jack Barchas,* who is the Chairman of Psychiatry at Cornell University Medical School. This is one of a continuing series of archival interviews of the American College of Neuropsychopharmacology. We are now in Boca Raton at the Annual Meeting of the ACNP, and today, is December 10, 2007. These interviews cover a wide range of areas and may be you could tell us first about your background and training

JB: I would be very happy to. First of all, there is no one I would rather be interviewed by than Stan Watson, because he is somebody very special to me, I have enjoyed working with him and he has been important in my life for decades. My career really was predetermined by my parents and my family. I lived most of my life in California and my mother and her parents had lived in California for many years. My parents were profoundly influenced by the Holocaust. I am one of eight children and my parents were very concerned with issues of education, fairness, and social justice. My father was a person who I never heard to make a discriminatory statement towards anyone. He was a man of enormous intelligence who graduated from college at eighteen, became a very good trial lawyer. His absolute love was the history of science and of ideas. It was something my mother shared with him; she was a housewife but would have loved to have been a medical researcher. When I was very young she would read me stories of people who had done medical research and about progress in medicine. I knew from an early age I wanted to be a doctor. I was always curious about how things worked and when I was four years old I took apart my grandfather's violin and tried to figure out where the sound was coming from. I remember my mother's look of concern but I explained what I was doing and she felt it was fine, that it was very important to figure out how things work. I had profound dyslexia as a child and when I told my teacher that I wanted to be a doctor, she said I would never be able to do anything in medicine, my intelligence wouldn't permit it. But I heard my father tell her, "my son can do whatever it is he wants to do". Both father and mother took my interest in medicine very seriously and when I was eight years old my father took me to a medical supply store and bought me a stethoscope. When I was eleven or so I told my mother I

* Jack D. Barchas was born in Los Angeles, California in 1933.

had decided when I grew up I wanted to study the brain. She turned to me and said that would be a wonderful thing. She still remembers having said that to me. When I was about thirteen, there was a spare room in our house my parents permitted me to turn into a laboratory. I got a used microtome and did paraffin preparations of plants and other things; I made slides, stained and studied them. I worked briefly in a pathologist's laboratory when I was in junior high school, until my mother found out there might be samples with syphilis. In high school, I worked cleaning glassware for a laboratory that studied thyroid; that was a very important experience because the glassware had to be scrupulously clean. I have had an appreciation of glassware washers ever since, in terms of what they do. I knew early on I was interested in psychiatry and my father introduced me to psychiatrists in West Los Angeles. They were, of course, all analysts, but were very nice to me and encouraging. Shortly after turning seventeen, I went to Pomona College. It didn't have much in the way of scientific research capacity but, otherwise, it was very nice. The first hour of the first day there, I met Patricia Courbet and fell immediately in love. She had an incredible impact on my scientific career and also became involved in the study of science. I have also always been appreciative towards my brothers and sisters for their patience with my intense involvement in science and my parents' commitment to that. I started scientific work very early on. At Pomona it wasn't possible to do much but I did dissect six cats for the anatomy lab and wrote a manual for the dissection of cats that was used for many years at the college. That experience had one negative impact; after Pat and I got married when I took my anatomy exam, I gave the professor at Yale medical school the feline names for parts of the human head and neck so he thought I was sassing him. He was the editor of Grey's Anatomy and took this so seriously he brought me up on charges before the committee on promotions. I had done very well in physiology and biochemistry so I was passed on to the next year, despite what he felt had been intentional high level sassing of a senior professor. I knew I still wanted to study the brain and went to the nearby UCLA Medical School, which had a new Brain Research Institute of which Doctor Horace Magoun was the first Director. He was in a kwanset hut because the Institute had not been built yet and had made it clear to his assistant she was not to allow any undergraduate students to meet with him. So I kept coming back once a month and just chatted with her. Finally she said, I'm going to let you meet Doctor Magoun. After that he agreed to let me spend time during the summer working in his lab. He assigned me to work with Carmen Clamente who

had me tracing sections of cat brains from text books so he could use them in his research. Shortly after, I was assigned to work with a new faculty member named James Olds. James was very young but already had a paper in Science. He was an absolutely remarkable man. He had trained in social relations at Harvard with Talcott Parsons and the first thing he had me do was index his book with Talcott Parsons, which was a very difficult book to understand. Olds was not trained in physiology, anatomy, biochemistry or neurophysiology, but he had an extremely inventive mind. He decided it would be interesting to study the brain, so he went to McGill and learned how to do implant electrodes in rat brains. He put electrodes in different areas of the brain and watched them as they woke up. What he noticed, which was simply brilliant, was if he stimulated the animal and woke it up the animal would walk around and return to exactly the place he had awakened it. So he thought perhaps the animal liked what he was doing. Then he took a Skinner box, which had never been used for this purpose, with a bar the rat could press to get an electrical stimulation. He found the animal learned to stimulate itself very quickly and would do it thousands of times an hour. On the basis of observations in one animal he wrote a paper he immediately sent off to Science, knowing it would be rejected. But during the interim he repeated the experiments and, then had the paper accepted. He was then hired to come to UCLA and was set up in the animal facilities area. So, here was this extraordinarily intelligent man, working in a two-room laboratory, one to house the animals, and the other where I would implant the electrodes. I was his first research assistant at UCLA and I would implant the animal while he was pacing back and forth, expounding theories about what a reward system might mean. I loved working with him and the environment at UCLA was remarkably stimulating. I decided to leave Pomona after three years when I had enough credits to graduate. In addition, Pat and I had a calm but very serious disagreement with the President of the University. We had gone to protest the college was not admitting minorities. He told us that if the college admitted them it would cut the number of deserving majority people so the policy should be continued even if the minorities excluded were of equal or greater talent. Based on that, we felt we couldn't stay there, so I then ended up spending only a year with Olds, who had a profound impact on me. He and I used to discuss the possibility there could be many neurotransmitters when, in those days, only a couple were known. I might add that Olds was a very significant mentor. We did studies, looking at bar pressing and rewarding, over the entire twenty-four hour cycle. Animals would bar press over eating, over sex, over anything

else and would bar press to exhaustion depending on the area of the brain involved. Olds was both creative and very demanding in terms of the rigor of the work. Doctor Magoun, who I talked to episodically, also proved to be a very important mentor. One hallway conversation, that lasted about a minute and a half, convinced me one can be a significant mentor in very little time. I was twenty or so and asked him should I get a PhD or an MD, and he said he had a PhD but there were times he wished he had an MD; since there weren't many people doing our type of work anyway, why didn't I get an MD. Then he added, "Maybe you should go to Yale, because they are very strong in neuroscience. And, by the way Barchas, it's very hard to find anybody interested in chemistry to work at the Brain Research Institute so why don't you study neurochemistry?" That conversation took less time than it does to tell. I did all three things with very profound gratitude in terms of my career and my future.

SW: Very nice! What was your first research project? And, how do you think that early period influenced you, in terms of themes and observations?

JB: That is a very important question. I asked Olds, what would be the effect of morphine on bar pressing and, as it worked out, that was a very important question. The answer was we could give low doses of morphine, which didn't effect the animal except to decrease the amount of bar pressing and neither of us could figure out what it meant.

When I went to Yale, I plunged into finding appropriate mentors and people to work with. During the first week, when people were going to orientation, socializing and getting to know each other in class, I was off meeting every neuroscientist at Yale. Very early on I met Daniel X. Freedman. Freedman, at that point, was a beginning instructor. He had an office in the basement of the Yale psychiatric institute at 333 Cedar Street, which was one of the great centers for severely ill patients. They hadn't much in the way of office space, so they gave him one that had been a padded cell for patients who needed seclusion. He kept everything in piles on the floor, so you had to walk carefully around them. He was working on a book on psychiatry, *From Theory to Practice*, with Frederick Redlich, which became a superb text, and he was also doing research with a man named Nicholas Giarman in the Department of Pharmacology. The Department of Psychiatry at Yale, which is now a powerhouse, had no laboratories at the time and the only assays for studying neurochemistry were bioassays that Giarman had. I proposed to Freedman that behavior might change neurotransmitters so we should study that, and he liked that idea tremendously. The assays we had were very poor at that time so he suggested I go to the Department

of Biochemistry and ask for a pH meter. The Chair of our Chemistry Department was a famous biochemist, a man interested in the history of science, who had written a leading textbook of biochemistry. I had been a student in his section and done extremely well so I told him I would like to get a PhD in biochemistry and he replied, "Barchas, a man has got to know what a man wants to do and you either want an MD or you want a PhD. You can't do both; it makes no sense whatsoever." But then, he asked, "What are you here for?" I told him I needed to borrow a pH meter because we wanted to study whether behavior or stress could change neurotransmitters. So then he said, "Barchas, it's very straightforward; biochemistry is a locomotive and behavior is the wind and the wind does not change the locomotive. We have pH meters, but I'm not going to lend you one for an experiment like that!" We tried to set up the assay without a pH-meter but it proved to be extremely difficult. We were able to use the student labs on the top floor of the medical school building but it was hot and humid. Richard Shrombren a Harvard medical student, who subsequently became a talented psychotherapist in the San Francisco area, worked with me. I would go home every night and explain to Pat, who was putting me through medical school, that the assay was not working. She would review the materials with me and at one point said maybe I should call the author. I said he is Swedish but she pointed out the paper was in English. So, I called the author and I talked to him across the Atlantic for about thirty minutes; that took two weeks of her salary which, in the late fifties, was one hundred and twenty dollars. He asked how we were measuring the pH, because it had to be 8.4 exactly. I replied, "Sir, we are using the finest European pH paper". I could hear him laugh over the phone! Exactly twenty years later I was running the Fourth International Catecholamine Meeting in Monte Ray with about eight hundred to a thousand people when Arvid Carlsson came up to me and said, Jack, I still remember our first discussion. So, that's the story of the pH meter,

SW: Very nice, very interesting! Can you describe what themes dominated your research and the observations that began to impact you after Yale?

JB: Just one last thing about the Yale period; I took a year off to work with Aaron Lerner to do organic chemistry and later I was able to continue the study with Freedman, which, in some ways, was a very important study, because it was a fundamental theme through the rest of my career. How does behavior impact neurochemistry and how does neurochemistry influence behavior. What Freedman and I found was that neurotransmitters or neuroregulators, serotonin and norepinephrine were differentially affected by stress. Our paper which influenced many other

investigators throughout the years became very important, and working with melatonin also became very important.

So, going forward I worked at NIH with Sidney Udenfriend, Herbert Weissbach and Sidney Spector, learning to do just plain good basic biochemistry and enzymology. I had arranged to work with Udenfriend to study serotonin and other mechanisms. When you went to work in his lab he handed you the next file folder on his big desk, which happened to be related to actinomycin D. So, I said I thought I was coming to work on serotonin and he replied, "Someday, you'll appreciate what I am having you work on". That began work on peptides and led to a paper in the *Journal of Biological Chemistry* after which I moved on to biochemistry, working out the biosynthesis of Actinomycin D.

When I went to Stanford, to Dave Hamburg's department, it was an opportunity to learn psychiatry because I had considered, at one point, moving to pharmacology, instead. Hamburg was interested in basic science, but he had no space so the first facility he gave me was a dog lab with a table in a room filled with dogs for Shumway's first study on heart transplantation. I went in and would have to wait ten minutes for the dogs to stop barking and, then slowly, I could do a few things. I kept reporting progress and never complained about the facilities but one day he said, "Jack, there is only one lab in this entire medical school I can find for you and that happens to be my own". He had just obtained a big grant he was very proud of and he was going to give it to me. I have always been incredibly appreciative for what he did. It gave me a chance to start to study neurotransmitters and behavior. The first student I had was Roland Ciaranello. He was an incredibly talented, creative, bright, hardworking and disciplined man, who became a dear friend. The theme was to study behavior, but what we were finding was there was so little known about neurotransmitters. That's why Roland and I began studying epinephrine formation, its' metabolism, and the effects of drugs. That work won a Bennett award from the Society of Biological Psychiatry. At the time I was a Professor and Roland was still a medical student. Roland and I showed the synthesis of these neurotransmitters could be controlled genetically, a study Doctor Hamburg urged us to do.

SW: Let me switch topics. Can you talk about your clinical operations and about your education in those areas?

JB: That became very important in later parts of my life. I was very fortunate in having superb teachers of clinical psychiatry at Stanford. Dave Hamburg had arranged that the very best of the supervisors, who had psychodynamic perspectives, would work with me. I loved clinical

work and it was great fun. I stopped doing it one day after I was seeing a graduate student, who was pouring out his psychosexual history, a troubled young man. He was telling me his girl friend and Mother were both bored by him and, in the middle of him saying all this, I suddenly had an idea for an essay I had been working on. I felt conflicted at what to do. I thought God had put this idea in my head, but what should I do with it; do I even write it down? I helped the young man through his difficulties but I realized there were about thirty thousand members of the American Psychiatric Association who could help him but only about a dozen people who can run my type of complex lab, so maybe I should stop that activity. However, it was very helpful, as Herb Yallum graciously said to me, that Dave Hamburg told him to make sure he trained me like a psychiatrist. After twenty five years at Stanford and four years at UCLA, Pat became so ill with a brain tumor I could no longer go back to the lab after dinner and I was asked to be the head of psychiatry at Cornell to help that great department move into neurobiology, imaging, genetics and developmental psychobiology while maintaining its clinical strength. So I am very pleased to have had that set of earlier therapeutic experiences.

At this point I would like to mention the transforming impact of mentee's on mentors. I referred to it in terms of Roland, but I have had a series of incredibly bright and able people, who pushed and pulled with me, as we worked out projects. Probably no one had more impact on me than Roland Ciaranello and Stan Watson, because they so brilliantly encouraged turning towards peptides, making me think about a whole host of new issues. Together, we were able to show where those peptides were; they could be changed by stress and runners could have elevated endorphins, which led to a search with Chris Evans, Jim Eberwine, Eckard Weber and others for new peptides and new ways to study them. One of the things I have learned is that the mentor and the mentee relationship is a two way relationship which involves changes for both and, when handled correctly ends up as a hybrid between friend and family; I feel that towards the people I have been talking about.

SW: Can you give us the sense of what you think your most important research contribution has been? What has made a difference?

JB: The question is a very interesting one. The answer involves the whole area of the endorphins and the opioid peptides that are endogenous in the brain. We had a lab that ranged from molecular neurobiology, biochemical neuroanatomy, analytical neurochemistry, and behavioral capacities, with the ability to study clinical physiology and pharmacology. When the endorphins were first discovered, we stepped

immediately into the area, used all of the tools we could and an enormous number of people became involved in the effort. For example, the very first demonstration that various endorphins were in different systems and parts of the brain was work done under the leadership of Stan Watson. Identifying those pathways and that work, published in *Nature*, was very important, because before that people thought they were all in the same location. We did the definitive study on the anatomy and, at the same time, we were studying the behavioral aspects of these substances. Huda Akil was able to demonstrate, with John Madden, that stress changed endorphin levels in the brain. In those earlier stress studies I described, the wind does change the biochemistry, and the pain threshold does change. This was the first mechanism by which one could explain stress induced analgesia. We pushed ahead, also, on the biochemistry, doing studies on the breakdown of enkephalins and enkephalinase and developing the first compounds that block enkephalins and change pain thresholds. These are examples of things we are doing that are integrative. With a variety of other people, like Eckard, Weber, and Chris Evans, we are also studying what substances are actually present. We developed new ways of assaying. Chris Evans developed a universal opioid assay antibody to pick up new substances and Ijo Maven maximized the ability to measure these materials. In very low concentrations, at the theoretical limit, we were able to show that BAM 18 was a new peptide. We were the first to identify metorphamide, the first amidated endorphin peptide. We highlighted dynorphin 1-8 and showed it was present in high levels and we showed that dynorphin 1-8 and alpha-endorphin are present in the same system, suggesting they might have, as was later found, the same precursor. These are examples of the things we were doing. We were also doing the behavioral studies. I described the stress induced analgesia studies, but we also were doing, with Richard Thompson and John Madden's involvement, studies dealing with learned helplessness and the role opioid peptides have in that process and in certain types of conditioned learning. We were able to study the effects of naloxone and show it reduced some forms of hallucinations. Huda Akil, with a colleague at UCSF, was able to show endorphins are released into spinal and ventricular fluid under certain conditions. All of this constituted a large story about endorphins at the very start of the endorphin period. We had the ability to bring together multiple technologies, all from the same laboratory, in an over arching program that was one of the more powerful ones in the country, and was extraordinarily satisfying. We did other things that were very important in the educational realm. A group

of us, Phil Berger, Glen Elliott, Roland Ciaranello and I did a *Textbook of Psychopharmacology*, which was very popular, and another group of us went ahead and wrote an invited essay, for *Science* magazine, titled *Behavioral Neurochemistry*, laying out our vision of the future based on studies of these neuroregulatory compounds which could be transmitters or modulators of neuronal activity and how there could be dozens and hundreds of these materials. In the longer term, it is essential to study them. We were having conferences about these different substances like neuroregulators and psychiatric disorders and took them very seriously; it was an important educational part of what we did. So, we're involved in both doing psychopharmacology and trying to advance it by developing people from multiple fields, who can enter into this wonderful and exciting discipline. That is the heart of what we are doing that will, hopefully, have an impressive, long term effect on the field.

Showing the wind does change the locomotive was very important. When you realize the context in which that took place, it was a very important thing to do. And, then we were starting to think about the necessity of understanding regulation. That was something we pushed, and the fact that there could be families of peptides doing very different things. One of our discoveries was BAM-18 which can oppose some of the actions of morphine. It's an opiod peptide; here we have these great families of opiod peptides, a couple of them doing different things in different ways and antagonizing or being synergistic with each other. The fifty years I have been in this field have been thrilling and exciting and we knew we were after things that were important. But, this next fifty years is going to be unbelievable because we finally have real genetic tools, real imagining tools, and real biochemical tools to study the multitude of systems and neurotransmitter systems. The ways of thinking about these which have been pioneered by people like yourself will now be applicable to severe illness. We will stop thinking about depression as depression, just as we don't think about pneumonia as pneumonia. So, at the end of the next fifty years we are going to see a true major revolution in our diagnostic abilities. And what we will find is what we know from epigenetics, the wind does change the locomotive and vice-a-versa.

SW: So, something you started years ago has grown very fast and very large?

JB: Sure. First of all the research funding is important; remember the Federal Government is a critical vehicle that should be encouraged. A lot of my effort has been focused getting the Federal Government through my

work on medicine. We had a doubling of the NIMH budget before a doubling took place for all the NIH budgets. Many people participated in that, including my fifteen year old son, Issac, who helped write part of that for the Institute of Medicine. But, it's easy to forget the importance of the program officers within government, people like Earl Usdin, Steve Koslow and all the other people who have so profoundly impacted on the science and what can be done. The private sector is also important, it can be a tug boat that adds resources but it is one arena in which, as a field, perhaps we have not done enough. People tend to think immediately about private donations in cancer, heart disease and other areas. But, that has been missing in neuropsychopharmacology. We were fortunate enough to encounter the Pritzker Family, early on, and their support came in the laboratory and the Chair; although, much of that was after I left. Out of those relationships, they decided to see how scientists could work together, how they could share and what types of things could be done working together. Jay was a remarkable man of enormous intelligence and high integrity directed to helping science and his children, Tom, GiGi and other members of the family; Penny, Mick and, earlier, John, Lisa and Bob all helped in various ways. But, Jay felt particularly strong about collaboration and that led to setting up the Pritzker Network for seeding young investigators, which included Stanford with Alan Schatzberg, and Michigan with Stanley Watson, Huda Akil, and myself. We would discuss the projects and help them get started. We had a few projects which went across institutions; that was great fun and led to the Pritzker Consortium, an effort that involves Biff Bunney, inspired by his important work in genetics and messengers in the brain, expressed in different diseases. These are very difficult studies and we don't know if the effort is going to be successful, regardless of what lab is involved. I might add how extraordinarily satisfying it has been to see the lab I started at Stanford now under other leadership, first with Roland Ciaranello as the Director, until his tragic death from a heart attack, and now, in the brilliant leadership of Rob Malenka. He is doing important research with help from the private and public sectors, and also the Department of Psychiatry at Stanford, which thrives under Alan Schatzberg. It is pleasing to have worked in an Institution and see good things happen to it through the decades.

SW: Thank you. One area that interested me was your outreach work through the Institute of Medicine, and also your publications and editorial work. Can you comment on those?

JB: That's my interest in social policy. Pavee was first started through my father. He believed in social justice, doing good and improving the

world; trying to get people to collaborate, who would normally not work together. He was President of the Sixteenth Congressional District Democratic Party in California and would take me, as an eight year old, to their meetings and sit me beside him on the sofa. After the meeting he would say, let's talk about what happened, who said what, why did they say it, what were they trying to do? I had all this experience in thinking about those types of things. That education had many manifestations I've already told you about, like the experience with the President of my College, in terms of civil rights. As a medical student, I did a study of teaching rounds, showing that doctors did not talk to patients very much. A paper on that was published in the *New England Journal of Medicine*, and became a classic, because it was one of the first articles the Journal had done of that sort. David Hamburg was inspirational in terms of public policy. He and I had regular sessions while I was a resident, in which we would talk about his activities in the public sector. I became a member of the Institute of Medicine and I was asked to Chair its Board on Biobehavioral Health and Mental Disorders, which I did for twelve years. I would testify on behalf of those issues to Congress and that became very important to me. And after Daniel Freedman passed away, who had been editor of the *Archives of General Psychiatry* I was asked to take the role and loved doing that. When Pat died, I married Rosemary Stephens, who profoundly influenced me in all of these later activities. I would do the editing work on the train from New York to Philadelphia, since she was Dean of Arts and Sciences at the University of Pennsylvania. I believe, as responsible scientists, those of us who want to, should become part of the public arena. I spent five years as Chair of the Board of the New York Academy of Medicine, a group of twenty two hundred physicians. I am now chairing a part of the American Psychiatric Association, a group concerned with some of its' educational functions, and in the past I chaired the Association for Research and Nervous and Mental Disorders Board. All of that I did out of concern for how to benefit those aspects of the field grow and how to help young people and seniors. You asked earlier about my hopes and concerns; one of my concerns is that, right now, it is much harder for young people to get started than it should be. We create processes, like obtaining a first grant, extraordinarily difficult with multiple revisions, some of which are trivial and might be better handled by a letter of stipulation; they shouldn't have to resubmit the grant. I am also concerned we are not funding senior investigators throughout their careers so some programs have been dropped, which I think sends a bad message in a field that is incredibly exciting. People have to feel there is

a true career path within it. We have got to fund and be prepared to continue to fund basic science, no matter what the science is; it can obviously be in neurobiology or psychopharmacology, but also in psychosocial or social neuroscience areas. Out of that can come translational research. We, ourselves, have done a tremendous amount of translational research. You and I did studies on naloxone in hallucinating patients, showing that in some patients severe hallucinations were diminished with naloxone and that was a form of translational research; we did it when it was time and ready to be done. I am worried we are defining translational research in a way that may be inhibiting basic science. So, part of my becoming involved in these activities is out of a love for the field. That is one reason I so like ACNP as it brings together everyone who might be relevant in a way that encourages communication. It has done that the entire time I have known of it, and it was nice I could come back and tell you how excited I am about the ACNP meetings. I deeply appreciate that and the chance to have this discussion with you.

SW: That's very nice, Jack. Last question, do you want to add anything? Are you happy? Do you want to make any comments about where you think this is taking you?

JB: That is a very interesting question. I tend to be a happy optimistic person and that may be genetic, because I have a mother who is bedridden, paralyzed and more or less blind but still optimistic, not about her condition, but about the world. Maybe I get my optimism in a basic genetic way. I do find I'm very happy and have experienced a level of happiness in my marriage to Rosemary I never expected, because you know how close Pat and I were. She, of course, was incredibly fond of you and Huda. I am also very happy about my son, my grandchildren and about our field. I feel that we are really making progress.

SW: Thank you very much, Jack.

JB: Thank you.

SW: A real pleasure.

JB: A wonderful pleasure, Stan.

SAMUEL H. BARONDES

**Interviewed by Andrea Tone & Thomas A. Ban
San Juan, Puerto Rico, December 9 & 10, 2003**

AT: I'm Andrea Tone. It is December 9, 2003, and I am interviewing Samuel Barondes.* It is the 42nd Annual Meeting of the ACNP in San Juan. Thank you for coming.

SB: It's my pleasure.

AT: Why don't we start at the beginning? Tell me a bit about your upbringing and your early education.

SB: I grew up in Brighton Beach, a seaside community in Brooklyn. My parents were immigrants from small villages in Eastern Europe who came to America in their late teens and met while working in New York. Neither had much formal education but both were autodidacts. They were also very idealistic and my father was particularly interested in socialist causes.

My elementary and high school education was in Jewish parochial schools, first the Yeshiva of Brighton Beach and then the Brooklyn branch of Talmudical Academy. Both of these schools provided me with a traditional religious education as well as a standard secular education. I then went on to Columbia College where I benefitted greatly from its famous Core Curriculum.

AT: Do they still have that?

SB: Yes. I'm pleased to say they do. It's a survey of great literature and ideas that form the foundation of western civilization. I really enjoyed it.

AT: When you were in high school, were you interested in biology or medicine?

SB: I was already interested in all kinds of science in elementary school, and this continued in high school. I liked to go home and do simple experiments with things around the house. And I kept a science notebook describing the experiments we did in class. I just loved science as a kid.

AT: Why Columbia?

SB: I applied to two colleges, Brooklyn College, which was my local school, and Columbia, which was also in New York. And I found Columbia to be really impressive. I particularly remember there were brick sidewalks, which I had never seen. It seemed like a different world, within subway distance of my home. My parents insisted that I live at home. We didn't have much money, so that was a given. I didn't consider it a hardship to have to take 90-minute subway rides each way between Brighton

* Samuel H. Barondes was born in Brooklyn, New York in 1933.

Beach and 116th Street in Manhattan. I felt lucky to be able go to Columbia because it seemed like a great new adventure.

AT So what course of study did you pursue?

SB: Columbia College did not have required majors. You had to take the Core Curriculum, and then you had to take a certain number of courses in various subjects. Among the requirements was a science course, and in my second year I took psychology, which was taught as an experimental science. The textbook, written by two Columbia professors, was based on experimental work pioneered by B.F. Skinner, who was a professor at Harvard. This Skinnerian emphasis distinguished Columbia's psychology department from almost all others, which were much more eclectic.

During my time at Columbia, as an undergraduate, Skinner's book, *Science and Human Behavior*, was published. Skinner believed everything was learned, and that all human behavior could be explained by simple mechanisms of learning. He demonstrated that people pulling levers on slot machines in a gambling casino showed patterns of behavior that looked just like rats pressing levers in order to get an occasional pellet of food. Graphs of human lever pulling or rat bar pressing looked very similar. I was interested in that kind of stuff because I liked to see experimental results presented as graphs. So all of a sudden I encountered the work of this scientist studying behavior in a way I liked. His approach was in startling contrast to that of Freud and the psychoanalysts, who were the other major force in psychology during that period. Instead of just speaking in vague qualitative generalities like the analysts, Skinner confined his attention to behavior you can measure and summarize in graphs. Based on my immersion in the work of Skinner I considered becoming an experimental psychologist.

AT: Based on this one course?

SB: Based on this one course and on my predisposition to be interested in these kinds of issues. And then what happened is I had a talk with my mother's brother, Joe. Joe was the pioneer immigrant in my mother's family. He came to America before the First World War, was drafted by the US Army as soon as war began, was sent to France, and was gassed in the trenches. Fortunately he recovered. And as a reward for his service he got support for education, a sort of a G.I. Bill, and he wound up becoming an accountant. With that financial background he bought and operated a small furniture company, and then started buying apartment houses that kept growing in value. By the 1950s, when I was in college, he had become a rich man and the patriarch of our family.

Since I was the first of the new generation, he was very interested in me and often came over to our house to talk.

I vividly remember one conversation that changed my life. It began with asking me what I wanted to do after graduating from college. I replied I wanted to become a professor of psychology, teach and do research. He then said something like, "Well, that's a wonderful thing to do, but first you have to go to medical school". When, I asked why he explained, "Because that way you'll make a living. Teachers of psychology don't earn any money. But once you get a medical degree it will increase your earning potential, and then you'll get a really good job and be in a better position to do all the science stuff."

AT: You're about the fourth person I've interviewed at this meeting who has told me a similar story.

SB: It was certainly in the spirit of that time. And it's a paradigm that is still alive and well. I often wonder how the course of my life would have been had I not had that pivotal conversation with Uncle Joe, which immediately sunk in. He was clearly trying to be helpful. And I respected and liked him, there was something very sensible about his advice. So I decided why not go to medical school.

AT: Did Uncle Joe have any qualms about you wanting to study psychology or psychiatry because at this point of time psychiatry wasn't a profession that had the same kind of stature as surgery.

SB: Not at all. In fact, he thought it was fine. He liked the idea. He thought I should follow my own interests, but he was just providing me with some sort of financial hedge in case things went bad. Because I had grown up through the depression as a kid, and my parents struggled, and Joe had come from a little village where people were all poor, the idea of having a profession where you could make a living was very attractive. The advice had an immediate and wonderful consequence because it made me take a course in physics that was required to get into medical school. Fortunately the distinguished Columbia faculty had started teaching a course that today might be called "physics for dummies." It was based on a book written by Gerald Holton, a historian of science. It was called *Introduction to Concepts and Theories in Physical Science*. It was a conceptual physics course, and was just perfect for me. I loved it. It taught me how the field developed historically as well as conceptually. So I owed my new understanding of the world of physics to Uncle Joe. Having passed the course with flying colors, I wound up going to medical school at Columbia.

AT: Why did you choose to go there?

SB: It wanted to stay in New York, and I didn't apply any place else. I was almost at the top of my class at Columbia College, was assured I would be accepted at Columbia Medical, and that seemed fine. I even got a scholarship from NY State, based on a competitive exam. I decided to live in the dorm, because Columbia Medical School was on 168th street, further away from Brighton Beach, and my parents were ready to allow me to leave. They did this with some reluctance because I was an only child, and they liked to have me around. They also feared for me in the world because, to them, the world was a scary place in that many of their siblings who remained in Europe were killed in the Holocaust. There was also residual anti-Semitism, even in the America of the 1950s. For me, in contrast, the wider world was exciting and interesting because I was moving from one culture to another.

When I started at Columbia Medical School in 1954 my intention was to be a psychiatrist. But when I arrived I was extremely disappointed because the psychiatry department was very rigidly psycho-analytic, whereas I had come from an experimental Skinnerian tradition of psychology. Although I loved reading Freud, the psychiatry professors I met were remarkably orthodox and narrow in their views. Having emancipated myself from the narrow Talmudic tradition I had grown up in, I had stumbled upon a new bunch of Talmudists who were quoting Freud in a biblical way! I didn't like their reluctance to consider alternative points of view, and since I tend to speak my mind, it was clear psychiatry was not going to work for me.

So I decided in the course of the first couple of years that I would become an endocrinologist. The reason was because hormones affect the brain, and it seemed endocrinology was a medical science I could apply to the study of human behavior and behavioral disorders. It was already clear that hyperthyroidism gave rise to severe anxiety and that excessive cortisol, in Cushing's disease, could cause mania and depression. So studying endocrinology was a way of maintaining an interest in behavior without getting myself involved with psychoanalysis. So when I graduated medical school, at the top of my class, I had decided to become an endocrinologist.

AT: How large was your class?

SB: 100 students.

AT: I was reading about the history of medical education and it suggested they still had quotas at a lot of universities for Jews.

SB: They did at some medical schools, even then. But I don't think this persisted at Columbia Medical School, when I went. There were quite a few Jewish kids in my class.

AT: When you graduated you had abandoned thoughts about becoming a psychiatrist?

SB: Absolutely. So I went to the Peter Bent Brigham Hospital, one of the Harvard teaching hospitals, for my internship and residency in medicine. One of the reasons I went there was that the chief of medicine was George Thorn, who was a famous endocrinologist. He was particularly interested in Addison's disease. It was time for me to leave New York, and going to Boston into the Harvard system was exciting. So I had two wonderful years in internal medicine at the Peter Bent Brigham which, like Columbia College and Medical School, is a place I adored. I really loved medicine, and became an excellent doctor.

But, again, a circumstance happened which changed my life. The rule at Brigham was you could not finish residency without taking a break to do research full time for at least two years. Then you could return to the program and finish your clinical training. Furthermore there was also a doctor's draft. Doctors were deferred but with the requirement that once they were finished training they had to serve in the military for a couple of years as a doctor. One way to satisfy the Brigham's requirement and the doctors draft was to join the US Public Health Service as a commissioned officer and get stationed at the National Institutes of Health where you could do research. So, a number of us from the Brigham applied for positions at the National Institutes of Health.

Fortunately, I was chosen by Ed Rall, head of the endocrinology branch at NIH. But when I arrived Ed had decided he was not going to keep working in a lab himself. He told me I could join any laboratory I wanted provided I did a bit of clinical service, which meant running the thyroid clinic once a week. In searching for a lab to work in I met Ira Pastan, who remains a very dear friend to the present day. He was a year ahead of me in the endocrinology branch. Presently he's the head of the molecular biology lab at the National Cancer Institute. When I arrived Ira befriended me and, when he learned I had no significant lab experience, taught me how to do the basic techniques of biological research. To start I joined Ira in the lab of an endocrinologist named Jim Fields. In choosing a project, I decided to work on the pituitary gland, which is directly connected to the hypothalamus at the base of the brain. Using techniques that Ira taught me, I decided to study the effects of serotonin and norepinephrine on the metabolism of glucose in the pituitary gland. Since serotonin and norepinephrine are found in the hypothalamus I hoped to learn something about the way the brain controls the pituitary that, in turn, controls the hormones in the body.

AT: Kind of fortuitous?

SB: One of the wonderful consequences of this plan was it led me to meet Julius Axelrod who was doing brilliant work on norepinephrine. It was a great time at NIH, its golden age, and everyone was open and available to novices like me. Julie was very welcoming and gave me reagents and friendly advice. Soon I was getting interesting results, and I started publishing papers. It seemed I was pretty good at this.

AT: What were you publishing on?

SB: My first paper was on the effects of serotonin and norepinephrine on glucose metabolism in the anterior pituitary. I would go to the slaughterhouse up in Frederick, Maryland, where you could get pituitary glands by digging them out of the skulls of cattle that had been slaughtered. They cost 25 cents each. I would put them on ice, take them back to the lab and make slices of the glands. Then I put the slices in an apparatus with radioactive glucose and other chemicals, with or without norepinephrine or serotonin, and measured the formation of radioactive carbon dioxide. I found that norepinephrine or serotonin greatly increased the metabolism of glucose in the pituitary slices. So my first paper was published in the *Journal of Clinical Endocrinology and Metabolism*. It was a big thrill. But I wasn't sure it was an important result, and I wondered if I might be better off trying another line of research.

As I was mulling over what choice I should make I had another amazing experience. It was the spring of 1961, and John Fitzgerald Kennedy had just become President. And guess what disease Kennedy had? He had Addison's disease! This was top secret at the time, but is now well known. Considering that Addison's disease is potentially fatal, the decision was made to find a member of the uniformed services to travel with him and to be available to provide emergency treatment. At the time, there were not many people in the uniformed services (which included the Public Health Service) who had experience treating patients with Addison's disease. I was one of them, because I had experience with Addison's disease at the Brigham. They came looking in the endocrinology branch at the NIH, and somehow found me and I was asked if I would do it.

AT: They asked you specifically to come to the White House and serve?

SB: They asked if I was willing to be considered for this assignment, and if I would be willing to travel with the President and be available in case he had an Addisonian crisis. I felt confident I could do it since all I would have to do is to give him some cortisone. I probably would never have been called upon to do this. But they wanted a backup. They told me it was top secret and I couldn't reveal he had Addison's. When I was approached I already had a security clearance to go to the NIH but in

order for me to take on this duty they decided they had better do a serious security clearance on me.

AT: I guess they found out your father was a socialist and that excluded you.

SB: What they found was the following. That my father was a socialist was a small part of it, although I know they had evidence of that in my FBI file, which I obtained many years later. But both my parents were very strongly anti-communist. They thought Stalin was a fascist. Nevertheless Brighton Beach, where I lived when I was a child, was a major center for the US Communist party. And it turned out that a card-carrying member of the Communist party was living in my parents' basement. He was a friend of my father, an artist, and he lived in the basement, pro bono, no rent. I remember that my mother called me during this period and told me that government agents were asking about me. She thought I was in some kind of trouble because I didn't tell them the reason they were investigating me. It was completely secret.

AT: So, it wasn't just the Addison's disease that was off limits.

SB: That's right. And I didn't expect them to send federal agents to Brighton Beach. Be that as it may, they called and said they had decided that since Kennedy was in the Navy they wanted somebody from the Navy rather than the US Public Health Service. I still wonder how it might have worked out if they decided to use me.

Meanwhile, at just around that time, I had another amazing experience. I met Gordon Tomkins. Gordon was an endocrinologist with a PhD in biochemistry who decided to give up clinical work to become a full-time scientist. He was just seven years older than me but had been named chief of a new unit right around the corner from my lab in Building 10 at NIH. People said I should go and talk to Gordon because he was interested in endocrinology. He was very open, friendly, and truly charismatic. And my meeting with him, like my meeting with Uncle Joe, changed my life.

To make a long story short, when I first met Gordon he took me into his tiny office and promptly introduced me to a completely new way of thinking about endocrinology. He had come to the conclusion that hormones worked by a mechanism I had never heard of, called regulation of gene expression. Gordon's idea was that hormones work by activating or inhibiting the expression of certain genes in particular cells and organs – an idea which is now common knowledge but was revolutionary at the time. He also believed that hormones probably do this by binding to certain proteins and controlling their shapes, and that activation of genes led to the manufacture of more of the messenger RNA that

the activated genes encoded. This was in early 1961, and it was truly visionary. Furthermore, Gordon had come to the conclusion that the most important tool for studying endocrinology was molecular biology, a field I had never heard of. Or, as he put it “endocrinology is really molecular biology.” In the course of my initial meeting with Gordon, which may have lasted two hours, he taught me this whole new way of thinking about hormones and biology. I walked in knowing nothing about this new approach; I walked out knowing the big picture, because of the way he explained it. Although it was revolutionary, it wasn’t hard to understand.

Amazed by what Gordon taught me in our first meeting I said, “Great, I want to work with you.” and was disappointed in his reply. He said, “You can’t work with me because you don’t know enough yet to work in my lab. Besides, I’m going to France in a year to do a sabbatical, and I’m not taking on new people. You need to learn how to work on this kind of stuff. But there’s a guy down the hall who I just hired who has only one post-doc. So he needs help and he’ll teach you how to do this kind of stuff. Why don’t you work with him?”

After talking it over with my friend Ira Pastan, I went to see this new guy, named Marshall Nirenberg who said he would take me on. He was at the time completely unknown. In fact, Gordon was one of the few people who thought he was promising and gave him a position to continue his work on the mechanism of protein synthesis. Gordon’s judgment proved to be correct, because three weeks after I joined his lab, Marshall discovered a way to figure out the code by which DNA, and the messenger RNA it gives rise to, determine the structure of particular proteins, a discovery that brought him a Nobel Prize.

The way he did it is a long story. A lot of it was serendipitous. The key was to use synthetic polynucleotides rather than natural messenger RNA. RNA has four different nucleotides, and one of them is uridylic acid. Marshall decided to study the effects of polyuridylic acid which is a chain of uridylic acids, without any of the three other nucleotides. When he and his postdoc, Heinrich Matthaei, added polyyuridylic acid to an extract derived from bacteria, the extract started making protein, and that protein, it turned out, had only one amino acid in it, which was phenylalanine. We now know the reason for that is that the code for phenylalanine is a string of three uridylic acids.

DNA has all of our genetic information. It’s encoded in four different nucleotides: A, C, G & T. And then what happens is information gets copied out of DNA onto a messenger RNA and instead of the T you get a U. RNA has A, C, U & G but no T. The T becomes U. Once

the language of DNA is copied into messenger RNA it is translated into proteins.

One of the great mysteries of biology was the language of DNA and the way it is translated into the language of proteins. We now know that the units of DNA, A, C, G & T, are arranged in specific sequences. For example you might have A-A-C-G-T-A. What does that mean? And how is that translated into proteins? Well, as it turns out, units of three nucleotides called triplets, say A-G-T, mean a specific amino acid. There are 20 amino acids in proteins, and there are 64 different triplets you can make from the four units of DNA. It turns out that these 64 possibilities are redundantly used, so that several different triplets may specify the same amino acid whereas some amino acids are specified by only one. And three weeks after I had arrived in his lab, Marshall had stumbled upon a way to figure out which triplets specify which amino acids, by making a large number of different synthetic polynucleotides and finding out which amino acids they direct into proteins. It was a great breakthrough. And within a few years Marshall and his growing number of postdocs went on to work out the entire genetic code.

Having arrived at the beginning of this great new line of research, just as the effects of polyuridylic acid were discovered, I was given the project of figuring out how it worked. There were two interesting questions I answered. One of the questions was: is a copy of messenger RNA used just once? Or is it used over and over again? Big question! I showed that it is used over and over again. It is used catalytically, not stoichiometrically. The other question concerned the interaction of polyuridylic acid with structures involved in the manufacture of proteins. I showed that it associates with structures called ribosomes, which are part of the machinery for making proteins. These were both very important findings, so I wrote a paper about each of them. Marshall, meanwhile, was busy working on the rest of the genetic code; there was a huge competition with another laboratory. So he was immersed in the competition, and I was left pretty much on my own with the problems I was given. Having written these papers I decided now it was time to work with Gordon. I also wanted to go to France, where Gordon had gone for his sabbatical.

AT: Did you know how to speak French?

SB: I knew some French. I also went to the local high school in Bethesda and took night classes in French. So I arranged to leave Marshall's lab and to work with Gordon for the last three months Gordon would be in France. People told me, "You're crazy. You know, this guy, Marshall is going to win a Nobel Prize." But, I said I had done my stuff, and I wrote

these two papers. I gave them to Marshall and said, please send them to the *Journal of Molecular Biology*, which was the great journal for this kind of research at the time. And he said, fine, so I went to France and did some work with Gordon at a lab in Gif-sur-Yvette.

Gordon, his wife Millicent and I had some great adventures in France. And then we all came back to NIH where I spent another nine months in Gordon's lab. We became good friends and remained friends until Gordon died at the age of 49 of a brain tumor; it's a long, horrible story. His wife, Millicent, and I are still good friends. She is a wonderful artist, and many years later, after a term as Chair of Psychiatry at UCSF she painted my portrait. It's hanging in the psychiatry department at UCSF, along with the other past department chairs.

When I went to France I was already thinking about the possibility of applying the molecular biology I had learned to my earlier interest, the brain. If endocrinology can be studied with molecular biology, maybe brain science can also be studied with molecular biology. It's just more complicated than endocrinology. So I talked to Gordon about this, and he said, "You can work on that sort of thing in my lab. Do whatever you want."

So I started collaborating with a person I knew as an undergraduate teacher at Columbia College. His name is Murray Jarvik and he happens to be one of the earliest members of ACNP. He is a psychopharmacologist interested in the storage of memories. And I was interested in the possibility that storage of memories depends on regulation of gene expression and on the synthesis of messenger RNA and proteins. So Murray and I started injecting mice with a drug called actinomycin-D which blocks the synthesis of messenger RNA to see if it would prevent mice from remembering. I would continue with this work for a number of years. It was a way of getting back to my interest in behavior, including psychiatry.

Having learned to do science I was not enthusiastic about going back to the Brigham to finish my residency in medicine. I thought maybe I would do something different and follow my interests more. So that is what I did.

But before telling you about that I'll tell you another story, about the two papers I left with Marshall before leaving for France. When I came back three months later they were still lying in the identical position on Marshall's desk. He was too busy to deal with them. After all, he was solving the genetic code. He had very little to do with my papers, so he just left them be. When I came back I was very disappointed that he hadn't done anything with the two papers.

But the story takes an interesting twist. As it happened, Phillip Abelson had just become the new editor of *Science* magazine. And he was looking for new kinds of things to feature; he had gotten word that molecular biology was hot and Marshall Nirenberg was hot. So he wanted papers from our lab. Meanwhile, Jim Watson, one of the double helix guys, had come to the lab to find out what Marshall was doing. So Marshall tells him about the stuff I did; and Watson says, "Gee, that's really interesting, because there's a guy at Harvard who's doing the same stuff and getting the same results." This was Walter Gilbert who subsequently went on to win a Nobel Prize as well. So Marshall decided we should publish this stuff, Watson thinks it's pretty good. Besides I was bugging him to get it published.

Since Abelson was looking for papers for *Science*, Marshall sent them. Abelson had them reviewed; and a few days later called back. They would like to publish the papers. But there's only one problem. The papers are written in the format of the *Journal of Molecular Biology* while *Science* has a very different format without a section devoted to details of experimental methods. So Marshall calls me in, and says "would you mind rewriting these papers in the *Science* format." And I, being utterly naive, and not knowing how prestigious it was to publish in *Science*, said that I don't understand why they can't publish them the way they are. And so Marshall sent me down to one of the senior staff editors at *Science*, Eleanor Butz, who said, "Well, you know, we don't publish papers like that." We went back and forth, and they finally decided, OK, we'll publish them. There were some scientific issues they wanted clarified, so we fixed those. Within a month or so I had two papers published in *Science*, back to back with me and Nirenberg as the authors.

The reason I backtracked is that these were really important papers, and they got enormous visibility because they were published in *Science*. Suddenly I was somebody to be reckoned with, and this encouraged me to use molecular biology to work on the brain, and even go back and do training in psychiatry. I suddenly saw I could be a psychiatrist who did science. By becoming a resident in psychiatry I could learn all the interesting stuff I wanted to about psychiatry, but I would also continue to do laboratory research. So I arranged a three year psychiatry residency at McLean Hospital, which is a Harvard teaching hospital. But they also gave me a lab and a small budget to continue my work on protein and RNA synthesis and memory.

AT: At McLean?

SB: Yes, they gave me a lab at McLean. There were several scientists working there, including Jordi Folch-Pi, who worked on myelin. They were not psychiatrists; they were PhDs and they were happy to have me. I soon acquired a graduate student, Harry Cohen, who did his PhD thesis with me. So while I was a resident, I worked on the question of whether brain protein synthesis is required for long term memory storage.

The idea behind this goes back to Gordon: if regulation of gene expression, which controls protein synthesis is so important for adaptive processes controlled by hormones, the same mechanism might work in the brain to control its functions by laying down memories. To test this hypothesis we studied mice learning to terminate a mild foot shock by making a correct choice in a maze. Some mice were injected with drugs, such as puromycin or cycloheximide, which inhibit protein synthesis, given either shortly before or at various times after training. Controls got saline. At that time similar studies were being done by Louis Flexner who also used mice, and by Bernie Agranoff, a member of the ACNP, who studied memory in goldfish. Harry Cohen and I found if you give one of these drugs in doses that wipe out brain protein synthesis, and then teach animals to choose the correct limb of simple maze, they could learn it perfectly and retain the information for about three hours; then the memory disappeared. So, in order to store it in the brain they had to turn on genes to make proteins, which, at that time, was a very radical idea. Now it's commonplace.

At about the same time I started working on the transport of newly made proteins in nerve cells called axoplasmic transport. I did this because the machinery that makes RNA and proteins is concentrated in the cell bodies of nerve cells whereas much of their action is at nerve terminals which may be even a few feet away. So the new proteins have to be transported to the nerve terminals through axons. I was interested in the speed with which this happened because I wondered how long it would take for changes in gene expression to occur in the nerve terminals, where one nerve cell communicates with others. While doing this laboratory research I also dutifully did my residency, which included psychotherapy and caring for of a lot of schizophrenic patients. I really learned clinical psychiatry and I liked it. My hope was that just as my colleagues in medicine were using molecular biology to figure out how hormones work for endocrinology, I would do the same thing in psychiatry. It was a simple idea, but it was novel at the time.

AT: When you were a resident at McLean, what portion of patients were given drug therapy?

SB: They were very reluctant to use drug therapy at the time. I was a resident from 1963 to 1966, so Thorazine was a well-established treatment. Imipramine was also available. Lithium, had been discovered in 1949, but was not yet approved in the U.S. But Thorazine, the MAO inhibitors, imipramine, and related tricyclic antidepressants were already available. Also the benzodiazepines were introduced; Librium and Valium came in 1960 or 1961. Amphetamine had been around for decades. So there were already a lot of drugs, including some we still use. I recently wrote a book called *Better Than Prozac*, which traces the history of these drugs.

AT: I've seen it.

SB: So drugs were available and I was very interested in them. But they were frowned upon at McLean at that time. I had two schizophrenic patients I treated during the whole three years I was a resident with psychotherapy but no medications. Both were adolescents with paranoid schizophrenia, one more primitive than the other. I would see them three times a week for one hour in psychotherapy. And my sessions were taped. My supervisor was Alfred Stanton who was the chief of psychiatry at McLean. He had worked with Harry Stack Sullivan who was very interested in the psychotherapy of schizophrenia. Stanton and I would meet once a week, listen to the tapes, and he would make encouraging comments. But there was no discussion of medication.

AT: Did you advocate it?

SB: Unfortunately I did not. I was, after all, a trainee being instructed in what was considered the best treatment. In those days they believed drugs interfered with the psychotherapeutic process. In the course of my conversations with Dr. Stanton I did raise the issue of why these kids aren't getting medication. And he would say, in our experience drugs really don't work very well for these kids because they're pretty high functioning, and do better with psychotherapy. This is not to say no drugs were used at that time at McLean. In fact I had some experience using the various drugs then available. But there was real reluctance to use them.

AT: At that time was McLean different from other hospitals, specifically public hospitals, where Thorazine was widely used?

SB: Yes.

AT: The results with Thorazine suggested it was very efficacious.

SB: Absolutely. But their view was that drugs were a last resort and should not be used with high functioning patients. And my two schizophrenic patients did improve somewhat over the three years I worked with them providing psychotherapy which included advice about ways they might

conduct themselves. Furthermore, I was continuously reassured I was doing a great job, and I learned an enormous amount about manifestations of schizophrenia. For example, one of the patients believed with total conviction that a street downtown Boston, which had lots of tall buildings, had been constructed so if he walked there the buildings would fall on him. That was his delusion, so he would not go into downtown Boston. It did not budge in the time I saw him. He learned to keep it to himself, but if I asked about it he would acknowledge he still believed it. In retrospect, I think this delusion would have dissolved if he were treated with Thorazine. I feel sad he wasn't treated properly because my teachers believed drugs didn't work very well or interfered with therapy and were too toxic to use. It's ironic that over the years McLean became a major site for research on psychopharmaceuticals. I'm sorry it wasn't at the time I was there.

AT: They were giving ECT?

SB: Yes. And they had done lobotomies. There were patients I saw who had had lobotomies, but they weren't doing them anymore. Maybe their bad experience with lobotomies made them wary of the new psychiatric drugs. One of the Kennedy sisters had a lobotomy, and I wouldn't be surprised if it was done at McLean.

AT: It failed.

SB: Absolutely failed. And we had the wife of a well-known Harvard professor who was a casualty of a lobotomy and an inpatient when I was there. ECT was certainly used at McLean, so there was openness to that type of somatic therapy. But Stanton, my supervisor, was primarily interested in adolescent schizophrenics, and he felt they could be treated by psychotherapy. That was how it was in those days and I look back at it with discomfort.

But I knew the field would change. I already had the dream that eventually molecular biology would come to the aid of psychiatry. It was clear to me, even in those days, that psychiatric disorders had some genetic basis. There was already literature on that when I was a resident. But it was pooh-poohed by the establishment that trained me. And it didn't seem to really make any difference. What were you going to do about it anyway? It was not at all apparent in those days that one could find the relevant genes, and use that discovery to identify treatments or as a basis for diagnosis. Genetics was very primitive in the 1960s.

I finished my residency, and they wanted me to become a faculty member at McLean but I needed to move on. I was offered a job as an assistant professor at Yale, which I considered, but I was married, had

one child and another on the way. My wife Ellen and I were from New York, and our parents were there. So we decided that we wanted to go back to New York which we remembered as footloose and fancy-free young people, not parents with little kids. So I took a job as an assistant professor at the Albert Einstein Medical School. One of the attractions was it was the first medical school in the country with a department of molecular biology. They offered me a joint appointment in the departments of psychiatry and molecular biology, which was perfect. I had colleagues in psychiatry, whom I respected, and also colleagues in molecular biology. I must say I really liked it at Einstein!

But everything changed a year or so after I arrived when my wife developed breast cancer. She had a mastectomy, and we thought she was cured. But through all the ensuing turmoil it became clear we didn't want to settle permanently in New York and raise two little daughters there. One problem was I wasn't earning a lot of money and I was being recruited all over the place. I was offered a full professorship at Stanford, which I looked at, and then I gave a talk at the Salk Institute in La Jolla, in San Diego. I was invited by their external advisory committee, which was full of Nobel Prize winners. Salvador Luria invited me. In the audience were Francis Crick and Jacques Monod. It was an incredible event. Also in the audience was Arnold Mandell, a member of the ACNP, who had just been appointed Chair of Psychiatry at the medical school at UC San Diego, which had just been founded; he invited me on the spot to come as a full professor. And in less than a year we were there. We arrived in December of 1969. We loved UC San Diego and coming to a brand new medical school that was clearly going to be excellent, and living in this little seaside town which was startlingly beautiful. I don't know if you know La Jolla. It has become very crowded, but in 1969 it was this idyllic little beach community. Houses were cheap and the salaries were good.

AT: The good old days!

SB: We bought a house for \$50,000 with an ocean view so it was a great move. And we believed my wife was cured. But shortly after we arrived it became clear that she had metastatic cancer, and she died a year and a half later. And I was left with two little girls who were five and seven years old.

That terrible tragedy put a real crimp on my life. I became the sole parent. Be that as it may I had a wonderful career at UC San Diego. I helped found an excellent department; after all, I was the first faculty member. There was Arnie, the Chair, and there was me, and for the first

six months I was doing everything, teaching classes, taking care of the patients. I loved it!

AT: What would you say your single most important contribution to your department, but also to research in psychiatry was at this point?

SB: I helped bring molecular science to psychiatry. I basically took what Gordon told me, which was that endocrinology is molecular biology, and said psychiatry is also molecular biology. I took the view one should study the brain as a molecular entity, that is, one should just break it down into its constituent proteins, study how these were made and how the brain developed.

Very shortly after I arrived in San Diego, while I continued my work on learning and memory, I became interested in developmental biology. I decided the brain was too complicated for the molecular technology of the time so I started working on slime molds, *Dictyostelium discoideum*. I became interested in how cells form connections, how they stick to each other, because I was interested in how synapses are formed in the brain. It has now become much easier to study it in the brain, and there have been great discoveries about the process, but then it seemed hopeless to study the development of cellular connections in the brain.

I became interested in the role of protein-sugar interactions in cell-cell connections and set up a research program using *Dictyostelium*. This organism generally exists as a colony of single amoebae, which each wander through the soil and eat bacteria. What's interesting is that as long as there are bacteria around, each cell keeps eating them and dividing to make daughter cells. But when the food is gone it changes from being an individualist to being a social organism. As this change occurs the individual cells start signaling each other using a compound called cyclic AMP, and they stick together in a very specific way, which is important for further development. When thousands of cells come together they begin to differentiate into two cell types. Some become stalk cells, which die but raise-up the rest of the cells, which become spore cells. The whole point of the aggregation and differentiation is to get some cells to a new place where they might find food. So the spores are disseminated to other places, including some where there are bacteria, and those lucky spores, sensing the bacteria, again become amoebae, so the life cycle goes on.

The reason this interested me is this whole developmental process occurs over the course of 24 hours. So slime molds go from being single-celled amoebae to a differentiated organism with 2 cell types in the course of a day. So instead of studying the course of human

development, which takes many years, developmental biology could be studied in a 24-hour period. These creatures can live and develop in Petri dishes so they are easy to study. In those days, working with nerve cells in culture was very tricky and difficult. All the things we take for granted now in terms of modern neuroscience were developed over the course of the past 30 years. And all the genetic tools for working on humans have been developed over the course of the past 15 years. At that time, when I was making critical decisions about what to work on, slime models were an excellent organism for studying how cells form associations with each other. So I started studying them in the naïve belief this would be a model for how nerve cell connections are formed in the brain.

Each scientific project has a life of its own. So, in the course of this work, which was guided by the hunch that sugars on and around cells are important for them to stick to each other, we started making some important discoveries about sugar-binding proteins in slime molds. We were interested in sugars and sugar-binding proteins because all cells are covered with sugars. That's true of slime mold cells, and it's true of nerve cells. And there is a code embedded in the structures of chains of sugars, which has still not been fully deciphered. Just as proteins are chains of amino acids, many proteins are decorated with sugar chains with complicated and specific sequences. It was clear that those sugar chains, right on the surface, must communicate information as they talk with each other. Some of the information about how cells interact was probably encoded in those sugars so I started looking for proteins that bind to sugars, some of which had been discovered in plants and named lectins. In the course of this work I and a post doc, Steve Rosen, discovered a couple of lectins in slime molds, which we named discoidins, that play a role in cell interactions. Then I started looking for similar proteins in mouse tissues, including brain, and discovered lectins in many chicken, mouse, frog and human tissues, which we named galectins. So my major research interest shifted to sugar binding proteins. I stopped working on memory because techniques for identifying the proteins involved in the storage process were not available at that time.

Since then Eric Kandel and others have made great progress in identifying brain proteins involved in memory storage. In fact Eric Kandel won a Nobel Prize for this work. But in the 1970s, I thought the problem was too hard to work on at the molecular level, whereas slime molds and lectins were easier to study with the tools available. Nowadays, as it became so easy to do elegant molecular experiments with human cells, there's less interest in slime molds. But some researchers are still using them to answer some fundamental biological questions.

Despite all the new knowledge about the biology of the brain, psychiatric problems remain very challenging. I was at a session here at the ACNP about new drug discovery, and people were bemoaning the fact that, with all the modern molecular and genetic technology, it is still hard to make a new drug, and we continue to rely on drug discoveries that were made in the 1950s by accidental means. So we've developed amazing basic science, but solving psychiatric problems still remains very difficult.

AT: You've written, within a short time, three books designed for the general public. Your most recent, published in 2003, is *Better Than Prozac*, which seemed to have an optimistic view about what we can achieve in drug development based on the research you and others have done. Can you say more about that?

SB: Well, I'm optimistic that, in the long run, we will be in position to identify very important targets for new drugs. I hope we will do this by finding genes that predispose to psychiatric disorders. This will open a path for drug development that is completely different from the serendipitous drug development of the 1950s, which we still are living off. So I'm optimistic that we will not have to depend purely on accidental discoveries anymore. But I recognize it will still be very hard to make new drugs. This was the theme of the symposium I was at this afternoon, which included Arvid Carlsson who has had an incredible history in drug development and is a Nobel Laureate.

The reason I'm optimistic is because of the Alzheimer's story, which I talk about in my latest book. Alzheimer's disease, in its early onset form (with symptoms by the age of 50), is caused by mutations in any one of three different genes. Most cases of Alzheimer's disease are of the late onset form, which strikes people in their 60s and above. The mutations in genes responsible for the early onset form have been found, and a lot has been learned about them. Each of these abnormal gene variants has a similar net effect on the development of a pathogenic substance in the brain called A-beta. So even though they are different genes, they work through the same final common pathway. That in turn has led to a proposed treatment by creating drugs that would block an enzyme that makes the pathogenic substance, A-beta. So through this knowledge about the genetics of Alzheimer's disease, pharmaceutical companies are trying to make a drug which might make a huge difference in the treatment of patients, including those with the late onset form who also accumulate A-beta. In fact such drugs could conceivably prevent the disease. Will they work? We don't know. There are a number of drug companies investing huge amounts of money in this project. This

is an example of how gene discovery is leading to development of what may be a profoundly important drug for a severe mental disorder.

AT: Some would say whether tricyclic antidepressants were discovered by accident or through rational cunning doesn't really matter.

SB: It doesn't.

AT: We already have this buffet of drug choices that work. But you're also saying we need better drugs.

SB: The title of my book *Better Than Prozac* comes from the statement of a patient who is helped by Prozac but dislikes certain side effects. She has sexual side effects and also feels it makes her thinking fuzzy. She's a very intellectual person. So she says "Thanks, I'm really grateful to you doctor, but I'm looking forward to the time when we have a drug that's better than Prozac." So I think Prozac and a lot of medications we have are remarkably useful and the fact they were discovered by accident is no different than the discovery of aspirin or digitalis. I don't think that psychiatrists need to be defensive about the accidental origin of the medications we have. If they were perfect, we wouldn't have to go any further. But they're not. They're limited not only by side effects but also because they don't always work. With Prozac, for example, about a third of patients with depression don't get any benefit at all. If you diddle around with combinations of drugs or with different ones, you can increase the number of patients who benefit. But there are still a lot of people with treatment-resistant depression; even people who benefit aren't necessarily completely relieved of their symptoms. And some people find the side effects enormously troubling. There is a huge variation in the sensitivity different people have to side effects. And by the way, genetics will be very useful for them, because there's this whole field called pharmacogenetics, which is the study of genetic variations that lead people to metabolize or respond differently to drugs. Identifying these genetic variations will help in drug selection. Part of my book is about the great promise of pharmacogenetics.

I'm also optimistic about the rational creation of some new psychiatric drugs. Nevertheless, all the optimistic people we heard today pointed out that it takes at least 10 years to go from discovery of a potential drug target to a successful drug. There are all kinds of impediments along the way, and frequently drugs that look good turn out not to work or turn out to have bad side effects. So as we accumulate knowledge about psychiatric disorders from genetics and from physiological studies of psychiatric disorders we will still have a long way to go before we can translate that knowledge into effective new medications. But I am optimistic that we stand on firmer ground than when I started

out. I wrote *Better Than Prozac* because I wanted to review the accomplishments of the field for a general audience to help people understand where psychiatric drugs came from, their strengths and limitations. And I devoted the last half of the book to how we hope to take the next steps. But I never said it was going to be easy.

AT: Let me ask you a final question, which will take you back to your parents.

SB: My parents?

AT: Who you said were socialists. It costs a lot of money for pharmaceutical companies to develop these drugs, and one of the complaints both politically and economically is that even though it costs firms a lot of money to develop these drugs, it costs consumers a lot of money to buy them. I was interviewing a specialist in geriatric depression this morning, and he was talking about how difficult it is for people over age 65 to afford something like Prozac, which is now off patent. So, thinking about the future, is there going to be a gap between the availability of these drugs and the ability of ordinary people to reap the benefits of this remarkable revolution?

SB: Absolutely. I think that this is an enormous social problem in America. And it's a very complex issue. It involves the way drug discovery is funded, our dependence on the pharmaceutical companies to do a lot of drug discovery, their dependence on their shareholders and their intense profit motive. The symposium I was at addressed this issue in much more detail than I can in this very short time. We would all be most pleased if we could find drugs that are practical and readily available, as well as totally effective. That is a major goal of psychiatric science.

Will we ever be able to solve all the problems of psychiatry with science? My next book has several tentative titles. One of them is *The Hope of A Science*, and it comes from William James. In 1892 William James wrote the short version of his famous book *Principles of Psychology*. In the final paragraph of that book, he says, "psychology is not a science, it is the hope of a science." So I think psychiatry in 2003 remains still the hope of a science, the hope of a science that will one day be so rich and so facile that it can bring a lot of benefit to a lot of people in a very efficient way. But despite all we've learned and all we are about to learn in the immediate future, fixing all the mental suffering of people is a tall task. And I'm not talking about just the dysphorias. I'm talking about the more serious problems like bipolar disorder and schizophrenia, which completely disable and ruin people's lives. These are big, big problems, and fixing them is not going to be easy. But we'll get there. And my hope is that the science we are accumulating now, these molecular approaches and understanding of the genes that

- predispose to these disorders, will eventually pay off. So I have the hope of that science, but I don't think it's going to be easy.
- AT: We should probably end on that. Do you have anything you would like to add?
- SB: Not for now. But we could talk more about the later part of my career. I think it's great to have these records. I like history myself, and I think it's priceless to have records of individual people and to see what they're like.
- AT: You have a wonderful history.
- SB: Thank you for giving me the opportunity.
- TB: This will be the continuation of the interview with Dr. Samuel Barondes for the archives of the American College of Neuropsychopharmacology. It is December 10, 2003. I am Thomas Ban.
- SB: I spoke with Andrea yesterday about my early background. But we ran out of time. What I thought I would do today is to summarize my later activities in four categories. The first was my time at UC San Diego from the founding of its department of psychiatry in 1969 until 1986. This was the period when I was most active as a researcher.
- TB: In Arnie Mandell's department?
- SB: Yes, in fact, Arnie Mandell was the chair, and I was the whole faculty for a while so I will describe my time there. Then I will tell about my move to UC San Francisco as the Chair of the department of psychiatry, which I did for about 7 years, and then assumed a new duty as director of a Center for Neurobiology and Psychiatry. After that I will tell you about some activities with the NIMH and especially with the McKnight Foundation, which were important parts of my professional life. And finally, I will tell about becoming a book writer in more recent years. So while I direct the Center for Neurobiology and Psychiatry, I've also written three books, and, my major activity in the future will be in the area of writing for a general audience about molecular approaches in psychiatry. I will cover those all briefly.
- TB: Very good.
- SB: I'll start with UCSD. I told Andrea yesterday that I met Arnie Mandell in 1969 at a meeting at the Salk Institute where I was giving a lecture, and he had just been appointed as the chair of psychiatry. UCSD was a brand new medical school, and we hit it off, and he invited me to become a professor in the department. And so, after consideration and formal visits and all that sort of stuff, I decided yes, this was great. And La Jolla at the time was a beautiful, wonderful place. It was just a lovely beach community.
- TB: It's still beautiful.

SB: It still is beautiful, but it was more untouched, in its more natural state. And there was going to be this great university, and we were getting in on the ground floor. So I jumped at the chance, and so I became, after the chair, the first faculty member of this department and was appointed as a full professor, which was quite wonderful. Arnie was very energetic, entertaining and a very interesting man, and we tried hard to build a department which was heavily research oriented. My interests were in basic science as it applies to psychiatry, although I'm fully trained as a psychiatrist. So I helped recruit the various other people. Lew Judd was the next person who came.

TB: So, it was you who recruited him.

SB: Well, Arnie and I did. Arnie knew him at UCLA and Lew eventually became the chair and has had a wonderful career. And I continued my research on the role of protein synthesis in learning and memory.

TB: Pioneering research.

SB: I was trying to bring molecular biological techniques to psychiatry, and so I was, at the time, studying protein metabolism in the brain and the effects of blocking protein synthesis on memory formation, which has since become a very popular and well established area. But it was a pioneering field at the time. And I had graduate students and post-docs and some of the people who came to work with me have gone on to wonderful careers. Larry Squire worked with me for several years and remains at UCSD. He's a very distinguished professor. Irwin Levitan came as a post-doc and is now the head of neuroscience at the University of Pennsylvania. So I attracted a bunch of young people, many of them PhDs, to work on learning and memory.

I also began work on the way that cells interact, because I believed that one could study the way synapses form – which seemed hopelessly complicated in 1970 - by using a model organism, a slime mold. It's a very simple organism that has, as I told Andrea yesterday, the property of forming cellular connections. So it could be used as a way of studying cell-to-cell connections in a simple biological system. And so I worked very actively on that, and we discovered some proteins which seemed to be involved in this process. I was very interested in the role of sugars on the surface of cells as a coding mechanism for cells recognizing each other. And we discovered some sugar-binding proteins, and this became a very important area of research for me. We found these sugar-binding proteins called lectins, first in slime molds and then in mammalian cells, including brain cells.

TB: Was it all laboratory work you did at the time?

SB: I was also doing a little bit of clinical work, but I was basically a laboratory person, doing basic research, but with an eye toward building up basic knowledge in biology and neurobiology as it could relate to psychiatry. I felt that foundation was necessary, and indeed that was correct. I mean, now the foundation has been built by thousands of people.

TB: Thousands of people.

SB: Yes, each contributing in his or her way, and also training students and post-docs to move the field forward. I had many interesting students and post-docs in my early work on brain proteins and memory. Later I had many others who worked on cell interactions and lectins, such as Steve Rosen, who is now a professor of anatomy at UCSF.

TB: Working on cell interactions?

SB: Cell interactions, was a very important area for me. So I continued in this way at UCSD for about 16 years and had a wonderful time. And then the opportunity arose to move to UC San Francisco as chair of the department of psychiatry. As I told Andrea, I lost my wife to cancer very shortly after I moved to La Jolla. I had two little children, and after 16 years they had grown up. They had both gone off to college at UCLA, and I felt free to go do something else, and UC San Francisco, at the time, was really eager to build up their much larger department of psychiatry to create more of a basic science presence. I was recruited and promised great resources in terms of lab development and recruitment of faculty.

So I became chair and wound up recruiting excellent faculty, like Rob Malenka and a number of other young people, some of whom are now members of the ACNP. All were psychiatrist scientists doing basic laboratory research as it relates to psychiatry. By this time, it was becoming easier to bring laboratory research to psychiatry because the body of relevant biological knowledge was accumulating. Genetics was becoming a really important area, and I became very interested in the genetics of bipolar disorder. And this interest continued when I stepped down as chair at the end of '93.

TB: But you continued your work in the laboratory?

SB: I did have a lab as chair, although it was difficult because I had heavy administrative duties and was doing a lot of recruiting. I would also supervise residents from time to time.

TB: What about clinical practice?

SB: I would see mostly VIP patients; I always maintained a small clinical practice. And I do that to the present. I insisted that all faculty I hired who were basic scientists, mainly MD/PhDs, spend four hours a week doing clinical work.

TB: A few hours a week.

SB: About four, so they would maintain contact with clinical psychiatry. I think it's critical, otherwise, they could just as well be PhDs. After I stopped being chair, I founded The Center for Neurobiology and Psychiatry, which is funded by NIH and private gifts. It helps young faculty start new projects, helps recruit young faculty to the department and helps build new laboratories. We decided to recruit people on the basis of excellence. So rather than recruit people to well-defined positions, we recruited the best people we could find and said do what you like. And we provided a good environment for them to interact with each other. We have excellent young people; people who already have made a name for themselves. People like John Rubenstein who is a member of the College now, Larry Tecott, Mark von Zastrow, Allison Doupe.

TB: You trained excellent people

SB: I did, although I closed my lab several years ago.

TB: So, you closed your lab when you retired from the chair.

SB: Not immediately. But while I was chair the balance shifted away from the lab, and I gradually turned it over to people I had trained. In the process I assumed a lot of advisory roles, which I liked. I was on the extramural science advisory board for the NIMH, I was the chair of the board of scientific counselors for the NIMH, and I spent a lot of time with the McKnight Foundation, which has been a very important part of my career.

The McKnight Foundation is based in Minneapolis and now has assets of about 2 billion dollars, so it's a big foundation. And one of their interests has been neuroscience, so they've set up the McKnight Endowment Fund for Neuroscience, which I helped found, was on the board of for almost 20 years, and was President of for 10 years. We fund young assistant professors in neuroscience and have a program for technology development in neuroscience. We also have a program to support neuroscience research on brain disorders, including psychiatric disorders. So I was very much involved in working with the Foundation, selecting grant recipients, working on the committees. I am extremely proud of what we accomplished, because the McKnight Foundation was giving us between 2 ½ million and 4 million dollars a year for this program – not a huge amount of money – but we used it to good advantage to help many, many excellent young people get started. Many of them are leaders in the field of neuroscience now. My view was that this was a way of helping to build a foundation in neuroscience, necessary for psychiatry.

Now we have a brain disorders award specifically to help bring basic scientists to work on clinical problems. I've always been interested in getting psychiatrists to work as basic scientists, but it's also clear to me that the other direction is going to be very fruitful. That is, basic scientists have much to teach us. There are many, many more of them than there are psychiatrists. And so what we are trying to do now is to give outstanding basic scientists small grants to help them start working on clinically relevant problems. So that's been another important activity of mine I have taken great pleasure in.

Finally, as I've grown older and decided that I don't want to work in the lab forever, and other people can do it better, I've written three books, all of them on molecular research as it relates to psychiatry. The first was called *Molecules of Mental Illness*, and it was published by Scientific American Library. It is a very beautiful book. Scientific American Library produces these beautiful full color books.

TB: I should read them.

SB: You should. They are actually quite interesting books. *Molecules of Mental Illness* was my first solo author book. It was published in 1993. The second, *Mood Genes*, was published in 1998. That was about the search for the genetic basis of manic depression, a book for a general audience which was quite popular. It's an introduction to how one thinks about genetics of mental illness, how one goes about searching for these genes. It gives a very good background in terms of how genetics works, and how it can affect the brain, and how this genetic research will change psychiatry, which is happening. And I just published a book this year called *Better Than Prozac*.

TB: Tell us about it.

SB: It's about making new drugs. In fact, much to my pleasure and surprise, Don Klein mentioned it very favorably yesterday in his lecture on drug development. He said he thought it was a great book and he really enjoyed it very much. Coming from Don Klein, that was an unexpected and great compliment.

TB: Yes, it was.

SB: So that was the last book, but I'm a scribbler and planning to write more.

TB: What will be next?

SB: I write slowly. I spend a lot of time thinking and reading. I have two possible titles for it, but the concept is probably going to be similar. One of them is *The Hope of A Science* a title that comes from a quote by William James. William James, in 1892, published a short version of his classic *Principles of Psychology*, and in the last paragraph he says

something like: “psychology is not a science... it is only the hope of a science.”

TB: Psychology is not a science; it is only the hope of a science.

SB: It's a lovely phrase. So that might be one title. Another I'm thinking of, which is different, is *A Secular Priesthood*, about psychiatry as a secular priesthood. It's a good topic because it speaks to me personally. I think that a lot of my interest in psychiatry has been not only the scientific issues, but also the ethical issues and how one should live one's life. I think that in our culture, psychiatrists have played a significant part in dealing with these issues. And now as we become more scientifically based we are called upon more and more by the popular media to give advice grounded in science.

TB: The Hope of a Science and A Secular Priesthood...

SB: Those are two topics that I am really interested in. I don't know which book is going to emerge.

TB: Is there continuity?

SB: There is continuity.

TB: Each complements the others.

SB: That's right. But I want to dole it out in portions which will allow me to keep active indefinitely. So I don't want to finish it.

TB: You are very productive.

SB: I will be 70 this month. But I hope to have many more years of productivity.

TB: Did you give up lab work completely?

SB: I have now. My last scientific papers were about the structure of galectins. Galectins are sugar-binding proteins, which we find in all sorts of creatures, including people. I named them galectins because they bind galactose residues in complex carbohydrates found on and around cells. There's a family of about 15 or so galectins, many of which we discovered. And we cloned the genes for many of them.

TB: Would you tell us something about the relevance of this research to psychiatry?

SB: The relevance that I envisioned for psychiatry came from our knowledge that the surfaces of cells, including nerve cell, are coated with complex sugars. I believed that the complex sugars on the surfaces of cells are one of the codes which determine how cells, including nerve cells, associate with each other. There has been a great deal of work over the past decade showing that protein-protein interactions of various kinds play central roles in the control of cell-cell interactions, including synapse formation. But there is also evidence that protein-sugar interactions are important. To make a pathway of nerve cells in the brain you want certain cells to associate with specific others. The connections

have to be selective to form specific circuits. My vision was that the sugars would be very important in making specific cell contacts and that by finding proteins that interacted with those sugars we could learn something. And that remains true, although it's now clear that sugars are not the major players in this story. There are many proteins that interact with other proteins to control specific cell associations. But this whole field of glycobiology, sugar biology, which has emerged in the last few decades, is gaining prominence. So we were prophetic in that regard 30 years ago.

TB: And on this note, we conclude this interview with Sam Barondes; a distinguished neuroscientist, clinician and author, and a fellow of the ACNP. Thank you very much.

SB: Thank you, Tom. It was a pleasure.

FRANK M. BERGER

**Interviewed by Leo E. Hollister
San Juan, Puerto Rico, December 14, 1995**

LH: I am privileged this morning to interview Dr. Frank Berger.* I am Leo Hollister. Frank and I have known each other for almost 40 years. It is quite a pleasure to welcome him at the annual meeting of the ACNP for this interview. I think Frank's name will always be associated with the drug meprobamate, the first tranquilizer developed in history. Tell me, Frank, how did you begin? What was your training, and what led you to do drug research?

FB: I was born in Czechoslovakia and got my MD in 1937. I worked first as a microbiologist at the Czechoslovak National Institute of Health and studied various typhoids and paratyphoids. When Hitler occupied Czechoslovakia in March 1939, I got married, left the country, managed to get into England, and spent the next year or two as a general physician in a refugee camp. In 1941, my medical degree from Prague was recognized and I got a position in a hospital for infectious diseases in Manchester. It was a lovely job. I learned English while I looked after patients.

LH: So, you were a practicing physician in those days.

FB: Oh, yes. I was taking care of about 800 patients. It was a most interesting period of my life. There was highly toxic diphtheria in the community with something like 15 admissions a day. They were mostly babies and quite a few of them died.

LH: That was a tragedy because diphtheria antitoxin had been developed earlier.

FB: Apparently it was not prepared or used properly. It was a strenuous job because one felt that the survival of the baby was dependent on one's ability to administer diphtheria antitoxin intravenously. This was a major undertaking in a one-year-old baby in shock.

LH: How did you do it? Did you have to go through the skull?

FB: I did it as I could. I had also patients with polio, meningitis and all kinds of other diseases.

LH: When you talk about diphtheria and polio and all those diseases, it reminds me how much progress has been made. We no longer need to bother about any of them.

FB: Yes. Few physicians of your generation have ever seen acute, bull-neck diphtheria.

LH: It had to be frightening.

* Frank Berger was born in Pilsen, Czech Republic in 1913. Berger died in 2008.

FB: Oh, it was. And so was polio. We had about nine iron lungs going at all times to keep them alive. That is another disease eradicated now.

LH: Except in the developing countries. I guess we still have a way to go there. But, theoretically, it could be eradicated just as smallpox was.

FB: Then, in 1942, I got a job in a bacteriology laboratory in Wakefield. It was shortly after that Florey and his collaborators purified penicillin and the effectiveness of penicillin was shown in experimentally induced infections in mice and patients suffering from staphylococcal and other infections. To extract penicillin, they acidified it and in the course of this process lost 90% of the precious substance.

LH: Didn't you get a better job that time?

FB: It was with the British Drug Houses, a company that was supposed to produce penicillin on a large scale. Of course, I was delighted to have my salary double and promptly moved to London. In those years penicillin was supplied in solution and the antibacterial effect of penicillin solution was lost because of penicillinase-producing bacteria that everything is contaminated with. My assignment was to find a non-toxic substance that could be added to penicillin solutions for selectively inhibiting penicillinase-producing bacteria. There was one such product, but it could inhibit the bacteria only a little bit. It was phenoxitol, a phenyl-ether of glycol.

LH: How did you come across that one?

FB: It was known that phenoxitol has that effect. So, my boss, Bill Bradley, told me that we have to find a non-toxic agent that is like phenoxitol but a thousand times more potent in inhibiting penicillinase-producing bacteria. We prepared all kinds of glycerol, erythrisol and other ethers and substituted phenols in our search. I supervised the testing of these substances against penicillinase producing bacteria. There was one substance I particularly liked because it very nicely inhibited the growth of bacteria while it preserved penicillin in the solutions. It was called mephenesin.

LH: Was mephenesin at the time on the market for clinical use?

FB: No, it was a new product of Bradley.

LH: Now is this the same Bradley whom I associate with electrophysiology?

FB: No. My Bradley was a chemist, pure and simple.

LH: He must have been.

FB: An excellent chemist. To test the toxicity of mephenesin I injected it into mice and other animals. It was not toxic. But while studying its toxicity I also found that in large doses it produced tranquilization and muscle relaxation limited to voluntary muscles. It did not affect respiration or

the heart. About that time somebody in Philadelphia discovered much better ways to preserve the activity of penicillin and interest at British Drug Houses in mephenesin was lost. I was told to forget about it.

LH: So that was the first use of mephenesin.

FB: Yes. But I could not forget the unique behavioral effects of the drug in animals. No other compound I knew about produced a state of paralysis in animals in which consciousness was maintained. The animals looked at you, could not move, but continued to breathe. Since no autonomic disturbance seemed to be associated with the paralysis of voluntary muscles, I thought that mephenesin would be wonderful in operations and asked permission to develop the drug for human use. I published my findings on mephenesin in 1946 in the *British Journal of Pharmacology* and in my article I pointed out that the compound has a tranquilizing action.

LH: Did you use the term tranquilizer?

FB: Yes, in the first paragraph.

LH: That must be one of the first uses of the term.

FB: I was particularly struck by its effect on guinea pigs, which are nervous animals that are not easy to catch but after a small dose of mephenesin became tranquil. I also collaborated with several physicians on the clinical development of mephenesin. More than 10,000 surgical patients in England received the substance for relaxation during operations. But I had to stop with my research in England because we received our visas to the United States and my late wife persuaded me to move here. So in October 1947 we moved to the States. At the time it was not permissible to enter the United States with a prearranged job. I know that this sounds unbelievable now. There was also a British regulation that did not permit us to take more than about 100 pounds, that is about \$150.00 out from the country.

LH: So instead of landing on these shores with just a dime, you arrived with 100 pounds and no job.

FB: But I had a typewriter and knew a few people who were interested in my publication on mephenesin. I went to see them, offered my services and was very fortunate in getting several job offers. The one I accepted, on the recommendation of my good friend George Brecher, head of hematology at NIH, was at the University of Rochester Medical School. It was an assistant professorship in pediatrics of all things.

LH: My goodness, from infectious diseases to pediatrics.

FB: Since infectious diseases are usually caught by children they thought they need somebody on their staff who knew a little bit about them. So that was the job. I got it after six weeks of our arrival. It did not pay well.

LH: You made up for it. Don't worry.

FB: I remember they paid me \$5,400, which at the time was much more than it is now, but by getting a license to practice I was able to supplement my income very nicely by taking night calls. I was fortunate because I got all kinds of grants and was able to start clinical trials with oral mephenesin.

LH: For what did you use it in children?

FB: I used it in everything.

LH: Just exploring?

FB: Right. Although I was assistant professor of pediatrics, I had access to patients with Parkinsonism, stroke, multiple sclerosis, and cerebral palsy.

LH: Anything where there may be muscle spasticity?

FB: Muscle spasticity and involuntary movements. We found it quite effective in cerebral palsy and in some post-stroke paralyses. We also found the spasticity that results from the disturbance of reciprocal innervation between contraction and relaxation could be corrected by the drug. I published a paper on mephenesin in 1948 in the *Journal of the American Medical Association* that helped Squibb to get the substance on the market. By the end of 1948 Tolserol was one of the best selling Squibb products.

LH: That was something.

FB: I also presented some evidence in my paper that mephenesin has a very short duration of action. Using the diazo-reagent I found breakdown products already 10 to 15 minutes after taking the medication.

LH: So it is very rapidly metabolized.

FB: That is right. And I said that we need to produce a drug that would be many times as active and longer acting than mephenesin.

LH: So that got you to other glycerol derivatives.

FB: That is right. Shortly after the publication of my paper I had several offers from pharmaceutical firms. I was anxious to find a better paying job because my wife was expecting a baby. That was in 1949. The baby is now a big boy. I believe you know Frank.

LH: Oh, yes. You have two sons, don't you?

FB: Yes. So I had various offers, and I accepted the offer from Carter Products, that shocked everybody at Rochester.

LH: Because they were only known for liver pills.

FB: "You must be insane, you should join a more reputable firm, like Lederle or Squibb," people told me. I was warned that Carter had a minuscule pharmaceutical business which at the time perhaps yielded about \$80,000 a year. But they offered me more than most of the others. I

- remember the salary they paid me was \$12,000 a year. I really felt I was a rich man.
- LH: In the late 1940s that was not bad pay.
- FB: But there was one other reason to be honest with you why I joined them. I said: "If I develop a better drug than mephenesin, I want to get a little bit from the sales. If I make a firm out of you, I want to get royalties." And the only firm that was prepared to pay me royalties was Carter. Then we addressed the issue why mephenesin is so rapidly metabolized. I didn't know any chemistry, but Carter-Wallace, or Carter as it was called at the time, had a fine chemist, Bernie Ludwig, and we found that mephenesin's rapid deactivation by oxidation of its terminal hydroxy groups could best be blocked by carbamates. It was also necessary to make several other structural changes in the molecule.
- LH: So you ended up with a carbamate.
- FB: That is exactly right. So when that happened we synthesized a few hundred carbamates. Meproamate seemed to be the best of them all around. It was patented in the fall of 1949. So I had a lot of fun developing it. And I will never forget the help you have given. You conducted one of the first clinical trials with meproamate.
- LH: That was trivial.
- FB: That was not trivial. That was an act of great courage.
- LH: Tell me, how did you get the name Miltown?
- FB: We had about six or seven products and we named them after the various villages around New Brunswick where our laboratories were. One of the villages near New Brunswick was Miltown. Another one, and this would have been a much better name, was Hopewell.
- LH: Oh, boy. What a name for a tranquilizer.
- FB: One of the investigators rushed into publication and used the name Miltown in the paper he submitted to the JAMA. When the paper appeared, the compound was named. It was not a good idea to stick with that name at all. Carter-Wallace did not have enough people and money to promote the drug. It had to license it to other companies. One of the licensees was Wyeth Laboratories who gave it the name Equanil. That was much more acceptable to physicians who, as a result, prescribed three or four times more Equanil than Miltown.
- LH: So that was the beginning. When was meproamate introduced for clinical use?
- FB: In the spring of 1955 and I would like to say again that you played a very important role in it. Soon after the drug went on the market, either late in 1955 or early in 1956, I organized a big conference at the New York Academy of Sciences. Do you remember that?

LH: Oh, yes. You got Aldous Huxley to attend.

FB: He was very interested in drugs and especially in those that affect consciousness. He came and gave the introductory address. And you gave a paper too in which you reviewed all the publications on the drug. You discussed how difficult it was to decide what a psychotropic drug should be used for.

LH: It still is.

FB: You examined the whole spectrum of possible indications for meprobamate.

LH: So from 1955 until around 1960 when Librium came along, Miltown had the whole field.

FB: That is right.

LH: And it became the most widely prescribed drug.

FB: Yes, it was widely prescribed, and it certainly made Wallace Laboratories. When I joined them, as I mentioned before, the sales were \$85,000 a year. By 1960, they were something like \$200 million a year.

LH: And guess who had a royalty?

FB: I had big problems with my royalty and spent a good part of my time fighting for my rights.

LH: While you were talking I was thinking of George Renshell who, as a graduate student, developed what ultimately became known as Benadryl. He had a similar arrangement with Parke-Davis and became one of the richest men around.

FB: But I was new in America. I signed a document that I did not understand. And once you sign something, it is very difficult to modify it. So that is how I failed to become the richest man in America. Since I failed to become the richest, I tried to become the happiest.

LH: Of course, Miltown was an astounding commercial success. Then Wyeth put it together with promazine.

FB: Yes.

LH: But you didn't have anything to do with that, did you?

FB: Not really. I was never enthusiastic about combinations. But regardless, our sales went up to \$200 million a year. I was everything at the company including sales manager and advertising manager. There was no other executive there and the firm was largely privately owned.

LH: By the Hoyts?

FB: Yes. And they hired a business advisor who told them that "this fellow Berger, who does not even know how to read a financial statement, is running a business of more than 200 million a year." He also told them that I ran it differently in that I would not employ detail men. So they

- decided to get people experienced in the pharmaceutical business to run it, and I did not like that.
- LH: Well, you know, even running a \$200 million a year business, without having anything to do with development, you should have been paid pretty well.
- FB: After the patent expired, I had no more royalties.
- LH: Now, as I recall, Wallace put out a combination product with benactyzine.
- FB: Yes, Deprol. It was one of the first products, I thought, that was effective in depression. And I remember that you did some clinical research with Deprol.
- LH: Well, I guess so. I cannot remember. But, I remember that we were having dinner together in New York around 1957 or 1958, and you were saying that you thought the next big development in the field would be the introduction of antidepressants.
- FB: Yes. I cannot remember now exactly when Deprol was introduced. It was in the late 1950s and at the time it was found effective in some depressed patients. But when the true antidepressants came along, Deprol faded out.
- LH: Yes. Now, let us see. I remember that both Carter-Wallace and Wyeth put out meprobamate for slow release by delaying absorption.
- FB: Yes.
- LH: And I studied both of them and came out with equal results. It turned out that both came from the same mill. They were different only in colors. That was sort of gratifying I could not find a bit of difference. Well, let us see, that gets us up to the late 1950s. What do you do for an encore after having something like Miltown?
- FB: Well, back in the 1960s I reverted to my first love that was bacteriology and immunology and started collaboration with people at the Pasteur Institute in Paris on the development of adjuvants, substances that increased immunogenicity.
- LH: I guess the only one at the time was Saponin.
- FB: That is right and Saponin is not suitable for use in humans because it produces swelling and is potentially carcinogenic. So, jointly with the late Werner Braun at Rutgers and Louis Chedid in Paris, we developed a chemically well-defined substance from the wall of acid-resistant bacteria, which had a potent adjuvant action. And my other interest was the development of a substance that would increase nonspecific immunity. My interest in developing such a substance was triggered by the well-known fact that not everybody who is exposed to an infectious agent catches the disease. Not everybody who is exposed to a carcinogen gets cancer. What is it that makes the difference? And I prepared

an agent from bacterial sources that increased nonspecific resistance in animals. I called the substance protodyne, and have published on it since 1968 extensively. If you shut down the immune system of mice, nonpathogenic bacteria will kill the animal. And this X factor of mine, protodyne, will protect the animal. This is what I have been working on for the past 10-15 years. It seems to work beautifully in vitro. I prepared a patent application for protodyne and offered it to every pharmaceutical firm in the world, but none of them got interested.

LH: That was, of course, before AIDS.

FB: Yes. But I don't really blame anybody. I was 82 this year. Most firms are not too anxious to start a research project with an 82 year old man.

LH: Well, something about aging takes the zip out of you, doesn't it? I remember talking to Paul Janssen about levamisol. They had no idea that it has adjuvant properties. But there was a Frenchman who tried the substance and it worked. Now levamisol found its place in the treatment of colon cancer.

FB: Yes. I think it is still used for that purpose. And a lot of work is being done to develop this area of research further.

LH: Well, from muscle relaxants to immunological boosters, you have traveled a long way. The last time I saw you, I think it was down in Louisville. John Schwab, who was then chairman of the department of psychiatry there, had the good sense to have you and Joel Elkes as visiting professors. What was your role there?

FB: Well, I think I had an opportunity to learn some psychiatry and see some psychiatric outpatients; I found it most interesting. My feeling was that most people we saw had really no psychiatric disorders. They were people, in my opinion, with problems of living, people who did not get along with their spouses, did not get along with their children, did not get along with their boss, and had not been taught, had not been educated, had not been prepared to handle all the crises of life. So they got stressed, broke down, and had to see a doctor, and the doctor did not know what to do. So he put one of the psychiatric names on them.

LH: That's right. You are absolutely right. So much of the general practice of medicine consists of people who have problems in getting along, and there is no easy cure for that. You should have started 30 years earlier.

FB: And, as you know, we don't get enough education how to handle problems of living. And I don't know what should be or could be done about it.

LH: I guess when religion had more influence people developed more of an ethical and moral sense than they do today. I am appalled at these young kids who think nothing of killing somebody for some trivial reason.

FB: Yes.

LH: They have no idea about the worth of human life. It is a kind of amoral society that we are engendering and we are paying the price for it. Well, that was an interesting career you had from microbiology to infectious disease, chemistry and back to the clinic, then more chemistry, running a drug company and becoming rich, and then, going back to immunology. What a checkered career. Would you do it over again?

FB: Oh, yes. I am not ready to die. I am ready to continue. Whether I liked it? Yes, I did, it was outstanding.

LH: Yes, I would say so. It kept you busy and interested all your life.

FB: Yes and still does. I have been very fortunate.

LH: I think all of us who have the opportunity to have a job that we like are blessed. You know, there are so many people who belong to the Thank-God-it's Friday club. I always say I belong to the My-God-it's-Friday club.

FB: Do we still have time?

LH: Sure. You want to say something more?

FB: Yes. I thought you were going to ask me what I would have liked to achieve or what do I think the contribution of those tranquilizers was to medicine?

LH: Good question. I am glad you asked it.

FB: I can tell you only what I think. I am sad, at times, that I have not been able to convey to more people my opinion about anxiety, meprobamate and all the new antianxiety drugs. And I find it hard to understand that there are so few psychiatrists who believe what I do about anxiety. Namely, that anxiety is a disease state. It is an inappropriate emotion that should be differentiated from fear. As you know, anxiety is apprehension of something you don't know.

LH: But fear you know.

FB: Fear is appropriate. Now Freud implied that anxiety is one of the great motivational forces in life. John Locke, before him, believed that we do things because we are anxious, we are afraid. That anxiety pushes us along. I think they were wrong.

LH: It hinders rather than helps.

FB: Exactly. And this is now well authenticated. You know Cattell, a leading psychologist at the University of Chicago. He did an extensive study on anxiety using factor analysis, and found that anxiety is not good for you. It decreases your productivity, your ability to perform, and everything else. Yet, there are so many psychiatrists who say: "Yes, too much anxiety is wrong, but a little anxiety is necessary." I don't think

that is so. I think the people who perform best are the people who are not scared, people who don't have this undefined feeling.

LH: Well, when you are always apprehensive about what is coming next I think it interferes with your thinking process and obviously decreases performance. I think in recent years there are more people beginning to subscribe to your notion that anxiety is pathologic and needs to be treated. But in so many people's mind anxiety is a kind of minor emotional disorder, akin to a problems of living so you don't need to bother too much about it. A lot of doctors are reluctant to prescribe medicine for it.

FB: Right. On the other hand tranquilizers are over-prescribed. For instance, a patient has a heart attack. He is brought to the hospital. The first thing he gets is a tranquilizer. I think that is a mistake. A person with a heart attack is not anxious. He is afraid. You know, there are some fine studies showing that anti-anxiety agents are effective only in true anxiety. They don't affect fear. Even if you load up somebody with antianxiety drugs and a car or a tiger is running towards him he will jump. So I think a patient brought to the hospital with a heart attack should not get Miltown or Librium or whatever. He should get morphine. He is in pain.

LH: Yes, but there was a very provocative study published a few years ago in which it was shown that during the stress of a heart attack catecholamines go way up and diazepam blunted that response. And since the circulating catecholamines may play a very significant role in fatal cardiac arrhythmia, diazepam might be just as effective as lidocaine in preventing it. It is unfortunate that nobody followed up that report because it might have given some justification for antianxiety drugs in patients with heart attacks. But, of course, we are talking about a very temporary use. People are increasingly recognizing that anxiety is pervasive in all disorders. We found in our depressed patients that anxiety was just as common a symptom as depression. And there is also a fair amount of anxiety seen in schizophrenic patients.

FB: What is called anxiety in schizophrenia might be fear. The schizophrenic is afraid of the content of his hallucinations.

LH: That's true. If voices are telling you what a bad person you are that awakes fear.

FB: Perhaps the "anxiety" of schizophrenics disappears if you do something about their hallucinations.

LH: Oh, there is no question about that. Well, what you are saying in effect then is that we need not be ashamed to treat anxiety. That we should

recognize it as a disabling disorder and consider it just as important as treating other illnesses.

FB: I think when we both were young physicians psychiatry had a taint and we should try to remove that by conveying to people there is really no difference between diseases of the mind and diseases of the body.

LH: Yeah. The old idea was that if you had stronger moral fibers you could pull yourself together and beat it.

FB: That is all nonsense.

LH: Well, of course, you know that Freud was a very dominant influence on psychiatric thinking when you and I were young. I think every department of psychiatry in the United States was headed by a chairman who was psychodynamically oriented. Now the pendulum has swung almost 180 degrees and almost every chairman is biologically oriented. Maybe it swung too far. Maybe, as one of my colleagues said, we are now talking about a mindless brain.

FB: Yes.

LH: So maybe we have gone a little bit too far. But the old idea that tended to lessen the importance of anxiety and made anxiety a kind of normal phenomenon is still hard to shake.

FB: Perhaps, but both you and I contributed one thing. We made psychiatry a part of medicine.

LH: Yes, I guess the drugs did that. I recently had an occasion to introduce Joe Coyle and I said, as far as I knew, he was the only chairman of a department of psychiatry who also had been president of the Society for Neuroscience. And that sort of an overlap is increasingly apparent now, even at this meeting. So by learning a lot about the brain we might be able to help patients better, which I think your discovery certainly played a role in. It has been a pleasure after all these years to have this conversation with you. I learned something about your career that I had never heard before.

FB: Thank you very much, Leo.

ARVID CARLSSON

Interviewed by William E. Bunney, Jr.
Las Croabas, Puerto Rico, December 12, 1998

WB: I have the honor today of interviewing Dr. Arvid Carlsson* from Gothenburg, Sweden, and I wonder if you'd start by telling us what your current position is and your title.

AC: I am Emeritus Professor of Pharmacology at the University of Gothenburg, Sweden.

WB: OK. Can you tell me what kind of training you have?

AC: I am a medical doctor, so I had my original training at the University of Lund, which is in the "deep south" of Sweden. My training in medicine and the work on my thesis in pharmacology were done in parallel and both were completed in 1951.

WB: What was the thesis on?

AC: That was on something entirely different from what we are going to talk about. It was on calcium metabolism. At that time radioactive isotopes had become commercially available and this of course, opened up tremendous opportunities for studying metabolism of various compounds, including calcium. So, that was what my thesis was about.

WB: How did you first become interested in psychopharmacology?

AC: Shortly after defending my thesis I applied for an associate professorship in pharmacology. We were two, who competed, and I didn't get it. The panel examining us let me understand that calcium metabolism wasn't really the thing that pharmacologists should be doing. So I went to an elder friend of mine, Dr. Sune Bergström, professor of biochemistry at the university and asked him whether he could find a laboratory in the US where they were doing some really fine modern work in biochemical pharmacology. He wrote to a friend of his at the NIH and it ended up with a letter of invitation from Dr. Bernard B. Brodie at the Laboratory of Chemical Pharmacology at the NIH.

WB: Who were your colleagues when you were there?

AC: Sidney Udenfriend, for example, was there, a very well known name. The person who was my immediate mentor was Dr. Parkhurst A. Shore and I must say that laboratory was kind of a Mecca of modern pharmacology. Brodie, together with Udenfriend and a doctor, named Bowman, had developed an instrument that turned out to be extremely important, because it was a very sensitive tool for measuring levels of both drugs and endogenous compounds in body tissues and fluids. It was called a spectrophotofluorometer. That was the instrument by which one could,

* Arvid Carlsson was born in Uppsala, Sweden in 1923.

for the first time, measure very low levels of various endogenous compounds, such as neurotransmitters. That was a breakthrough.

WB: My impression was that the Laboratory of Chemical Pharmacology was probably the hottest laboratory in the world, maybe, at that time, in terms of the people there.

AC: That's true. There was a stream of visitors all the time from all parts of the world.

WB: Wasn't Fridolin Sulser there for a while?

AC: Fridolin came later. One person, who came at the time I was there, visiting frequently, was Nathan Kline, and he picked up some things there. This was in 1955, by the way. Shore and Brodie had shortly after my arrival discovered that reserpine, an antipsychotic and antihypertensive drug used in those days, caused a virtually complete depletion of serotonin in tissues, including the brain. There was another person, Alfred Pletscher, who came from Basel, from Hoffman-LaRoche. He brought iproniazid, which was the first monoamine oxidase inhibitor, and the interaction between reserpine and iproniazid was so intriguing to Nathan Kline that it ended up with Nathan Kline actually demonstrating the therapeutic action of iproniazid in depressed people, another important discovery.

WB: He got the Lasker Award for that.

AC: Twice, he got it twice, for discovering the antipsychotic action of reserpine and the antidepressant effect of iproniazid.

WB: What was the work you were doing when you were in Brodie's lab?

AC: That was on reserpine. I was very lucky, because as I mentioned, only a couple of months before I came, Shore and Brodie had discovered the serotonin-depleting action of reserpine. I was given the opportunity to show, in in-vitro experiments in blood platelets, the action of reserpine on the storage of serotonin.

WB: And, how long were you there in Brodie's lab?

AC: Five months.

WB: OK, and, then, you went back and what did you do when you got back?

AC: Actually, when I was there, I asked Brodie, shouldn't we also look at some other compounds besides serotonin to see whether reserpine could act on those and Brodie said, no, he didn't think so. He was so sure serotonin was the most important compound insofar as psychosis was concerned he thought it would be a waste of time. So, I thought perhaps I can do that when I get home and I wrote to a friend of mine, an associate professor of histology in Lund, Nils-Åke Hillarp. He had just made the very important discovery that there are organelles in the adrenal medulla that are capable of storing adrenaline and noradrenaline

together with ATP. It was very intriguing. And, I thought, maybe reserpine acts on these organelles. That's why I wrote to him, asking if we should look at this and he agreed. Apparently reserpine acted in a similar manner on organelles in the adrenal medulla, in the noradrenergic nerves and in the serotonin-storing cells.

WB: So, all these monoamines are stored in a similar manner?

AC: Absolutely, all monoamines. Of course, dopamine was not being discussed at that time.

WB: So, take me through your career in terms of the high points of the research. I think that's what we really need to do.

AC: Hillarp and I did these experiments and found that also noradrenaline and adrenaline stores are depleted when you give reserpine. We also found that if you stimulated the adrenergic nerves following reserpine treatments, they didn't respond any more, so we believed that after the neurotransmitter had gone, the nerves couldn't function any more. This was actually opposite to the hypothesis of Brodie, because he believed that what reserpine does is to cause an ongoing release, so it's more or less the opposite from the point of view of the function of the system. But, we were in favor of the depletion hypothesis. Reserpine has a very pronounced behavioral effect; the animals become immobile and are heavily sedated. We felt that perhaps we can reverse this condition by giving norepinephrine or serotonin and then see which one is important. But we couldn't give the amines themselves, because they don't get into the brain; we had to give the precursors, L-DOPA and 5-hydroxytryptophan. We found a most striking effect when we gave L-DOPA. The animals started to wake up within ten minutes following an IV injection and, then behaved like normal animals.

WB: It must have been exciting when you first saw this.

AC: We were just as excited as the animals. It was really dramatic. We were so excited that we very quickly wrote a letter to Nature, sending a photograph of the response. They accepted the letter, but they didn't think the photograph was worthwhile. But at that time when we sent it off, we hadn't yet analyzed the brains. We were sure that there should be a lot of noradrenaline in those brains since the animals responded so nicely, and we were, of course, greatly disappointed when we found there was still no noradrenaline. In order to save our face, we thought, maybe at least, we could look for dopamine in the brain, because that is an intermediate between L-DOPA and noradrenaline. We had to develop a method for measuring dopamine and, then, we found that, sure enough, the response to L-DOPA could be correlated very closely to the formation and accumulation of dopamine in the brain. We also

found that dopamine does indeed occur in the brain under normal conditions and not just in those small levels you would assume an intermediate would have. Actually, the levels were a little bit higher than those of noradrenaline. From all these findings, we proposed that dopamine is an agonist in its own right in the brain.

WB: Was that the first time that was proposed?

AC: That was the first time. We were the first to identify dopamine in the brain, in 1958, and to propose a role for it in the brain. And soon afterwards we proposed that parkinsonism could be due to dopamine deficiency and that L-DOPA could have an anti-parkinson effect. We were very excited and went to a meeting shortly after that, Hillarp and I, in London, on Adrenergic Mechanisms. There were all the big shots, with Sir Henry Dale on top, and we reported on these things, but we were disappointed that they were not impressed. We got all kinds of questions such as, is it really true these amines could have a function in the brain? They didn't believe so. Marthe Vogt, for example, was very much against it, like many others, and the British pharmacologist Paton referred to some unpublished data indicating that these amines are in the glia, and had no importance. We were very disappointed. We thought, now we at least had to prove that these amines do occur in nerves. Hillarp was a very clever histochemist, so he developed a method that enabled us to see where these amines are located and, indeed, they are in the nerves. They are not in the glia and they had a distribution that was very much the same as in peripheral adrenergic nerves, where it was known already that noradrenaline is a neurotransmitter. That was very important to convince the scientific community that in the brain you have chemical transmission as in the peripheral system and not, as was generally believed, that signaling between the nerves in neurons in the brain was electrical only. Our findings triggered the concept of chemical transmission in the central nervous system.

WB: So, that opened up a whole conceptual field.

AC: Yes, absolutely. Before that, the kinds of questions that were dealt with in psychopharmacology and CNS physiology had to do with carbohydrate metabolism and the like. If you go into the 1970s, if you look at journals then, nearly all research in the central nervous system is centered around neurotransmitters, so that was a revolution in neuroscience.

WB: Now, take this into the pharmacology, in terms of the drugs.

AC: Brodie's interest in reserpine was due to the discovery a few years earlier that reserpine and chlorpromazine have such a dramatic effect in psychosis and schizophrenia. The discoveries just mentioned opened

up entirely new aspects of the mode of action of antipsychotic drugs and, as a consequence, new hypotheses about the pathogenesis of schizophrenia, for example, the dopamine hypothesis. While reserpine causes depletion of monoamines, the other major antipsychotic drugs, the ones that are now in general use, such as chlorpromazine, did not cause depletion of the amines, so we wondered how they could act. We discovered in 1963, for the first time, an effect of chlorpromazine, haloperidol and similar agents on dopamine and noradrenaline metabolism, that turned out to be in the direction of stimulation. This was opposite, in terms of function, to what reserpine did. On the basis of that and a number of other observations at that time, we proposed that chlorpromazine and haloperidol block dopamine receptors, rather than depleting the neurotransmitter. The outcome would be similar whether you give reserpine to cause depletion of the catecholamines or give chlorpromazine to cause blockade of dopamine and noradrenaline receptors. Further along, when our studies continued and others came in, it turned out that dopamine seemed to be more important than noradrenaline, even if we still could not exclude a contribution by noradrenaline.

WB: Wasn't this one of the major pillars and pioneering sort of framework upon which people started to think about mechanisms of action of antipsychotics?

AC: Yes, absolutely, and the antidepressants were discussed in similar terms.

WB: But, this was another first.

AC: That's right; the antidepressants came in somewhat later. First came iproniazid, which was a monoamine oxidase inhibitor that Nathan Kline had found was an antidepressant and then came imipramine and it was in the early 1960's that the first observations on an effect of imipramine on noradrenaline uptake was reported.

WB: And, some of that was done in Brodie's lab, too, wasn't it?

AC: The first observations concerning uptake of norepinephrine in the brain were in Brodie's lab and he was very much interested in that and had the idea imipramine didn't act on its own but was a pro-drug. They suggested that it was desipramine that was active. That was based on some behavioral experiments done in his lab.

WB: OK, then what happened in your career? What were the other high points?

AC: We worked for a long time to pursue our catecholamine work, but an entirely different thing came up a little later and went back to serotonin. What we found was that imipramine did not only block the re-uptake of noradrenaline but also serotonin. We went through quite a long series of tricyclic antidepressants and found that practically all of

them had effects on both the uptake of noradrenaline and serotonin, but there were differences. There was one compound, chlorimipramine, that was particularly strong in its action on serotonin, so we were very excited about that and I still remember I went down to Geigy in Basel and told them this is a compound you should bring to the clinic. They didn't believe much in it. They had another candidate, but, fortunately, the other candidate turned out to have a problem in toxicity, so they did develop chlorimipramine and it turned out to have a very interesting pharmacological profile, different, for example, from imipramine.

WB: Was it effective in depression and obsessive compulsive disorder (OCD)?

AC: That's right. That was the most important part with chlorimipramine, the whole area of anxiety, panic disorder and OCD. Regarding OCD, that was the first time one had a drug that really could do anything in this disorder. We started to look at other types of molecules to see whether they could have an effect on the uptake of serotonin and came across a series of antihistaminic compounds; one of them was brompheniramine. That compound turned out to be especially powerful. Like many other antihistamines it acted both on serotonin and noradrenaline re-uptake, but brompheniramine was relatively strong on serotonin. I collaborated with a very clever Swiss organic chemist, who was working in Sweden at the Astra Company and, together, we modified brompheniramine on two sites and, as a result, we came to zimelidine. Zimelidine was the first selective serotonin uptake inhibitor (SSRI). In clinical testing it was found to be an antidepressant and, later on, also found to be a powerful drug in panic disorders. I am not sure if they collected data also on OCD but I think they did. Unfortunately, zimelidine turned out to have a rare but serious side effect, so the Astra Company decided to withdraw the compound. In contrast to the tricyclic antidepressants, zimelidine didn't exert any anticholinergic action or cardiotoxicity.

WB: So, zimelidine was really the first in the family of the SSRI's?

AC: Absolutely.

WB: It was the prototype.

AC: It was the prototype for Prozac, for example. At Eli Lilly, they started to work on Prozac at about the time we submitted the first patent for zimelidine.

WB: OK, what happened next?

AC: What I would like to talk about is our interest in neurocircuitries. We started out from dopamine as a platform to see how dopamine interacts with other neurotransmitters. In that context we became interested in glutamate. We got into this at a very early stage at a little group of which both of us are members, which has a meeting in the Caribbean every

year. Actually, at that time, I remember the NMDA receptor had just been characterized and that phencyclidine had been found by Lodge and his colleagues to block the NMDA receptor. At one of these meetings in the Caribbean, I learned from you that phencyclidine is even more powerful than the amphetamines in mimicking schizophrenia, especially with respect to the negative symptoms. On that basis, we developed a scheme which started to evolve. According to this glutamate and dopamine are powerful controlling agents in the basal ganglia in the sense that they are antagonizing each other. The basal ganglia, in turn, control the thalamus, which we thought could work as a filter, and this could be important in the pathogenesis of psychosis. If this filter opens up too much the sensory input will overload the cerebral cortex and that might lead to psychosis. That was the concept of a circuitry from which we started out. Later on, when I started to test it pharmacologically, together with Maria Carlsson, we found much support for it, but also that it was more complicated. We had evidence that glutamate and dopamine can, under certain conditions, act in concert so there are pathways where they oppose each other and other pathways where they operate together.

WB: Which drugs did you study?

AC: There is no doubt that it was reserpine that was the starting point for our research and it's interesting that we have been using it ever since. Many people felt this is an obsolete drug, even in research, but we don't agree. I think reserpine is the drug of choice, if you really want to cause a depletion of the monoaminergic system and monoaminergic pathways and be sure you can disregard the presynaptic monoaminergic mechanisms. There is no other way, really, of being absolutely sure than to give reserpine and add inhibitors of the synthesis of these amines.

WB: You've listed a number of the famous people who've had impacts on your career. Are there others that should be mentioned?

AC: Well, I did mention the most important ones: Brodie, Hillarp, and Corrody. I've had, of course, lots of collaborators who have been very important to me.

WB: What do you think was your most significant contribution?

AC: I really don't know. I think I have been so excited all the way along by the various things that showed up.

WB: All right. How did you stay in the field and do science, rather than taking administrative jobs which I'm sure were offered to you on many occasions?

AC: I was very energetic in that context. I insisted that my secretary should do the work that I was supposed to do, so whenever one of those brown

envelopes came, I gave it to her and I'd say I couldn't care less about it; you take care of it. So, I stayed out of administration. I was on a couple of faculty committees but I didn't please the other members, so I got out of them rather soon.

WB: Are you happy with the way things turned out for you?

AC: Yes, I must say I have been very lucky in many respects. I was lucky at the very outset to get to this fabulous laboratory, and, then, to meet such wonderful people, like those I have mentioned already. So, yes, I have been fortunate and I am very pleased.

WB: Where do you see this field going in the next 5 or 10 years, and what new drugs might be developed? What illnesses might be treated?

AC: I have the feeling that in the area of depression, affective disorders and anxiety disorders, there have been really significant advances during the last few decades; in contrast, in the area of psychosis, where progress has been less striking. So I think that the most likely area where we are going to see some real breakthroughs is in the area of psychosis and schizophrenia. And, we see some signs of that already. I think that clozapine has opened up very interesting new avenues and points to the importance of neurotransmitters other than dopamine. Especially, serotonin is coming into the picture of psychosis in a very interesting manner. This is one avenue where some progress is now underway with new drugs that are clozapine-like, yet not toxic like clozapine. They seem to offer promise, even though I think that it's not going to be a very great step, but still significant in comparison to the drugs available now. Then, I think other new principles of different kinds will be related to glutamate. Furthermore, the newly discovered receptor subtypes have to be considered. We have the area of partial agonists that I believe are very promising.

WB: You've done a fair amount of work on partial dopamine receptor agonists such as 3PPP.

AC: That's one of my favorite areas, actually. And a clean 5HT₂ receptor antagonist; one such compound is actually now being tested in the clinic in schizophrenia. So there are at least three or four areas that offer great promise. Within the next 5 or 10 years, there has to be a breakthrough. I consider it almost unthinkable that all these four should be failures.

WB: What are the four again?

AC: It will be the mixed kind that clozapine offers with drugs such as olanzapine. That is number one. That is closest. We are almost there. Then, the pure 5HT₂ antagonists, this is probably somewhat related to clozapine, but still different. We have the partial dopamine receptor agonists

and, finally, we have the whole new area of glutamates. These receptors, for example, the NMDA receptor, is a very complicated receptor with many different binding sites that offers enormous possibilities. I mean, a lot remains to be done to characterize this receptor with its subunits and possible subtypes. You have one binding site where glutamate comes in. You have another one where glycine sits. There is a lot of effort now ongoing in the area of the glycine site. If we look a little bit more ahead, maybe, 10 years from now, I wouldn't be surprised if the glutamate area is going to be very important in the field of psychosis.

WB: Are there any other issues that we should have covered?

AC: I might like to talk a little bit about some of our post mortem studies, which I think are interesting. What we did was to examine various monoaminergic indices, in other words, levels of dopamine, noradrenaline, serotonin and their metabolites and precursors in post mortem brains, in schizophrenics as well as in controls. And, we did first conventional statistics on the measurements we had done and didn't find much. Then came a young man who was very talented in multivariate analysis who fed all the data into a computer and used some clever programs; out came patterns in which all these variables were viewed at one time, a multi-dimensional body that could be projected to a two dimensional picture to see whether there were any clusters. What showed up was one area where you had all the controls and two others where you had the schizophrenics that were quite different from each other. One of them turned out to be paranoid and the other one non-paranoid schizophrenic. So, from that starting point, I very strongly believe in the methodology of multivariate analysis and we're using it, not only on post mortem material, but also in our preclinical work. For example, I had the privilege of having in my group a number of clever organic chemists. They are synthesizing compounds for us and if you wish to characterize the pharmacological profile of the various compounds on behavior or the chemistry of the brain, then, multivariate analysis is extremely powerful and I think should be used a lot more.

WB: Any other areas?

AC: I think we'll stop now.

WB: OK. Let me just say that Dr. Arvid Carlsson is, in my view, one of the pioneers in the field of neuropsychopharmacology. He was recently selected for the Japan Prize among all neuroscientists and individuals in psychology and psychiatry and I consider that a great honor, well deserved, and a timely recognition of his pioneering contributions to the field of neuropsychopharmacology and to neuroscience.

AC: Thank you.

ANNICA B. DAHLSTRÖM

**Interviewed by Andrea Tone
San Juan, Puerto Rico, December 13, 2004**

AT: My name is Dr. Andrea Tone and we're at the 2004 ACNP Meeting in Puerto Rico and this afternoon I have the great honor of interviewing Dr. Annica Dahlström.* I want to start with how you became interested in medicine and how you became, in particular, drawn to the work you do.

AD: My grandmother was a midwife who did a lot of charitable work for poor people in Stockholm, and I had an uncle, who was a wonderful pediatrician. My brother and I were very happy whenever we saw him because we knew that we'd have a nice time. All my life I've been curious about how things worked. I had the opportunity to go to an excellent secondary school which I think was the best in Stockholm. When I talk today about differences in the brain, between males and females, and why things are developing in a very funny way, sometimes in society, I advocate separate schools for boys and girls, because, I think that gives girls a better opportunity to learn, and I think, it also, gives the adults and boys a better opportunity to concentrate on school.

AT: I have a four-year-old girl and I've often wondered about that.

AD: My family discussed whether I should study medicine. I was, at that time, a very good pianist and my piano teacher wanted me to go on with music, but my parents said, well, you know, if you break a hand, it's not really a good prospect for future life and I said, okay, let's be practical. I would really like to study medicine, but they said, no, it's better to be a teacher, because as a teacher you can have a family and, during summer holidays, you have plenty of time to see them. Then, my uncle said something which really pushed me over the edge; "You see, Annica, it is better if you study biology or chemistry, because going to medical school at Karolinska Institute, that's much too hard for a girl." Wow, is it too hard for a girl? I have to check that out. So, I started studying medicine! My intention was to become a renal doctor, or possibly, a surgeon, pediatrician, or pediatric surgeon, and do something for people who needed me. I completed my first scientific work on the effect of estrogen on tissue culture in mouse uterine epithelium.

AT: That was your first publication?

AD: My very first publication. I had nice teachers, but they talked too much and didn't inspire me. Then one day, Hillarp came to the tissue culture room, and, fortunately, I was still there. That was a lucky moment for me. He was, at that time, rather young. I mean, he was fifty-five, which

* Annica B. Dahlström was born in Stockholm, Sweden in 1941.

I consider now to be young, and he was extremely enthusiastic about the work he was doing.

AT: For the benefit of those who weren't able to hear your wonderful presentation last night, would you tell us why he was so important?

AD: Nils-Åke Hillarp and Arvid Carlsson developed a technique which made it possible for the first time ever to see neurotransmitters at their cellular localizations. Using a fluorescent technique, it was possible to see nerve cells that gave off axons, which travelled to the interior parts of the brain into nerve terminals, which contained noradrenaline that is released, influencing the brain. The same could also be shown with serotonin. It was a different set of nerve cells but with the same type of fibers sprouting into very dense networks of nerve terminals in clumps from where the release took place. I collaborated with Kjell Fuxe in this mapping of the monoamine pathways. Unfortunately, Hillarp died. He stimulated much of the work regarding an understanding of several neuropsychiatric and neurological diseases.

His predecessor was an old guy from the German era by the name of Hedquist who wore spectacles and had a little goatee beard but was not very interested in research. He wasn't interested in the students either and kept his precious microscopes hidden under plastic hooks with locks, so when you wanted to prepare for a teaching session with the younger students, and asked for the key, he said, "What do you want the key for? What are you going to do with the microscope?" You had to explain before you got the key. I remember the first time when Hillarp visited us. He had moved to Stockholm and he swept, like a hurricane, through the whole department and he said, "Dust is everywhere". He looked at these microscopes and said, "What the hell are these"? So, we moved them and got a brush. This was something new. We thought, we should stay and listen to what this guy has to say. He told us about his new method and what the method could do. He also told us many of the problems he had in his previous biochemical and pharmacological experiments which were unexplained but now, with the new methodology, we would be in a position to explain. We were four or five students in his class at the time and we felt like pioneers. So, when he asked whether we would like to join him in his research we said, absolutely, yes. It was exciting! Kjell Fuxe and I were given the central nervous system as our area to work on. Later on, younger people joined us who had heard about this fantastic person, Hillarp.

AT: Even in the short period of time he was alive, he was like a magnet.

AD: He came in 1962 and drew people like a magnet. In May 1964, he had a lump in his axilla. One of our collaborators, a very famous Professor of

Surgery cut it open while he was still on the operating table and when he looked at it and saw that it was black inside, he said, "Sorry, I have to tell you that this is malignant cancer. It's a metastasis of melanoma". Of course, it was a shock to Hillarp and to all of us. He gathered us about one week after and told us. "Sorry, guys, this is the end. We have only a few more months left to work. So, let us do our best. Let us work as much as possible". And we did. We took no holidays, no weekends, not even Christmas, and we produced a tremendous amount of work during that time under his guidance. I also admired his family, especially his wife, Eva, because she understood that for him, science was much more important than she was. She could understand his priorities in life and she accepted them. She knew it when she married him; she was there, all the time, by his side.

AT: In the lab?

AD: No, not in the lab, at home. He was no longer able to be in the lab, so we visited him in their home two or three people at a time. He read, criticized and discussed our papers. It was a very intense period. When he got too ill to be at home, Eva sat with him in the hospital, and when he could no longer write, he dictated to her, and she wrote the notes that were passed to us. The idea that he had to do this scientific work kept him afloat for a long time. At least, his doctors said they were amazed that he lived so long after he was diagnosed.

AT: Was he a very passionate person?

AD: He was passionate, yes. I remember when he was in pain and the nurses would knock at the door and say, "Professor, shouldn't you have your morphine shot now"? "No, no, no, wait until later". After he had finished his work with us, he leaned back and said, "Now, please ask the nurse to come in; I can't stand it anymore". He was, in a way, a hero. I don't want to make it into a tear jerker; I'm just telling you exactly how it was. We were very, very devoted to him.

AT: When you showed that picture of people in the lab in the mid 1960's you were all smiling. It was a very joyful picture. I don't want to overemphasize gender, but you had a lot of women in that lab.

AD: Yes. Two of us were science students and the rest were technicians, but the technicians were treated just the same as we were. Sweden is said to be a very democratic society; the lab certainly had a democratic atmosphere and everybody contributed to the research.

AT: To put the work you were doing in a broader historical and international context, how was it different from work that was being done in France, Germany or elsewhere? You were considered real pioneers in neuropsychopharmacology. Can you put that into context for us?

AD: We were the ones who for the first time saw these nerve cells and fibers in the brain and mapped the structures to see which nerve cell groups were related to which areas of the brain. That basic knowledge was lacking until then. Having this knowledge enabled the labs in different countries to take a leap forward in scientific research. I remember mapping the pathways of the catecholamine and serotonin systems when we found the cell groups were mostly located in the brain stem and we were trying to establish the location of these cell groups with known anatomical structures in the rat brain atlas but we were unable to do so. What we had to do was to name them as (a) green fluorescence cells which were the catecholamine, norepinephrine and dopamine cells, and (b) yellow fluorescence cells, which were the serotonin cells. Then we found that the nerve cells we identified had many ramifications. I mean, their dendritic trees were widespread, but they had only one very long axon that led to a totally different part of the brain. The axon was very thin, less than one micrometer, one tenth of a millimeter thick; before that nobody had been able to see these fibers under the microscope. There we were, twenty-seven year olds from Sweden, trying to tell people in the United States that we see fluorescence from the monoaminergic pathways joining into the medial forebrain bundle and spreading out to innervate all the different parts of the cortex. We were questioned, "How do you know that?" And we were told, "That's not true. No one has seen this. You're making it up". We had a hard time trying to convince scientists how we could see what nobody else had been able to before.

When you cut an axon, the distal nerve terminal network degenerates, because it can no longer have any nourishment from the cell body. The cell body is the center of metabolism of a nerve cell and if you cut an axon, you have reactions in the cell body, which indicate that the nerve cell body has been injured. You can see that under the microscope. So, by doing this type of lesion experiment, we could map out the whole system. Then, we were trying to convince people!

AT: You were far ahead of what was going on in other parts of the world. What was the psychiatric community saying about your work in Sweden? Was there an immediate rush to figure out how to translate your findings into drug development or new treatments?

AD: Our work generated a lot of interest, but we had in Swedish psychiatry, as in other parts of the world, the problem of people not believing in the biology of psychiatric disorders. I think that battle is finally over with the realization something is wrong with the monoaminergic pathways in some psychiatric disorders. The reasons could be manifold and since

these monoaminergic neurons are genetically regulated, as everything else in the body, you have individuals with genes that create strong neurons and others who have genes that do not create strong neurons. My idea is that, if you have these weaker systems, anything influencing the system from the outside can break the system and throw the person into depression. These monoaminergic systems can be influenced both from the inside and the outside.

AT: In Sweden was psychoanalysis as prominent as it was in France, at this time?

AD: Yes, I think it was. A lot of people still undergo psychoanalysis and some people say that it's wonderful. For me, it would be a waste of time.

AT: Let's go back to your research. After Hillarp's death, what kind of research did you do?

AD: I was mostly involved in studies on central nervous system pathways, but, then there was Kjell and some others working in the same area. Kjell was the first from our group to have his MD thesis ready by the autumn of 1965.

Hillarp was very clear that it would be a good thing for Kjell and me to split up and not work together. We were both very strong characters and, sometimes, we butted heads. Anyway, I continued working on something that we had observed during our "lesion experiments." If you cut an axon what happens is that, on the cell body side of this axon, one can see an accumulation of fluorescent material, whereas on the distal side everything disappears. So, what was the piling up of fluorescence material due to? For me, it was very obvious; something was transported from the cell body towards the nerve terminals. At that time, the only person talking about transport in neurons was Paul Weiss at Rockefeller University who had described a slow flow of axoplasm from the cell body towards the periphery. It was funny, but he described the rate of flow as something like two or three millimeters per day while what I was seeing under the microscope was clearly much faster than that. Having this observation in mind, I studied different nerves in the peripheral nervous system to find out which contained noradrenergic fibers that could be used in further studies of this presumed transport. So, my thesis in 1966, dealt with the Fast Intraneuronal Transport of Granules Containing Noradrenaline from the Cell Body Site Down to the Nerve Terminals. I combined the microscopic observations with biochemical measurements of noradrenaline. My first paper on this topic was published in 1965. In this paper I said that the axonal transport must be much quicker than 2 to 3 millimeters per day and suggested that another type of transport mechanism that

was active. Paul Weiss was very interested in my work and invited me to Rockefeller University, which I finally did. He also said that there must be something wrong with my calculations. Then I saw a publication by Lillian Libensky from Poland that appeared in 1965, the same year as mine. She had used the histochemical staining method on cholinesterase, the enzyme that breaks down acetylcholine and she could also see the piling up of material very quickly. She stated in her paper that it took place much faster than described by Weiss and his group. Strangely enough, about the same time, a young guy in the United States was collaborating with an electron microscopist in France. They injected radioactive amino acids in the neighborhood of a cell body, watched the start of the incorporation of amino acids into radioactive proteins and followed the transport of these radioactive proteins down to the nerve endings. This French group had always waited for about a week after the injection of the amino acids before they started to follow the transport of the radioactive proteins but this young, about twenty-five or twenty-six years old guy, couldn't understand why he had to wait so long. Although the others told him it wasn't a good idea, he started to follow the radioactive proteins a couple of hours after the injection, and could see a big wave of radioactivity moving rapidly. He also reported his findings of fast axonal transport in 1965. So, it was in 1965 that fast axonal transport was discovered.

AT: Let's continue to follow your research career. We want to find out what you consider your key contributions to the field.

AD: I think my most important contribution was the mapping of the monoaminergic pathways in the brain, and almost equally important was the discovery of the axonal transport mechanism. Since then, I've worked on this transport mechanism and I have had a lot of very good collaborators and students studying it. There are certain specific ATPase molecules which are the motors driving the fast transport; there is one group driving transport from the cell body toward the nerve endings and another group of ATPases that take care of the retrograde transport. This is not only transport toward the nerve endings; it is also transport back to the cell body for recycling.

AT: You stuck with research rather than clinical work?

AD: I started medical school in 1961 and finished my studies after I moved to Goteborg. I was a medical student for a total of 18 years, for the longest time in Sweden. I was the last one who had my internship according to the old system, but I am a fully qualified medical doctor.

AT: Why did you decide to finish medical school?

- AD: I started off to become a doctor and I still wish to deal with patients. Rats and hamsters are very nice, but human beings are even nicer. So I wanted to have contact with patients and I did clinical work one day a week up to 1987. After I got my professorship in 1983 I tried to continue to do clinical work one day a week, but finally it became impossible. In 1987 I gave up clinical contacts. I still have a few patients calling me and I prescribe medicine for them, for my family and for myself. It's very convenient.
- AT: I didn't know you could do that. I thought there were ethical guidelines that physicians couldn't prescribe medicines for themselves.
- AD: For themselves? Why on earth not? I don't understand the ethical point there.
- AT: I am not familiar with the history, but I think the concern was that if a doctor, had a narcotics dependency problem they would be feeding the problem instead of being cared for by another doctor.
- AD: Narcotic prescriptions are registered and computerized. So, as soon as somebody writes out an unusually high amount of a narcotic it is noted and the person is interviewed. So in Sweden this is not a problem.
- AT: What kind of patients were you seeing?
- AD: I was mostly seeing patients who had to talk to somebody to find out what was going on in their brains.
- AT: What kind of patients were they?
- AD: Psychiatric patients. Some of them were complaining of certain types of pain related to monoaminergic systems in the brain. They felt I would be more able to help them than other doctors.
- AT: Along the way, you had children?
- AD: Yes.
- AT: How did you juggle all of that?
- AD: For me, it was very important to have children. I think that's built into most people, especially in women. My first marriage did not produce any children. So, I decided, okay, I have to try another route.
- AT: I know what you mean.
- AD: I worked with my first husband but that's not very good for a marital relationship as I found out. I didn't marry again for a long time. I had some relationships and one of the guys really wanted to marry me, but I said no first. But then I said, "If you can make me pregnant, I'll marry you, but not before". He did but I didn't recognize my pregnancy for some time because it was so unexpected. I was assisting at a surgical operation and, all of a sudden, everything blacked out and I was pulled back by a nurse, who saw that I was fainting. They took me outside and put me on a gurney and the surgeon finally came out and patted my

hand and he said, “Congratulations, Annica”. I said, “What, congratulations for fainting in an operation? I’m embarrassed.” He said, “You haven’t done that before, have you”? “No, no, no, I haven’t”. “Well, it’s clear, you must be pregnant”. “No”. At that time, I was still not a qualified doctor; I was doing research and I was trying to combine this with clinical work. I didn’t have time to think about what was happening, but the pregnancy was really great. I had a daughter, and about three years later we had a son. Then my husband decided it was too much of a problem being married to somebody with such a heavy workload as mine, so, he decided to leave.

AT: You did it as a single parent?

AD: More or less. I had very good help from people around me. I had babysitters, girls who had just left school and didn’t know what they wanted to do with their lives, so they did a year of babysitting. My children would choose the ones who played the best with them, and it worked out fine. Then they went to Montessori School. Both of them decided not to follow in their mother’s footsteps. I said, “Okay, that’s fine. Why would you”? My daughter told me “I’m not going to study medicine.” “No,” I said, “That’s fine”. She was a child who studied very hard in school and had the best grades in every subject, so she could choose what she wanted to do. She was naturally talented and was able to go to France to study French. Afterwards, she realized that, maybe, being a language teacher was not really very profitable, so she started to read physics at a Technical High School. After one semester, she told me, “Mama, I can’t do it. It’s so boring. It’s so utterly boring. I understand it and everything is fine, but it’s so boring. What shall I do”? I said, “Well, why don’t you just see what medicine has to offer, just for a couple of months, and if you don’t like it, you leave it for something else”? She said, “OK, I’ll do that”. She also knew she’d have a chance to study nursing. She was clever enough to say, I want to meet people, not only dentists and medical students, but all kinds of people. So, she went to Uppsala. At the end of the first semester she called me one evening and said, “Do you know how utterly smart the immune system is”? I said, “Yes, I have some idea”. She said, “Oh, it’s fantastic”. She had found what she was interested in. She is a qualified doctor, now. At first she wanted to go into orthopedics because she’s a vigorous skier and has seen all the fractures of skiers, but, oddly enough, she’s now stuck in a psychiatric clinic as a house doctor.

AT: That’s interesting.

AD: I asked, “Anna Marie, do you think you can really manage this”? So she said, “Yes, this is very interesting”. She tells me about different patients

and I have a feeling she puts too much of herself into it, which makes her a good doctor, but at the same time, I'm not sure she will be able to take it for very long, because it's a very demanding to be a good psychiatrist. My son had a good time when he went to school, but he also had very low points. He wanted to become a psychologist, but went into economics. I thought it was fine to have an economist in the family. Then, he suddenly comes and says: "Well, I've done this admissions test at the university". He was admitted to medical school and he's now in his 7th semester, I think. Both kids are now in medicine in spite of saying they were not interested.

AT: That's funny.

AD: I think there must be something in the genes.

AT: Maybe hard wired. What does he want to do?

AD: He hasn't decided yet.

AT: You must be proud of them.

AD: Yes, and they're also very active physically. My son has a passion for diving: he can hold his breath for almost 7 minutes and he dives without any help 69 or 70 meters. He participated in European championships and won second prize. Unfortunately, he could not enter the World Championships in this very crazy sport, because he had an exam to do. He chose, very maturely, to do the exam rather than the diving competition.

AT: It's a very terrifying sport for parents.

AD: Yes and when we discussed this he said, "Ma, I am very careful, so don't you worry".

AT: Going back to you, for a moment. You've done a lot of different kinds of work. You've been a clinician; you have been a researcher; you've been a full professor in the department of histology; you've, also, been the Vice-Chancellor and Vice-President of the University. Why did you decide to do all these varied things?

AD: I think because I'm a woman. I think women tend to look at the whole picture, and not just digging down into one separate problem, much more than men. I think there's a gender difference there and lately I have been going through the published material related to differences in the wiring of the brain between males and females. There is an amazing amount of literature on it.

AT: I would love to hear more about that.

AD: For instance, the retina is narrower in heterosexual males, which means that they have some type of tunnel vision. Homosexual males see wider, like women. Let me give you an example that I found many times, when you enter a flight and say your seat number is 27, then you bump into a

big guy in seat number 7. You are trying to make him understand there is somebody behind him who wants to pass but he doesn't move. Finally, he says, "Oh, I did not know you were behind me." That never happens with women.

AT: That's true.

AD: Women go to the side, because they can see somebody approaching. I have come to realize that it's not out of disrespect, or trying to be a bad guy that the men do not let those behind pass. It's just that they don't see them. With the middle ear, the way to decode sounds, is different in men and women, possibly because a woman needs to be able to interpret the different noises that a baby makes. Most men can't understand how a mother can differentiate between cries due to hunger or tiredness or need to change a diaper. A woman can do that, but men can never pick up these differences. I'm talking about heterosexual females. The wiring of the brain is decided very early, during gestation. In cases where there is something wrong with the balance between the two sex hormones, the brain of the baby could be very different from what the peripheral genitals indicate. There is wonderful literature on this topic coming from the United States. Marion Diamond, for instance, is somebody who has done relevant work. But in Sweden it's politically incorrect to say this.

AT: So, you got interested in this field, because you knew that there was good research and thought it had yet to be imported to Sweden?

AD: It had to be told because there is so much going wrong in Swedish society. The social democrats want everybody to be treated the same and that's fine, but they also want everybody to be the same, and that is an impossibility. There's a feminist section of Sweden, which has declared there is no difference between the male and female brains. The only unique thing for women is to give birth to children, and soon, they will try to make men able to nurse babies and things like that. Why would you like to be similar to a man in your brain? I wouldn't. I'm very happy being a female.

AT: I am, too. I like my brain.

AD: I think that everybody should have the same pay for the same type of work but we don't need to be exactly like each other. We have these normal distribution curves of interests for women and men, which intersect. So we have part of the population with both male and female interests.

AT: Yours is a message that has political implications?

AD: Yes, for sure.

AT: Are your views making much progress in Sweden?

AD: People love to listen to my talks, but there's still a long way to go. Some of the newspapers in Sweden are aghast that somebody with a scientific background is telling the truth. But, the real question is, do the politicians listen? I think that's the same problem everywhere; politicians don't listen.

AT: How did you come to be so highly placed in administration? Clearly, you're a public intellectual? That is not the case for everyone with your background. How did that come about? You are very articulate and engaging. That must have been something you wanted to become I assume?

AD: I never strived for it. I have been asked to do certain things and initially I always said no. A woman always says no when she's asked about something important. Then men say, and that's a mistake, that women never want to do anything, because they don't want to accept responsibility. But this is not the case; it's just that women need time to think. Women have to consider the implications for their family before accepting anything. If you come back to her and ask again she might say that would be fun. This is something else we need to publicize. You can't treat males and females the same way; they respond differently and you have to approach them differently if you want something from them. My appointment as professor at the university was a very interesting experience for me. At times it was difficult but I learned a lot. As a scientist I could make my own schedule. Then, all of a sudden I was in a position in which I was expected to make use of administrative personnel and I had to wait, for example, until they typed a letter. You want to have things done promptly. It was very hard for me to accept the delays and the bureaucracy. So I ended up doing everything myself. I typed and sent my letters and, of course, I wasn't very popular, to say the least.

AT: Was computer software available?

AD: Not really. They didn't have much there. I think the people sitting there used the old typewriters. They wanted to stick to their old ways. They didn't want to be rushed by computers. It was resistance against progress. Many of them are now retired, so we are in a new era.

I had to travel to different universities in the Middle East, because we felt we had to have contacts not only with international universities in America and France but, also with people who thought differently from us, to incorporate their experiences in our teaching. I went to Teheran, for instance to have a discussion with the head of the university and that was an interesting experience. I had been told, before I saw him, that I was not allowed to look him in the eyes or touch his hands. I said: how on earth am I going to conduct a serious negotiation

with somebody without looking into his eyes? So, I was looking very hard into his eyes and that made him feel uncomfortable. I could see that. I heard afterwards that he complained that my scarf did not cover enough of my hair. Parts of my hair were exposed, so one of these little black women came up to me and said, "Would you please cover your head?" I said, "Why?" She responded, "Because, someone has asked me to speak to you about it." So, I said, "But, if he wants me to do that, he can tell me, himself." It is interesting, but we had, for some years, collaboration with that university, anyway. Then, I was in Jordan, at the University of Amman and I was invited to the medical faculty club. There were a lot of women; the percentage of women at the Amman medical faculty is 20 to 21 percent.

AT: Have things changed a lot in this regard since you entered the medical field?

AD: Yes. We now have more than 50 percent female medical students. As to PhD students, it's also around 50 percent. But when it comes to higher positions, it's much lower. I think 17 percent of medical professors are women. People complain about that, but usually women are honest enough to realize there are other things in life more important than a career.

AT: I want to ask you about the brain map you showed us yesterday.

AD: That was the first schematic drawing of the different neurotransmitter-systems in the brain.

AT: That was done in the early sixties?

AD: Yes, what I was showing was published in 1964. It was a schematic drawing of a cross section of the spinal cord, the brain stem, pons, medulla oblongata and the hemispheres. It indicated on one side the noradrenaline and dopamine fibers and nerve cells in green and on the other side the serotonin fibers and cell bodies in the midline and raphe area. We have indicated how the axons from the nerve cell bodies collect in the median forebrain bundle.

AT: So, was that mapping of the brain your work?

AD: The work was done by Fuxe and me. I don't want to take all the credit myself.

AT: It's remarkable.

AD: We did the "lesion experiments" to see which nerve cell groups innervated which areas and we could see the accumulation of noreadrenaline or serotonin in the cells. Sometimes, it was difficult for people to accept these new pathways nobody had seen before. The fluorescent microscope could pick up structures which are less than one micron;

every little granule lights up like a lamp. It sends rays of light in all directions; you don't see the structure itself, but the light it produces.

AT: Yes, the light you showed us last night was very pretty. I can almost imagine a gallery full of art.

AD: It was so rewarding to do that work.

AT: Wonderful. I want to ask you where you see neuroscience heading; what you think the burning questions are that still need to be answered, that can be answered in the next thirty or forty years?

AD: The most important thing is to have the politicians and society understand the importance of what happens in the brain, because people still regard the brain as an organ like a heart, liver or kidneys, when, in fact, the brain is the essence of everything. The heart is there to pump blood to the brain, but, without the brain, people don't exist. It would be important to make politicians understand we must dig further into the secrets of the brain in order to be able to continue to develop society in a positive way. It would be important to make them understand that a lot of problems in society could be managed rather simply if we could understand everybody is an individual person with their individual genetic make-up and that behaviors can emanate from a dysfunction of neurons in the brain, not just from upbringing or external factors. Children should be treated differently in order for their brains to develop in the best way, mature and blossom. The way education is organized today, at least in Sweden, does not create the best possibility for a brain to develop. I'm not just talking about intellect. I'm talking about social competence, about how to live in a society and make the best of one's abilities. Greed today is something I consider almost a disease and greed creates so much negativity in society. If we could figure out what creates greed, much could be solved.

AT: Could you give us a concrete example of how a school might reorganize itself to give children greater opportunities?

AD: Of course, the parents are important. I would very much like to introduce a "driving license" for parents before they create children, because so many treat their children totally opposite to how they should be treated. Parents don't know about the development of a child's brain and the different periods and phases of brain development the child is confronted with. Then, of course, there's the school. Children should have also much better access to adults. In Sweden, today, economics has forced a drastic cut in doctors, nurses and teachers, which means too many children are let loose to play in totally uncontrolled ways. The brain needs teaching. You can't leave a child to develop automatically by nature. It's not possible. A healthy social environment is needed for

the brain to develop correctly. As for psychiatric diseases, it's the gene map that allows us to look at individuals for small changes in genes for auto receptors or transporters; that opens up the possibility to make drugs specific for each individual. Politicians are still fairly generous with research grants for basic research, because, as the name indicates it is the basis of everything. You cannot do clinical research unless it's based on experiments in basic research. But, as was said yesterday, clinicians and basic scientists should work hand in hand so that cross-fertilization of ideas can occur. But we must nourish basic research. That's something Sweden is forgetting more and more, unfortunately.

AT: You mentioned that last night. It was very interesting to listen to the language you used when you described how politicians need to support basic science. In Canada I hear that a lot too, but in the United States it seems although the NSF is fairly generous, and actually more generous than NIH, more and more funding is coming from the pharmaceutical industry. Is this something that concerns you?

AD: It was really wonderful in Sweden when Astra, the Swedish drug company, and the university worked hand in hand. During that time many excellent discoveries were made. It was without any strings or bonuses from Astra to the university. It was proper collaboration. These days, drug companies are much more restrictive when it comes to supporting research. They want to direct what kind of research is being done and that is disastrous. You cannot command discoveries, they have to come spontaneously. Then, there is all this talk about centers of excellence, I do not like that. You have to put that label on yourself, otherwise, nobody would consider you worthy; that is something which, to my mind, is typical male behavior. Much more support should be given to smaller groups and these should be given freedom to make contact with other groups. I think small groups are important, and not just large centers of excellence which are like factories. A factory-like organization is counterproductive to the generation of new ideas. This is something I feel very strongly about. In the old days nobody told us what to say or do. They were giving us support to open up new directions and it was up to us to do it.

AT: Let me ask a final question before I ask if you have anything to add. Coming from Sweden, are there significant differences in the kinds of things that interest neuropsychopharmacologists here at the ACNP meeting compared to Europe and other places? To what extent can we say, in the year 2004, we've become truly global in neuropsychopharmacology. To what extent do culture and national politics still matter?

AD: I would say neuropsychopharmacology is the same all over. There might be differences when it comes to funding; some governments might not consider supporting research in schizophrenia with the same high priority as research on how to stop people being addicted to alcohol. There could be minor differences, but basically it's the same. It is even possible for Swedish labs to get funding from NIH. I don't see any cultural differences in our ways of looking at neuropsychiatry either.

AT: Does a patient's experience with a psychiatric illness vary?

AD: Yes. Patients, in Sweden have a very bad time, because the government made cuts in the number of psychiatrists and in funds for psychiatric inpatient treatment. We have a lot of patients, unfortunately, who go untreated despite having tried to get medicine on the streets, which is the reason for some of the unfortunate homicides we've had during the last year. Strangely, the Swedish authorities do not understand they need to increase funds for psychiatric research and treatment. They are still cutting back. You have no access to the inside of a politician's brain. They listen to you and say, yes I understand, but not a word has gone in. How could we change that?

AT: I don't know.

AD: I think we have to change our government, but I'm not sure it's going to improve things. Politicians also have to change.

AT: I wonder if there's a study on how to enter a politician's brain!

AD: We need to know a lot more about our brains and before somebody becomes an influential politician, they should have their brain examined with CT scans and things like that.

AT: As someone yesterday said, George Bush took a physical but no one asked him to take a mental exam.

AD: Exactly. That goes for many politicians.

AT: Is there anything you want to add?

AD: Just that I feel I have been given so much in life. I was given good parents, good genes, and I was at the right place at the right time. I had a fantastic kick-start in my career and enough mental energy to accomplish everything I wanted. Also I was lucky enough to have children, two husbands and things like that. On the whole, I'm very grateful.

AT: Thank you. It was wonderful.

AD: Thank you very much.

JAMES V. DINGELL

**Interviewed by Leo E. Hollister
Washington, DC, April 15, 1997**

LH: It's Tuesday, April 15, 1997, and we're here in Washington, DC to continue the series of interviews on the history of psychopharmacology, sponsored by the American College of Neuropsychopharmacology. Our guest today is Dr. James V. Dingell,* who has been long associated with the National Institute of Mental Health. Is this correct?

JD: Actually Leo, it was Heart, Lung and Blood, Cancer and Drug Abuse.

LH: Well no matter which institute he works with and I'm welcoming him here.

JD: Well, thank you. Very good to be with you!

LH: I always like to know a little bit about how people got to where they wound up.

JD: It has been an interesting story, punctuated by a great deal of good fortune. I began my training in chemistry at Georgetown University in 1950 and planned to go onto Law school upon graduation in 1954. However, this was the time of the Korean War and I had taken a double major, Chemistry and Military Science, to be prepared for my almost certain military service. But the first stroke of good fortune occurred when I took a course in Biochemistry in my senior year that changed my whole outlook on a future in chemistry. I was excited by chemistry, and law school ceased to be a future plan. My good fortune was to continue at Georgetown, as Georgetown had offered me a teaching assistantship in chemistry and the army agreed to allow Second Lieutenant Dingell to go on in graduate school. However, after about a year, I found that things were a bit difficult living on one hundred dollars a month and I met Leo Gaudette, a fellow graduate student, who advised me that NIH offered opportunities for graduate students to do their studies at night and thesis related research during the day. It was in June 1955 that I went to NIH and after more than a dozen interviews had the good fortune to meet Dr. Bernard B. Brodie, who took the time to describe the exciting work that was underway in his Laboratory of Chemical Pharmacology on drug metabolism, reserpine, norepinephrine and the development of the spectrophotofluorometer with Dr. Bowman. I will always remember Dr. Brodie's words. He was not looking for civil servants but graduate students because he knew they would work harder!

LH: That was a wonderful opportunity. Out of eighteen interviews, this one caught you, right?

* James V. Dingell was born on Detroit, Michigan in 1931.

JD: Indeed! Dr. Brodie's enthusiasm was irresistible. Just remember these were the early days of studies with the microsomal drug metabolizing enzymes, the revolutionizing drugs chlorpromazine and reserpine, and new instruments for the measurement of drugs and biogenic amines in biological materials. I will always be grateful for the opportunity I was given to become associated with scientists like Drs. Brodie, Axelrod, Udenfriend, Bert La Du, and of course, Jim Gillette who mentored my thesis research.

LH: Dr. Brodie must have been quite a charmer.

JD: He was indeed! He could be difficult to get along with but when you faced difficulties, as I know from personal experience, Dr. Brodie was the friend to have. He was devoted to his people and was always there and ready to go that extra mile for his people.

LH: Now, you went there in 1955.

JD: In June, 1955.

LH: Was Axelrod still at the NIH?

JD: Julie had left. He got his degree in 1954, and he'd left Dr. Brodie but he bequeathed us a legacy with his early studies on the microsomal drug metabolizing enzymes.

LH: Of course Brodie had been long in the field of drug metabolism.

JD: Dr. Brodie was probably the father of modern pharmacokinetics, modern pharmacology. He came with that wonderful group from Goldwater Memorial Hospital to found the Heart Institute in 1950. His most notable accomplishment before coming to NIH was involvement with the anti-malarial program that had been going on at the beginning of the war. As you may recall, the first thing that happened, when the war broke out, was the Japanese overran Southeast Asia and with the loss of our source of quinine, malaria became a considerable problem. There was an interesting compound, Atabrine (mepacrine) which showed promise but when it was used by troops showed considerable toxicity. Brodie and his group, including Julie Axelrod, developed a method for measuring the levels of the drug in plasma which had to be maintained to be effective against the invading organism. With an adjustment of the dosage schedule to provide adequate plasma levels malaria ceased to be a major problem in the South Pacific. Some actually credited Dr. Brodie with a major role in winning the war in the South Pacific.

LH: Well, by golly.

JD: He was right up there with General Mac Arthur.

LH: There were more troops disabled by malaria than by bullets.

JD: Yes indeed! It was a wonderful time when I joined the lab, because it was spring for the NIH, things were in bloom! We had a sympathetic

Congress; we had men like Lister Hill interested in development, using money spent during the war on other things, to develop and exploit the opportunities in science. And it goes without saying we had a truly magnificent director of NIH in Dr. Jim Shannon.

LH: Shannon was the one who recruited Brodie.

JD: Indeed, and Brodie brought with him Julie Axelrod, Syd Udenfriend, and John Burns, all of whom deserve enormous recognition for their contributions.

LH: It sounds like a Who's Who in Pharmacology.

JD: It was.

LH: Was Jim Gillette part of that team?

JD: Jim Gillette joined Brodie in 1954. Jim was interested in the biochemistry of drug metabolism and his main focus was the enzymatic mechanism of drug metabolism. He did very early, very solid and well recognized studies with TPNH oxidase which led into the Cytochrome P450 System. I was privileged to work with and learn from Jim Gillette the good habits of careful work in the lab, the importance of analytical methodology and the ability to work long hours.

LH: That was trademark in Brodie's lab, wasn't it?

JD: That was, indeed.

LH: And, unusual hours, too, if understand it.

JD: Yes, unusual hours. The graduate students, those of us at Georgetown, would work all day and our classes were at night. Those at George Washington, like Ronnie Kuntzman and Julie Axelrod, took time during the day to attend classes and would work later hours at night.

LH: And Brodie was known for being on an entirely different rhythm.

JD: That's the other side of the coin. Dr. Brodie kept very strange hours. He would arrive late in the morning, but you could be sure that if something hot was going on in the lab, you would receive a phone call at an early hour be it two or four a.m. in the morning, to hear about those hot results. He was a remarkable gadfly! He kept the lab energized from one end to the other; it was a genuine experience working with him.

LH: He used to throw out very interesting new ideas and be enthusiastic about them.

JD: He did. He had a philosophy that if an idea struck you as having promise, test it and collaborate. This was the beauty of NIH in those days. The opportunities for collaboration were wide open, be it Evan Horning's people at the other end of the hall in organic chemistry or with Bob Bowman and his group for instrumentation.

LH: It must have been a wonderful time to work there.

JD: It was a truly remarkable time at the NIH.

LH: What was your first assignment in the lab?

JD: Working directly with Jim Gillette on model systems for dealkylation, an enzymatic mechanism. What I did at the time stayed with me for a number of years and paid off well. We were able to come up with several nonenzymatic systems which effectively removed methyl groups from compounds such as aminopyrine.

LH: Didn't you do some of the early studies with tricyclics such as imipramine?

JD: Those studies were both interesting and very rewarding for me. After I finished work for my Masters Degree at Georgetown, Dr. Brodie suggested that a new drug, imipramine, could give me some experience in pharmacology that would be of value if I chose to go into the drug industry in the future. As I recall, imipramine was originally synthesized as a potential tranquilizer. However, it was an astute clinician in Switzerland named Kuhn who recognized its antidepressant activity. Interestingly, Kuhn found that when the drug was administered to bipolar patients it did little or nothing to calm their excited phase but dramatically reduced their depressed phase. I well remember Dr. Brodie's words that although it might just be an interesting placebo, it was worth studying. He advised: "Why don't you take a look at this compound and see what you get?" The obvious first step was the development of analytical methodology for the measurement of the compound and its potential metabolites. Experience told us that most likely the drug would undergo both hydroxylation and demethylation. Since a simple method for measuring formaldehyde on demethylation was at hand, I found that copious amounts of formaldehyde were formed on incubation of imipramine with preparations of liver microsomal enzymes. This was interesting since the tertiary amine methyl groups of imipramine were on a side chain and the prevailing thinking at the time was that for dealkylation to occur they had to be located in near proximity to an aromatic ring. These were the days before advances in gas and liquid chromatography, and therefore it was necessary to develop a fluorometric assay method that used solvent extraction to separate imipramine from its demethylated and hydroxylated metabolites.

LH: Hadn't Geigy already done some work on the excretion of imipramine?

JD: They had done some studies, as I recall. It was in the rabbit and they found that hydroxylation is the major route of metabolism in that species.

LH: What about dealkylation?

JD: They didn't know a great deal about dealkylation from their studies. But the story at this point was becoming very interesting because my dear friend Fridolin Sulser joined Brodie's lab and was challenged to

find a way to unmask the antidepressant action of imipramine. The drug didn't reverse any of the drug induced syndromes that were known at the time. In fact, it potentiated the action of ethanol and barbiturates.

LH: It wasn't, in that case, much different from chlorpromazine.

JD: Exactly. So, Fridolin and his technician Jim Watts turned to the well known depression induced by reserpine model in the hope of finding it reliable. I'm sure, Fridolin has described in detail this interesting detective story, but they found that although a single administration of imipramine to rats potentiated the reserpine induced sedation, chronic administration of imipramine before reserpine administration not only prevented but dramatically reversed the expected drug induced depression. Their model mimicked what was seen in patients, a lag period before the antidepressant action of imipramine became apparent, and, their findings actually suggested that imipramine might act through an active metabolite. This fit hand in glove with results of my studies on the metabolism of the drug in rats. These studies showed that the secondary amine metabolite desmethylimipramine not only had a longer half-life than its parent compound in rats but accumulated in tissues including brain after the administration of imipramine.

LH: Wouldn't the hydroxylated metabolites be more likely to be short lived?

JD: Being conjugated with glucuronic acid or sulfate they would be rapidly excreted in urine and rendered inactive. Our attention now turned to the likely suspects, the dealkylated metabolites; to make the story short, a generous sample of desmethylimipramine was obtained through the courtesy of Dr. Franz Haeffliger of Geigy and tested in the reserpine model. A single injection of desmethylimipramine reversed the action of either reserpine or RO 4 -1284. Thus, desipramine was born along with an insight into the putative mechanism of action of tricyclic antidepressants.

LH: Desipramine was shared with Lakeside, wasn't it?

JD: That's another interesting story. As I recall it, Geigy's legal staff, in Switzerland, was not aware of the holiday on George Washington's birthday and they were a day late in submitting their patent with the result they had to share the patent with Lakeside. I think one had the patent on use and the other on the synthesis.

LH: That was a close call, wasn't it?

JD: Yes and a lot of money lost because of that.

LH: I remember Brodie thinking that the active metabolite desipramine would work much more quickly than the delayed action seen with tricyclics.

JD: Right.

LH: But, that didn't seem to be the case.

- JD: It didn't, and, that's been an interesting story.
- LH: It only takes a few hours before the dealkylated metabolites accumulate.
- JD: Indeed. We studied the metabolism of imipramine in several species and found marked inter-species differences in the pathways and rates of metabolism of the drug. Importantly, in rats where the anti-reserpine action was seen, the half life of desipramine was considerably longer than the parent compound. But in rabbits where the antireserpine action was not apparent, hydroxylation was the main pathway of metabolism and desipramine did not accumulate in tissues. About this time the technique of gas-liquid chromatography (GLC) was in its infancy; it was just being developed in the laboratory of Dr. Evan Horning down the hall from Dr. Brodie's laboratory. On a hunch I thought we might be able to further confirm the identity of the metabolite isolated from brain using GLC. With the blessing of my friend and mentor Jim Gillette I took a sample of the material isolated from rat brain to Dr. Bill Van Den Heuvel, who injected it into their early gas chromatograph. Needless to say, we were delighted to see our first sample give us a beautiful peak, characteristic of desipramine. We had confirmed the accumulation of desipramine in rat brain and the validity of our extraction assay. But back to your original point, we can only say that desipramine is an active metabolite, but whether or not imipramine acts through its metabolite remains an open question. Desipramine is still on the market, to my knowledge.
- LH: It's kind of unique among the tricyclics, being a specific uptake inhibitor of norepinephrine. It also seemed less sedative and anticholinergic.
- JD: That's right. It's a remarkable compound and has been an important tool. The philosophy I learned from Dr. Brodie is that first you've got to have good methods that are both sensitive and specific for the compound. Secondly, drugs are the most formidable tools we have for probing the function of the central nervous system. Just remember how naive some of our experiments were, grinding up the whole brain and trying to relate chemistry to function. I'll never forget Fridolin telling me, "Jim, we have to get beyond this, because a homogenized brain doesn't think".
- LH: You mentioned Syd Udenfriend. I think, in this whole series, he's been neglected. I hope we can get hold of him, but what was he doing in this laboratory?
- JD: Sydney was one of the early members of Dr. Brodie's lab and he was Brodie's right hand before Erminio Costa joined the lab. But, Sydney developed and later had his own lab, around the corner. You of course know of his development and leadership at the Roche Institute. That's a capsule of the time with Brodie and Jim Gillette that opened opportunities for me. We had Dr. Milton Bush from Vanderbilt in the lab doing his

sabbatical, just as I was finishing up my imipramine program. Vanderbilt was interested in a program in psychopharmacology. So this takes us into the next part of my career; seventeen years at Vanderbilt.

LH: Did you move there at the same time Fridolin did or before?

JD: Our paths crossed again and that's an interesting story. I went to Vanderbilt at the end of October 1962. I remember driving to Nashville while military convoys were moving to Florida during the Cuban Missile Crisis. I had left my wife and baby son in Maryland to move there. I went with the charge from Dr. Allan Bass, who was the Chairman of the Pharmacology Department to help start the program in psychopharmacology. Allan Bass wanted to develop space for psychopharmacology research made available by the Department of Mental Health of the State of Tennessee, at Central State Hospital. Dr. Bass and Dr. Frank Luton, who was the Director of the hospital, took me out to show me the area I would have to develop as a laboratory. I went home that night, after seeing the sorry state of the place; I would have to put the lab into a hydrotherapy room with all of the odors that permeated the hospital, and I was physically sick that evening. But, not being one to turn tail and run, I moved to Central State, started a lab with one technician and, lo and behold, things were going fairly well. Those were days when I didn't have a lot of collaboration going on. I had several projects with different problems so, when I hit an obstacle I could move to something else, waiting for inspiration to solve the problem. As things went well, another old friend and old hand from Dr. Brodie's lab, Danny Efron, came to see what was happening and what the potential was at Vanderbilt for developing a psychopharmacology program. Danny was taken with the possibility and suggested that we put in a center grant application. NIMH had money in those days and the amount involved was several hundred thousand dollars, which, although modest by today's terms, was quite handsome in the early 1960's. I remember, I worked with Allan Bass and Milton Bush in that small department of pharmacology at Vanderbilt which had only five members. We put together a center grant application, were site visited and funded with only one person, Jim Dingell in the whole program. The problem was then to find a Director to develop the program further. After approaching several of the old timers in psychopharmacology, we came up blank. I remember talking to Danny Efron on the phone suggesting one person I thought ought to try for this position. He asked "Who's that"? I said, "Fridolin Sulser". He replied, "Jim, he's very happy where he is". I suggested he ought to give Fridolin a try and lo and behold, about two weeks later I got a phone call from Dan Efron telling me, "Jim, we found a Director

for that program”. I said, “Who is it”? He said, “Fridolin”. We were able to start the program with an old colleague as my boss, which couldn’t have been a better relationship. It was a very fruitful time for us.

LH: That became quite an Institute.

ID: It did. Indeed that small lab became the Tennessee Neuropsychiatric Institute and, when I left at the end of 1975, we had thirty or forty people. Allan Bass is a man of great wisdom and great farsight. Allan’s philosophy was one must get competent young people, then give them opportunities and support. And that is what he did with me, with Fridolin and another outstanding scientist, who is now Chief of Medicine at Vanderbilt, Dr. John Oates.

LH: What were you doing down there, once you got your laboratory set in those undistinguished quarters?

JD: I worked on problems, such as the effects of calcium deficiency on drug metabolism, and the effects of carbon tetrachloride poisoning on the microsomal enzymes. With Fridolin, we studied the amphetamines. Fridolin’s early days at Vanderbilt also offered the opportunity for us to renew our interest in the tricyclics. Other investigators had observed the ability of desipramine to potentiate the action of amphetamine and suggested this action could provide a model for unmasking the antidepressant action of new drugs. We knew from its long half life in rats that desipramine would accumulate in tissues and also that it was localized in hepatic microsomes. It therefore seemed reasonable to assume that desipramine’s ability to potentiate amphetamine was a biochemical rather than a pharmacological interaction, i.e., an inhibition of the metabolism of amphetamine rather than an interaction at the receptor level. By using the original extraction procedure for amphetamine we were able to measure the levels of the radiolabeled drug in the brains of rats after administration of desipramine. What we found was a striking prolongation of the half life of amphetamine in rats after pretreatment with desipramine. We later found that the ability to prolong and enhance the psychomotor stimulation of amphetamine by inhibition of its metabolism is not just a characteristic of antidepressants but was even seen with chlorpromazine.

LH: How did that work and which pathway was involved?

JD: In the rat, it would have been the major pathway of para-hydroxylation rather than deamination which predominates in rabbits. This brings up an interesting side light. The first pathway of drug metabolism in hepatic microsomes was deamination. This was found by Julie Axelrod using rabbit liver preparations to metabolize amphetamine. Since this was the research for his doctoral dissertation, he was fortunate that he

- had not chosen rat liver preparations to investigate the metabolism of amphetamine.
- LH: We ordinarily think of drug interactions of this sort as being bad, but could some be of positive clinical value?
- JD: Well, you certainly recall the history of SKF 525 A. It was first thought that it would have value as what was called a prolonging agent, but later it was found to be only an inhibitor of the microsomal drug metabolizing enzymes. I think that a poor ratio of benefit to risk would doom the therapeutic use of drug metabolism inhibitors.
- LH: You left Vanderbilt in the mid seventies.
- JD: Yes, after finishing a series of studies on the metabolism and excretion of delta 9 tetrahydrocannabinol, I took the opportunity to return to the Washington area to work with Dick Adamson in the Laboratory of Chemical Pharmacology of the National Cancer Institute.
- LH: So, you left Vanderbilt before Fridolin got interested in the effects of drugs on the down regulation of the β adrenoceptor coupled adenylate cyclase.
- JD: Right. That was his next area of interest. I didn't share those studies with him, but was pleased to see them done.
- LH: It was a good unifying hypothesis; unfortunately it left unanswered questions.
- JD: Leo that reminds me of another "Brodieism.". Discussing the importance of a hypothesis, Dr. Brodie made the remark that "you always have to start with a hypothesis that is so simple that it almost has to be wrong to begin with because any simple wrong hypothesis will, ultimately, evolve into a more accurate complex hypothesis".
- LH: That's a good aphorism.
- JD: And words of real wisdom.
- LH: So much of what you see written today is what I call a straw man hypothesis. I suppose you, like almost every other person in science that I've ever talked to, have no regrets about your career?
- JD: None. My career was determined by good fortune, good fortune in meeting men like Dr. Brodie, Bert La Du, Jim Gillette, Fridolin Sulser, Dan Efron, Danny Freedman, Morey Lipton and so many others, men of enormous ability, willingness to cooperate, be helpful and so on.
- LH: And these were very nice people.
- JD: They were, absolutely, yes. Dr. Brodie was not always the most easy person to get along with, but when you needed a friend or had a problem, he was there. I would probably, had it not been for Dr. Brodie, ended my career in science in 1960, because the United States Army had decided they were tired of granting me delays and called to active

duty. Dr. Brodie decided that he would make every effort to get me transferred into the Public Health Service and keep me with him to finish up the imipramine problem, so, again, a man of great friendship.

LH: He gave you a practical opportunity.

JD: Indeed.

LH: You mentioned Erminio Costa in passing, and Brodie had a couple of people from Sardinia. Didn't he have Luigi Gessa?

JD: That's right, and also from Italy, Rudolfo Paoletti.

LH: I remember, I think it was in 1970, when the Nobel Prize was announced, that one of my friends came bustling in and said, "Guess who won the Nobel?" I guessed Brodie or Euler. But he said, "No, it's Axelrod" I replied, "Brodie's heart must be broken".

JD: I'm sure it was. I think it was a very unfortunate occurrence. Dr. Brodie did so much in opening so many fields. The only thing that I think might have weighed in the balance was that Julie chose to stay with an area and kept moving on in depth. Dr. Brodie would open up an area and move on.

LH: Yeah, he was a pioneer.

JD: When I was at Vanderbilt everybody assumed that Earl Sutherland was going to get the Nobel Prize. I remember lying in bed one morning and flipping the TV on to clear my head when the news came on about the Nobel Laureates and I was astounded to hear among them was Julie Axelrod. I jumped out of bed, laughing my head off, because everything had been prepared for Earl. He had won the Lasker Award and it was assumed it would be automatic for him to get the Nobel Prize but here was this wonderful gentleman, Julie Axelrod, who was chosen. I remember firing off a telegram right away, congratulating him.

LH: The ACNP was meeting at that time; Danny Freedman was President and he composed a telegram from the organization, congratulating Julie and I never saw an audience more sympathetic. Everybody was jubilant!

JD: You know Julie's history. Julie didn't get his PhD until he was about forty-five years of age and his plans to get into medical school in New York were thwarted because of quotas, so bless his heart, he worked as a technician.

LH: He had a tough life.

JD: The gods reward good people.

LH: Well, you had to work for your PhD, too.

JD: Yes, but I didn't have to face the hardships that Julie did and Julie was always a very kind, thoughtful and giving person, one of those friends you're really proud to have.

- LH: One person that comes in mind, who won a Nobel Prize, who, as far as I know, didn't have a doctoral degree, was Gertrude Elion.
- JD: Yes, wasn't that nice! She did it with George Hitchings. That was another one of the good turns of science that restores your faith in it; people, other than those that speak directly to God, can win the Nobel Prize.
- LH: A few years ago I had an opportunity to make nominations and I was trying to promote pharmacology, so I put up Hitchings and Black for methods of developing new treatments, but I had forgotten that Elion was such an essential part of the Hitchings team.
- JD: Some people never get the recognition they deserve. In the case of Dr. Brodie, I think it was unfortunate. It would have been nice, looking back from the point of view of drug metabolism, if Brodie could have shared the Nobel Prize, perhaps, with Professor Williams from St. Mary's in London. But so be it, those days are gone, Brodie had his share of recognition; he received the Gold Medal for Science and I believe that was a reward for his work with the anti-malaria program and pharmacology development.
- LH: You were lucky to be part of that wonderful team.
- JD: Fortunate, indeed.
- LH: I imagine that between the two of them, Brodie and Axelrod were responsible for more influence on psychopharmacology than any two people I can think of.
- JD: In terms of the development of people, I humbly admit I was among the least of Brodie's graduate students.
- LH: Well, I want to thank you for coming. It seems like we've been trying to get together for a long time.
- JD: It's amazing how the time goes by.
- LH: We talked about Brodie more than you, but that's good.
- JD: I think it was important that his enormous contributions be recognized. My later years have been spent in administration at both, the National Heart, Lung and Blood Institute and the National Institute of Drug Abuse. Looking back it is hard to believe those many years have flown by so fast.
- LH: We are all getting older and that's why we are doing these interviews to catch us while we are still here.
- JD: As you say, it's unfortunate that we don't have some of those old timers, who gave us so much; how wonderful it would be if we could have had Danny Freedman sitting here, Morey Lipton and Brodie. You're fortunate, you had Axelrod.

- LH: After Danny became editor of the *Archives of General Psychiatry*, I was talking to him and I said, “Danny, now that you’re the editor, every time I send a manuscript in, forget it’s me. Judge the manuscript on its merits; otherwise, my Presbyterian conscience will suffer”. He said, “Don’t worry my Jewish conscience would suffer equally!”
- JD: Danny and Morey were the epitome of what one should be in psychiatry. Wonderful people!
- LH: That’s the other pleasant part of our career, having known such lovely, smart, inspiring people. I can think of several dozen who could have interviewed you more intelligently.
- JD: Thank you, my friend, thank you.

SALVATORE J. ENNA

**Interviewed by Elizabeth Bromley
Waikoloa, Hawaii, December 12, 2005**

EB: Would you tell me your name and where you were born?

SE: My name is Salvatore Enna* and I was born in Kansas City in December, 1944.

EB: And, tell me about your family.

SE: My parents were children of immigrants. My grandparents on both my mother's and father's sides came from Sicily and had very little formal education. My father was a high school graduate and my mother a grade school graduate. I was one of five children, the second of five.

EB: So, you have one older sibling?

SE: Yes, I had an older brother and I have a younger brother and two younger sisters.

EB: And, when did your parents come to the United States?

SE: My grandparents came to the United States. My parents were both born in the United States. My grandparents came to this country in the 1890's.

EB: And, what was the set up in your house, a lot of siblings? Were your grandparents in the house?

SE: No, by the time I was born, only one grandparent was left and she died when I was very young. We had a very modest home, two bedrooms and one bath. In this house lived five children, two parents and my great aunt. It was a crowded situation but it was wonderful. It was fantastic. I never felt deprived.

EB: You went to public school?

SE: No, I went to a private Catholic grade school and high school.

EB: And, what was that like, your high school experience, junior high and high school?

SE: Fabulous, fabulous. I had a great adolescence. I had a lot of friends and was very active in sports, theater, and other extracurricular activities.

EB: What kind of sports?

SE: Football. That was back when you didn't have to be particularly large to play high school football. Today I don't think I would make the team.

EB: You could run faster.

SE: Yes. I went to a Jesuit high school, an all male school. We had a very good time, and I received a good education.

EB: Were you a good student? Did you like school?

* Salvatore Enna was born in Kansas City, Missouri in 1944. Known as Sam to his colleagues, in his publications he is typically listed as S.J. Enna.

SE: I loved school. While neither of my parents went beyond high school, they believed strongly that education was the way to get ahead. This was stressed in our household. The great aunt who lived with us was a school teacher, so there was a lot of discussion about school, education and doing well. So, school was a priority. Attending school and doing well was just something that one did. You know, you had to go to school. That was your job.

EB: Something that was comfortable to you. Did you have special mentors or teachers at that time in your life?

SE: No.

EB: Someone in your family or family friends?

SE: No, not really.

EB: Did religion play an important role in your family?

SE: My family was Catholic and they were fairly religious, although not extremely so. We went to church every Sunday, that sort of thing.

EB: Now, you said they expected you to devote yourself to school and get an education. Did they have more specific expectations for you?

SE: No. They worked very hard to see that I went to the best school they could afford. Again, that was their job and it was made clear that my job was to do as well as I could in school. In terms of any particular career direction it didn't matter. The important thing was to get a good education.

EB: And, what was your thought about your future?

SE: Well, in high school, I didn't really give it a lot of thought. You know, high school is pretty well laid out for you. You don't make a lot of decisions in terms of subject matter. In college, most of my friends went into business. I found that pretty dull. That didn't excite me at all. So I took science, with majors in biology and chemistry, almost in rebellion to the idea of going into business. I just didn't want to pursue a business degree. At that point I wasn't particularly drawn to science, although I found it interesting. The important thing was that it wasn't business.

EB: Rebellion against your peers.

SE: Not in an aggressive way, but, if they're going to do that, I don't want to.

EB: Where did you go to college?

SE: I went to the local Jesuit College in Kansas City, Rockhurst College.

EB: Rockhurst?

SE: Right.

EB: And, did you live at home then?

SE: Yes. Oh, I couldn't afford to leave town for college. My family didn't have any money and I worked to pay the tuition. And this great aunt who lived with us helped me with the tuition, as well. She was unmarried

so it was a family kind of thing. Everybody said, "If Sam wants to go to college we'll figure out a way to pay his tuition". And that's what they did.

EB: And, so, how did it go with the science?

SE: Fine. I really enjoyed it and, then, when I was a junior or senior I started thinking about career options. You know, I needed to make a living. I considered all the conventional possibilities, medicine and dentistry, since most of the science majors go on to professional and graduate schools. I'd never considered pharmacology since, like most people, I hadn't heard of it in high school and college. I remember very distinctly, a fellow named Ed Walaczek, who was the Chair of Pharmacology at the University of Kansas Medical School who gave a talk to the science majors at Rockhurst. His description of pharmacology opened a new world to me. I was struck by the fact that pharmacology is a practical application of biology and chemistry. I had no interest in going out to discover new plant or animal species. But, with pharmacology it appeared you could use your training in biology and chemistry for something interesting, for something that's really useful. So, that's when I was first introduced to pharmacology and became interested in it as a possible career choice. When I graduated from college I made an application to graduate school at the University of Missouri-Kansas City School of Pharmacy and was accepted.

EB: You felt comfortable enough with that and applied?

SE: Yes, I applied to graduate school and was accepted. The campus for the University of Missouri was walking distance from my home. I continued living at home because I couldn't afford to move out. Of course, graduate school is a bit easier than undergraduate school because I was able to get a scholarship to cover my tuition and some other costs. While the graduate program was small and not world famous, it was a good program.

EB: What year did you start there?

SE: I began graduate school in 1965, the year I graduated from college. I received my Master's degree in Pharmacology in 1967 and my PhD in 1970.

EB: And, what was it like there?

SE: It was great. For my PhD I worked with a fellow named Louis Schanker, which turned out to be a critical decision in terms of my own career. Schanker had worked with B.B. Brodie. I don't know if you know Brodie, but a lot of biomedical scientists today are his descendants. Brodie ran one of the early laboratories at NIH. He had a tremendous breadth of interests in science and pharmacology. He and his group

made seminal contributions in a variety of areas, including drug metabolism and neuropharmacology. Many of the giants in the field of pharmacology trained with Brodie. Do you happen to know Julius Axelrod?

EB: I do.

SE: Axelrod was Brodie's technician who ultimately received his PhD. He was given his own lab at the NIH and ultimately received the Nobel Prize for his work. Arvid Carlsson, another Nobel Laureate, worked in the Brodie lab at one time. Sol Snyder worked with Axelrod during the Brodie era. So Brodie had this huge group at NIH. One member of his laboratory was Lou Schanker, who became quite famous for his work on drug absorption. Schanker, who was originally from Kansas City, was offered a position at the School of Pharmacy there. He arrived at the University of Missouri-Kansas City School of Pharmacy about the same time I entered graduate school. He asked me to join his lab and I was happy to do so. For my PhD, I worked on animal models for studying drug absorption. We published two or three papers in the field. However, I knew I didn't want to stay in the drug absorption area. I was more interested in neuropharmacology.

EB: Why was that?

SE: From what I'd read and people I'd met in the field. It was just an area that interested me more than drug absorption.

EB: Was that the new frontier at the time?

SE: It was developing. You know, I can't point to any one specific reason why it interested me. It just seemed a bit more glamorous and exciting than drug absorption, although I have nothing against drug absorption. It's an important area. Also, I'm sure I was influenced by a couple of other graduate students in school with me at the same time, who were working in neuropharmacology. I was taken by their enthusiasm and the interesting aspects of their work. Anyway, after I was awarded my PhD, Schanker recommended that I do postdoctoral work with Parkhurst Shore, a neuropharmacologist and former colleague of his in the Brodie lab at NIH. At that time Park was a professor at the University of Texas, Southwestern Medical School in the Department of Pharmacology. He was internationally recognized for his work on monoamines. I believe he was one of the original members of the ACNP. In 1970 I went to Dallas and worked with Park for two years. We did some work on drug receptor binding assays, very primitive stuff. One of the more popular topics at the time was finding new ways to identify more precisely the sites of drug action. Axelrod had pioneered the use of radiolabeled drugs and transmitters to address some of these issues. Working with Shore I did some studies with radiolabeled reserpine in an attempt to localize its site of action and

to explain some of its pharmacological properties, such as its prolonged duration of action. Park and I published a number of papers on this topic. One day I was talking with Park and said, "You know, my wife, Colleen, and I would like to spend some time in Europe. Do you think I could do some postdoctoral work over there?" I suggested that I could probably work with Silvio Garattini, who, at that time, was head of the Mario Negri Institute in Milan. I knew Garattini's work and that he and Park were good friends. Park replied, "Well, Silvio is a nice guy and does nice work, but I would recommend you try to get a postdoctoral position at Hoffmann-LaRoche in Basel, Switzerland where they are doing some very interesting studies and have significant resources". Park suggested that I look into working with Alfred Pletscher, who was director of research at Hoffmann-LaRoche at the time. Alfred and Park had become good friends while both were working in the Brodie lab at the NIH. Again you can see how important the Brodie group was to my career development. Park volunteered to write Pletscher to see if they had postdoctoral fellowships at Hoffmann-LaRoche in Basel. Pletscher replied in the affirmative and offered me a position on the strength of Park's recommendation. So, in late 1972, Hoffmann-La Roche flew me, my wife and our newborn to Basel where I worked for the next 18 months as a postdoctoral fellow with Alfred Pletscher.

EB: You were working for a drug company, weren't you?

SE: Yes.

EB: Was there any concern about doing that?

SE: No, because as a postdoctoral fellow my position was quasi-academic. I had no responsibilities with regard to the commercial operations of the company. I could conduct any research that interested me, under the direction of Alfred Pletscher. The people at Hoffmann-La Roche were wonderful and very open. For example, I was allowed to attend scientific sessions covering their commercial research projects where I learned a great deal about drug discovery and development, and the challenges faced by industrial scientists. So, during my time in Basel I learned a bit about the pharmaceutical industry, although that wasn't my objective. My own research in trying to identify sites of drug action continued at Hoffmann-LaRoche. Since at that time Hoffmann-LaRoche was becoming quite wealthy from the benzodiazepines, money for research was virtually unlimited. It was a wonderful time to be there. And, of course, Colleen and I very much enjoyed living in Switzerland and made numerous contacts and friends in Europe, many of whom we still see on a regular basis 30 years later.

EB: Couldn't you do that work in the United States? Did you need to go to Europe?

SE: Oh, no. I could have pursued these studies in the United States. However, we went there because my wife and I wanted to have the European experience and because of the close personal relationship between Park Shore and Alfred Pletscher. After I'd been in Basel for nearly a year I began to make inquiries about obtaining a permanent position back in the States. By the end of my term in Basel I would have been a postdoctoral student for and a half years and, with a growing family, we felt it was time to settle down. I communicated with Park Shore about this and he indicated the difficulties associated with obtaining a job back in the States while working abroad. He suggested I do another post-doc with someone in the States, which would give me an opportunity to investigate permanent job opportunities in a more organized manner. To this end he recommended I get in touch with Sol Snyder, a young faculty member at Johns Hopkins Medical School. I believe this was in 1973. I remember Park saying "This Snyder guy is doing a lot of exciting stuff and you might want to consider working with him to make your re-entry into the States". By coincidence Sol was coming to Strasburg for a meeting I was also attending. Park arranged for Sol and I to get together and we met and discussed his research programs and my interests. At the end of the meeting Sol indicated he would be happy to have me join his group when I completed my stint in Basel.

EB: So, what was exciting about what he was doing?

SE: Well, remember the emphasis of what I had been doing as a post-doc was on the localization of drug sites of action. Sol was gaining notoriety with his development of an assay for identifying the opiate binding site. In the early 1970's, Sol became quite famous, in both the scientific community and among the lay public, for identifying the site of action of opiates in brain. This was universally hailed as a major breakthrough in the field. To achieve this Sol had adapted a radioligand binding technique that had been used by Pedro Cuatrecasas, a faculty colleague of his, for studying the insulin receptor. Sol's findings were considered particularly exciting since they made it possible to localize precisely the sites of action of opiates in the central nervous system. It also made possible a more detailed study of the pharmacological differences among members of this drug class. The receptor binding assays developed by Sol and his lab became very popular tools for both academic and industrial scientists since they are technically simple and yet are powerful for discerning the sites of drug actions and for developing

new drugs. Moreover, this simple technique could generate an enormous amount of important information in a very brief period of time. At the time he and I met in Strasburg, articles were appearing in the New York Times, Time magazine and other lay publications about Sol and his opiate receptor discoveries. While Snyder was a generation behind Park Shore, Park knew him because Snyder had worked with Axelrod, a close friend of Park's from their time together in Brodie's lab. It's all very incestuous. So, thanks to Park's recommendation, and the fact that Sol's lab was attracting a great deal of money, Sol welcomed me to his group. In June 1974 my family and I returned to the States and settled in Baltimore. I spent two years with Sol at Johns Hopkins and they were, without question, the most productive two years of my life. Sol's laboratory was the most dynamic place in the world for neuroscience research. You had this constant feeling that every day something new was being discovered that was really, really important. In addition, Sol is a wonderful leader. He infused in all of us enthusiasm and a sense of excitement about discovery. I couldn't wait to get to the lab each day and I was reluctant to leave in the evening. However, by this time Colleen and I had two small children, Anne and Matt, and I had important obligations to them. This period with Sol is the fondest memory of my professional life, and the most productive time. We used to joke that because the receptor binding assays were so simple we could perform an experiment in the morning and collect the data and write the paper that afternoon. Every experiment yielded something new and exciting. For example, in one series of experiments we examined neurotransmitter receptor binding in brain tissue samples obtained at autopsy from people who had suffered with Alzheimer's, Parkinson's or some other neurodegenerative disease to learn which receptors are missing or over-expressed in these conditions. Such data had important implications with regard to drug therapy. Thus, if a particular receptor is missing from a critical brain region, why administer a drug known to interact with that site? Or, if these receptors are overabundant that may mean there is a lack of this particular transmitter, so some kind of replacement therapy may be appropriate. In short, our work had direct clinical implications which made it all the more exciting. Sol and I co-authored 20 or 30 papers during that two year period. Besides the work, I was fortunate to be in Sol's lab then since it housed so many others who would go on to great careers in the neurosciences. Among my contemporaries in Sol's lab were Henry Yamamura, Ian Creese, David Bylund, Jim Bennett and Gavril Pasternak, all of whom were either pre- or postdoctoral fellows. Junior faculty in the group at that time included Joe Coyle, Mike

Kuhar and Elliott Richelson. Most of these individuals are now members of the ACNP. Having achieved some notoriety because of the number of papers we published, I began receiving invitations to present lectures and seminars at various institutions, to give symposium presentations, and to write book chapters and review articles. As for my area of specialization, this was chosen by Sol who assigned each new member of the team a neurotransmitter receptor. I was assigned GABA, and have remained in the area ever since. There was some logic to this since I had worked at Hoffmann-LaRoche and was aware of the work being conducted in trying to link GABA receptors with the mechanism of action of the benzodiazepines. So I devoted my entire two years at Johns Hopkins to defining the GABA receptor and to developing methods for studying this site.

EB: Is all of that based on a suspicion that was how the benzodiazepines were working?

SE: Well, there were data supporting this hypothesis, but it was indirect.

EB: And, you said, fine? That seemed all right with you?

SE: It didn't matter to me. GABA was clearly an important transmitter substance.

EB: It didn't matter to you?

SE: No, no. Just being in that laboratory was a treat and being the GABA guy was fine. We had a serotonin guy, Jim Bennett, who's a neurologist now at the University of Virginia. Ian Crease, who's now in Newark, was the dopamine guy, David Bylund, who until recently was the chair of Pharmacology at the University of Nebraska, was the β -adrenergic guy, and Hank Yamamura, now at the University of Arizona, the cholinergic muscarinic guy.

EB: Did your work start to have, at this point, some kind of overriding objective? Did you start to think about what you were doing in a broader prospective, what your particular contribution would be?

SE: Yes. I had this GABA assignment and since we were all able to use this new and powerful receptor binding technique, my job was to define the role of this receptor in central nervous system function. There were an endless number of experimental possibilities and leads to follow. Some of the questions being asked included what role does GABA play in epilepsy, in schizophrenia, and in depression? I could pick a disorder and look at it from the standpoint of the neuropathology and the pharmacology, could directly examine to what extent the drugs being used now to treat these conditions interact with the GABA receptor. From these results we could possibly come up with new pharmacological tools to manipulate the GABA system. So at that time my whole life

was focused on finding out how alterations in GABAergic transmission explain some of the symptoms of various conditions. This was particularly exciting because something like 30% to 40% of all neurons in the central nervous system are GABAergic, and another 40% glutamatergic. So, GABA and glutamate are the two most important, quantitatively at least, neurotransmitters in the central nervous system. Because of its widespread distribution, it is likely that every neurological and psychiatric disorder involves GABA in some way as does every drug that's given to treat neurological and psychiatric disorders, if it's administered for a long period of time. So yes, as I said, there were an endless number of possibilities in terms of experiments and every experiment led to a discovery. I mean, that was what was fantastic about this assignment. I was the first person in the world to discover this little factoid, you know, and that's really fun. That is really fun. By 1976 my time at Johns Hopkins was coming to an end and I needed to move on. I had to start earning a decent living to support my family. So I began looking at job opportunities, which were plentiful given Sol's fame and the visibility of our work. Everyone coming out of Sol's lab was eagerly courted by potential employers. I received excellent job offers from industry and academia. My wife and I discussed at length which to pursue. We leaned towards academia because we felt I'd have more freedom. I had all these research ideas. Ultimately we chose to accept a faculty position at the University of Texas, Medical School in Houston. One reason for this was our positive experience living in Dallas and we still had friends in the area. At the time the University of Texas, Medical School at Houston was a new institution. I believe it was established in 1970. Texas was investing a lot of money in medical education. That was a boom time for medical schools, with many beginning operations in the 1960's and 1970's. Because it was still new, there were a lot of young faculty, some of whom were friends and acquaintances from earlier days. The chair of pharmacology was Alan Robison, who had made his reputation at Vanderbilt working on cyclic AMP. Given his background and interests he understood the implications of what I was doing. He and I got along very well. He's a wonderful person. I joined the faculty in Houston as an Assistant Professor in 1976 and was an Associate Professor by 1978, and a full professor by 1980. Since things were going well with my career I was glad we had chosen Houston.

EB: And, you set up your own lab?

SE: Oh, yes. I got my own lab going. I received funding right away. The lab grew and at its peak I probably had about twenty people working there at any given time.

EB: Do you have a lab now?

SE: Yes, but not that size. I have a collaborative research program with another faculty member at the University of Kansas. EB: What do you like about lab work?

SE: Well, the students you work with are one of the most rewarding aspects. I was fortunate to have some outstanding graduate students and post-doctoral fellows. They come up with the greatest ideas and that's the way I learned. Again, the joy in this work is in the pursuit of ideas and the excitement of discovery.

EB: How have students changed over your career?

SE: I don't think they've changed that much. Most individuals coming into pharmacology don't really know what they're getting into, because, as was the case for me, there isn't much exposure to pharmacology in undergraduate work. The students have a vague notion about the discipline and most are more interested in neuroscience than pharmacology. They're attracted by the possibility of studying depression, schizophrenia or Alzheimer's disease since they are familiar with these conditions.

EB: They're interested in neuroscience. What do you find that they think they're going to do? What are they interested in about neuroscience?

SE: I think they're interested in understanding the brain and behavior. I mean, one thing that has changed to some extent is that students are more interested in what is happening at the molecular level than was the case when I first started studying in the area. At that time the emphasis was more biochemical, more behavioral. Now, students are more interested in what is going on at the level of the gene. They can ask questions now that we couldn't when I was in training because of the availability of new tools for studying these issues. And, so, one of the things I do with students is make sure they appreciate the whole picture, from basic molecular biology to behavior since you are limiting yourself if you focus on only one level of inquiry.

EB: Genes?

SE: Yes, they have to know molecular biology. They have to know how to conduct research at the molecular level. But I try to make sure they also appreciate what's happening at the biochemical and the behavioral levels as well because you can manipulate genes all you want, but are missing important insights unless you can phenotype the animal as well. You know, you can over-express or under-express genes quite readily. Unfortunately, for many students today, both inside and outside the neurosciences, the consequences of these manipulations are unknown unless there is an obvious phenotypic change, such

as the head falling off or the whiskers drooping. This is unfortunate because there is a wealth of information to mine from an animal following a genetic manipulation. Some may be very subtle changes, which require an understanding of animal behavior and basic biochemistry to fully appreciate.

EB: Where did you get that perspective from?

SE: Well, that was the way I was trained. At that time one approach to research was to match a behavior, or a physiological response, to a disorder. In this way you'd identify an animal model of a particular condition. Then you'd begin studying what's going on with this animal and how it differs from a normal animal. So, for neuropharmacology, it was the behavior that drove the questions. Now, in many instances the questions are being driven by what can be achieved at the molecular level. What happens if we modify this gene, the expression of this particular protein? What does it mean in terms of brain chemistry or the response to drugs? But, again, I think it's important to ultimately define what it means with respect to behavior, the final end-point for our discipline.

EB: Is that something, in terms of the lab, that's become more specialized or more focused since there isn't as much need for work with the animals?

SE: Well, a lot of it is driven by that and the expense associated with animal studies. Most of the emphasis, however, is driven by the NIH since it provides the funds for research. As the molecular approach gained popularity, as science became more reductionistic, the NIH review panels and committees began directing money to those engaged in this approach. In addition, these review panels became more and more populated with people doing this kind of research, which is perfectly fine since they are best able to judge the quality of this science. But, as more and more money went to support such work then, to maintain your laboratory you had to do these kinds of studies. This, in turn, determined the type of training received by the students. As the number of molecular neuroscientists grew,, the number of those familiar with traditional techniques, such as behavioral and biochemical assay, shrunk, as these approaches were considered old fashioned. Fortunately, this attitude is changing now, with the NIH beginning to appreciate that we're losing this expertise. NIH is funding initiatives now to train more rounded scientists.

EB: Fairly recently, in the last couple of years?

SE: That's right. Having been for many years a department chair I know for a fact there are students who have completed dissertation projects on say the expression and regulation of proteins that are thought to

affect cardiac function, but know little about cardiovascular anatomy and physiology. Many graduate students have never had the need, or the opportunity, to work with an intact animal, to learn how to handle a live rat or mouse, to give an injection. Rather, they spend their entire graduate training working with cell lines. While vital information is obtained from such studies, it is difficult to claim you are a neuropharmacologist or cardiovascular pharmacologist if you have had little or no exposure to the phenotypic changes that occur in intact animals following modifications of these critical organ systems. Pharmacologists, and other biomedical scientists for that matter, must learn to appreciate the inter-relationships among organ systems, a concept that can't be taught or appreciated by focusing only on cell lines. However, because funding for organ system and whole animals studies has diminished over the years, there are fewer experts qualified to teach students these principles. This must change or we will severely compromise our ability to place the results of basic biochemical and molecular studies into a clinically meaningful context.

EB: Knowing that it matters?

SE: In fact it's very critical.

EB: Now, have you done or have you had exposure to clinical work or to working with clinicians?

SE: No, not directly.

EB: But, in your training, you worked a lot with animal behavior and whole systems.

SE: Right.

EB: And, in terms of your sources of funding, how was your lab funded?

SE: Primarily NIH, though I have had Department of Defense (DoD) and National Science Foundation (NSF) funding over the years.

EB: You had DoD funding?

SE: Yes, Air Force funding, funding from private foundations, the Pharma Foundation, small amounts from drug companies. The main source of funding has been the NIH.

EB: And has that been fairly secure over your career?

SE: My funding was quite secure, and in fact continued to improve each year, during the ten years I was on the faculty at the University of Texas Medical School in Houston. Then, in 1986 Sol Snyder, invited me back to Baltimore to be Director of Research for a small biotech company he had founded a few years earlier.

EB: What was his company called?

SE: Nova Pharmaceutical. Not surprisingly, this company was built around the idea of exploiting the receptor binding technique for drug discovery.

It sounded like an interesting opportunity. After all, I'd had some exposure to drug discovery when I was at Hoffmann-LaRoche, although it was very limited. Also, while in Houston I'd spent a great deal of time working as a consultant with many of the major pharmaceutical firms so I had some idea about the challenges faced by the industry, its approach to drug discovery, and its use of the receptor binding technique. I accepted the position at Nova and we moved to Baltimore. Of course, I gave up all of my NIH and other funding when I took this position. I found my experience in industry very stimulating and educational. In some ways the stresses were not different from those associated with my academic appointment. For example, by the time I left Texas in 1986 I needed about \$400,000/year to maintain my laboratory operation. With Nova, I, together with other executives in the company, had to raise millions each year to keep the operation afloat.

EB: You spent some time raising money.

SE: Oh yes. That is a critical part of the job when you are trying to build a company that as yet has no revenue stream from product sales.

EB: Why did you go? You know, were you looking for something different, a different kind of work?

SE: No, I wasn't actively looking at the time. However, I have a great deal of respect for Sol. I knew he would be fun to work with and was certain that anything he was involved in would be interesting. As I said, I had had some modest experience in the industry and thought this would be a chance to be involved in developing new medications. This differed from what I had been doing up to then, with its focus on basic research.

EB: Then, looking again for some practical application for what you are doing?

SE: That was one of the attractions.

EB: At that time, in the mid 1980's, there was a possibility of making a fair amount of money with the drug development opportunities, too?

SE: Yes, those were heady times, when stock options and other financial opportunities were quite abundant. While I was given a nice employment package, there was no guarantee of a financial windfall. The amount I would receive was dependent on how well the company performed. At any rate, the financial possibilities were an attraction, although they were not the main driving force. After all, I was financially secure in my position in Houston. In any event, I returned to Baltimore and worked for Nova. We initiated a number of drug discovery programs and came up with some interesting findings. I enjoyed myself very much.

EB: Did it seem that it would be possible to go back into an academic setting?

- SE: I didn't really think about that. You know, I didn't know what was going to happen in the future. I had enough confidence in myself to feel certain I'd find employment in either academia or industry once the Nova experience ended. I had enough self-confidence that I didn't worry.
- EB: It didn't worry you what would happen if you had to move to another setting?
- SE: No. My experience has been that if you do a good job of whatever you're doing now, tomorrow will take care of itself. Basically, in terms of our current incomes and positions, we all live off of what we accomplished yesterday. The same is true for athletes or any other occupation. You're getting paid for past successes, with the expectation you'll do as well or better tomorrow.
- EB: I failed to bring you back to the same kind of question about the overriding goal for your work. You mentioned a couple of times taking a step back in order to do something more practical, but, also, great excitement about discovering and mapping out steps and just pure excitement about that kind of science. How does that work for you?
- SE: You mean, in terms of a balance between those two, a percentage?
- EB: Some people have always wanted to find a cure for something and that's been the motivator.
- SE: That has not been my primary drive. Over my career the most excitement I've had, was at times when I was conducting basic research. Having an opportunity to develop drugs, being involved directly in the development of drugs that will help people, is also a motivation and is one of the things that I like being involved in, but that hasn't been my primary driving force. Rather, my primary motivation has been curiosity and the exhilaration of being the first person ever to see a significant piece of data. I mentioned that earlier. When you see the data and something works out as predicted, or there is a surprise that all of a sudden clarifies an issue, that's the biggest high a person could have. I'm the first person in the world to know this!
- EB: What's the most exciting thing that you've discovered in your career?
- SE: I've never thought about that. It's all been very exciting and important. It's like asking you to choose among your children. I've done some things that are more or less important, but, I guess, the one thing I take the most pride in is my corpus of work defining the biochemical properties of the GABA receptor system. I was involved in that from the very early days. That's probably what I'm best known for. It is also gratifying to know this early work contributed significantly to major discoveries made by others as, for example, the identification of the mechanism of action of the benzodiazepines, and the studies demonstrating an

involvement of the GABA receptor system in numerous psychiatric disorders. Also, my work helped provide the tools used by others in attempting to develop new classes of therapeutic agents. So I see my work in the bigger picture. That's not to say that these subsequent findings wouldn't have ultimately occurred without my contributions. However, the fact is my work played a role in getting to where we are today in terms of understanding the neurobiological and pharmacological significance of the GABA receptor system. That's what is fun and exciting about my profession, and that's what motivates me to continue with this line of work.

EB: So, you went to Nova?

SE: I went to Nova. I was there for six years. In 1992 Nova was acquired by another company, Scios, which was located in the San Francisco Bay area.

EB: Another biotech company?

SE: Yes. They were interested in some of our chemical leads in the inflammation area. Since they already had their own research director, and I wasn't particularly interested in abandoning my interest in neuroscience, I exercised my option to leave the company. While at the time I had no specific plans regarding my next job, I was asked to interview at a couple of drug companies and at the University of Kansas, Medical School, which is in Kansas City. As Kansas City is our hometown, this opportunity had particular appeal since both my wife and I had family in the area. They asked me to interview for the chair of pharmacology since Ed Walaczek, the individual who had first introduced me to the discipline some 30 years earlier, was stepping down.

EB: Full circle.

SE: So, I accepted the position at the University of Kansas. We had lots of friends and family there and my mother was still alive at that time, as were both of my wife's parents. That was about twelve years ago. We were both pleased to be able to move back home after being gone for nearly 25 years. It was also good from the standpoint of my professional career since it gave me a chance to be a department chair and to grow a department.

EB: You were doing less and less science?

SE: When I took the job as chair in late 1992 I took it with the understanding that I would remain in that position for a maximum of ten years. In my experience, after about eight years most chairs begin to lose their effectiveness since institutional resources are needed for many things, with an established chair and an established department being low on the list of priorities. For example, chair recruitment is an ongoing activity

at most places, with current resources needed to attract qualified candidates for these posts. So, I agreed to the offer with the understanding that I could step down in ten years. At the end of that time I requested release from the Dean who asked me to stay on a bit longer since she had other chairs she wanted to fill first. Finally, after twelve years as chair, I was able to step down and resume my career as a professor. Since I'd gotten off the NIH merry-go-round for six years before returning to academia it was a real challenge attracting funding while taking on new administrative responsibilities. With regard to obtaining grants it was like being a new faculty member again. You have to re-establish your research credentials.

EB: Even though you were Chair?

SE: Oh sure. There are no guarantees for NIH funding. While most people taking a chair bring a funding package and a research team with them, I had to rebuild from scratch while undertaking all of the administrative responsibilities of the position. This included recruiting new faculty, overseeing laboratory renovations, reorganizing the teaching programs, and all the rest. As I was re-entering the academic orbit it was a challenge to find the time to attract outside funding to reconstruct my research program. As I indicated earlier, this was accomplished, in part, by collaborating with some of the faculty I recruited.

EB: Are you still doing that, after you stepped down as Chair?

SE: Yes.

EB: Where do you see your lab going in the next five or ten years?

SE: Our interest now is regulation of receptor expression with regard to a particular kind of GABA receptor. There's a GABA receptor that was discovered about fifteen years ago that we've studied in detail and published extensively on. Because it is unusual in being a heterodimer G protein-coupled receptor, little is known about how it is regulated and expressed. This receptor, termed GABA-B, is very important for normal central nervous system function. It plays a key role in the mediation of pain and emotion, two areas of interest to us. For example, people with chronic pain are often depressed, and depressed individuals seem to be more sensitive to painful stimuli. Women tend to experience pain more than men, and females tend to suffer from depression more than males. This suggests the possibility that hormones may be influencing these processes. What is the relationship between, say, estrogens, GABA-B receptor expression and function and the pain threshold? What effect does chronic pain have on the GABA-B receptor system? Does pharmacologic manipulation of the GABA-B receptor modify the transmission and perception of pain and/or the emotional response to this type

of stimulus? Anyway, our emphasis is on understanding how the regulation of the GABA-B receptor at the molecular level is influenced by, and influences, the perception of pain and the affective component of pain syndromes. Pain is a wonderful vehicle for studying conditions such as anxiety and depression because they appear to be closely related to one another. In the long term I would hope that our work would reveal the role of the GABA-B receptor in mediating pain and the emotional response to it with the aim of developing drugs that could be used to ameliorate these conditions. Does this make sense?

EB: Yes. What was the role of technological innovation in the development of your science?

SE: Indispensible.

EB: Like what?

SE: Being able to manipulate gene expression makes it possible for us to ask questions we couldn't even conceive fifteen or twenty years ago. It has already told us a great deal about the possible function of GABA-B receptors.

EB: In terms of balancing your family life and your work life, you mentioned a lot of moves and shifts in your schedule trying to squeeze in a little bit here or there; how do you balance outside work?

SE: The most important thing is to have a spouse who is understanding and supportive. Also, I don't consider myself a workaholic. I'm not a 24/7 kind of guy when it comes to my work. I believe it is important to have something outside of your work, with the family being the top priority. I've always made it a point to spend time with my family, to spend weekends at home, especially when the kids were young. Moving around has been great for all of us. In fact, I'd recommend it to everyone. There's no better education for children, or for yourself, than living in other countries and other parts of this country. This opens your mind and gives you an opportunity to learn about different cultures. I know our children benefited enormously from the moves but there are times in a child's life when it is more difficult to move. The high school years are especially difficult in this regard. We had to do this in our move to Baltimore in 1986. Our eldest, Anne, was just entering high school at the time. However, she thrived in her new environment. In fact she graduated top in her class. So I think the travel demands of my career were a boon for my family. My wife and I agree our life has been full and interesting. We've met so many people, been to so many places and been involved in so many things. While our children have now moved on with their own lives, they all enjoy traveling. Each has chosen to live

abroad for a time. For them traveling and moving is just a normal part of life.

EB: You have two kids?

SE: Three. Our third, Katie, arrived ten years after the second, so we sort of had two separate families.

EB: Are they scientists, doctors?

SE: My son Matt is a physician. He's in his last year of residency in orthopedic surgery at Brown University. He's the second child. The oldest, Anne, attended Yale as an undergraduate and received an MBA from Stanford. She's in investment banking in the San Francisco area. The youngest, Katie, just graduated from Columbia University in New York and is working at Christie's auction house. Her undergraduate degree is in art history. So, only one of our children pursued a career in a medical field. However, my wife and I were very careful never to push our kids into a career path, preferring instead to have them make decisions in their own way. That's the way I was raised. As my parents taught me, the important thing is to get a sound education and find something you enjoy doing. That's the way we raised our children. They've done their own thing.

EB: Also, it mixes the practical and the desirable.

SE: It's true. We don't know how this art history thing is going to work out, but that's Katie's choice. Katie has many talents. I know she will make a success of any career she chooses.

EB: Actually, I just have a few more questions about your career. Do you have any patents?

SE: No.

EB: You had experience in the academic world and in the private world, where do you think we are with that new science and what role do you want for industry to play in science? What do you think would be ideal as far as a relationship between industry and academia?

SE: You know, I haven't really given it a whole lot of thought. Perhaps the cleanest way to deal with that issue, because of potential conflicts, is to work through foundations. I think industry does have a responsibility to help support basic research in academia because they benefit from it. I'm not as extreme on this as some members of the Congress who believe that all drug companies owe some of their profits to the government because of the work done by the NIH. In terms of drug discovery and development, industry adds quite a bit of value to the overall process.

EB: So, industry adds to the value?

- SE: Yes, right. I don't agree with the philosophy that a company owes compensation to the government because they developed a compound that may have first been discovered at the NIH or some other government laboratory.
- EB: Because it goes the other way?
- SE: Because the company had to risk five hundred million to a billion dollars to develop this agent. Without their willingness to take this financial risk the drug would never have been developed. Indeed, most new chemical agents don't make it through clinical trials. I doubt the government is considering compensating companies for failures.
- EB: You also mentioned that in your career, working in industry, you brought things back to your academic lab.
- SE: Yes, that's right. And most of the companies, the big ones, provide money to foundations or establish their own foundation which provides funds to investigators. Some companies also pay for fellowships to help foster training in the biomedical sciences. In my experience, working as an academic dealing with people in industry, I've found them to be very generous in providing compounds, reagents, and other materials in support of basic research. Obtaining this type of support from industry has become more difficult in recent years, due in large measure to new government and institutional regulations. That's unfortunate. It used to be I could pick up the phone and call a colleague in industry and ask him to send me a sample of a particular compound. He would ship it off the same day. Now you are required to complete a number of forms for both the university and company, and these must be seen and approved by various layers of administrators at both institutions before the compound can be shipped. I've seen this process take up to a year between when the request went out and the material finally arrived in the academic laboratory. I can't help but think it is slowing down science. The process certainly makes me think two or three times about doing a particular experiment if it's going to take that long to get the compound for study. Usually, by that time, I will have moved on to something else.
- EB: Industry has changed too, when you could call up your friend at Lilly and get the compound. Are companies still working that way where they would give their compounds to other scientists to do research?
- SE: Most companies aren't working that way now. You have all this paperwork you have to do; fifteen years ago you didn't have to do that. They were very, very open about it. But, it's a more complex issue now. For example, one thing driving caution on the part of industry is the litigious nature of society. One of the expressions that's sometimes used in this regard is "There are certain skunks you don't want to poke". Say, for

example, you have a successful product and some academic calls to obtain a small sample for some studies. After doing his experiments he reports that this agent shortens lifespan. Now this conclusion may be false, or the experiments performed improperly, but nonetheless you as the manufacturer have to chase down this possibility while at the same time defending yourself in public by assuring consumers the agent is safe if taken as directed. Anyway, it seems to me there was a more collegial nature, a less suspicious nature, between industry and academia twenty years ago.

EB: Do you worry that there's less openness in science than there used to be?

SE: There is no doubt there is less openness among scientists than in earlier years. This is due in part to the fact or the perception that academics and academic institutions have made a lot of money by licensing patents on their discoveries. However, there has always been a certain amount of secrecy among scientists to avoid getting scooped and losing credit for ones discoveries.

EB: And it's still there regardless whether there's money involved or not.

SE: Right.

EB: You're someone who did go to work for a start-up company, that new element in the culture of science; some people who made a lot of money on a risky decision, other people who made less and some who never made a risky decision.

SE: I've known people in all those groups. However, their decision in this regard has not affected my relationship, either personal or professional. Take Sol Snyder for example. Last month I attended a banquet in his honor when he stepped down as chair of the Neuroscience Department at Johns Hopkins. On the day of this dinner the Baltimore Sun published a press release from Hopkins announcing that Sol had donated \$30 million to endow the department. Now, Sol, and his wife Elaine, come from modest backgrounds so the \$30 million isn't inherited money. Rather, Sol achieved financial success through ventures like Nova Pharmaceutical and other activities. His wealth, and the way he made it, hasn't changed my relationship with him, nor to my knowledge has it changed the feelings of others. He always has been, and remains, a highly respected scientist for the work that he's done, his scientific contributions, and now for the financial contribution he has made to support research and training at Hopkins.

EB: I wonder if there are shifts in the questions asked in science because there's money in certain areas and not in others.

SE: Sure. I stated earlier, the willingness of NIH to fund a certain avenue of research drives scientists in that direction. The same applies to commercial research. There are certainly some academics that are focused on working in areas that could potentially make them independently wealthy. However, this approach is difficult to maintain unless your research is supportable by the NIH since such work is costly. It is very difficult for an academic to find outside private investors willing to support work on the chance it may have commercial potential. Academic institutions are also aware of this and looking to exploit it. You'd be hard pressed to find a major academic institution that doesn't have an office dedicated to protecting intellectual property and to commercializing patents generated by members of the faculty. So, academics are being pressured to conduct research that could be of financial benefit to their institution.

EB: As in, *What Is Up With Kansas?*

SE: Did you read that book?

EB: It's a great book, very smart.

SE: To me it was an interesting but misleading book. The author grew up in the neighborhood where I live now, in Mission Hills, Kansas. Anyway, in the book he goes on about how Mission Hills is loaded with people who made their money illicitly. He stated that Mission Hills is now filled with greedy bankers and CEOs who have taken advantage of the masses. He flatly states there are no longer any professionals living in this neighborhood since they have all been driven out by greedy corporate types. Well, I don't consider myself a greedy corporate type, nor do I think my neighbors belong in this category since I have radiologists living in the houses on either side of me, an orthopedic surgeon in the house behind me, a gastroenterologist in the house directly across the street from me, an attorney next door to him, and a neurosurgeon and a cardiologist living in the two houses on the corner of my block. This is only one block in the neighborhood. It's hard for me to believe that all of the physicians and lawyers congregated on my block, leaving the rest of the neighborhood for those greedy CEO's. After reading this section of the book I had to conclude the author was either a liar or he hasn't been back to his neighborhood in decades. Clearly he didn't know what he was talking about. As far as I'm concerned he has no credibility. Unfortunately, most people, like yourself, don't know the facts so you have to take his word for it. With this author that's a mistake.

EB: Sure.

SE: Still, the book presents an interesting idea. It does not seem to be in the best interest of the majority of the people of Kansas to be conservative, and, so, why are they conservative? That's why I talk a lot.

EB: Not much, just for my benefit!

SE: That's fine.

EB: I'm wondering if you have any regrets about your career, decisions you've made, opportunities you missed?

SE: No, no major regrets. I've enjoyed my career. I could probably think of a couple of decisions where I'd like to have a redo but, overall, it's been a fantastic ride. I've been able to travel the world, live in many interesting places, work with intelligent and creative people, and make contributions to society. I've been a faculty member, an executive, and a department chair. What else is there in this line of work? It's like I've been to a fancy buffet and had the opportunity to taste a bit of everything. So, yes, I've had a wonderful time. It's been a great run. I think this is due in large measure to the fact that I received such wise guidance and counsel from my mentors, Drs. Schanker, Shore, Pletscher, and Snyder. These guys really took care of me. They fostered me and my career. They encouraged me and provided support when it was needed. I hope I am remembered as fondly by my own students. I try to guide them to postdoctoral experiences with scientists who are known for their work, but also who are known to care about their students and to have a long-term interest in their careers. In looking back, I can say with confidence I was more blessed than most when it comes to having had supportive mentors.

EB: Do you have a least favorite part of it?

SE: No, I've had people ask me if I preferred industry over academia. Again, it's like choosing between your kids. They're just different, neither better nor worse. They both have their challenges and rewarding aspects. I do dislike bureaucracies, but that's the same whether you're in a commercial enterprise or an academic institution. A lot of what we were talking about in terms of the problems with science can be traced to bureaucratic problems.

EB: Right, or fund raising?

SE: That's a necessary evil in all lines of work. I served for twelve years on NIH study sections, three different study sections. I've reviewed grants and been on many site visits. There is no question the process is cumbersome and can be flawed and unfair. However, I still believe the peer review system is important for maintaining high standards and for identifying the most important work. If you can't get the funding, if your ideas are not fundable, if people are not finding them interesting, then you need to change direction. That's the way the system works. It's Darwinian.

EB: Anything we should have talked about that we haven't covered?

SE: Not that I know of.
EB: Good. Excellent!
SE: Okay.
EB: All right. Thank you.
SE: Thank you very much.

HANS CHRISTIAN FIBIGER

**Interviewed by Thomas A. Ban
San Juan, Puerto Rico, December 8, 2003**

TB: This will be an interview with Dr. Hans Christian Fibiger* for the archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the college in San Juan. It is December 8, 2003. I am Thomas Ban. If you could start from the very beginning and tell us something about where you were born, something about your education?

HF: I was born in Copenhagen in 1943 and spent the first five years of my life in that beautiful city. My parents decided to move to Canada in 1948, probably primarily because my father had five sisters in Copenhagen that he needed to get away from! But, seriously, my parents always told me the reason for moving to Canada was that they felt the future for the kids would be better in Canada than it might have been in Denmark. And, as I think back on it, it was the right move for me, for my sisters and brothers. So in 1948 we got on a big ship in Sweden and made the trip across the Atlantic and landed in New York. Then, we took a train to Montreal, another train from Montreal to Vancouver, and ultimately ended up in beautiful Victoria, British Columbia. That is where I spent my youth and went to school. We had a lovely home. Victoria is one of the most beautiful cities in North America, and I had an absolutely idyllic childhood. I continued my studies at the University of Victoria where I enrolled in 1960 and, unfortunately, did not graduate until 1966. I spent six years as an undergraduate because I kept changing my mind about what I wanted to do in life. My parents told me I had always been good at math and, therefore, I should become a chartered accountant. As I looked into that opportunity, I decided quickly that wasn't the right life for me. I started to read Freud as a high school student. I became very, very interested early on in the human mind and trying to understand its dynamics. And like so many other people in that era, the more I thought and read about it, the more it became evident that the key to understanding the mind was to understand the biology of the human brain. So during my undergraduate training, I eventually shifted to major in psychology and chemistry and graduated with honors in 1966. I then wanted to go to graduate school, applied to a number of places, and finally decided to accept an offer at Princeton. That turned out to be a very good experience for me as well. At the time I arrived in Princeton I was interested in physiological psychology but the advisor I ended up

* Hans Christian Fibiger was born in Copenhagen, Denmark in 1943.

with was a person who had nothing to do with physiological psychology. He studied infant-mother interactions, and so I spent a good part of the first year behind one-way mirrors watching mothers and infants interact and scoring various dimensions of their behavior. Then there was an opportunity that came up in the Department of Psychology to work with Dr. Byron Campbell who suddenly received a very large grant in psychopharmacology from the National Institutes of Mental Health, and was looking for new graduate students. I quickly knocked on his door and asked whether he would consider me to work in his lab. He graciously agreed, and I ended up spending the next three years with him. I took a year off from graduate school, tragically, because I had a young brother who, at the age of 16, died of leukemia. But I went back to Princeton and completed my degree in what was essentially psychopharmacology in 1970. I had a very good experience at Princeton and made some great friends while there.

TB: Could you tell us something about the research you did with Byron Campbell?

HF: We were studying the effects of psychoactive agents on rat behavior as a function of age; it was developmental neuropsychopharmacology. Dr. Campbell had an interest for a long time in developmental biology from a behavioral perspective, but it was an area of research he himself did not know much about. So we learned together and, perhaps through no choice of his own, he let the students train each other, which was a great way to learn I came to understand.

In 1970 I left Princeton and accepted a post-doctoral position in Vancouver to work with Drs. Patrick and Edie McGeer, who were two very well-renowned neurochemists in the Department of Psychiatry at the University of British Columbia. I also planned to spend half my time with a neuropsychologist, Dr. Harry Klonoff. It was meant to be a joint post-doctoral experience that was funded by the Medical Research Council of Canada. With Dr. Klonoff I was involved in studies that applied neuropsychological batteries to individuals with schizophrenia. We published one of the very first papers on a neuropsychological assessment using standardized tests in patients with schizophrenia. That field has grown and expanded enormously, but this was back in 1970. I remember having heated debates with Dr. Klonoff about whether the reduced test scores really reflected true cognitive deficits as opposed to an inability of these patients to attend to or stay with the test we administered. The deficits were very broad and not specific. Subsequent events have shown that the cognitive deficits are not just an artifact of a psychotic process, but a true core feature of

schizophrenia. I think back fondly on the debates I used to have with Dr. Klonoff about that.

TB: What tests did you use for measuring cognitive deficit?

HF: What we used at the time were conventional neuropsychological tests, like the Benton visual retention test, various subtests of the Wexler intelligence scale, etc.

TB: Didn't you use conditional reflex measures?

HF: We didn't; we used just neuropsychological tests. I did, with Dr. Klonoff, one of the first studies on the neuropsychological effects of marijuana. This was during the height of the "marijuana period" in North America. We did an interesting study on how people performed after smoking marijuana in a simulated driving test. That study was placebo controlled. The subjects would smoke either marijuana or marijuana from which THC had been removed. As one might expect, there were adverse effects on cognitive function. It was interesting to see the number of people who reported getting high when they smoked the placebo. That was a lot of fun.

Most of my time in Vancouver during my post-doc, however, was spent with Pat and Edie McGeer. We did a lot of interesting work together. The McGeers were focused on analyzing human brains postmortem and looking at the activity of various neurotransmitter synthesising enzymes. They were interested in Alzheimer's and Parkinson's disease. We would obtain fresh brain tissue by an arrangement with the coroner in Vancouver. I remember that we would go and harvest these brains whenever we got a call, in the middle of the night or some other part of the day. We had to get the brains quickly to the lab, put them immediately on ice, dissect them, and run the neurochemical assays. I think we were one of the first labs to show that there was a decrease in choline acetyl transferase activity in the brains of people with Alzheimer's disease. We confirmed the classical studies showing that dopaminergic neurons were damaged in Parkinson's disease and we conducted a lot of animal work during that period. I also studied axonal transport in the central nervous system by injecting microliter quantities of radio-labeled amino acids which could be incorporated into the cell, synthesized into proteins and transported up the axon to the nerve terminals. I did this experiment after hours because Pat McGeer thought it was "a crazy idea." When the data worked out extremely well, and I showed him the data he became very interested and wanted to be a co-author on the paper. What I learned from that experience was to trust my students and let them follow their instincts. The young, untrained, creative brain often comes up with ideas that those of us who have been

indoctrinated for longer periods of time wouldn't think of. I have always managed my students that way and gave them probably more room to operate than others did. It didn't work for every student, some needed more guidance than others. But I always tried to provide as much freedom as they could handle because of my own personal experience as a post-doc pursuing ideas my advisors told me not to, but which worked out well.

After my post-doc with Klonoff and the McGeers, I applied for a Medical Research Council scholarship in Canada. I was offered a position to stay in Vancouver as an Assistant Professor in the Division of Neurological Sciences, which was in the Department of Psychiatry at UBC. I got my own lab space, and was very lucky to get an MRC scholarship that supported my salary for five years. I also was successful in getting funding for my first grant application. That was the initial period of 27 years as a professor at the University of British Columbia.

TB: What was your first research grant for?

HF: The first grant was to pursue further studies on axonal transport in the central nervous system. But I soon hooked up with a person who turned out to be a long-term friend and colleague, Tony Phillips, who had just joined the Department of Psychology. Tony's interest was in studying brain stimulation and reward mechanisms. He was able to show that by implanting electrodes in certain regions of the brain animals will work to stimulate that part with small electrical currents. That was the area Tony focused on while I was becoming more and more interested, as an independent investigator, in pursuing the neurochemistry of learning and reinforcement. Tony and I partnered to do some studies into the neurochemistry, neuropharmacology and neuroanatomy of brain stimulation and reward. We submitted some joint grant applications and began a very productive and successful long-term collaboration which lasted about 25 years.

TB: Wasn't that area of research opened up by James Olds with his findings at McGill.

HF: Yes. We used the technique developed by Olds. It was an area of research Tony had a great interest and expertise in. I had become very interested in intravenous self-administration of drugs as a tool to understand addiction and received a grant from a Canadian funding agency created by concern about illicit drug use. I was very lucky to get that grant to study the biology of addiction. It fit very nicely into the work I was doing with Tony Phillips on brain reward mechanisms from an intracranial self-stimulation perspective. An early result of that work was the discovery made by David Roberts, the first graduate student in my

laboratory, that the nucleus accumbens is a key structure in the brain that mediates the reinforcing effects of cocaine. Now we all know that today, it is well accepted and understood. Dave's work in my laboratory was the place where all that started. We had animals self-administer cocaine, and would make very selective 6-hydroxydopamine lesions in the nucleus accumbens and other areas to study what effect they would have on the cocaine self administration. To our amazement and delight it turned out that if you destroy the dopamine terminals in the nucleus accumbens, animals stop taking cocaine, even though they took it before. It's as if they lost interest in cocaine. That discovery has spawned a whole industry in academic research, which is still going on today. But I feel very proud and pleased that work started in my laboratory. We opened up this new field which was something we felt very good about. Dave Roberts, who is now a professor in North Carolina, and still working in that area, deserves a lot of credit for having done that outstanding research. So that was one of the things that we did. We did many, many other things as well. My laboratory in Vancouver became a place for interdisciplinary research. We did a lot of work in neuroanatomy during which we studied the anatomy of the extrapyramidal nervous system using emerging new techniques dependent on axonal transport. My previous interest in axonal transport fit nicely with that new technology. We got more and more into immunohistochemistry and all the modern tracing techniques that exist in neuroanatomy. So we had a long studying the detailed connections of the extrapyramidal system. We also were amongst the first to map the distribution of cholinergic neurons in the brain. It culminated in a very big review paper that I published in *Brain Research Reviews* in which I synthesized the research findings in this field. I think that was a useful contribution. There were many other labs working in the same area and I think we helped define the anatomy of central cholinergic neurons which have become of interest because of their role in Alzheimer's disease and in arousal function. We became very interested in understanding the role of the locus ceruleus, a noradrenergic nucleus that sends projections widely through the forebrain and has descending projections to the spinal cord. We did a lot of work trying to understand the role of those projections on behavior. I think that was very important research. There was a big debate at the time in which Larry Stein, a member of this College, and I were involved. Larry felt that the noradrenergic system coming out of the locus ceruleus was a very important reward-related system, and we had a heavy debate about that. I think history has shown Larry was wrong; that the locus ceruleus is not significantly

involved in reward mechanisms. Now we know, partly on the basis of our work and partly on the work of many others, that the mesolimbic dopamine system, starting in the ventral tegmental area and enervating the nucleus accumbens, is the key component of the neural circuitry of reward. The other work we did on the locus ceruleus and the so-called dorsal noradrenergic bundle got me involved in my first, and hopefully last, case of scientific fraud in my laboratory. I had what looked to be a profoundly gifted student whose name was Steve Mason, who received his PhD. with Susan Iverson in Cambridge. He came to my lab to do a post-doc. Unfortunately, it turned out that Steve Mason published some data that couldn't be replicated. After he left my lab, I spent part of the next three years publishing retractions and redoing many of the experiments. In those days it wasn't as big a deal as it is today. Today, and rightfully so, scientific fraud is something the scientific community takes much more seriously than it did 20 years ago. But that was a very disturbing period that we had to try to clean up. And, of course, I did my very best after that to make sure that Steve Mason never got a job again in science. My view of scientific fraud is that that is the capital crime of our business. It deserves capital punishment, meaning you don't work in science again.

After that period, we did a lot of neurochemistry. We were among the first to get into brain microdialysis in a big way where we could study neurotransmitter release in awake animals. We did some really nice studies showing that you can actually study neurotransmitter release in animals that are performing different tasks. One of the most enjoyable experiments we did was to look at dopamine release in the nucleus accumbens during various stages of sexual behavior in male rats. You could watch dopamine release in the nucleus accumbens go up a little bit when a female was introduced into an environment close to the male, and then as they started to copulate, dopamine release would shoot up, showing that this was not just a system cocaine works on, but has something to do with mediating natural reinforcers. We did similar kinds of work with food intake. We also did a whole lot of interesting pharmacological experiments looking at acetylcholine release using microdialysis. That provided us with useful information about what acetylcholine is doing in the brain during different kinds of behavior. It also told us a lot about how you can pharmacologically manipulate central cholinergic neurons.

The last thing that I'll mention in terms of work we did at UBC was concerned with immediate early genes and, as always, it was something one of my students brought in. He was a new post-doc whose name

is George Robertson. George had become, as a graduate student at Dalhousie University, very interested in immediate early genes, such as c-Fos. He was interested in continuing some of that work in my lab, and I have to admit that before I met George I practically knew nothing about immediate early genes. This was an area that was exploding at the time, but an area I had not personally followed. I tried, as usual, to give my students as much freedom to follow their interests as long as I could be convinced it was worthwhile. And George certainly had. I didn't need much convincing. So what we started to do with this technique was to study the activity of central neurons as reflected by the extent to which they were expressed in c-Fos. With this immediate early gene, you can see changes in either messenger RNA or protein very quickly in neurons activated by some sensory or pharmacological stimulus. We used early gene expression to do a functional mapping of the brain in many different circumstances. One of the things we did was to place animals in environments that caused a lot of anxiety because they had been foot shocked in that environment before. It was amazing to see that when the animals were returned they were obviously stressed by being back in that environment. You could see the neural circuitry involved light up. We mapped that out and defined some of the circuitry. That nice work was done by a colleague, Charles Beck, a professor from the University of Alberta in Edmonton, who spent a sabbatical in my department. One of the really interesting things that George had done was to map the distribution of neurons in the forebrain that are activated *in vivo* by antipsychotic drugs. We could show very nicely that atypical antipsychotics activated a different set of neurons to a significant extent than did typical neuroleptic agents. That work has now been confirmed by many other labs.

TB: Was there any overlap between atypical and typical neuroleptics?

HF: There was some overlap. But the bottom line is that whereas the typical neuroleptic agents targeted the striatum as much as the nucleus accumbens, the atypicals are much more active in the nucleus accumbens, which is quite consistent with their lack of extrapyramidal side effects that are mediated in the striatum. We also showed other differences as well. So the atypicals clearly had a different signature in the brain than do the typicals. This has now become a technique used in the pharmaceutical industry as an assay to guide drug discovery.

TB: Is it used for the screening of new atypical drugs?

HF: Right. We did a lot of other work with immediate early genes, but those were a couple of the highlights, I think.

TB: Wasn't some other work going on with early genes about the same time?

HF: Yes. The immediate early gene work we did was not unique. We didn't discover this technique, but we applied it in interesting ways. And we were amongst the first to understand how you could use this technique to map, in great detail, the activity of neurons in the brain.

Another comment I would make is that, in my experience, every laboratory goes through great periods and not so great periods; over 25 years my lab went through some absolutely fabulous periods and produced some very innovative science.

TB: What year did you become an independent investigator?

HF: I started as an independent investigator in 1972.

TB: How long did you stay at UBC?

HF: Until 1998, so it was 26 years. In 1998 I had an offer to become Vice-president of Neuroscience at Eli Lilly and Company. That was a very difficult decision. My lab was still well funded and we were still doing lots of interesting work. But the question I asked myself at the time was how good would I be at doing something else. And one thing that happened during those 26 years, almost inevitably, was that I wasn't as excited about what I was doing as when I was getting started. The arrival is not as interesting as the journey. I had been Acting Head of the Department of Psychiatry for about three years; that taught me I did not want to be an academic administrator. I could have considered in Vancouver become vice-president of research or something like that but I wasn't really interested.

TB: When was this?

HF: I acted as head of psychiatry on two occasions for about 1 ½ years each. It was in the 80s and 90s that I did this. I enjoyed it, but it was not something I wanted to do. The problem with academic administration is that you have responsibilities without real authority. That's not a good equation. If there are tenured professors who are not pulling their weight or who have gone out to pasture there is very little you can do because, in the Canadian system, salaries are paid by the university, so they are not dependent on grant funding at all. Persuasion is OK, but it's not a very effective tool to make things happen. So this opportunity at Lilly came along. I got a call from David Leander, a very senior behavioral pharmacologist at Lilly, who told me they were looking for a Vice-president of Research and asked would I be interested. I initially said no, I hadn't even thought about moving to industry. Then, we had some additional conversations. He finally convinced me to visit Indianapolis and I liked what I saw. There was a terrific group of people at Lilly. The other thing that was happening was my own lab was moving more and

more into molecular neurobiology and what I wanted to do was very expensive.

TB: What kind of molecular neurobiology did you want to do?

HF: I wanted to study transcript profiling in primates, because the primate brain is very different from the rodent brain, and I wanted to understand something about gene expression in primates.

TB: Early gene expression?

HF: Right. Using transcript profiling, performed with chip technologies, like affymetrix chips. But it was terribly expensive to do and probably beyond what one could do in Canada in terms of the level of funding one can get. I discovered, as I visited Lilly, that a company of that size has incredible resources. We could start to do that kind of research, so it was very attractive and I decide to go to Lilly and try my hand at running a very big organization. Lilly Neuroscience had a research site at headquarters in Indianapolis and a research site just outside of London in a place called Earl Wood, so it was an international operation. Still, it was a very difficult decision. I think anybody who makes the jump from academia to industry always wonders if they're doing the right thing, particularly when their academic life is going just fine.

TB: It made it possible for you to do what you wanted to do.

HF: Oh, absolutely, and as I said, it would have been hard to get the money to do what I wanted in Canada. Eventually, after going to Lilly, we did those experiments. They were very expensive, but we did them. It was tough moving from Vancouver, which is probably the most beautiful city in North America, to Indianapolis, which is a pretty plain vanilla town in the Midwest. But Lilly was a great company and I had a terrific time there. My family enjoyed it in Indianapolis and my kids were in a wonderful school. I have never regretted the decision to try my hand at industry. It was a great time, and I'm glad I did it. In the last last two months I left Lilly for an absolutely wonderful opportunity to join Amgen, the largest biotech company in the world, and certainly the world's most successful. Amgen called me earlier this year and asked if I would like to come to Thousand Oaks in California to head up a new neuroscience department. The goal at Amgen is for me to build neuroscience into a very powerful force in discovery. I went for a couple of reasons. It wasn't I was in any way unhappy at Lilly. There were some things I didn't like but the overwhelming reason for going was to have a chance to build something in a company that has absolutely outstanding leadership, has lots of resources, and do something different. Hopefully, five or seven years from now I will be able to look back on my time at Amgen and feel that I built something unique and very good; that's certainly my goal.

TB: Before moving into that could you tell us more about what you did at Lilly? I understood you did some research in early gene expression. What else did you do and how did your research in early gene expression translate into the development of new drugs?

HF: Well, that's a very good question, Tom. Most of what I did at Lilly was manage a big organization, to make sure that Lilly Neuroscience continued to be very productive, and to try to put new molecules into the clinic. We were very successful at doing that. It was a very productive period in my life. In the gene expression study we tried to understand whether one can use gene expression to identify new targets for the treatment of psychiatric disorders. We would treat monkeys with phencyclidine chronically, which is supposed to be a good model for schizophrenia, or treat them with amphetamine which produces psychosis and then we looked at how gene expression was changed. We were interested to see whether we could use early gene expression as targets to identify new treatments of schizophrenia. It turns out that the answer is no. The difficulty is that there are so many changes as a result of these treatments and these vary by brain region. Gene expression may go up in the frontal cortex and down in the amygdala. What are you supposed to do with that information?

TB: When we worked with phencyclidine, in the late 1950s, we found that in different doses it also induced different psychopathologies in patients with different diagnoses.

HF: You can't deal with that. And even a place like Lilly, with all the resources you couldn't run proper dose response studies in that situation. Nevertheless, we had to do those studies to decide whether our approach was useful or not. The conclusion I reached was that it wasn't a useful approach to for identifying suitable drugs for the treatment of schizophrenia. Some people probably are still doing the kind of work we did, but I don't see it as being particularly useful for identifying new targets in the brain for treatment. Most of my work at Lilly was to try to manage a big portfolio and recruit new talent. Olanzapine (Zyprexa) was discovered in Lilly's facility at Earl Wood, in the United Kingdom. They were very proud of that but what I inherited was a group who had been sitting on their laurels for 15 years, saying don't forget we discovered olanzapine. That was OK for a while but sooner or later I had to get that organization to be more productive. So I changed the leadership and brought in new people; now it's a very good organization.

TB: So, olanzapine was discovered before you joined Lilly?

HF: It was discovered back in the mid 1980s.

TB: Structurally where did olanzapine come from?

- HF: Olanzapine is a derivative of clozapine. It's a very similar structure. The advantage is that pharmacologically it's much more potent than clozapine, so you can give much lower doses. And because of the much lower doses, you don't get agranulocytosis.
- TB: It's a great advantage.
- HF: Oh, absolutely.
- TB: So the starting point was clozapine?
- HF: Clozapine was the starting point for olanzapine. I think what they were asking at the time it was developed was whether they could change the molecule in some minor way to maintain the therapeutic profile of clozapine without risking agranulocytosis. Lilly was successful with in doing that and the rest is history. Zyprexa will probably sell four billion dollars this year.
- TB: A very successful drug.
- HF: Right.
- TB: In your new job your task will be to set up and organize a new institute. Looking back at your career it was a kind of step aside to become acting chair of a department of psychiatry.
- HF: Why did I accept the acting chair?
- TB: Yes.
- HF: Probably because there wasn't anybody more qualified to do it. The Department of Psychiatry at Vancouver was not a strong department. The Division of Neurological Sciences within that department was very strong and had people like Pat and Edie McGeer, Juhn Wada, and Judah Quastel, very strong basic scientists.
- TB: I hadn't realized you had Judah Quastel.
- HF: Judah Quastel had retired from McGill when he came to UBC, but he was one of those people who had no intention of slowing down just because he reached retirement age, and he continued to do some very good work in Vancouver.
- TB: With hindsight do you think you were successful as acting chair in a clinical department?
- HF: I think I was; everybody was pleased with the administrative work I did there. It was one of these rare cases when a non-physician ends up being head of a clinical department.
- TB: Actually, there were several heads of psychiatry departments in Canada who were not psychiatrists.
- HF: One of them is Glen Baker, who is head of the department in Edmonton.
- TB: It seems that most of the non-psychiatrist heads do just as well if not better than the psychiatrists. Do you think you had an impact on transforming the profile of the department of psychiatry?

HF: I think I did. I clearly turned the department more biological. But I think the whole field was going through a movement towards more biology. It wasn't anything I was doing out of the ordinary, but we did recruit during my tenure some very good psychiatric researchers. Probably the best of them was Peter Little, a superb clinical investigator in schizophrenia. He left unfortunately and went back to England. We recruited some good people there during my tenure.

TB: Did you also recruit some good people to Eli Lilly?

HF: I recruited some wonderful people to Lilly.

TB: Would you like to name some of them?

HF: We recruited Ian Reagan, who headed up the new Earl Wood site. We recruited Beth Hoffman, who is an outstanding molecular biologist. We recruited Calpana Merchant just at the end of my tenure from Pharmacia. She's a terrific scientist. We also recruited George Nomikos, who has done some great microdialysis work, and Yang, a very gifted electrophysiologist. Both, Nomikos and Yang worked with me in Vancouver.

TB: You obviously trained a lot of people. Would you like to mention a few?

HF: I had many, many graduate students. I'm worried about doing this, because I'm a afraid I will miss some of them. I think I have already mentioned David Roberts, Jim Nagy, Bill Staines and George Robertson. I must have had 30 or 40 graduate students or post-docs during my academic career. I paid a lot of attention of trying to be a good mentor. I took the task of training graduate students or post-docs very seriously. And I think, in the vast majority of the cases, I launched them into a good career.

TB: Did I understand you correctly that in your new position, you are expected to build a research institute?

HF: Yes.

TB: From scratch?

HF: Not from scratch. Amgen has about 50 people in its neuroscience department, and my goal is probably to build that to a group of between 200 and 300 people over the next five years.

TB: What will you expect them to do?

HF: They will discover breakthrough therapeutics.

TB: Clinically more selective and effective drugs?

HF: That's the challenge. What I want to try to do is something different than what most pharma companies do. The sad fact is that the current business model the pharmaceutical industry uses is not viable. Companies cannot discover and develop drugs quickly enough to meet the goals that investors expect. If you want to grow the value of your company by 15% a year, which is what Wall Street would like to see, nobody

is able to discover and develop drugs, quickly enough to meet that target. As we speak, Bristol-Meyers is in huge trouble, Merck is on its knees, Schering, I don't know what they're going to do, they're in terrible shape. Among all of them I would say Lilly right now probably has the best pipeline.

TB: So, Lilly is OK?

HF: But also Lilly has got a huge problem starting in 2010, because in 2011 it will lose Zyprexa, a loss of between four and six billion dollars a year. That's the expectation. And Lilly, right now, hasn't the ability to make up for that loss in terms of new innovative products. And this is true across the industry. R&D and other expenses have been going up and productivity, in terms of new launched molecules is going down. The investment is not producing what we had hoped. There are many reasons for that. It's a very complex issue. The bottom line is that the current business model is not viable. What I'm working very hard on right now is to try to think about how we can create a new model, how to come up with new approaches to developing novel therapeutics for important human diseases that will sustain the growth companies need. It's a very, very complex question and I don't have all the answers.

TB: Would the field of psychotropics that had clinical end-points with better predictive validity help?

HF: It would help. I believe society is willing to pay for true innovation. And I think they are willing to pay for a medication that you can say in advance is going to work for the patient. So the dream for the future is the genotype. You determine, on the basis of the genotype, that there is a very high probability the medication will work or will not work for this particular patient. So don't waste time and money giving the drug to somebody for whom it is not going to be effective. We have seen the first example of that in the treatment of breast cancer. That's the future. And society, I think, will be more than happy to pay for those kinds of advances. But it requires a combination of diagnostics and therapeutics, and most companies are not doing that.

TB: Do you think genotyping will be the answer?

HF: I'd be in a much better position to answer that question a year from now, because I am working through these kinds of questions. And what I have to decide is where Amgen neuroscience is going to place its bets. We will certainly do some work in neuropsychiatry.

TB: Glad to hear that.

HF: But I think one of the good things about this meeting, is that I'm starting to see some changes I've been advocating for a long time. There is more and more discussion today about how schizophrenia is not a

useful concept for research. It's too vague. The way that DSM describes schizophrenia, as somebody pointed out at this meeting, is that you can have two patients with schizophrenia who essentially don't share any symptoms. That may be OK for clinical practice because it doesn't make any difference. We don't have any differential treatments right now anyway. Remember the old story about schizophrenia being the graveyard of neuropathology. Schizophrenia will be the graveyard of molecular biology. It will be the graveyard of imaging. It will be the graveyard of any technology that you try to apply to it, because it is simply too diffuse a concept to be useful for research and development purposes. Now what is happening at this meeting, which is very encouraging, is that people are starting to take this idea of endophenotypes seriously. So let's focus on the cognition of schizophrenia. Let's focus on positive symptoms of schizophrenia. The biology of those things, are going to be different and therefore the medications are going to be different. It's interesting that the pharmaceutical industry is still trying to kind of grapple with this. There is the mantra over the last few years that we need to develop very potent, very selective compounds, and these compounds will be a good treatment for depression, for example. I don't think that's going to be true. I think it might be that very potent, very selective compounds might be good for treating one aspect of this thing we call depression, but not the whole thing. And maybe the reason that SSRIs have been so successful is that there is only one target for SSRIs, the serotonin transporter. But, remember, there are 17 serotonin receptors whose activity is being impacted by that SSRI. So, in fact, an SSRI, is a very "dirty" drug because its immediate post-synaptic consequences are mediated by at least 17 receptors that we know about.

TB: Now, before closing, is there anything else you would like to add?

HF: No.

TB: I have one more question. Could say something about the ACNP? When did you become a member?

HF: I joined ACNP very early in my career. I felt very privileged to get into the ACNP. I think I must have been one of the very few Canadians who were accepted for membership, and I think I was accepted in 1976, 18 years ago. And I think I have attended just about every meeting since then. Without question, if I could only go to one meeting every year, it would be the annual meeting of the ACNP. I had the privilege of serving as the journal editor for Neuropsychopharmacology for a few years. Unfortunately, I had to give that up when I joined industry. But I enjoyed doing that very much, and I was honored to contribute in that way. And I've been on Council for the last three years. Today, in fact, is my last

Council meeting. And that's been a lot of fun too. So, I felt very close to the College and I've, without exception, enjoyed my interactions.

TB: Just one additional question; what would you like to see happen in the neurosciences in the future?

HF: Probably exactly what we just talked about a minute ago. Let's get rid of these useless concepts or syndromes, useless for research purposes. Let's start focusing on endophenotypes. Hopefully, we'll have better luck there. Let's start treating patients for their specific symptoms, so maybe this kind of medication for psychosis, this kind of medication for cognition, a different kind of medication for negative symptoms, etc. If we can genotype patients so the physician can be helped in understanding what will be in the best interest of his patient that would be a wonderful step forward.

TB: Well, on this note we should conclude this interview. Thank you very much.

HF: It's a pleasure. Thank you.

ALAN FRAZER

Interviewed by Stephen H. Koslow
Scottsdale, Arizona, December 9, 2008

SK: We're doing an interview right now with Dr. Alan Frazer.* It is December 9, 2008. We're in Scottsdale, Arizona at the Annual Meeting of the American College of Neuropsychopharmacology. Dr. Frazer is currently the Secretary of the ACNP and is doing a marvelous job, but I'll let him tell you about the rest through questions and answers. Good morning, Dr. Frazer.

AF: Good morning, Dr. Koslow.

SK: I think we need to start at the beginning. So, where were you born?

AF: I was born in Philadelphia, Pennsylvania in 1943 in a hospital.

SK: Excellent, a good place to do that. What would you say were significant events in your childhood that led you to take this career of Neuropsychopharmacological Research?

AF: Somewhere around eleven, twelve or thirteen, I read a book called *The Microbe Hunters*. I believe it was by somebody named De Kruif and, clearly, in retrospect, it just fascinated me. It was mostly about microbiology and the people who made the discoveries of many of the bacteria that were causing diseases. I thought it was so neat, the way they lived their lives. Fortunately, I guess, even at that time, science classes in mid-level school and high school seemed fairly easy to me, so that combination made me think about a career in biomedical science. I didn't know what area of biomedical science, but I was stimulated by that book and, then continued in that vein.

SK: So, you sort of came into being at the time when drugs first started to be used for mental illnesses? Did your training occur in any unique way that brought you into psychopharmacology, or did you, at first, take a broader approach to education? Where were you educated?

AF: A good question. Based on this idea that I wanted something in, perhaps, biomedical science, I went to the Philadelphia College of Pharmacy and Science for my undergraduate degree, which was in chemistry, not in pharmacy. One of the advantages of being in that school was, at that time, and perhaps even today, it was the only undergraduate school that had pharmacology as a discipline in a pharmacy school. Although I couldn't take pharmacology as a chemistry major; I was able to modify my curriculum in a way that allowed me at least to take physiology. Clearly, the best lecturer at that school was the chairman of the pharmacology department, G. Victor Rossi. And, while I didn't take a

* Alan Frazer was born in Philadelphia, Pennsylvania in 1943.

pharmacology class with him, I was able to do undergraduate research under his tutelage on LSD and I thought that was pretty neat. So, at that point, I decided to go for a doctorate in the biomedical sciences. I had taken by then biochemistry and physiology but I thought that pharmacology sounded like a pretty neat discipline and decided to get a PhD in pharmacology. I applied to a number of schools and got accepted into the University of Pennsylvania. Again, being from Philadelphia, it was easy for me to go there. So, I went to Penn, which is where I got my degree in pharmacology, but nothing dealing with brain function. My thesis work had to do with the effects of thyroid hormone on the heart.

SK: That's a big jump from the heart to the brain. What was the significant event that got you working on the brain and on the effects of drugs on the brain?

AF: I thought you'd never ask! The significant event was that I had a post-doc position lined up for Mass General at Harvard with an eminent biochemist whose research, if you want to put it into a clinical perspective, was cancer. I was planning to start in the late spring of 1969, but I had married in 1968 and as soon as I returned from my honeymoon my father was diagnosed with cancer. It was pretty bad colon cancer. It had metastasized and it was clear he was not going to make it. I was an only son, who just got married and here was my mother living in Philadelphia, with her husband in a very difficult situation. I felt very uncomfortable leaving the city at that time. So, I made a decision. I called the scientist in Boston, who was going to be my post doc mentor and explained the situation. He was a real gentleman and understood completely, even though he had held a project for eight months for me. I told my graduate student mentor that I wanted to stay in the city and if she heard of any available job to let me know. Shortly thereafter, a young man came around who had been hired to develop an affective diseases research unit in the department of psychiatry at Penn and said he wanted a PhD scientist who could help them with analytical methodology to measure things in patients, and also develop a pre-clinical component to his program. I asked my mentor if she knew anybody and she said she did. And I remember saying to her, I don't know anything about the brain and she said, you don't know anything about cancer either, but you're a scientist and you will do okay. And that's how I got into neuropsychopharmacology.

SK: Who is that mentor you went to work with?

AF: Well, it wasn't really a mentor relationship. The head of that research unit was somebody originally from South Africa who had spent time in North Carolina as a resident. His name was Joe Mendels. He was in

charge of the Affective Disorders Research Unit, which was centered in the VA Hospital on the campus of the University of Pennsylvania. Many people around the country have in addition to their academic appointments also appointments in the VA, and that was helpful to me throughout my career. By being in the VA, I was able to get VA grants, as well as NIH grants.

SK: The field, when you first entered was pretty young. How would you describe it at that time?

AF: This was in the early 1970's, and I would say it was in the 1960's, and the late '50's, when many of these new psychotropic drugs were becoming known. They were all discovered by serendipity and the 1960's were really spent, in my view, trying to understand their clinical uses, the doses, the kinds of patients most likely to respond, side effects, etc. That was the clinical side. The pre-clinical side was obviously focusing on how they might act. Around that time, the biggest emphasis was on the discovery these drugs had prominent effects on biogenic amine systems. Particularly the antidepressants, which I was interested in, in different ways they seemed to enhance noradrenergic or serotonergic function. So the big emphasis at that time was attempting to understand what these drugs were doing acutely, to serotonin and norepinephrine. Did they have any effects on dopamine? Obviously, theories arose at that time about the illnesses themselves, which I've often thought were a little simplistic in the sense that if the drugs did this, then, the disease must be due to that. Nevertheless, the data were substantial about the acute potent effects that these drugs had on transporters, monoamine oxidase, etc. There was a lot of enthusiasm also from work being carried out at the Karolinska Institute where they were able to visualize the biogenic amine systems in the brain using fluorescence histochemistry. So a lot of the best and brightest were trying to understand brain function. Techniques were becoming available, which historically we may look at as being sort of not all that sensitive, specific or sophisticated. But for the first time in history, a variety of fluorescent techniques were becoming available for measuring brain function to an extent we could not do previously. There was a tremendous amount of excitement around that.

SK: So, to some degree, you were one of the first translational scientists to come along to bridge basic and clinical research in mental disorders. What was the first hypothesis that you tested? What were the first experiments you thought about doing to investigate the underlying mechanism of the action of these drugs and of the disorders they were used in?

AF: It's interesting you mentioned the translational aspect, because as a PhD member of this Affective Disorders Research Unit, we had to attend research rounds weekly and one of the things that was being investigated, not so much in our research unit, but in the field at the time, was whether adjunctive therapy of treatment non-responders with thyroid hormone could enhance the effect of a drug such as imipramine. Data were being published that this seemed to be so; a certain number of non-responders could be converted to responders or that the onset of the antidepressant effect could be shortened. Nobody seemed to know why. At the time it was felt, as it is today, that imipramine, by blocking norepinephrine uptake, could enhance the effect of norepinephrine at alpha or beta noradrenergic receptors. It was thought that thyroid hormone might sensitize β -receptors to the effect of norepinephrine. From my going to rounds, weekly, I had this epiphany that patients are not treated just once with a drug but multiple times, often for weeks if not months, so if was going to design an experiment with imipramine that might have clinical relevance I should treat the animal more than once. When I went to the literature, and this was 1971 or 1972, to find a protocol for treating an animal with imipramine, a drug that had been around since 1958, more than once, there was a single paper in the literature. All the others were on in vitro work or giving it once and measuring its effects fifteen minutes or so later. So, I said let's give it for five days. Why I chose five days was that it didn't involve a weekend. So I thought, let's treat the animals with imipramine; let's treat them with thyroid hormone; let's remove their brain and measure the ability of norepinephrine added to brain slices to increase cyclic AMP, which I had measured for my thesis work. It was much more difficult to measure it in those years then now.

SK: Why cyclic AMP?

AF: Cyclic AMP was known to be linked to β -adrenergic receptor activation. So the idea I had was that if I would add norepinephrine to the brain slice of an imipramine treated animal, I would see a bigger increase in cyclic AMP than I would in a non-imipramine treated animal and when I gave thyroid hormone plus imipramine, the increase in cyclic AMP would even be greater, showing a potentiation of the effect. The results were quite different from what I expected; in the imipramine treated animal, norepinephrine had a diminished ability to elevate cyclic AMP and the addition of thyroid hormone did nothing. So, my hypothesis was proven wrong. The interesting question was why was chronic treatment with imipramine, which was thought to enhance noradrenergic function, not doing so, but instead, diminishing noradrenergic function.

I speculated at the time, in an added note on the proofs to a paper published in 1974, that maybe the chronic overexposure of beta receptors to norepinephrine by chronic treatment was causing subsensitivity and a down regulation of the response. And this idea was correct. At that time ligand binding techniques on homogenates for receptors were becoming available, so we used a ligand for beta receptors and showed there was a time dependent decrease in beta receptors after chronic treatment of rats with despiramine. I think we were the second to show it. From my perspective it was not necessarily that down regulation was important in the antidepressant effect, but that we showed, almost for the first time, what we now refer to as plasticity; that chronic treatments were doing different things from acute treatments. Ours was one of the very earliest, if not the earliest, papers showing that you do need to look at what these drugs are doing in animals with repeated administration. The results could be quite different from what you see acutely and that made me think about drugs as sort of insults to the body, whereby the body has a variety of compensatory mechanisms that come into play to try to maintain homeostasis. That has been a theme of mine for the rest of my career, looking at chronic drug effects.

SK: So, in essence, you found the chronic effect different from the acute effect and that was surprising. How do you deal with the fact that these drugs are used to treat an illness in humans and that rats in which they are tested are probably not depressed? How do you overcome this issue? Do you have an established animal model for depression?

AF: That is a good question. Obviously, if we had an established, well-validated, universally accepted animal model of depression, everybody would be using it. The fact of the matter is we don't. Most of our models are based on stress. Certainly in human depression there's a stress component, but that is not necessarily universal. In terms of looking at the pharmacological effects of drugs, which is primarily what I do, the rationale I use is that effects seen in the normal rat, such as inhibition of uptake or down regulation of beta receptors, are the same things occurring in humans. Often times, when the drugs are given to human controls who are nondepressed, you see very similar effects in the non-depressed and depressed humans. Now, it's always possible that the illness itself causes biological changes that could alter the effect of the drug, but so far there hasn't been much data I've seen that substantiates that view. Instead, the pharmacological effect of the drug seems similar in depressed patients, non-depressed patients and in a laboratory rat, as best as we can measure those effects.

- SK: This first experiment you did was pretty radical in terms of the thinking in the field at that time so I presume when you had your results you were pretty excited about them and presented them at a meeting. How were the results received?
- AF: I don't recall where I presented them. It may have been a biological psychiatry meeting. But, I can tell you where it had an impact and really affected my career, and that was at an ACNP meeting where I wasn't presenting them. It was at a plenary session where Fridolin Sulser, who was doing a considerable amount of similar research and a very senior person, got up and was talking about his data and very graciously mentioned he thought some of the finest work in this area was being carried out by me. And, suddenly, after he finished, people came up to me at the coffee break and asked what I was doing that Fridolin mentioned. That was great. I've always had a warm spot in my heart, both for the ACNP and Fridolin, because of that; it shows the importance of having quality people at a meeting where many of the movers and shakers in neuropsychopharmacology attend. But, back to the point you made, I would also say that if I did not attend those rounds, I probably would not have thought about designing the experiment with chronic treatment. Based on my own career I can't overemphasize how important is to have PhDs truly understand the clinical domain, make research rounds and interact with clinicians to understand the illness and treatment in a way you may not get out of textbooks.
- SK: And so, this was your beginning. Where did it take you? You've had a long and very successful research career, working in the same area, but going in many different directions. Maybe you could summarize some of the major pathways you've taken and the impact they've had on understanding pharmacological treatments.
- AF: I've always pursued, at the pre-clinical level, a systems approach in terms of long term drug effects on various measures in brain. We have more recently started, in a more serious way, to add behavioral outputs to the neurochemical outputs including immediate early gene expression, but always using drugs in a way that is therapeutically relevant. At the same time, I've carried out a number of studies with my clinical colleagues, primarily dealing with issues of onset of action. The common idea is that many antidepressants don't begin to have their beneficial effects for two, three or four weeks after treatment is initiated. Certainly, their optimal therapeutic effects don't occur before four, six or eight weeks, but optimal therapeutic effect and the initiation of a therapeutic effect are different. Together with primarily Marty Katz and Charlie Bowden, in the follow up to a multi-center study, we found if you look early enough

you certainly don't see optimal improvement, but you do see, in one or two weeks, improvement in some symptoms in patients who ultimately respond after six weeks to different types of antidepressants. That has a lot of not only practical but theoretical implications as to when important pharmacological effects are happening. So I've always tried to go back and forth between the clinical and pre-clinical domains, and design pre-clinical experiments that have therapeutic relevance. It has been very helpful to my career working at the translational interface that has long been what the ACNP is all about. It certainly makes significant sections of grants easy to write and that's how my career has developed.

SK: From the time you started to do research in the field it has exploded, in terms of the number of people doing research and the number of drugs available. Who else would you say is doing similar work to yours and what impact did it have on your work?

AF: People doing work similar to mine are folks like Pierre Blier in Canada and Paco Artigas in Spain, both doing work on chronic effects of antidepressants. Irwin Lucki, who was a post doc of mine, has developed an international reputation in his own right. There are lots of people looking at chronic effects of antipsychotics and other kinds of drugs, but from my perspective what they were doing is not competitive, but complimentary. For a while I felt I was more focused on the noradrenergic system and Pierre and Paco were focused more on the serotonin systems. But, then I also moved to work on the serotonin system but keeping an interest in the norepinephrine system. So I would say these are the major people working in the same area. But there was a whole coterie of people looking at chronic drug effects in all kinds of psychotherapeutic drugs.

SK: Did any of their work have a significant impact on the directions you took?

AF: I don't know if it was their results as much as it was the development of techniques that had more of an impact. For example, moving from homogenate binding to autoradiography, developed by people like Tom Rainbow and others coming out of Bruce McEwen's lab, made it possible to look for neuroanatomical specificity among antidepressants; that was a big advance for us. So using techniques that have anatomical specificity is the way we went. These techniques weren't necessarily developed by people who were looking for chronic effects. They were asking other questions but we fairly quickly used their techniques for questions we were interested in. Now, for example, we use the technique of in vivo voltammetry to look at transporter function in vivo on a millisecond time scale and we do that in the hippocampus. We're one of the

few labs in the country that do it for serotonin. Again, this was developed in the chemistry lab at Kansas but people like Greg Gerhardt, and I apologize for blocking on the name of the individual in North Carolina, are probably the biggest proponents of this methodology. But they use it primarily for dopamine. With the help of Dr. Gerhardt, another member of the ACNP, we have adapted it for serotonin and find it very useful. So it wasn't so much advances made by those in the same area of research, but other kinds of basic science advances and advances in techniques, such as the cloning of transporters, by people like Randy Blakely, Susan Amaro, both ACNP members. This allowed the whole transporter field to expand tremendously in terms of regulation and identification of proteins involved in that trafficking. It's more those kinds of advances that have influenced how I proceeded with my own research.

SK: What would you say was your biggest contribution to the field?

AF: I think that early paper I've alluded to was significant in terms of its impact because it did begin the shift for the whole field from acute to chronic drug effects. That paper got a lot of people very interested in chronic drug effects.

SK: You spent most of your career in Philadelphia, but I know you did move. Maybe you want to mention something about where you moved to and where you are now.

AF: My career from 1969 through 1993 was spent at the University of Pennsylvania, both in psychiatry and pharmacology. Then, I was offered the Chairmanship of the Department of Pharmacology at the Health Science Center in San Antonio and moved there in 1993, and that's where I am, currently. We have built a department that has a neuro-orientation and I'm pleased that two members of my department, Charles France and David Morilak, are members of the ACNP. Hopefully we will have more members in the future. My orientation as Chair has been to recruit good people. Charles, for example, is a very major figure in the substance abuse area. It's nice to have people who understand the importance of the ACNP and are proud to be members of the organization.

SK: Doing research is pretty much a full time job and in addition to doing research you belong to a number of professional organizations and have major academic responsibilities. How do you balance all of these things and be successful at each?

AF: The trick is time management and surrounding yourself with very good people. You're absolutely correct, being a Chair of a department has administrative responsibilities and no matter how good the people are in a department, there're always issues. Being Secretary of the ACNP

is not overly time demanding and I'm happy to do it for this wonderful organization. I'm also the Editor in Chief of the International Journal of Neuropsychopharmacology, the official publication of the CINP, and that takes a certain amount of time. But from the research perspective, if you have very good people working with you and I've recently not just got very good people as "second in commands" but also people in the laboratory who can carry out the day to day work independently. So a lot of the research I now do, I can manage at arms length. So, the trick is to have outstanding collaborators.

SK: Was it the first time you came to the ACNP where Fridolin talked about your research?

AF: I don't believe so. In fact, I know it was not. I actually think I came to the ACNP first because Dr. Mendels was either a member or was coming to the meeting. I heard about it and was able to wrangle an invitation from a member, who I knew peripherally. That was probably in the early 1970's, right around the time my paper was being published. I think I came one or two more times after and became a member in 1981. The meeting where Fridolin spoke was probably around 1980 or 1981.

SK: Why did you decide to become a member?

AF: I felt that in the area in which I was carrying out research, this was far the most prestigious group of people in the field. What I liked was this mix of pre-clinical and clinical people who could speak each other's language. It also had representatives from the pharmaceutical industry who were knowledgeable about drug development and had drugs, some of which I would have liked to get my hands on. It was a good networking place and quite prestigious, so, for me, it was a very easy decision. This was the organization I wanted to be a member of.

SK: So, it was the content of the ACNP and the people at the ACNP?

AF: Absolutely.

SK: Who will you name as some of the key people who attracted you here?

AF: There was just about everybody here from biological psychiatry who I felt if I could interact with. Those people who would be a benefit to my career.

SK: Did attending the annual meeting enhance your career?

AF: I think it has. It has helped in getting feedback from these people on our presentations and, just as importantly, in having an opportunity to meet and chat about the issues they or I have, outside the meeting halls in the informal atmosphere we certainly used to have at the ACNP. It's been a little more difficult to maintain that informality as the size of the meeting and the membership has grown, but we still have it at least as

much as at any other major meeting and that has been very helpful to me.

SK: So do you think we should go back to smaller meetings with small groups like we had in San Juan sometime ago?

AF: You know, there's a natural evolution to things. I don't think we can go back to that unless we form a different society. We haven't yet reached the tipping point in terms of our meetings starting to feel more like, for example, a meeting of the Society for Neuroscience. We're nowhere close to that. My guess is you don't have to get to twenty thousand before you start to have a very different meeting. I don't know if it occurs at twenty-five hundred or four thousand. We're not there yet and I still think the ambiance of this meeting is closer to what we had when I first started, but I am concerned about its growth changing the nature of the meeting. One thing that has occurred already, that is unfortunate, is our growth has made us too large to go to the Caribe Hilton, which did play such an important role in the whole history of the ACNP. Having that venue for the meeting led to the success of the ACNP.

SK: You currently serve on the Executive Committee of the ACNP as Executive Secretary, but I know you have also served on committees. May be you can talk about that a bit, which committees you served on.

AF: Two committees come to mind that have probably the most impact on the ACNP; the Credentials Committee, which I served on and chaired, and the Program Committee, which I've served on multiple times but have never chaired. I've been fairly impressed with both committees. The Credentials Committee, which is the committee that selects new members, has a difficult task. What I've been impressed has been the very good applications and that, by and large, people allowed their personal feelings to be left at the door and really looked at the data from the CV's. It is a honorable job of selecting new members, knowing that there will be people who are going to be very unhappy who did not get in. The Program Committee also has a difficult task. I think it is an improvement that people are leaving the room if they have a conflict of interest related to a proposal. We, perhaps, didn't do that as much in the Program Committee at the time I was on the Committee as I would have liked, but sitting in now on current Program Committee meetings as a member of the Executive Committee, I think they now do an excellent job.

SK: You have said that attending the annual meetings enhanced your career?

AF: Yes, being a member of the ACNP, has academic bona fides and advantages associated with it. When you say at your institution you're

a member of the ACNP, every once in awhile somebody has to find out what that is and when they do there's sort of an "Oh". That's something. It's not like the Society for Neuroscience where you pay your money and you're a member. There's a certain stature you get at your institution by being a member. But the most important thing for me has been just the wonderful people I have developed personal friendships with at annual meetings, such as yourself. The professional associations I develop here have been a very important part of my life, and it has been very good to me, in terms of helping with my science.

SK: Would you care to share with us some of your fond memories of things that have occurred at the ACNP meetings?

AF: I just have very fond memories. Very often, and at this meeting, my wife accompanies me. Occasionally, when our children were younger and the meeting was at the Caribe Hilton, they would come too, to enjoy the beach. It was a very relaxing atmosphere. My wife has made many friends here as well and finds that she enjoys the people she interacts with at the meetings. So it's been an overall wonderful experience although I'm not sure I could think of any single incident. I just have a tremendous number of fond memories, many of which are my interactions with you at this meeting and other good friends and having wonderful suppers.

SK: If you could do it again, what would you do differently with the ACNP and career wise, research wise?

AF: You know, I hate to say it. I'm not sure I would do anything terribly differently with respect to the ACNP. I've always enjoyed the meetings. I think many of us find that it is an organization that we're the fondest of; that's the case with me. I think I did get involved in an appropriate way with ACNP activities. You've alluded to some of them. I'm actually quite honored to have been elected to the Secretary of the ACNP, because, again, some of my fondest fun memories involve Oakley Ray, who, to me, was the public face of the ACNP. When I was coming to the meetings early, I wasn't sure who the President or Treasurer was, but I knew who Oakley Ray was. He was the person you went to if you had a problem, if there was an issue, and he solved them. Fortunately, with Ronnie Wilkins, who really takes a lot of Oakley's responsibilities, I don't have to do everything that Oakley did for the ACNP, nor could I, because as you've indicated, I do have a full time job. But I'm gratified to help the ACNP at this time with the history series and other things that I've been charged with working on. ACNP has been a wonderful part of my life and my family's life.

- SK: Changing the tone there are a lot of elements that feed into the field of mental disorders and drug development; industry, government, this and other organizations. What do you think about that?
- AF: ACNP consists of a prestigious group of people who have not only focused on the science, which is very important, but have taken public policy positions. They have gone to Capitol Hill to lobby for things that are relevant. They have good interactions with advocacy groups, so I think they have been politically responsible. The quality of the science conducted by ACNP members and the quality of the science presented here have been excellent. We've also taken a leadership role to attract new people into this discipline through our Travel Awardee program, sponsored in part by industry but with no strings attached. We get outstanding junior people, residents, young faculty, to come to this meeting and put them together with a mentor, trying to ensure they have successful careers in neuropsychopharmacology. So I think the ACNP has functioned at multiple levels including quality of science, political activism, trying to facilitate young people entering the field. The ACNP has done an excellent job in all these areas.
- SK: Looking into your crystal ball, what do you see in the future as the greatest opportunities and challenges to both the ACNP and the field in terms of moving ahead to come up with preventive measures and cures for mental disorders?
- AF: There're several things; there's the science and there's the politics. Certainly, we're in a difficult time right now with regard to the public perception of the pharmaceutical industry, some of which is probably well deserved, but other aspects are not. The pharmaceutical industry has become a whipping boy for politicians, in terms of the price of drugs. Conflict of interest, which has certainly reared its head in the last few years, has to get resolved for us to move forward. The idea that academic people cannot interact with industry because doing so tarnishes them or that projects supported by industry are not valid, seem to be foolish. I understand it, but it's foolish and I don't think it will help patients, because you want people from industry, who are responsible for developing drugs, to be talking with people who understand the illnesses best and are the leading lights in research. We have to figure out how industry, academic and government relations are going to work to erase the perception that whatever we do is influenced by the pharmaceutical industry, which I don't think is correct. Yet, I understand where the perception is coming from. I think that's a big challenge. Scientifically we have made some wonderful advances with new genetic and other techniques but we have not had innovative

drug development in the last thirty years. But I believe we're poised in the next fifteen years to see totally novel targets for drug development producing new drugs. We have to reassess our diagnostic criteria to better reflect biology than current criteria do.

SK: Can you add some insights into why you think these things will happen?

AF: New techniques have become available, which will allow us to move ahead more rapidly. This is just the way the science in our field is going to develop.

SK: Alan, it has been fun interviewing you. You've done a great job, as always, but I'd like to give you a chance to add anything else we may have missed that you feel you want to say.

AF: You've done an outstanding job of interviewing me. The kind of friendship we've developed and friendships we both developed with other members of the ACNP are one of the most important components of being a member of the ACNP. Meeting you in enjoyable places annually has contributed. So, that's it!

SK: Good job.

KJELL G. FUXE

**Interviewed by Thomas A. Ban
Waikoloa, Hawaii, December 8, 2001**

TB: We are at the annual meeting of the American College of Neuropsychopharmacology in Hawaii. It is December 8, 2001, and I will be interviewing Professor Kjell Fuxe* from Sweden for the archives of the College. I'm Thomas Ban. We should start from the very beginning, if you could say something about your early interest and education, and then we go on to your professional activities.

KF: I will do my best to summarize my life. It all started in 1938 when I was born in Stockholm on the 25th of April. It was very peaceful in Stockholm in those days but the second world-war, was about to start with the Nazis. Thank heavens I was out of it growing up in Stockholm, away from the war. I will always be grateful for that. So I had a good beginning to my life with a very wonderful Mother who loved me like a Jewish mother, and protected me all my youth until I entered the University. I guess early on I unconsciously realized that having my home with my mother's love, the safe streets, and the food and milk to fill an empty stomach, I could survive. My interest was only to have a good time. However, when starting school at 7 years of age I found out that within me I had this thing of wanting to compete. I also felt good about going to the Adolf Fredrik's elementary school because I had to have something to do, being full of energy that has kept me going my entire life. Starting to learn offered a way for me to invest my energy in something that seemed worthwhile. Learning was a way to survive. I probably was not aware of these thoughts at the time since I was just a boy who liked to study. So, this was life during my first twelve years in school, with the last eight years at Norra Latin, a combined secondary grammar school and senior high school where I got a classic education. It was located in the north part of Stockholm, close to home. I was lucky with that school. It gave me a chance if I got good marks to enter the Stockholm University. I never worked as hard as when I was a senior high school scholar in Norra Latin. I was lucky enough to be accepted by the Karolinska Institute, the medical faculty of Stockholm and my intention at first was to become a doctor. The medical studies began in 1957 and I took my medical bachelors degree in 1959. Already in 1958 I began to work as an assistant in the Department of Histology at the Karolinska Institute. In fact, histology was my first course and gave me my first contact with science. During

* Kjell Fuxe was born in Stockholm, Sweden in 1938.

these years, from 1958 to 1961, I was trained in histology, histochemistry and fluorescence microscopy, by Dr. Bengt Fredricsson and Dr. Ove Nilsson, and in biochemistry by Prof. Sune Bergström. As a student with Dr. Ove Nilsson I began to work on the lipid granules of the uterine epithelium and its hormonal regulation. In this analysis I was excited by being able to visualize the epithelial cells with the use of fluorescence microscopy, making it possible to understand in a small way their structure, with focus on the lipid granules. Then, in 1962, Professor Nils-Åke Hillarp came from the University of Göteborg to become the chairman of our histology department. I was very grateful that I became his first pupil in Stockholm. So, I switched from the uterus to the brain with the analysis of brain structure and histochemistry since Hillarp brought with him something very fantastic. He gave us this gift, namely the method to demonstrate catecholamines (CA) or serotonin (5-HT) at the cellular level with fluorescence histochemistry, the Falck-Hillarp technique. Suddenly you could do studies you had only dreamt of. You could study the putative dopamine (DA), noradrenaline (NA) and 5-HT transmitters and their regulation at the cellular level, which was at this time revolutionary. I was allowed to select my thesis project, and I chose the brain because in my mind it was just a black box. So, this was the beginning of my life in neuroscience. Carlsson, Falck and Hillarp had in 1962 published a supplement in *Acta Physiologica Scandinavica*, on the cellular localization of CA in the hypothalamus and demonstrated for the first time their localization in varicose nerve terminals, similar in appearance to the autonomic ground plexus of nerve terminals discovered many years earlier by Hillarp. This was one of his several outstanding contributions to science. It was a sad and highly tragic event for all of his students and for Swedish medical science when he was struck by a malignant melanoma in 1963, discovered too late for effective treatment. He died in March 1965. He left behind a large number of very young, enthusiastic students at the department including me who had looked up at him for being a highly creative and brilliant scientist and a wonderful human being. I believe he would have received the Nobel Prize together with Arvid Carlsson had he stayed alive. It was not easy for Sweden to lose such a scientific giant. However, he left behind his group of young Swedish medical scientists, the so-called amine group, who could continue his work, and build up a new neuroscience tradition in Sweden based on his achievements. The amine group was formed in the histology department after his death in 1965.

I defended my thesis on “Evidence for the existence of central monoamine neurons in the brain” in April 1965 about one month after

his death. My work with Hillarp began with setting up the Falck-Hillarp technique in Stockholm developed by Bengt Falck and Nils-Åke Hillarp at the department of histology, University of Lund. It was a tough task to set it up since there were variabilities in the reaction of monoamines with formaldehyde gas. Sometimes the reaction was too weak and the monoamines could not be properly detected. Sometimes there was a diffusion of the monoamines and no monoamine localization to cells and their terminals could be observed. Bertil Hamberger, now a professor of surgery at the Karolinska Institute, with other colleagues from the amine group, developed an important method to standardize the formaldehyde fluorescence technique of Falck and Hillarp. He discovered that the water content of the paraformaldehyde powder used was crucial and developed a method with the optimal amount of water in the reaction. This was an important contribution for which he should be properly acknowledged. It was just a one-page publication in 1965, but a very important page, that had a major impact on the field. In the 1960s we mapped the major DA, NA and 5-HT pathways. We discovered the nigro-striatal dopamine system, the meso-limbic dopamine system, and the tubero-infundibular dopamine system. We also contributed to the mapping of the meso-cortical dopamine systems. We mapped the major descending and ascending brainstem NA systems from the pons, mainly locus coeruleus, and the medulla oblongata to the spinal cord and the telencephalon and diencephalon, respectively. We also mapped the brain stem 5-HT systems from the caudal and rostral raphe nuclei with projections to the spinal cord and the telencephalon and diencephalon, respectively. This work was very much a team effort, and I was happy to collaborate with Annica Dahlström, two years younger than me, who is now professor of Neurobiology at the University of Göteborg. We worked well together in the early years from 1963 to 1965 and had a lot of fun doing so. We also had a nice collaboration with Arvid Carlsson and his group in the 1960s. They helped out very much in the mapping of the monoamine pathways since they provided the biochemical counterpart. Knut Larsson from the department of psychology at the University of Göteborg made an important contribution by performing lesions of the monoamine systems. Dr. Nils-Erik Anden in Carlsson's group played an especially important role in this collaboration. In 1966 we summed up part of the work in a review article we wrote together. It was based on a lecture I gave in 1965 in New York at a symposium on the biochemistry and pharmacology of the basal ganglia. The proceedings of this meeting, the Second Symposium of the Parkinson Disease Information and Research Center, was edited by E. Costa, L. Cote,

and M. Yahr, and published by Raven Press, New York. In 1971, Urban Ungerstedt, now professor of pharmacology at the Karolinska Institute wrote a beautiful thesis on monoamines, based in part on the Falck-Hillarp technique. All these works together represented truly important contributions. I believe it was the dawn of chemical neuroanatomy. The Cajal-Golgi mapping with the silver impregnation technique was followed by transmitter based mapping. I believe this was fundamental also for neuropsychopharmacology since pharmacologists could begin to understand better how all these neuropsychotropic drugs acted on the neural circuits of brain and where their primary targets were located. In fact in the 1960s we began a fine collaboration with Arvid Carlsson to understand in a better way the mechanism of action of the classical antidepressants, like imipramine. With Anden and Hans Corrodi we gave functional correlates to the postulated DA receptor blocking activity of classical neuroleptics like haloperidol and chlorpromazine as pioneered by Carlsson. We elucidated also the mechanism of action of hallucinogens of the indolalkylamine type, like d-LSD, based on the discovery of their ability to act as postjunctional 5-HT receptor agonists, a property that may mediate their hallucinogenic activity. In 1967, with evidence that apomorphine may be a DA receptor agonist, in collaboration with Anden and Corrodi we began to discover novel dopamine receptor agonists for the treatment of Parkinson's disease. So, there was a world full of neuropsychopharmacology, which interacted with the mapping world and vice versa and I was there in both of them.

Our antidepressant work with Arvid Carlsson began in 1965. It showed that classic antidepressant drugs blocked the uptake mechanism for NA in the plasma membrane of the central NA neuron systems but not of the DA neuron systems. In contrast, d-amphetamine in this analysis was shown to be a DA and NA releasing drug, which probably mediated its rewarding actions. In this period I started to believe that we must have an uptake-concentration mechanism for 5-HT in the plasma membrane of the 5-HT neurons similar to the NA uptake-concentration mechanism. Ungerstedt and I could demonstrate, after reserpine depletion of the monoamine stores and intraventricular injections of 5-HT, a nice uptake of 5-HT in the 5-HT terminals. Then, I told Arvid Carlsson about our findings, and we continued our collaboration by analysis of the effects of antidepressants also on the 5-HT uptake. We found that the classical antidepressant drug, imipramine had a significant blocking action on the 5-HT uptake concentration mechanism. This was the beginning of the story on the effect of antidepressants on 5-HT neurons with the development of SSRIs.

TB: When did that happen?

KF: The paper on the intraventricular injection of 5-HT was published in 1967 in the *Journal of Pharmacy and Pharmacology*. The following year, in 1968, in the same journal, Carlsson, I and Ungerstedt published the first observations that imipramine could block the 5-HT uptake-concentration mechanism in the central 5-HT neurons. In the same year Corrodi and I could also show, as published again in the *Journal of Pharmacy and Pharmacology*, that imipramine reduced 5-HT turnover in the brain using the tryptophan hydroxylase inhibition method. In 1969, Corrodi and I published a follow up paper with a number of imipramine-like drugs. Thus, our original story was published in these three small papers. They are almost never cited but the first observations are there. The work with Arvid Carlsson was continued with two papers published in the *European Journal of Pharmacology* in 1969, showing that some antidepressant drugs may preferentially block the 5-HT uptake concentration mechanism in the surface membrane of the central 5-HT neurons while others may preferentially block the NA uptake concentration mechanism in the surface membrane of the central NA neurons. Arvid Carlsson, together with Hans Corrodi and others at Astra, went on to develop novel compounds with rather selective actions on the 5-HT uptake-concentration mechanism, the most famous one being zimelidine. However, neuropathy developed in a few patients and its clinical development for treatment of depression was stopped. Instead, fluoxetine with the same mechanism of action came along and took over the scene.

TB: So the original observations on 5-HT uptake in the brain were made in the late 1960s?

KF: Yes, our first observations were made in 1967 and 1968.

TB: Fluoxetine was introduced almost 20 years later?

KF: Yes, something like that.

TB: Actually 15 years later?

KF: Yes. It is nice to have been part of this discovery. The neuroleptic work performed mainly with Anden and Corrodi was a follow up of Arvid Carlsson's pioneering neurochemical findings in the brain suggesting that neuroleptics may mainly act in schizophrenia by blocking DA receptors. The evidence obtained in our work as published in 1966 in *Acta Pharmacologica et Toxicologica*, and in 1970, in the *European Journal of Pharmacology*, we gave further neurochemical evidence, and a functional correlate to Carlsson's pioneering biochemical findings, showing that in fact DA receptor blockade was involved in their actions. Of importance was our suggestion in 1970 that the anti-schizophrenic actions

importantly involved a blockade of limbic DA receptors, as published in a book on neuroleptics edited by Bobon, Janssen and Bobon. In the period from 1968 to 1974, together with Anden and Corrodi, we also obtained evidence that hallucinogenic drugs of the indolalkylamine type were able to activate postjunctional 5-HT receptors in the brain and the spinal cord as shown in studies on 5-HT turnover and in functional tests. The first paper in this area of research on d-LSD appeared in 1968 in the *British Journal of Pharmacology*. We wrote a review on the subject in 1976 in a book with the title *Schizophrenia Today*, edited by D.Kemali, G.Bartholini and D.Richter. The hypothesis was advanced that activation of certain postjunctional 5-HT receptors in the brain may be responsible for the hallucinogenic effects of these drugs. In contrast, Aghajanian and his group, in the same period proposed that activation of the 5-HT autoreceptors on the dorsal raphé 5-HT cell bodies was responsible for the hallucinogenic actions of d-LSD type of drugs. A major achievement by our group working with Anden and Corrodi in the period from 1967 to 1979 was the development of novel dopamine receptor agonists. It began with studies on the DA agonist properties of apomorphine in 1967, supporting Ernst's work in 1966 and '67, followed by the discovery of the DA agonist action of the French compound ET495 (piribedil) in 1971 and of bromocriptine in 1973, leading to the introduction of these drugs in the treatment in Parkinson's disease, and also to the introduction of dopaminergic ergot derivatives in brain research.

The important functional model in these DA agonist experiments was Ungerstedt's. It showed that unilateral 6-OHDA (6-hydroxydopamine) injections in the medial substantia nigra lead to a dramatic disappearance of striatal DA terminals on the lesioned side without touching the striatal DA terminals on the unlesioned side. When these rats were treated with DA agonists or L-DOPA they turned contralaterally to the DA denervated side. The explanation of this lay in the existence of supersensitive striatal DA receptors on the DA denervated side. After treatment with a DA agonist, the DA denervated striatum will become overactivated in comparison to the intact striatum in terms of DA receptor activity. It is this imbalance of DA receptor activity that leads to an asymmetry in the basal ganglia activation of motor neurons in the brainstem and spinal cord with the appearance of contralateral rotational behavior. Ungerstedt's model was excellent since the number of turns could be easily quantified.

I was interested in bromocriptine since it produced a marked lowering of prolactin secretion, and, based on a large number of

neuroendocrine experiments, Fuxe, Hökfelt and Nilsson, formed the hypothesis that the tuberoinfundibular DA neurons were involved in the inhibitory control of prolactin and LH (luteinizing hormone) secretion. Thus, bromocriptine became a new interesting tool in this analysis. I then discovered that bromocriptine reduced DA turnover in the striatum, using the Falck-Hillarp technique together with semiquantitative and quantitative measurements of CA fluorescence that I published in 1974 with Agnati. The results were also corroborated biochemically by Corrodi. Then we found that bromocriptine produced contralateral rotational behavior in the Ungerstedt model. Thus there was evidence that it was a DA receptor agonist and probably a novel antiparkinson drug. And bromocriptine became an important drug in the treatment of Parkinson's disease (PD.) The DA agonist action of the substance also explained its prolactin lowering actions. My old friend and mentor Dr. Menek Goldstein, was also excited about the bromocriptine story and Menek showed its antitremor activity in his monkey model of PD. It was a unique moment in my life when I met Menek in 1969. We immediately liked each other and became true friends for the rest of his life.

TB: Where did you meet?

KF: It was at the Second International Neurochemistry Meeting in Milan. We had an exciting time there and decided to work together on the continued mapping of the central CA and 5-HT neurons. Menek had developed highly specific antisera against the CA synthesizing enzymes and had made pioneering discoveries on the biochemical properties of the central CA neurons. We truly felt that this could be the beginning of a great novel mapping of the central monoamine neurons using immunohistochemistry and would lead to the introduction of that technique in chemical neuroanatomy. We were happy to be together and took a train-ride to the Stresa region and enjoyed the spectacular beauty of this part of Italy on a warm summer day. We felt very close and our strong friendship and scientific collaboration lasted for almost 30 years until his death in 1997, leading to large number of interesting publications.

TB: Let me interrupt here and clarify a couple of things. Am I correct to say that you started as a medical student to work in the Department of Histology at the University, and you have stayed in the same Department as of today?

KF: Yes, that is the way it was and it is an interesting story.

TB: You got first involved with mapping of the monoamines and then in the functional aspects of their activity?

KF: Yes, and also the pharmacological aspects.

- TB: Would it be correct to say that yours was one of the first major publications on serotonin uptake?
- KF: Well it was one of the first, and it was a very significant contribution, based on work I did parallel to mapping. And my second contribution was the discovery of the DA agonist action of bromocriptine.
- TB: They were two major lines of research you were involved in beginning?
- KF: Yes, it is true.
- TB: So, just to clarify again, the serotonin uptake research started in the late 1960s?
- KF: Yes.
- TB: The dopamine agonist research related to the treatment of Parkinson's was done about the early 1970s?
- KF: Yes. This is true for bromocriptine but the DA agonist story started in 1966 with the discovery of the DA agonist action of apomorphine by Ernst and Smelik in 1966 and Anden, Fuxe and their associates in 1967.
- TB: It took about 20 years until it moved to psychiatry?
- KF: Well, zimelidine, a selective 5-HT uptake blocker, was developed by Astra in collaboration with A. Carlsson for the treatment of depression in the early 1980s. So we are talking about 10-15 years.
- TB: When did you become professor?
- KF: I became a prosector of histology in 1968.
- TB: What is a prosector?
- KF: Prosector today corresponds to a full professorship but in 1968 it corresponded to an associate professorship. However, it was an important position since it was with tenure and it had almost the same benefits as a full professorship. My prosector position was converted to a professorship in 1979. The prosector position had a special significance since it allowed the newly formed amine group to remain at the histology department and work in peace.
- TB: Would it be correct to say that all the research you described so far was based on fluorescence techniques?
- KF: First it was amine fluorescence, then immunofluorescence. The former is in fact more elegant since you could demonstrate the cellular localization of the transmitters DA, NA and 5-HT by converting them into fluorescent compounds by condensation with formaldehyde leading to a ring closure followed by a secondary dehydrogenation.
- TB: Then you moved from amine fluorescence into immunofluorescence?
- KF: Exactly.
- TB: When did this take place?
- KF: This took place after I had met Menek in Milan in 1969 and began our unique collaboration.

Let me mention that we had a tremendous demand for quantification of amine fluorescence. So in the early 1970s Jonsson, Agnati and I developed quantitative and semiquantitative methods for the evaluation of amine fluorescence.

- TB: You mentioned before that you had published several papers with Menek.
- KF: The first paper from our work was published in 1970 on the location of DA beta-hydroxylase in the brain by using immunoreactivity. The good news for me in the 1970's was that I got a very important scientist to my laboratory. His name was Luigi Agnati and he became professor of human physiology at the University of Modena some years later. He came to my lab in the early 1970s and stayed for a year. He was an outstanding scientist and became a genuine friend. We have by now, worked together for over 30 years.
- TB: Let us move ahead now and tell us about your research in the late 1970s and early 1980s.
- KF: In this period Luigi and I began our fundamental work on receptors leading to the development of the concept of intramembrane receptor-receptor interactions. There were many new peptides discovered and we did not understand how the integration between peptide and monoamine signals took place. We felt that one way could be through direct reciprocal interactions between the peptide and monoamine receptor subtypes in the surface membranes of neurons regulating the affinity and density of the participating receptors. Such direct interactions would be a fine way to tune receptors and send conditioned receptor signals to the ion channels and enzymes controlling the excitability and metabolic state of the nerve cells. This would be a new fundamental integrative mechanism in the cell, operating at the membrane level. We began the experiments in a small way, and had lots of problems. We had to work at least a year before getting any results at all. Finally, we got results in membrane preparations from various brain regions and could observe modulations of the binding characteristics of monoamine receptors by agonist activation of peptide receptors in the membranes. However, the modulation of affinity and density by peptides, e.g., CCK peptides and Substance P, was small e.g., 20-30% changes of KD values. No one except our team believed that this could have any possible physiological significance. But Luigi and I, with our teams, struggled on. We very much believed in this form of receptor plasticity involving direct receptor-receptor interactions. Of course in those early days we did not know the molecular mechanism bringing the two receptors together. Our first papers appeared in 1980 and 1981. We organized an International Wenner-Gren Center symposium

on receptor-receptor interactions in 1986 with the proceedings published in 1987 by Macmillan Press. There were other groups working on receptor-receptor interactions but at the meeting few believed in our story. It did not have an impact at the time. The major thing at the meeting was Greengard's important story on indirect receptor-receptor interactions via intracellular loops causing phosphorylation or dephosphorylation of the receptor. This work did have an impact. However, Luigi and I with our teams, struggled along leading to the publication of a large number of papers on intramembrane receptor-receptor interactions. In a review paper we published (Zoli et al) we proposed that the direct receptor-receptor interactions were the result of receptor heterodimerization. This was in 1993.

In 1998 and 1999 the breakthrough came when several groups gave experimental evidence of GABA-B receptor heterodimerization. In the year of 2000 we obtained evidence through the collaboration with the Franco team in Barcelona for the existence of functional A1/D1 heteromeric receptor complexes that gave the molecular basis for the antagonistic A1/D1 receptor-receptor interactions. At the present meeting I will speak on the antagonistic A2/D2 receptor-receptor interactions and their relevance for treatment of Parkinson's disease and schizophrenia. In 1991 and 1992 we proposed the introduction of A_{2A} antagonists in the treatment of Parkinson's disease and in 1994 the use of A_{2A} agonists in the treatment of schizophrenia. We believe that we will develop many new drugs for neuropsychopharmacology based on the receptor-receptor interactions taking place via the interface of receptor heteromers in the surface membrane. I just would like to mention that in 1982 the Agnati-Fuxe teams published a paper in *Medical Biology* introducing the hypothesis of "the receptor mosaic hypothesis of the engram". We postulated that the formation and stabilization of clusters of receptors and mosaics, in the surface membrane with multiple receptor interactions represented the molecular mechanism for learning and memory. It has been a fully forgotten paper. Now 20 years later it seems to be a true story.

TB: Did the work on monoamine receptor interactions start in the late 1970s?

KF: Yes, it began in the late 1970s.

TB: Then, in the 1980s?

KF: Another important story in the 1980's was the introduction of the concept of volume transmission (VT), by the Agnati-Fuxe teams. We first published on it in 1986 in *Acta Physiologica Scandinavica*. We stated that there exists in the CNS, besides the rapid wiring transmission,

(WT), with synaptic transmission as the prototype, a slow mode of communication in brain involving the diffusion and convection of transmitters and modulators in the extracellular fluid and CSF. This concept was based on a number of observations like the detection of spread of CA after their microinjection into the brain, the appearance of diffuse neuropil CA fluorescence after amphetamine treatment, detectable by the Falck-Hillarp technique, the discovery of non-junctional monoamine varicosities in the brain by Descarries and colleagues, and the demonstration of ion diffusion in the extracellular space. The observations of transmitter-receptor mismatches were a major factor for our introduction of the concept of VT. To Agnati and me it represented the architecture for slow, long distance VT. The best identified signal for long distance VT appears to be Interleukin-1- β , as shown by Jansson and colleagues in 2000. This is the mode of brain communication mimicked by drugs acting on the brain and therefore of highest relevance for neuropsychopharmacology. Luigi and I are actively pursuing this story of VT vs. WT in the regulation of the cellular and molecular networks of the CNS.

TB: So what would you call your most important contribution, the discovery of receptor-receptor interaction?

KF: Yes, I think so. The receptor-receptor interactions have been the most important contribution made by the Agnati-Fuxe teams. We were 15 years before any other team. But the introduction of the VT concept with evidence for its existence, also by our teams, takes a strong second place.

TB: It seems that at the beginning the scientific community was skeptical about receptor-receptor interactions, but apparently this is not the case 20 years after.

KF: Yes, it has been a tough battle but the intramembrane receptor-receptor interactions survive over the years. You just have to endure, and if you endure long enough, you finally get a story accepted if it is true. The receptor-receptor interaction story has now been accepted and recognized as a novel principle in molecular neuropsychopharmacology.

TB: Are you a medical doctor?

KF: Yes, but I was never a clinician with the exception of having had a temporary position as a doctor in the summer in the islands off the northwest of Sweden.

TB: I understand that all through your professional life you did research. What was your first paper on?

KF: It was on preservation of cholinesterase and its histochemical demonstration. It was done with Bengt Fredricsson, my first teacher, Bo Holmstedt, a famous neuropsychopharmacologist, and with Folke

Sjöquist, now a famous clinical pharmacologist. The collaboration was again initiated by me in 1972 to study with Holmstedt the effects of the hallucinogenic compound 5-methoxy-N, N-dimethyltryptamine. That led to a paper on the central monoamine neurons that was published in the *European Journal of Pharmacology*; and work with Folke Sjöquist on the actions of apomorphine on body temperature in the mouse also led to a publication in the *Journal of Pharmacy and Pharmacology*.

TB: When did you publish your first paper?

KF: This first paper was published in 1960.

TB: What was the last paper that you published?

KF: One of the last papers I published (2001) was related to volume transmission. It was on 5-HT terminals and their relationship to the 5-HT_{2A} receptor immunoreactive processes giving structural support for VT in 5-HT neurotransmission. Another recent paper of mine, on mGluR5/D2 receptor interactions was just published in *Neuropsychopharmacology*. This was done in collaboration with the Patrizia Popoli team in Rome and is a good example of the ongoing work on receptor-receptor interactions.

TB: You are still very active?

KF: Yes, I think I have never worked as hard as during these last years with the exception of my school days at Norra Latin.

TB: You started to attend ACNP meetings quite a number of years ago?

KF: Yes, thanks to my old friend Menek Goldstein. He brought me into the ACNP.

TB: Do you remember when approximately?

KF: I became a member in 1994 but Menek invited me to participate in ACNP panels in the 1960s and 1970s. The ACNP meeting was in Puerto Rico at the time when I was young. I still remember how much I enjoyed the meetings.

TB: Is there anything else you would like to mention?

KF: I would like to just mention the tremendous importance of having had Menek as my mentor and big brother during a large part of my life. We have had tremendous fun in science and we enjoyed working together. Science was always the focus, because we were both crazy about it. I would also like to state simply that it is vital to have a life also outside of science. I am genuinely grateful to my family who has not given up on me even though, because of my activities in science, I spent too little time with them.

TB: Are you married and have children?

KF: Yes. I have a wonderful wife, two sons and a daughter. They are a very crucial part of my life and at the core of my existence.

TB: On this note we should conclude this interview with Professor Kjell Fuxe from Sweden. Thank you very much for sharing this information with us.

KF: Thanks

SILVIO GARATTINI

**Interviewed by Leo E. Hollister
San Juan, Puerto Rico, December 12, 1995**

LH: I'm Leo Hollister and today, December 12, 1995, it's my privilege to interview Silvio Garattini.* Dr. Garattini is the Director of the Mario Negri Institute in Milano, one of the pre-eminent pharmacological institutes in the world. Welcome to San Juan.

SG: Thank you.

LH: You were quite a young man when you became Director of Mario Negri. How did that happen? What was your training up to that point?

SG: I was born in 1928. I went to school during World War II and had to resume my education after some interruption. At the time no-one in Italy knew what was going to happen, so my father said, "It would be best if you study something that will provide you with security" so I started my career in chemistry. Chemistry was considered a safe occupation so I studied and became a Certified Chemist. I had an excellent training because, at that time, the teaching of chemistry in Italy was not only theoretical but included some laboratory work which I enjoyed very much. Then I worked as a chemist in a steel factory, but I wasn't happy. After the war ended I decided I would like to get a university degree and in 1948 I passed the admission examination. I decided to read medicine with the idea that, with my training in chemistry – something that other medical doctors would not have - I could combine medical with chemical knowledge. When I was taking my pharmacology exam in pharmacology I realized that it really appealed to me. Pharmacology studies the biology of chemicals, the interactions between chemicals and the living organism, and I decided I would like to pursue pharmacology as a career. My family could not afford to keep me while I was at university and I had to work while I was studying. So I started my career in the Pharmacology Department at University of Milan while I was following the courses and taking the exams necessary to get my medical degree, which I got in 1954.

LH: What did you do after you got your MD?

SG: In 1955 I got a "Libera Docenza" in chemotherapy and in 1957 in pharmacology. For a short period I stayed on as an assistant professor in the Department of Pharmacology at my University, and then I moved to the University of Milan. The head of the Department of Pharmacology was Professor Emilio Trabucchi, a well-known pharmacologist, who played an important role in my professional development. In Milan I had the

* Silvio Garattini was born in Bergamo, Italy in 1928.

opportunity to organize a team of young pharmacologists to work with me on projects in psychopharmacology while I continued my research in the laboratory, publishing papers. 1957 was a significant year in my life because I had an opportunity to spend three months in the United States and to visit laboratories, including those at the National Institute of Mental Health and at the National Heart Institute, and to meet many people I knew from the literature, like Bernard Brodie, Julius Axelrod and others. I was very impressed that research was already a profession in the United States. This was not the case in Italy. At the time in Italy, research served as a means of collecting credits and publishing papers to improve one's university career, but it was not a profession in itself. I was also struck by the variety of institutions doing research in the United States. There were public universities, state universities, private universities, private laboratories, and research laboratories of the pharmaceutical industry and of foundations. I found the idea of a "foundation" especially attractive because it is a relatively free organization that is not subject to the anonymous bureaucracy that is ever-present in Italian universities. Since foundations are not for making profit, one should be able to work in a foundation in the interest of the public. This was another attraction. In my somewhat naïve way of thinking I saw foundations as private places at the service of the public. So after I returned to Italy, I got together my team in the department and told them that if we were serious about our intention of doing research we would have to decide whether to move to the United States and work there, or create a facility that had a different organizational structure from any in Italy. We decided we should stay and create a suitable setting for our research. Then, as a naïve young man I went around asking people for help to establish a foundation.

LH: That wasn't so naïve.

SG: Well, it seemed very simple and apparently some people responded to it favorably. In fact while doing the rounds asking people for support I met, by chance, Mr. Mario Negri, an industrialist in Milan who was primarily in the jewelry business, who had no children but was always interested in young people. And when I asked Mr. Negri, like I asked everyone, "Why don't you help us set up a foundation where we can do independent research?" he responded simply, "Why not?" Then he added, "But you are too young. Let's think about it. Let's see what can be done". After that we had many meetings at which we discussed not only what should be done, but what kind of research we should do, how an organization of this kind could obtain support, and what kind of rules of operation the foundation should have. After a series of such

discussions I was confident that he was ready to do it. But then, tragically, he got cancer of the liver. I was shocked. My dream that seemed so close to materializing was fading. But then, about a couple of weeks before he passed away, he called me and asked me to visit him in the hospital. He told me: "Don't worry. I have done what we discussed and whatever happens to me everything will be fine." Mario Negri died in April 1960. When they opened his will, everything we had discussed was written down, each single point we had talked about was there. He named me as the director of the institute to be established, that he wanted to be called The Italian Mario Negri Institute of Pharmacological Research. So my dream became reality.

LH: That was very noble of him.

SG: It was also something extremely risky for him. It was hard to set up a research foundation in Italy, where most research at that time was done at state universities and even at drug companies: research was in a very early stage of development. Mr. Negri left the equivalent in Italian lira of about one million US dollars for the creation of the foundation and we had to decide what to do with the money. One possibility was to put it in a bank and use the interest to fund some of our research. The other was to use the capital to build an institute that would then have to survive by competing for grant support. To doing something significant in Italy we knew we would need a building, so we decided to use the money Mario Negri left to build the institute we envisaged. By the end of 1961 the Institute was recognized as a non-profit organization by the US Treasury. We needed this recognition in order to obtain support for our research from the USA. We were already collaborating with American groups.

LH: So it was established as a foundation to get tax-exempt status.

SG: Exactly. First we were recognized by the American government and then, later, by the Italian government.

In February 1963, 20 researchers moved into the Institute to set up laboratories so we could continue our research. We had three groups of researchers; one was working in cancer, one in psychopharmacology, which was just starting to develop, and one in cardiovascular disease. It was a difficult start. We actually got much more help from foreign than from Italian groups. We were something new and unusual in Italy, and were asked again and again, "What kind of organization are you? Are you a university? Are you industry?" Our answer, of course, was that we were neither university nor industry. It took some time before people recognized that this type of organization had not existed in Italy before.

I would like to acknowledge here the strong support we got from Sir Henry Dale, the chairman of Burroughs Wellcome. I had the privilege to

discuss our initiative with him and he was very sympathetic and encouraging about our project. Then we also got support from the Gustavus and Louise Pfeiffer Research Fondation in New York.

To operate the Institute we implemented three simple rules. The first is that we don't spend money that's not available. We thought it was important to resist the temptation to borrow money, so as to avoid running into problems. The second rule is that in order to maintain our freedom we do not accept any donation, grant, or contract that is more than 10% of our total budget. In this way, we thought we could avoid becoming dependent on any single body. The third rule is that we never check people's working times. We thought that everyone would do what they possibly could and that self-discipline was everything. These are three simple rules that I believe are important regarding the operation of the Institute.

As soon as the first scientists moved in we started research. Then, to complement the research with educational activities, we established two schools, one for technicians, and one for post-doctoral fellows. These schools are still running. It was also an early decision that all scientific papers from the Institute would be written in English.

LH: A wise decision.

SG: At that time English was the language of science and if we wanted to communicate our findings to the scientific community we would have to do it in the lingua franca of science. We use Italian when we process data in the Institute but English to communicate our findings with the world. So far we have six thousand scientific publications.

We also decided that not only the scientific community but also the physicians in the community and the public should be informed about our findings. This was unusual at that time. But we felt it was important for people to be informed, so we wrote articles for newspapers, talked on the radio and appeared on television. In Italy, it was considered improper for academics to talk to laymen. But we were convinced it was important to let the public know about progress and problems in science. In Italy in those years people were not accustomed to make donations to support science. Donations were usually given to the church or to the arts or humanities. By communicating with the public directly we tried to convince people that it was just as important to contribute to scientific institutions.

LH: Did you get on any list of organized charities over there?

SG: No, we did not, but now we have a number of institutions that support our research with grants. An important one is the Agency for Cancer

Research. Right now, we have maybe 20 or 30 organizations helping support various kinds of research in different fields.

LH: Do you have anything comparable to the National Institutes of Health?

SG: No, not really. We have the National Research Council, but that has much less money to distribute than the NIH. Actually, we have been very lucky because at the beginning we had several grants and contracts from the NIH. There was a period, I believe between 1965 and 1970, when the Mario Negri Institute was receiving more grants from the NIH than any other European organization. After 1970, the Institute was gradually accepted by Italian academia and we became part of the Italian scientific scene. But the beginning certainly was very difficult in this respect.

In the meantime, the Institute was growing so fast that the building we built in the beginning could no longer accommodate all our researchers. So we added first a new floor, then a six-floor extension, which we called “the Tower”, because we needed more space for laboratories. We also got a grant from an American foundation to build a guest-house where people from other countries working with us could stay. Later we built another building to accommodate epidemiology and molecular biology, two areas of research we became interested in. We also set up a second Mario Negri Institute in Bergamo, concentrating on renal diseases. We built it in Bergamo because we were able to arrange collaboration with the local hospital so we could build a bridge between laboratory research and clinical work. Then, we built an institute in the south of Italy, because we wanted to help young researchers in the south get involved in scientific work. Just recently we established a clinical research center devoted to rare diseases near Bergamo. Why rare diseases? Because I think that people with rare diseases are twice unlucky; because they have the disease and then again because it is such a rarity that industry is not interested in developing a treatment for it.

LH: Can we focus in on that rare disease center?

SG: We were able to extend our activity into this area and remodel a splendid building in its own enormous park, thanks to the generosity of the Daccò family. In gratitude, the building was called the Aldo and Cele Daccò Center. There are about 5000 rare diseases and they account for more or less 10% of all pathology. The clinical research center serves as an information center where people - physicians, parents, relatives or anyone - can get information on all the different rare diseases we know about. In addition to a small hospital, the Center also has an outpatient clinic and a school for rare diseases. The rooms in the hospital are the old

bedrooms of the villa, finely decorated in lovely colors. So patients can walk out from their rooms into a park and beautiful surroundings.

LH: Sounds like a palace.

SG: Yes. Physicians usually see not more than one or two cases of any of these rare diseases in their whole career. So our idea is to have 20 people with a given rare disease together in one place. It's something no-one ever did before.

LH: People with rare diseases are scattered all over.

SG: We will have room to receive foreign scientists interested in one or other of these diseases, so they can stay for a week or so to do studies that could help these patients. The Daccò Center started work in 1992. We started, as I told you, with about 20 researchers in the Milan Institute and we now have about 900 people. So the family has grown.

LH: Maybe your use of the term, naive, at the beginning was correct, because I don't think anyone except a naive young man could have dreamed such an empire could develop.

SG: I have been very lucky with my colleagues. Some of my early collaborators have, unfortunately, passed away, including Professor Alfredo Leonardi, who became the General Secretary of the Institute. He was an MD, but he took care of the administrative aspects. You may have known Professor Valzelli; he was involved in psychopharmacology and did a lot of work on aggressive behavior. Each of my collaborators has his or her own scientific personality. They work on their own grants. The Institute is a union of independent researchers.

LH: It's an amazing development. Now, let's talk about psychopharmacology. You have a book that was published in 1957.

SG: *Psychotropic Drugs* is the book you are referring to. It is the proceedings of a meeting held in Milan in the early years of psychopharmacology. A lot of clinicians and scientists involved in psychopharmacology from all around the world attended it. At that time we already had chlorpromazine, reserpine, meprobamate, iproniazid, and obviously, amphetamines.

LH: Some of the prototype drugs.

SG: One of the opening presentations was given by Professor Blaschko, a well-known biochemist and enzymologist, who reviewed all the various forms of monoamine oxidases known at that time.

LH: When was this conference held?

SG: In Milan, from 11 to 15 May, 1957.

LH: Didn't you have at the opening session, besides Blaschko, also Abe Hoffer, Erminio Costa, who must have been a very young man, Hi Denber, and Ernst Rothlin from Sandoz?

- SG: Yes. Rothlin was there from Sandoz because Sandoz had LSD and some other hallucinogenic agents. We had many important people from the field of psychopharmacology at that meeting.
- LH: I think your book was published in the same year as Abraham Wikler's book *The Relation of Pharmacology to Psychiatry*.
- SG: Well, the Milan Symposium was a very interesting meeting in that one could sense from the presentations the direction psychopharmacology was taking and the tremendous amount of work that still needed to be done to understand brain function. I see psychotropic drugs as tools to understand how the brain is functioning, to generate knowledge that could provide ideas to open new avenues for developing new drugs, more than just treatments. Actually only a few psychotropic drugs proved important in treatment.
- LH: Neuropsychopharmacology is a bootstrap operation. We get ideas from our drugs, which we use to treat our patients for developing new drugs.
- SG: Exactly. And the brain is so complicated that probably there are no other ways but using drugs for learning about its functioning.
- LH: I imagine you still have a large division devoted to psychopharmacology?
- SG: Yes, and our research in this area is not restricted to psychopharmacology but also includes neuroendocrinology and neuroimmunology. These are newly emerging areas of research. Our work in psychopharmacology ranges from basic molecular biology, to clinical work in psychiatry that we do in collaboration with others because we have no clinical arm. We are doing research with drugs in biochemistry, neurophysiology, behavioral pharmacology, endocrinology, and immunology. We also do research on psychiatric epidemiology, as well as evaluation of psychiatric service in general hospitals because, as you probably know, we no longer have psychiatric hospitals in Italy.
- LH: So the psychiatric service is provided in a general hospital?
- SG: It is provided by general hospitals. So it is very important to see how the psychiatric service works in these settings. In psychopharmacology – as you can see – we have quite a wide spectrum of activities. Serotonin has been a continuous interest of mine. In the proceedings of the Milan symposium we reported our findings on measuring serotonin in the brain. At that time, we needed ten brains from mice for one measurement of serotonin in the brain. Now, with new techniques like isotopes, ultraradiography and mass spectrometry, we can do a hundred examinations on a single brain.
- LH: Major changes.

SG: Yes, there have been a lot of important changes during the past 40 years but there is still a great deal of interest in serotonin at the Institute.

LH: It was interesting that during the 1960's, most people in this country put their bet that the important neurotransmitter in depression was norepinephrine, and serotonin was kept alive mainly in Europe. But now we've come around to thinking more about serotonin, especially with the new class of serotonin uptake inhibitors.

SG: I think that both chemical transmitters are important in depression, and possibly also some of the other neurotransmitters.

LH: We know of many transmitters now.

SG: We know that there is an interaction between serotonin and norepinephrine, and also between these and some of the other transmitters. If you touch one neurotransmitter you induce a lot of interactions.

LH: Then, in addition to neurotransmitters, we also recognize receptors and receptor subtypes.

SG: Plus transport mechanisms. New micro-analytic techniques are becoming important. Before we could measure only a mixture of serotonin, free and bound in vesicles, together. Now, with microanalysis, we can measure the serotonin that is free and is acting on receptors or various other targets. We now have ways of measuring serotonin release that causes changes at the presynaptic or postsynaptic receptors.

LH: Bernard Brodie didn't live long enough to see the resurrection of serotonin.

SG: I learned a lot from Bernard Steve Brodie. I had the privilege to be in contact with him and spend time with him. He was certainly an exceptional man, one who was able to ask the right questions. I will remember hours of discussions I had with him; it was a way for him to get new ideas.

LH: I'm glad there's a laboratory dedicated to his memory in Cagliari.

SG: And I'm glad too that we have this laboratory in Italy, because he was always very interested in science in Italy.

LH: He trained a lot of people from Italy, like Gessa and Costa.

SG: Exactly. In 1959, about two years after my first visit to the USA, I had the opportunity to see Steve Brodie again, and at that time he told me, "You should come and stay with us for a period. Why don't you call me?" I would have been very interested to spend time with him. But in 1960 I felt obliged to follow the directions in Mario Negri's will. Shortly after the will was opened I went to Miami for a meeting where I met Steve and told him that I would not be able to come because I was committed to building an institute. That was when I introduced Erminio Costa to Steve Brodie.

- LH: Is that right?
- SG: And so in a way, Erminio Costa...
- LH: Took your place.
- SG: He was senior to me, but that was when he met Steve Brodie for the first time.
- LH: What a small world!
- SG: It sure is!
- LH: As you look back on psychopharmacological experience in your laboratory, what would you think are your major achievements?
- SG: We were probably the first to show the antagonistic effect between serotonin and chlorpromazine but we didn't get any recognition for it because we were obliged by the university to publish in Italian. We were doing experiments at the time with serotonin in isolated organs.
- LH: So you followed up on Gaddum's old experiments with serotonin and LSD?
- SG: Yes, exactly, and as I said we tried chlorpromazine, among many other substances, and were surprised to see the great antagonism between chlorpromazine and serotonin. We did our experiments in several isolated organs and also did some studies in vivo.
- LH: Let me interrupt you here. This antagonism of serotonin by chlorpromazine, along with its dopamine blocking action, makes chlorpromazine somewhat similar to the newer atypical antipsychotic drugs?
- SG: Exactly. There is really no difference between chlorpromazine and the new atypical antipsychotics except that chlorpromazine is also very active on norepinephrine. I don't know if that is significant or not, but in any case there is this difference.
- LH: Interesting.
- SG: Another contribution was based on research that I did with Erminio Costa. We were the first to show the antagonism between reserpine and imipramine, the first tricyclic antidepressant. Imipramine was considered to be a chlorpromazine-like drug.
- LH: Neuroleptic.
- SG: Neuroleptic, but Dr. Kuhn in Switzerland recognized that it had antidepressant activity. Although there was already some experience with iproniazid, a monoamine oxidase inhibitor, which seemed to have an effect on mood, there was some scepticism in those years about whether a drug could have antidepressant effects. There was no animal model for depression we could use to show antidepressant activity. So since some clinical experience indicated that reserpine might have caused depression in some patients treated for hypertension, we used some of the behavioral effects of reserpine as a model for depression.

We induced changes like hypothermia and ptosis in the animal with reserpine and tried to see if imipramine antagonized these changes. It worked, and reserpine reversal became an important pharmacological test for screening and developing new antidepressants. Reserpine was replaced by tetrabenazine, a benzoquinolizine derivative, with similar pharmacological actions to reserpine in the test but, because it could be given intravenously, it was easier to work with. It was interesting to see that imipramine was an antagonist of reserpine and chlorpromazine was not. So I think the development of an animal model of depression that could be used in screening for antidepressants was also an important contribution we made.

LY: Yes, indeed.

SG: In the late 1950s we studied the effects of electroshock and showed that it produced changes in serotonin. Later on this was also shown by others, using more sophisticated techniques.

LH: So you found changes in serotonin after ECT?

SG: We made contributions to the understanding of the mechanism of action of benzodiazepines too. We have done a lot of work to characterize what was present in the brain after the administration of a benzodiazepine. For instance, diazepam is metabolized to form methyl oxazepam that is metabolized to oxazepam. These metabolites are at least as active as diazepam. So, when using diazepam, or benzodiazepines in general, one must always be aware of the possibility that the drug might have active metabolites, just as active as or even more active than the parent substance.

LH: Methyl oxazepam has actually a much longer half-life than diazepam.

SG: Exactly, and that explains the longer duration of action of diazepam than would be expected from its half-life. We worked in several animal species so we learned that not all species metabolize diazepam the same way. We also did a lot of research with benzodiazepine receptors at the time the first reports on these were published.

LH: That was in 1967?

SG: Yes, some time in the late 1960s. We also invested a lot of research in the area of anorectic agents.

LH: Fenfluramine?

SG: Fenfluramine, and dexfenfluramine, the active metabolite of fenfluramine. We did a lot of work with these drugs in various animal species, studying their mechanism of action, and showed there was an increase in serotonin, responsible for the anorectic effect.

LH: It creates a feeling of satiety.

- SG: We could distinguish between amphetamine-like and fenfluramine-like mechanisms of action in anorectic effects. There are several other agents that are not yet used clinically that have exactly the same effect as fenfluramine, for example methylchlorophenyl piperazine, an agonist of 5HT_{1C} receptors which is a trazodone metabolite.
- LH: It was developed in Italy, wasn't it?
- SG: Yes. In the 1970s we were studying the effect of drug metabolites in the action of drugs and found that in some cases the action of a metabolite differed from the action of the parent substance. For instance, if you take buspirone, it is its metabolite that explains the anxiolytic activity of the drug. Buspirone itself is not an adrenergic α_2 agonist but its metabolite is. So unless you know exactly what you have in the brain, in terms of chemicals, you don't know what to expect from your drug.
- LH: We need to know the active metabolites.
- SG: Another example is dexfenfluramine which has an active metabolite, dextnorfenfluramine, that accumulates in the body differently from the parent substance. It also differs from the parent substance in that it is a 5HT_{1C} agonist, so it has its own action on serotonin too.
- LH: So there are lots of chemicals to be tested. Do you think fenfluramine damages the serotonin system? Is that a real concern?
- SG: With excessively high doses there is a long-lasting decrease of serotonin. If one looks into the brain with various techniques, including antibodies against serotonin, it is a fact that one cannot detect serotonin in the brain. One interpretation of these findings is that there is selective neurotoxicity with fenfluramine. There is a lot of discussion at present about what the dexfenfluramine-induced disappearance of serotonin means. My opinion is that it would not have been a clinical problem and it only appears at much higher doses than those used in humans. I think it would be a very interesting area of research to establish what the neurotoxicity is, because even if serotonin is not present for a long time after the administration of fenfluramine all its functions seem to be present, and that implies that serotonin synthesis is going on.
- LH: There are probably hundreds of thousands of people taking fenfluramine, and if they don't have a serotonergic system, it doesn't seem to cause any harm. It makes one wonder about the role of serotonin in brain function.
- SG: At the time of the Milan symposium, when I started my research with serotonin, it looked as if we would progress rapidly in understanding how the brain functions, and develop drugs to take care of all psychiatric diseases. After almost 40 years, though, I must say these expecta-

tions have not been fulfilled. It is certainly fair to say we have made a lot of progress, but maybe less than we expected.

LH: Than we hoped for.....

SG: If we look back at the last 40 years we have not developed any antipsychotics that are clinically more effective than chlorpromazine. In the anxiolytic field we have added benzodiazepines and buspirone to meprobamate but they don't offer major advances. None of the new antidepressants are superior to imipramine. The selective serotonin uptake inhibitors might have a different side effect profile from tricyclic antidepressants, although even on looking carefully through the literature that is not completely clear. In any case, what we have in new drug development is still disappointing at present. Maybe studies now going on in laboratories with peptides, cytokines, and so forth will lead to advances in treatment.

LH: One of the problems is that we used the drugs as tools, as you said, to find out what they do, and then we used that understanding to pick up new compounds. If one picks compounds this way, they are bound to have actions similar what we started with. But now we are accessing post receptor mechanisms all the way down to third messengers, we should find new points in the system that drugs might attack. Who knows whether it will be different blocking the system downstream rather than the receptor?

SG: We will probably have to look for drugs in the future that don't have the same wide range of activity as the drugs available today, and if we do that we might be able to develop drugs that are more selectively effective for certain subgroups of patients. In other words, we might develop drugs for a certain type of depression but not for all depressions. But to do that will require changes in our approach to drug development because industry will not be interested in developing drugs without a sufficiently large market to get back their investment. This is a problem that needs to be solved. In order to progress we need to find a way to dissociate the development of the drug from the question of profit. There is a conflict between our needs and what companies are developing that will have to be overcome.

LH: It could be done in an independent pharmacological institute.

SG: That's true. I think we shall have to find a way in the future to bring together the know-how of industry with the know-how of independent research institutions and reconcile their interests with the interests of the public. Possibly we shall need help from the government because if we don't get these know-hows together and don't reconcile the different interests we will still have difficulty developing new drugs. It is

time to think in a different way about how to develop psychotropic drugs. Take as an example the field of antihypertensives. If you are a drug company and develop an antihypertensive you want a drug for the whole spectrum of hypertensive patients, to widen your market. But maybe what we really need is a range of anti-hypertensive agents, each addressing only one mechanism that may be present in only a fraction of hypertensive patients.

LH: We have so many anti-hypertensives that work through different mechanisms.

SG: But we don't take advantage of that to prescribe the specific anti-hypertensive agent for each group of patients. This is more or less what is happening in psychopharmacology too, when we talk about the use of neuroleptics in schizophrenic or other psychotic patients. We have many neuroleptics and one or other of these may be more selectively effective in one subpopulation of patients or another.

LH: I spent about ten years of fruitless studies on how to pick the right drug for the right patient.

SG: Maybe all the drugs we have are similar because they have been detected by the same tests. Some time ago I organized a meeting in Milan on New Tests for New Drugs, because if we continue with the same tests as today we will just have more chemical entities of the same type. So, as I said, we should probably work to develop drugs that are selectively effective for one or more subpopulations of patients.

LH: Let me ask you a personal question. You look 20 years younger than your chronological age. How do you do that?

SG: That is a compliment. Time is equal for everybody: I have no secret. I am lucky to have good health and I am interested in my work, which is a privilege.

LH: It is a blessing to enjoy one's work.

SG: I hope to see other developments in the field of psychopharmacology.

LH: I hope you will. You have contributed a lot to the field; starting as a young chemistry major you have built quite an empire, and a very good one. Silvio Garrattini, I wish you all the best.

SG: Thank you.

PAUL GREENGARD

Interviewed by Eric J. Nestler
San Juan, Puerto Rico, December 1996

EN: We are at the annual meeting of the American College of Neuropsychopharmacology in San Juan, Puerto Rico. It is December 1996. My name is Eric Nestler. I'm a Professor of Psychiatry at Yale University and it's my pleasure to introduce Dr. Paul Greengard.* I had the honor of being a graduate student in Paul's lab in the late 1970's and early 1980's, so it's a particular honor and pleasure to be interviewing you today.

PG: Thank you.

EN: I'd like to start by asking you to comment on what you think your major contributions have been in the scientific arena, perhaps, starting with the area of cyclic nucleotides.

PG: In the cyclic nucleotide area, the most significant contributions we made were the discovery of several neurotransmitter sensitive adenylyl cyclases. In other words, we found that when we prepared membrane preparations a variety of neurotransmitters that had previously been unknown with respect to their mechanisms of action had increased the level of cyclic AMP. The first of these adenylate cyclases that we studied was the dopamine sensitive adenylate cyclase, which, as we learned later on, was attributable to the D1 subclass of dopamine receptors. This was a rather important observation, because at that time it was a total mystery as to what happened when a neurotransmitter combined with its receptor. In fact, it was even argued by several people that there was no such thing as a receptor.

EN: Right. Now, turning back the clock 30 years, we've talked many times that a neuron is like a black box. Neurotransmitters would bind on the outside of the neurons and produce effects on the cells. But how they would actually produce those effects was completely unknown and finding the coupling with the adenylate cyclase was a major advance in that area.

EN: What prompted you to first look at that?

PG: That was the work of Earl Sutherland, who had been studying the mechanisms by which glucagon and epinephrine, which control carbohydrate metabolism, caused the production of glucose in liver and muscle by breaking down glycogen. That was a very beautiful series of studies which I followed from the time I had been a graduate student. Then, during the five years I studied in England, I continued to follow

* Paul Greengard was born in New York, New York in 1925.

that literature. And, the thought occurred to me that the way hormones work in the periphery might have counterparts in the way that neurotransmitters might work in the central nervous system. It sounds sort of trivial now, because it's so well established, but it was by no means clear at the time that there was any homology whatsoever, between the endocrine system and the nervous system. And, as you said, people just considered the nerve cells a black box and had no idea in terms of the biochemical sequels what happened when a neurotransmitter attacked its target cells.

EN: Very shortly after you began looking at neurotransmitter coupling to second messengers like cyclic AMP or cyclic GMP, you began looking at the next step of signal transduction; at protein phosphorylation. What prompted you to look at that?

PG: What got me interested was that I heard a lecture by a man named Don Walsh, working at the time in the laboratory of Ed Krebs, who described how cyclic AMP caused the activation of this protein kinase, which they called cyclic AMP dependent protein kinase, that they thought was probably involved in the mechanisms by which norepinephrine and glucagon broke down glycogen. In other words, it was a follow up on the work of Sutherland.

EN: To get to the next step?

PG: Taking it to the next step in this signal transduction sequence. And so the possibility occurred to me that, perhaps not only the first, but also other steps might be homologous in the brain to what occurred in the periphery. They had shown in liver and in muscle that this enzyme existed and since I was interested in how the neurotransmitters might affect target cells in the brain, I wondered whether this same enzyme might be present in the brain. So, my colleagues and I tried to find out whether there is cyclic AMP dependent protein kinase in the brain; we not only found it was, but also that it was present in much higher concentrations than in the periphery. In addition, when we did subcellular fractionation, we found it was enriched in fractions that contained a lot of synaptic material. So, that gave us a lot of confidence we were on the right track when we hypothesized these neurotransmitter sensitive adenylate cyclases and the protein kinase might be involved in mediating the actions of neurotransmitters.

EN: You mentioned previously that that notion was far from clear at the time. How did the scientific community and the neuroscience community, in particular, respond to your proposal of an important role for second messengers and protein phosphorylation in mediating the effects of neurotransmitters?

- PG: Well, it did not respond homogenously. I would say that a large majority of people greeted this concept with a scathing response, to put it mildly. Interestingly, Earl Sutherland, with whom I had spent six months studying, thought that the idea might be right and said, even if it's only 90 percent right, it would be terribly important. I was quite sure my study was right, but since so many people were opposed to this possibility, it was nice to have a man, for whom I had such tremendous respect, support this as a realistic possibility. It took a remarkably long time until it was generally accepted, which had both disadvantages and advantages. The disadvantage was that people believed we were talking a lot of malarkey. The advantage was that, for almost 15 years, we had basically no friendly competitors in the field, and so it was possible to systematically work out a great deal of the basic principles of signal transduction in the brain without competitors helping us.
- EN: When I was in my early stages of training, I think the general view was that cyclic AMP and cyclic AMP kinase were mostly involved in regulating metabolic processes in the brain and not regulating synaptic transmission, which was your original proposal. When would you say that finally became accepted, when did the majority of the scientific community come around to your point of view?
- PG: It was a very gradual thing; it was incremental over many, many years and in many small steps. Probably, the most critical period in bringing over the majority of people to the idea that what we were saying was correct was when we published a pair of papers, one in collaboration with Felix Strumwasser and the other one in collaboration with Eric Kandel and Vince Castellucci, in which we were able to show that injection of the catalytic subunit of cyclic AMP dependent protein kinase into the target cells, was able to mimic the effects of the neurotransmitter in producing a physiological response.
- EN: So, that was really the first direct evidence that a protein phosphorylation mechanism would regulate ionic conductance?
- PG: Actually, slightly before that we'd been able to show, using avian erythrocytes, which have an isoproterenol-sensitive ion exchanger, that cyclic AMP dependent protein kinase regulated that. But people are not too interested in the regulation of avian erythrocytes, and even less willing to draw general conclusions from them about what is taking place in brain. And that is a reasonable basis for skepticism.
- EN: Although, some of the mechanisms did turn out to be homologous.
- PG: Very much so, yes.

EN: It wasn't too long after your discovery of the importance of the prevalence of cyclic AMP kinase in the brain that your laboratory also found other protein kinases in the brain.

PG: That's correct. The next enzymes we found were two more protein kinases. They were actually discovered by our group in the brain, and then shown to be present in other tissues. The first one was cyclic GMP dependent protein kinase. When we were purifying cyclic AMP dependent protein kinase from lobster muscle, we found another peak which came off a column. So, we had these two peaks and found that one was preferentially activated by cyclic AMP, whereas the other by cyclic GMP. And, that led us to characterize this new class of protein kinase, which mediates the effects of a different set of first messengers and neurotransmitters than the cyclic AMP dependent kinase. The next enzyme our lab discovered was the one which is now recognized as the calcium calmodulin dependent protein kinase, which turned out to mediate many of the effects of calcium in the target cells.

EN: Most textbooks of neuroscience, written today, would describe protein phosphorylation as the major molecular event with which changes in signal transduction in the brain are mediated and that, certainly, was a view that arose from your discoveries. At what point did you realize the widespread importance of phosphorylation, because this apparently, is the important cyclic AMP mediated mechanism?

PG: Let me change your question slightly; when did I first hypothesize or believe that it might be important. That was very early on in the late sixties and the early seventies. I remember, I was on vacation with my family and I was explaining what I was doing in the laboratory to my son, Leslie. As I was explaining it, I realized that this protein phosphorylation process might not only be important in brain function, but in mediating every type of biological regulation. And then, I have to say, I strongly suspected it had tremendous variety of uses, but even the broadest way of thinking that did not compare with how broad it was in reality. I had no idea, at that time, that tyrosine protein kinases existed or that they would control cell division. Basically, I felt there are all sorts of processes regulated by phosphorylation, but I did not think that every biochemical pathway would be controlled by it, which is the way it is.

EN: In fact, something like 60 or 70 protein kinases have been cloned and virtually every cellular process is regulated in a fundamental way by phosphorylation. Then, very early on, you began to examine some of the substrates for these protein kinases and, here too, your lab was probably the only lab, in the early days, looking at that type of thing. Tell us what drove you to look for those substrates and something about

a couple of your favorite substrates you've looked at over the last few years.

PG: The work we did on the brain, as I said, derived, in part, from the work that Earl Sutherland had done with adenylyl cyclase in forming cyclic AMP and the work that Ed Krebs had done in showing that cyclic AMP dependent protein kinase phosphorylated an enzyme, which broke down glycogen. But those didn't seem likely to lead down the path to understanding neuronal function in the brain. I thought there must be substrates in brain for the protein kinases, which could account for the actions of neurotransmitters and so we started looking for substrates and prepared different subcellular fractions. It was in the very early days of SDS polyacrylamide gels. Ed Johnson, a graduate student in the laboratory, was assigned this job and he did indeed find a very weak band on the gel. We purified this and it turned out to be a protein that, at the time, we called Protein 1, because it was the first phosphoprotein we found in the brain. And then, some years later, when we identified it as being in the synaptic region, we changed the name to Synapsin 1 and, in retrospect, the reason for that was that we found Synapsin 1 is present on all of the small synaptic vesicles in virtually all nerve terminals in the brain. So, the Synapsins are incredibly abundant. Synapsin 1 and Synapsin 2, together, represent one percent of total neuronal protein. And, since they're so abundant, that's why we discovered them first.

EN: You've learned quite a bit about what functions these proteins serve in brain with the development of your Synapsin knock-out mice and also, some of the neurodevelopmental aspects. Maybe you can comment briefly on what functional role this band on a gel ended up playing.

PG: Considerably before we had the knock-out mice in the lab, a major step forward was made by collaborating with Rodolfo Llinas at NYU. He's one of the world's great authorities on synaptic physiology and, particularly, on synaptic transmission in the squid. So, we undertook a collaboration in which we injected the dephospho and phospho forms of Synapsin 1 and showed that the phosphorylated form was ineffective but the dephospho form totally abolished neurotransmitter release. Next, we injected the kinase, which converts the dephosphorylated form into the phospho form and showed that it caused an enormous increase in neurotransmitter release. That provided very good evidence for the concept that the state of phosphorylation of Synapsin 1 controlled the efficiency of release. Then we were able to go on and discover molecular mechanisms by which it does that. Although this story is not final as yet, it seems as though the Synapsins regulate

the neurotransmitter release by cross-linking the vesicles to the actin cytoskeleton so that they are not available for release. And then, when a nerve impulse comes along, it raises calcium levels. This activates a calcium kinase which phosphorylates Synapsin, and the cross-linking of the vesicle with the actin cytoskeleton is disrupted and the vesicles are now available for release.

EN: Do you see Synapsins as being a major mediator of pre-tetanic potentiation and other processes where prior nerve impulses do lead to facilitation and subsequent nerve transmission?

PG: Yes, we think they are one of the major molecular bases for synaptic plasticity, that the efficiency of synaptic transmission is determined by the previous history of that nerve ending, and a major way in which that is achieved is through the Synapsin regulation of the number of vesicles available for release.

EN: What are the other major substrates your lab first discovered and then studied, such as DARPP32?

PG: After we had found the Synapsins and had obtained good evidence for their role in physiological processes in synaptic transmission, I wondered whether it might be possible to show that different phosphoproteins were localized in different regions of the brain, in different nerve cell types. At that time, Ivar Walaas and Angus Nairn started looking for phosphorylation in different regions of the brain and they found that the striatum had several substrates for a cyclic AMP dependent protein kinase. The reason this was so prominent is because the striatum is relatively large and relatively homogeneous, so, just like Synapsin 1 is a dominant protein in the whole brain, DARPP32 is a dominant protein in this region, simply because 95 percent of the neurons, which are called medium spiny neurons, contain DARPP32. After we found that cyclic AMP dependent kinase caused the phosphorylation of DARPP32, we started looking at intact cells in slices to see whether the neurotransmitters there might regulate DARPP32, and it turned out, as we had hoped, given the location of this protein, that dopamine was able to regulate it.

EN: The studies that your lab has performed on DARPP32 have provided important insight into the mechanisms of signal transduction within the basal ganglion, how it is that D1 and D2 dopamine receptor mechanisms can interact with one another and interact with glutamate?

PG: When we first found this protein, we called it DARPP32, because it was an acronym for dopamine and cyclic AMP regulated PhosphoProtein-32. It's now clear it integrates inputs from a large variety of first messenger systems so that name is a bit anachronistic. But, the name DARPP32 is well established and it didn't seem right to change it. But certainly our

understanding of this pathway now is that DARPP32 and the downstream effectors for DARPP32, provide a major role for mediating the actions of different first messengers, including the dopamine pathway, and, perhaps even more important, integrating the actions of these different pathways. I might mention that just as DARPP32 turned out to be much more important than just the dopamine pathway, the Synapsins have turned out to be much more important than just regulating neurotransmitter release. It's now very clear from studies we've done in the last few years, that the Synapsins play a critical role in synaptogenesis. The higher the level of Synapsins, the faster the Synapses are formed, and the lower the level, the more slowly they are formed. If you remove Synapsin from nerve cells during development, they don't grow axons. If you wait until they grow axons and remove the Synapsin, they don't form Synapses. If you wait until they form Synapses to remove the Synapsin, the Synapses disappear, and if you now let the Synapsin re-express itself, the Synapses grow again. So, it's clear the Synapsins play a very critical role in the formation of and stabilization of Synapses. We also believe that various neurotrophins have a component of their trophic actions mediated through the Synapsins. So, from starting as a band on a gel and then to transmitter release, this molecule has gone a long way.

EN: Absolutely, and provided new paradigms for other people's work, as well. I'd like to shift gears and ask you different types of questions. In addition to your scientific contributions, another way to measure your contributions to the field of science is all the trainees who have been in your lab. You've had a big lab, and do you have an idea of how many post-docs and grad students you've had in your lab since your early days at Yale, and, now, through Rockefeller.

PG: Well, I stopped counting after 10,000! Seriously, I would guess it's about 200 post-doctoral fellows or graduate students that have been through the lab. It probably averages about 6 to 8 people a year.

EN: You mean turnovers.

PG: Turnovers yes.

EN: I remember when I was in the lab there were a relatively large number of people from other countries. You can probably comment on that aspect.

PG: We've had a number of people from all over the world, which has made it a very pleasant lab. We have had an international community and sometimes we have these cooking days where people bring in food from countries all over the world. In old days, men's wives used to bring

the food in, but since half the lab is now women, the members of the lab or their significant others bring in food.

EN: Pretty much every continent is covered, I think. Where have your trainees gone on to over the years?

PG: Many of them have become very distinguished leaders in the field, as you, for example, a Professor at Yale University, and that gives me great pleasure. And there are two other full professors at Yale now, who trained in our laboratory. We have people who are now full professors at Harvard and Stanford and Cal Tech, in Chicago, and Hopkins and so on. Some people have become directors of research in major pharmaceutical companies. It's been a very gratifying part of my work. First of all, I love working with younger people. It keeps you on your toes all the time, keeps your mind stimulated continuously and stops you from getting too rigidly set in your ideas. It's been very gratifying to see these young people succeed, because, in a certain sense, you feel like they are part of your family and your children.

EN: Absolutely. When you go around the country, probably in just about every city, there are trainees from your lab; it must be very gratifying.

PG: I only go to cities where there are former trainees.

EN: The other thing that has always struck me has been the career path you took to where you are today. When I began working in your lab, it became clear to me that you started out in the pharmaceutical industry, and then made the move to academia. That is a direction very few people make. Some people start out in academia and move to industry, but very few do it the opposite way.

PG: Yes. After I finished my training at Johns Hopkins, I went to England and did post-doctoral studies there for 5 years. When I came back, I was offered and accepted this position at what was then Geigy Pharmaceuticals, because I was excited about the possibility of using my scientific training and knowledge to develop drugs that would be useful for folks. And, the reason I left was because I found it rather difficult or frustrating to have what I considered a very exciting idea but have to persuade a committee to pursue the path I wanted. Although some of the time I was successful, sometimes I was not, and it was very frustrating to be convinced you were going down the right pathway then have an organic chemist, a physiological pharmacologist and a clinician tell you they didn't like that idea and not be able to persuade them of its originality. So, I thought I would be able to do the things I wanted to do more readily in academia. It had nothing to do with basic vs. applied research. In fact, in some ways, my efforts in the drug development area were more frustrating, because it required more of this teamwork I was talking about.

- EN: So, what was the actual process by which you went from industry to academia full time? Didn't you have a couple of sabbaticals in between when you made that transition?
- PG: I took a job at the New York Institute for Mental Retardation on Staten Island. The Director was one of the leading figures in Downs research at that time. But, the Institute was not ready then. During the year, while it was being built, I had this half year at Albert Einstein College of Medicine in the Bronx and a half year at Vanderbilt University. During that year, they offered me a professorship at Yale, so I asked the New York Institute Director if he would object to my taking that position and he said, no, it's a wonderful opportunity and I should do it. So, I went directly to Yale without ever actually having been at the Institute on Staten Island.
- EN: And, it was during one of those brief stints that you worked with Sutherland?
- PG: Yes, it was that second six month period. He was at Vanderbilt and I went there; the main project we did was in collaboration with Sidney Colowick and Osamu Hayaishi and we were able to demonstrate that cyclic AMP was a high energy compound. In fact, you could make ATP from cyclic AMP. It had that high energy. Also at the time, working with Al Robinson, we began to look at cyclic AMP formation in the brain but we didn't get very far with. The first project, measuring the free energy of hydrolysis of cyclic AMP, was going so well I finally spent my full time at Vanderbilt on that.
- EN: Let me ask you about your earlier training. You grew up in New York?
- PG: Yes.
- EN: And, where did you go to college?
- PG: I went to Hamilton College in upstate New York, which is where my father and my uncle had gone. In those days you went where your parents told you to and the possibility never even occurred to me that I might go anywhere other than Hamilton College. I knew from the time I was 4 years old, that's where I was going to college.
- EN: Where did you go for your graduate work?
- PG: Hamilton was a very broad, excellent school.
- EN: It's a large college.
- PG: At the time, I'd majored in mathematics and physics. First, I went to the Department of Biophysics at the University of Pennsylvania. I decided that I'd like to use my knowledge of physics to apply to medicine, because that was not long after the second World War and I didn't like the idea of using whatever talents I might have in physics to increase knowledge that could be used for the development of more destructive

weapons. Instead the idea appealed to me of doing medical physics. And, at that time, there were only two departments in the country. One was the Radiation Laboratory at Berkeley, which was doing radioisotope tracing and the other was the Department of Biophysics at the University of Pennsylvania. That department was headed by Detlev Bronx. Soon after I got there he announced he was going to become the President of Johns Hopkins. So, he moved a bunch of us with him to Hopkins where a man named Keffer Hartline, a Nobel Laureate on vision, chaired the department and Detlev was the President of the University. I did my PhD in Biophysics there.

EN: What was your PhD on?

PG: At the time that I was beginning to look for a thesis, Alan Hodgkin came through.

EN: Of Hodgkin and Huxley?

PG: Of Hodgkin and Huxley. It was before their classic work was published and he described the ionic basis of the nerve impulse. The department I was in was very biophysically oriented and I thought, in looking at the situation as a graduate student, that Hodgkin and Huxley had made a tremendous discovery and I didn't see any way biophysics would move beyond where they were for decades. That turned out to be a correct prediction. So I decided what I would like to do would be understand the biochemical basis of changes in membrane properties, membrane potential and action potential and so on. I persuaded my mentors in the department to let me work in that area and I got Sidney Colowick, who was a very distinguished biochemist and wonderful human being, to help guide my thesis. He, as the biochemist, and a man named Frank Brink, an electrophysiologist, and I did my thesis on the biochemical basis of axon degeneration.

EN: That theme helped through the rest of your career; the biochemical basis of neurofunction.

PG: Yes, except for the gap when I was at Geigy for 8 years. During that time, because I was head of the biochemistry division, my responsibility was the biochemical component of drug development in whatever area the company was working, so my activities were not only in the nervous system but several other areas. But, when I left Geigy and went to Yale, I went back to trying to understand the biochemical basis of nerve cell function, what today we would call signal transduction; although that terminology wasn't used in those days.

EN: Let me finish by asking where you see the field of psychopharmacology developing over the next decade or so, both in terms of advances in

basic neuroscience and how that information will contribute to clinical treatments?

PG: There are now a vast number of signal transduction processes known. There's not only the first messenger, second messengers, second messenger-regulated protein kinases, there's the Jak-Stat pathway and the Ras-raf pathway. And there are many hundreds of protein kinases, all of which need to be cloned and characterized. And I've long had the belief that most diseases are going to be diseases of regulation because you can't have diseases of critical steps. For example, if you had a mutation so you didn't have any nicotinic acid receptors, it would be lethal. So, it's seemed to me for decades that most diseases are going to turn out to be abnormalities of these modulation processes. You don't function quite as well and then they eventually manifest themselves in the frank expression of the disease. With the human genome project, we'll get to know the basic effects in many of the major diseases and this is going to involve a lot of signal transduction components, so the knowledge being obtained on these will be of great value in designing new drugs.

EN: Do you think that there will be potential for identifying drugs or other types of treatment that manipulate or take advantage of some of these signal transduction pathways?

PG: I think so, yes. There are a number of examples already, but it's hard to see just where they're going to come from in the future, because it's impossible right now to make really wise guesses as to which pathways are going to be defective in the various diseases.

EN: OK, I think we're all set. Thank you very much.

PG: Thank you.

LESLIE L. IVERSEN

Interviewed by Thomas A. Ban
San Juan, Puerto Rico, December 9, 2002

TB: This is an interview with Dr. Leslie Iversen* for the Archives of the American College of Neuropsychopharmacology. We are at the Annual Meeting of the American College of Neuropsychopharmacology in San Juan, Puerto Rico. It is December 9, 2002. I'm Thomas Ban. Please tell us first where you were born and something about your education, and early interests. Then we would be interested to learn how you got involved in neuropsychopharmacology.

LI: It's a privilege to be asked to join in this program. I was born in the West Country of England in Exeter, but my parents were Danish, so I'm a first generation immigrant. I was educated in Exeter at a grammar school and at the age of eighteen, I got a scholarship to go to Trinity College, Cambridge, which was a great privilege. But, meanwhile, I had to do two years military service. It was not optional, and I joined the British Navy, teaching ordinary seamen English and Arithmetic. I was posted to the Mediterranean, where I spent two interesting years, learning how to snorkel, dive and sail the boats and forgetting all the science I'd ever known.

Then, I went to Cambridge in 1958 as an undergraduate to study botany, my boyhood passion. But after one term of botany I decided to change subjects, because the teaching was very, very old fashioned, based on systematic classification of plants. They hadn't even heard about biochemistry which I decided was much more exciting. So I switched to a three year degree in biochemistry, which was, and still is, a very strong subject at Cambridge. The department was buzzing with excellent people and good teachers, so I had a very good education and ended up in final year doing nothing but biochemistry along with fourteen other students. During that time, I became convinced I wanted to do research. I had read Aldous Huxley's books, *"The Doors of Perception"* and *"Heaven and Hell"*, which influenced me greatly. It was, to a biochemist, an extraordinary story, that a chemical like mescaline or LSD, a few milligrams of a pure substance, could alter the state of consciousness and the whole way one sees the world in such a profound way. It was almost miraculous and I thought, scientists should try to understand this better. So, I became determined to do a PhD in brain biochemistry. The problem was, I also wanted to get married to my fellow-student Susan, and we both wanted to stay in Cambridge to do our

* Leslie Lars Iversen was born in Exeter, United Kingdom in 1937.

PhD's, but I couldn't find anyone who could teach me brain biochemistry. I was getting quite desperate until I met, by good fortune, my future supervisor Gordon Whitby. Gordon was a member of the faculty in the biochemistry department, but he'd been on leave in the States working with Julie Axelrod where he had been involved in the very first experiments with radiolabeled norepinephrine and the discovery, with Julie Axelrod and George Hertting, of what is now called the norepinephrine transporter. Gordon Whitby returned to Cambridge just at the time I wanted a PhD supervisor. So I became his student and was lucky to be exposed to the latest data from Julie Axelrod's lab at NIH. We were the first people in the UK. to have radioactively labeled norepinephrine. It was very early days for the subject, and I was able to study the norepinephrine uptake process using the sympathetic nerves in rat heart as the model. I made a detailed study of the kinetics of the process and the many drugs that could inhibit it, including the synthetic phenethylamines, and psychotropic drugs, including the tricyclic antidepressants and cocaine. I was getting exposed to psychopharmacology and had a great time for three years. Largely because of Gordon Whitby's contact with the Axelrod lab, I was able to meet Julie and to persuade him to take me as a post-doc. Then, I was fortunate to get the award of a Harkness Fellowship, a specialist fund, sponsoring Fellowships in both directions across the Atlantic, not only for scientists but for journalists and artists as well.

TB: Are we in the early sixties?

LI: I went to Julie Axelrod's lab right after qualifying for my PhD, which was 1964.

TB: So in 1964, you went to the States.

LI: I got to Julie's lab when Jacques Glowinski was there and he and I worked very closely on catecholamine metabolism in the brain. I became exposed to the CNS part of the monoamine story and having access to radiolabelled tracers, we were among the first to do studies with them. I had a very busy and productive year and was exposed to Julie Axelrod with his unique creativity, which I'm still a huge admirer of. Just a few weeks ago I went to Julie's 90th birthday celebration at the NIH, having gone ten years earlier to his 80th birthday. I was delighted to see him still in good spirits and intellectually sharp. So my postdoc year in his lab was a great time for me. My PhD mentor in Cambridge changed from Gordon Whitby to Arnold Burgen. Gordon Whitby left Cambridge about half way through my PhD. Arnold Burgen had come back from the Montreal, Canada to be head of pharmacology in Cambridge. He took me on for the last year and a half of my PhD and

was an inspiring teacher. He was a friend and colleague of Steve Kuffler, the great neurobiologist at Harvard, and gave me an introduction there so I was able to do a second year of post-doc in the States at Harvard in the Department of Neurobiology. The whole concept of neuroscience was still very new and I think it was one of the first academic departments in the US that had a neuroscience program. That was, again, a period of great excitement. I worked with Ed Kravitz, the biochemist in the group but I also got to know many of the others; David Potter, Ed Furshpan and Steve Kuffler who was another remarkable genius in neuroscience. This was a privileged time for me. With Ed Kravitz I got to work on GABA. The group at Harvard had been working on GABA in the lobster where the peripheral muscles have both an excitatory nerve, which we now know releases glutamate, and an inhibitory nerve. Inhibition which occurs inside the central nervous system in mammals, occurs right down at the muscle level in crustaceans. GABA was suspected to be the transmitter for the inhibitory nerves, from a number of pieces of evidence the Harvard group had put together. My job was to make a final demonstration that, if you stimulated the inhibitory nerve, GABA was released. That might sound like a relatively simple thing to do, with a nice big muscle preparation from the lobster. We used the big crusher claw, which has a muscle that controls the finger in the inner part of the claw. The muscle, which weighed about a gram, was innervated by just one inhibitory nerve fiber, which we could expose and stimulate, while washing the muscle in sea water and measuring the released GABA. The problem was that trying to measure minute amounts of GABA in large volumes of seawater, which is a concentrated salt solution, proved technically very difficult. It took me and Ed Kravitz, together with a Japanese visitor Masanori Otsuka, two-thirds of my post-doc year to work out how to do this, and only in the last three months did we get some results. We showed that there was a calcium dependent release of GABA in response to stimulating an identified inhibitory nerve. This was the first real demonstration that GABA is released from inhibitory nerves. So, that was a fruitful period and a wonderful learning experience for me. My two years in the United States from 1964 to 1966, were enormously influential both in learning how great laboratories work and in making friends and contacts in the US who have remained for the rest of my career. After that, I went back to Cambridge and rejoined the Department of Pharmacology, not as a faculty member but as a Research Fellow, sponsored initially by Trinity College and then by the Royal Society on one of their endowed Fellowships. A few years after I got back, I was appointed Director of

a Medical Research Council Laboratory in Cambridge. We called it the “MRC Neurochemical Pharmacology Unit”.

TB: What year was that?

LI: It was 1970 when that started. The Unit was a self-contained laboratory in the Department of Pharmacology funded directly by Government Research Council funds. Looking back that was a dream job, because Medical Research Council funding was quite good, even if not enormously generous. It paid for staff, infrastructure, equipment, and all the running costs and we were able to attract a number of talented post-docs and students locally and from overseas. We had a number of very able young scientists from USA, Canada, Australia and Europe. So, I spent eleven or twelve years doing that enormously satisfying and very exciting, job and during those years some wonderful people came through the lab, like Ira Black, one of our post-docs and Ian Hendry, one of our PhD students. Many, many people, who’ve later gone on to have their own independent and highly successful careers came through the lab. Tom Jessell was another, who is now doing very well in the field of developmental neurobiology. So, this was great.

TB: Did you continue your research with GABA?

LI: I continued to be interested in GABA and we collaborated with Jimmy Mitchell in the Department of Pharmacology. We were able to do some GABA release studies from the mammalian cortex using super-fusion techniques. We discovered the GABA uptake mechanism, which exists for amino acids as it does for monoamines. We discovered a glycine reuptake mechanism also. But, the two most notable events in that period in Cambridge were working on the mechanism of action of anti-schizophrenic drugs and, secondly, getting involved in the field of neuropeptides. The anti-schizophrenic drug story was started by work done in Paul Greengard’s lab at Yale, with his student, John Kebabian, who first described a dopamine stimulated adenylate cyclase in the pituitary. That was the first biochemical test tube model for a dopamine receptor, before ligand-binding studies came along. To me it was very exciting, because I’d already been interested in the idea, promulgated by Sol Snyder and others, that dopamine was at the heart of the story in schizophrenia. A lot of indirect lines of evidence were pointing towards a key role for dopamine and for blockade of dopamine receptors in the action of anti-schizophrenic drugs but the idea, until then, was based on indirect evidence. We thought maybe, we have, for the first time, the opportunity of testing this idea. Richard Miller, who was a very bright biochemistry student, joined the lab as my PhD student in 1974 or 1973, and started work on this mechanism, using

the Keababian - Greengard model, not in the pituitary, but in the basal ganglia of rat brain. He was able to show very quickly that a whole series of anti-schizophrenic drugs, the phenothiazines and the thioxanthenes, did indeed inhibit the dopamine stimulated cyclase system and did so in the rank order or potency you'd predict from their clinical potencies and known effects in animal models. We thought we had finally cracked the problem, and this was how anti-schizophrenic drugs work. Richard published a number of papers. But there was a problem; certain classes of neuroleptic agents didn't work in this model, notably the butyrophenones, such as haloperidol, which everyone knows to be a very potent neuroleptic, both in animal models and clinically. These drugs just didn't work except at rather high concentrations. And, that was true for the whole class of sulpiride type drugs also. So we knew we must have stumbled on only part of the story. A few years later Sol Snyder's lab and Phil Seeman in Toronto finally nailed this down by showing what we'd been studying was the D1 receptor and it was probable that the D2 receptor, which they identified in radioligand binding studies, was more likely the target. And that's what everyone believes today. But we had a lot of fun with the D1 research, and I developed an interest in schizophrenia research, which has been with me ever since.

TB: Didn't you get involved also in research with Substance P?

LI: While I was at Harvard, working with Ed Kravitz and Steve Kuffler, Masanori Otsuka from Japan was working on Substance P as a possible transmitter substance and he maintained a strong interest in this after returning to Tokyo. He and I remained in contact about this. My own interest in Substance P stemmed largely from Masanori's very painstaking neurophysiological work, suggesting a role for Substance P as a sensory neurotransmitter. In the central nervous system, the work of Tomas Hökfelt and other Swedish histochemists mapping SP neuron groups was also important. Tomas was the first to publish a detailed map of Substance P pathways in peripheral nerves and in the many pathways within the brain. I got into this area knowing we had to generate antibodies and immunoassays to measure the peptide. But you couldn't buy the peptide at that time.

TB: Are we in the 1970's now?

LI: We are talking about early 1970's when Susan Leeman in Boston had only just described the amino acid sequence of the peptide for the first time. I wrote to a contact at the Merck Institute in Raleigh, New Jersey. The head of chemistry there, at that time, was Ralph Hirschmann, who had made a batch of synthetic Substance P for Susan Leeman. He was very kind and gave me a 25 milligrams sample, which was a priceless

treasure, because 25 milligrams was enough to sustain the entire program at Cambridge for many years. We were able to generate antibodies and to devise our own immunoassays and immunostaining. Claudio Cuello, a visitor from Argentina made his own very detailed map of Substance P pathways in the CNS. Cuello later went to be head of pharmacology at McGill and still works in Canada. My student, Tom Jessell, was able to set up an in vitro brain slice SP release preparation using a sensitive immunoassay. He was the first to show that if you took slices of brain stem, sensory nuclei or spinal cord dorsal horn, the release of Substance P in the sensory areas was powerfully suppressed by opiates such as morphine, and that effect could be blocked by naloxone. So, we discovered one of the possible sites of action for opiate analgesics in the CNS at what we thought was one of the primary sensory relay stations, in which Substance P might be one of the pain transmitters. That was exciting and Substance P was also the subject of a collaborative study, between my lab and my wife's laboratory in the Department of Experimental Psychology. She had developed her own psychopharmacology and behavioral psychology group. We were able to do collaborative studies in animals, using one of our monoclonal SP antibodies, showing that if you infused a monoclonal antibody into the brain to neutralize Substance P, stress-induced release of dopamine no longer occurred. We believed we'd identified a possible Substance P link relevant to Substance P antagonists as antidepressants.

In the early 1980's, along came a posse of people from US Merck Research Laboratories, led by Clem Stone the head of the CNS Pharmacology at Merck. They were looking to build a basic neuroscience lab in England, as part of the company's global expansion. They wanted to be seen as a company doing research, not only in the USA and Canada, but in other parts of the world, in Japan and in Europe. They'd chosen England as one of the first targets, knowing that basic neuroscience and neuropharmacology were relatively strong subjects here. They came to Cambridge and asked would I be willing to advise them on the project. Of course, I said I'd be very happy to. So I advised them on the project, which was to build an entirely new neuroscience laboratory on a site halfway between Cambridge and London and staff it with up to three hundred people, creating a major center for all basic and pre-clinical neuroscience for Merck worldwide. It was a multimillion dollar project. Of course, they were looking for someone to head the lab. I said initially not me, "I've got a perfectly good and secure job here in Cambridge working for the government, wonderful people come to work for me, I only have to write a progress report once

every three years and I get a site visit once every six years.” In fact the good times for the Medical Research Council were about to come to an end. Things were getting a lot tougher in the 1980’s than in the 1970’s. Eventually, I saw that the Merck opportunity was just too good to miss. It was a once-in-a-career opportunity to do something much bigger than I’d done before, so I accepted the offer and started working for Merck Research in 1983. We started off in a temporary location and began recruiting people and that went well. In 1983 and 1984 there were a number of academic people looking for jobs and the pharmaceutical industry was not actively looking for people. So, we were able to hire some really excellent scientists. We had, quite rapidly, a head count of over a hundred people within the first two years and by the time I’d finished, twelve years later, it was up to some three hundred people working on science. It was a big operation and I learned what it was like to work for a big company which was different from working for the Medical Research Council in a number of ways.

TB: In what way was it different?

LI: First of all, we had a lot more money to spend and we could buy all the up to date equipment we wanted. I was fortunate to work for a company that was and is very science driven. Unlike many big pharma companies, which are dominated by accountants and marketing people, Merck has always been led by scientists, and during my period there, a scientist, Roy Vagelos, was appointed to be Chairman and Chief Executive, which was unheard of, but it worked very well. It was a period of expansion for neuroscience and a huge period of expansion for the pharmaceutical industry. It’s always nice to join an industry that is in a period of log growth! It was double digit growth every year and if it fell below twenty percent the Wall Street analysts would say something must be wrong. Of course, everybody knows in their heart that can’t go on forever, but in the 1980’s it was expected. During the period with Merck, I was able to set up a number of different projects in research. I learned the hard way about research and development in the pharmaceutical industry. When I joined, my mentor, Clem Stone, told me to expect that out of every ten projects you start, you’d be lucky if one of them succeeded and became a product for the company. Being an arrogant academic, I thought the rules would be different for me, but they weren’t. Out of all the projects I started during the twelve-year period I was there, only one of them made it to the market and that was Maxalt (rizatriptan), the anti-migraine compound. Rizatriptan is one of the sons of Sumatriptan, the 5HT_{1D} agonist, which has proved to be a real breakthrough in the treatment of migraine headaches, with one of the first pharmacological

mechanisms where you could treat the headache after it had started and stop it in its tracks. Sumatriptan from Glaxo was the first compound, but Sumatriptan had a number of deficiencies that we were able to improve on, notably, rather poor bioavailability when given orally and our compound was better absorbed orally and acted much faster. It has done quite well, particularly in the US.

I suppose one of our big challenges during my period at Merck was in the excitatory amino acid area. That was a field I'd never worked in before and we got into the area almost by accident. Merck had, before I came along, discovered a compound, which was called MK-801 (dizocilpine) that had been selected by classical pharmacology screening in an animal test for anti-seizure activity and it proved to be active orally as an anti-convulsant. Merck had put it into development for epilepsy and wanted to know how they could make it better. So my lab was assigned to find out how MK-801 worked. We tried a lot of different things. First, we set up a radioligand binding assay. Eric Wong, a talented young biochemist, did that using tritium-labeled MK-801. We could then screen the entire Sigma catalog to see whether we could find anything to interact with that binding site and we found that pentazocine and phencyclidine were moderately active competitive antagonists for MK-801 binding. That didn't tell us very much, because these were opiates of obscure mechanisms. We really didn't understand it. But then, we learned of David Lodge's neurophysiology experiments in which he described *in vivo* neuropharmacology experiments where phencyclidine and pentazocine were NMDA receptor antagonists. That gave us a clue that MK-801 might be an NMDA receptor antagonist. John Kemp and Geoff Woodruff and others in our neurophysiology lab at Merck were very quickly able to show that MK-801 was indeed a potent non-competitive NMDA receptor antagonist. It was an open channel antagonist. In other words, the agonist had to be present for the antagonist to work. We were then able to show, in a number of animal studies, that this compound had a number of properties expected from glutamate antagonists behaviorally. Notably MK-801 was a neuroprotective agent. We were keen on the idea that in stroke or other cerebral ischemia injuries, glutamate release might contribute to the damage. There were a number of animal models of ischemia, involving ligation of the middle cerebral artery or other insults to the brain to deprive it of blood flow and oxygen, and we worked with Jim McCulloch in Glasgow with those models. He was one of the experts in this area and he generated a number of examples where MK-801, given *in vivo*, was a very powerful protector against damage that would otherwise occur when

these stroke models were performed. We could rescue up to two-thirds or more of the damage that would normally occur by giving MK-801, so we got quite excited about that. We wanted to get into the clinic and test this in stroke patients. But then, we hit a problem. John Olney at Washington University, St. Louis, who had been one of the pioneers of the whole idea about glutamate as an excitotoxic chemical in brain, published a paper in *Science*, reporting that in rats given a high dose of MK-801, one could see various signs of neuropathology in certain areas of the brain, notably, in the limbic areas in the cingulate cortex. What he observed was that some of the large neurons in those areas of the brain developed a pale structure with a large number of fluid filled vacuoles and looked pretty sick within a few hours after MK-801 administration. We rushed into the lab, repeated his findings and found that the great majority of those neurons recovered to normal when the drug was no longer there. However, we had to admit there were a small number of nerve cells that apparently died in those particular areas of the brain. That became a very hot issue with the Food and Drug Administration, who called a halt to all companies working with NMDA antagonists until this issue had been resolved. And, they set down a number of experiments they'd like to see done in primates and other animals before anything went into the clinic. Merck took a look at some other data that suggested a possibility MK-801 might prove to be a hallucinogenic molecule and decided to give up on clinical development. We were of course very disappointed by that; although in retrospect we now see all the other companies that tested NMDA antagonists in stroke failed miserably.

TB: What else did you do?

LI: We continued to be interested in the NMDA receptor and we were able to start developing cell models in which different sub-units of the NMDA receptor were expressed. We began to look at some types of selective drugs to be worked with in future glutamate pharmacology. We did the same thing for the GABA-A receptors, an epic project in retrospect, which started in the 1980's and, only twenty years later, is beginning to show some fruits for the Merck Research Labs. The GABA-A receptor has α , β , γ subunits each of which is encoded by multiple genes. So, the number of possible permutations of GABA-A receptors is absolutely enormous, but we figured probably most of these don't exist in brain and by making antibodies selective to the different sub-units we were able to work out that in the mammalian brain, there are not more than twenty or so of the thousands of permutations. So we were able to set the foundations for sub-unit selective GABA-A pharmacology, which is

continuing to this day, and Merck Research now has compounds in the development pipeline which stemmed from that research.

The other big focus for the Merck lab was neuropeptides. We had inherited, again, from previous work at Merck, a series of compounds that were pure, very selective, non peptide drugs working at cholecystinin (CCK) receptors in the central nervous system and the gut. CCK is one of the gut-brain peptides. In the gut CCK affects gut motility, pancreatic secretions, gall bladder secretions, and in the stomach, the closely related peptide gastrin, is a stimulator of gastric acid secretion. But, in the brain, CCK acts in multiple pathways. Its function is not yet understood, but satiety may be one of the systems involved. The particular focus we had was the curious phenomenon that CCK can cause panic in human volunteers. This was based on studies by the Danish scientist, Jens Rehfeld and, then, by Claude de Montigny and his colleagues at McGill, Kelly and Bradwejn, who had shown that if you give very small doses, of CCK4 to human subjects by IV bolus injection, you get an almost immediate panic reaction in a dose-dependent manner. It is a remarkable piece of psychopharmacology. With clinical colleagues at Merck and by working with Bradwejn and de Montigny and colleagues in Canada, we were able to show that if you gave the Merck CCK antagonist drug L-365,260, orally, one hour before giving the CCK4 injection, you could block the CCK induced panic. That showed our drug worked in the right place and at the right time. Then, our clinical colleagues went on and did a clinical trial in patients with recurrent panic attacks. It was a six week placebo controlled trial with forty patients and showed absolutely nothing. The drug did not work; it did not reduce the frequency of panic attacks or their intensity. It was a very clear negative finding. And, if you think about it the logic was very weak. The logic says "CCK causes panic therefore panic is due to CCK". Of course, the last part is a *non sequitur*. Management at Merck decided, quite rightly, that this whole program was not going anywhere and they cancelled the drug development. Despite the fact our lab in England had made a number of attractive looking second generation compounds we had to give up that whole thing. But, that's the way it goes in the business of developing drugs. We had another neuropeptide in the lab, which was still going strongly at Merck after my departure. That was Substance P. Substance P has been one of my interests since my days at Cambridge in the 1970's. At Merck, we tried to find drugs that worked as Substance P antagonists. We had the belief they might act in the spinal cord or brain stem, and represent a novel generation of analgesics, working in the central nervous

system by non-opioid mechanisms. That was the objective. We didn't know how to find a non-peptide drug working on a peptide receptor, so we tackled this in two ways. We tried rational drug development, using the peptide itself as a model, making peptide analogues by cyclizing some peptide analogues of Substance P. That chemistry program yielded some antagonist compounds but these were not bio-available. They didn't get into the brain, being peptides, and they were not absorbed orally, so they didn't really go anywhere from an in vivo pharmacology point of view. We also tried natural product screening to see if we could find a lead. That was how the cholecystokinin program had started at Merck some years earlier. We tried to do the same with Substance P. We plugged our assays into a large lab in Spain doing such screenings for Merck, and we ran screening, which we thought at that time was on quite a large scale, about 50,000 tests a year for two years. Nowadays, you do that in one week. At the end we had absolutely nothing, so we had to pull that program. By the late 1980's we had to admit that we hadn't got anywhere at all with our Substance P program, and were about to give it up. But then the first real breakthrough came in this area, the Pfizer SP antagonist was presented in a paper published in January 1991. This was a non-peptide antagonist molecule with sub-nanomolar affinity for the NK1 receptor relevant to the action of Substance P. The whole field broke open from that discovery. We discovered, along with many other companies, that if we searched the Merck chemical library using the Pfizer pharmacophore we could pull out other compounds that had reasonable activity at the Substance P receptor, and could develop our own chemical series. We went into this in a very big way, with chemistry on both sides of the Atlantic, and, generated multiple series of NK1-selective Substance P antagonists. We tested them in a number of animal tests, thinking naively, that once you had the Substance P antagonist, you'd be able to understand what Substance P was all about very quickly. And, of course, life isn't so simple. We found that in pain models these compounds were not particularly good analgesics. In fact, in most acute pain tests, in which morphine works well, the Substance P antagonists didn't work at all. Only in chronic models of pain did the SP antagonists appear to have some beneficial effects. More than twelve clinical trials have been reported by Merck and others for different types of clinical pain in which the SP antagonists have not been found to be effective pain relievers. Our original idea just didn't work but by the time I left Merck, we'd developed another idea.

TB: When did you leave Merck?

LI: I left in 1995. By that time, we had picked up on the idea that the vagus nerve, has a large proportion of SP-containing sensory fibers and one of the functions of these fibers is in the vomiting reflex. The vagal nerves go to the nucleus tractus solitarius and then to the nearby area prostema and that's the vomiting reflex circuitry. We showed in animal models that Substance P antagonists were very potent antiemetic agents and they worked against a wider range of emetic stimuli than the classical 5HT₃ antagonist drugs, then the clinical gold standard. They also worked in the "secondary phase" of vomiting seen in cancer chemotherapy with agents such as Cisplatin (cis-diamminedichloroplatinum) that can go on for several days and is relatively unresponsive to 5-HT₃ compounds. The Merck development compound 'Emend,' a Substance P antagonist went into clinical trial, just after I left the company and was, indeed, very effective as an antiemetic against the secondary phase nausea in cancer therapy. It was subsequently approved and marketed.

The other discovery made after that was what I call a 'rainy afternoon experiment' by one of our scientists. When you finish your week's work on a Friday afternoon, particularly if it's raining, and do an experiment because you have a good idea, that is what I call a "rainy afternoon experiment." Nadia Rupniak in the behavioral lab at Merck did something like that. She did a Substance P antagonist study using an animal model predictive of anxiolytic-antidepressant activity. In the model the infant pup is separated from the guinea pig mother and the pup emits distress by vocalization than can be picked up and recorded. If the animals are treated with antidepressants, such as fluoxetine or with anxiolytics such as diazepam, this phenomenon can be prevented or reversed. Nadia showed that the Substance P antagonist she had available did so in a very potent way. Then, she went on to show similar activity in a number of other of these compounds. Merck senior management took the bold move of going straight into the clinic for a trial in depression, doing a head to head comparison study with paroxetine, one of the SSRI antidepressants and showed that the Substance P antagonist used in that study was as effective as paroxetine and lacked the sexual dysfunction side effect that seemed to affect a high proportion of SSRI treated patients. That compound went on to further development and Merck management learned some of the rules about antidepressant drugs, namely, that they don't always work in clinical trials. They were very disappointed by a second study done in 650 patients, a dose- ranging study, using fluoxetine as the positive comparator. Fluoxetine didn't work and the Merck compound didn't work and the probable explanation is that the patients included in the study were

suffering from mild depression, and the placebo effect, which is well known to be greatest in mild depression, killed the outcome. Having worked with neuropeptide pharmacology for thirty years, it was gratifying to see some practical outcome with 'Emend' from all that.

Those are some of the highlights of my time at Merck. Some of the other things that could have happened, but didn't happen, might be worth mentioning. When I first joined in the early 1980s Merck had just completed a large scale clinical trial in the USA and Canada with one of the first SSRI's, zimelidine. Zimelidine was developed by Arvid Carlsson and the Astra Company in Sweden, and by that time it was already on the market as an antidepressant in Europe. The findings in the Merck clinical trials with zimelidine looked wonderful, with very good clinical data. I think it was a 4,000 patient, very large scale, Phase 3 study. I was there at the Clinical Neuroscience Group at Merck, when they were packing up all the papers that go from floor to ceiling for the FDA NDA submission. They hired a truck to take the papers to Washington. Merck could have been first in the U.S. market with an SSRI, but the compound developed serious complications. In Europe, there were some Guillian-Barre Syndrome episodes, and Astra, rightly decided to pull the compound off the market. So, it never got to the market in America. Merck had another shot at this, a few years later with another SSRI, fluvoxamine, licensed from Duphar, a Dutch company. That went into early stage clinical trials and caused nausea, vomiting in a large proportion of patients and Merck stopped further development.

I've been enormously privileged to work in world class labs in the US and to work for a world class company, which has been a huge learning experience for me. A great deal of good science has come from the Merck lab, and I was given a great deal of autonomy in the scientific direction of an entirely new program of neuroscience projects.

TB: What did you do after you left Merck?

LI: I'll just add a couple of notes about my interests since leaving Merck. Since leaving Merck, I have developed quite a strong interest in cannabis pharmacology. Again, as with many things in life, partly by accident, I was recruited by the UK Government's House of Lords, inquiry into the medicinal use of cannabis about five years ago, and had to advise their Lordships on what questions to ask and what witnesses to call on this issue. I had to learn quickly about the field myself, which I hadn't worked in before. I became very interested in the subject and the House of Lords produced a report, suggesting there may be some grounds for the medicinal use of cannabis in certain conditions, particularly, multiple sclerosis, and left it at that. The government of the day, in 1998, said we

don't want to know about that, because we know we're not going to do anything on this issue. They looked at the medicinal use of cannabis as a gateway into legalizing the drug and didn't want to take this up. This was in 1998. And, it is interesting to see how the field has developed with the discovery of cannabis receptors, endogenous cannabinoids and the prospects of a whole new pharmacology evolving. The potential for developing new medicinal agents in this area is very great. Attitudes to the medicinal use of cannabinoids have changed quite markedly just in the last two or three years. The Medical Research Council in Britain sponsored two quite large scale trials of oral cannabis extract vs. pure tetrahydrocannabinol vs. placebo in patients with multiple sclerosis, a 600 patient study, and in patients with chronic pain, which is a 200 patient study. This is, for the first time, a proper scale clinical study on whether cannabis works or not. There's also a commercial company in Britain, G. W. Pharmaceuticals, who are doing their own clinical trials of a herbal cannabis extract in MS and pain and a number of other indications. Our government has said that if adequate clinical data can be produced to the regulatory agencies, they will declare cannabis no longer to be an illegal drug for medicinal use and they will sanction and license it. That will be, if it happens, a large advance. On our side of the Atlantic, things are happening. Even politicians are getting the message that the way in which we're waging war on drugs is not working. We try to convey to young people that cannabis is a poisonous, deadly drug. This is something that is counter-intuitive to them, because they see their peers and even their parents smoking cannabis without harm. So, they just don't believe the government message.

TB: What are you working on right now?

LI: In my present job, I'm a part-time academic at King's College, London. In the merged medical school of Guy's and St. Thomas hospitals at Kings College we're building a new research center for age related disease on the Guy's campus. Indeed, we have already built the center, courtesy of a large charity grant from Lord Wolfson and his Foundation. I'm trying to help them build that into a world class center for Alzheimer's disease research, a topic which is very much neglected in Europe.

TB: So, that's what you have been doing these years?

LI: In addition, I have been advising small companies how to get off the ground in the biotech pharmaceutical area. I work with a small company in California, one in Germany, and one in Denmark. I have my own small company in England. I advise venture capital funding in Denmark. I do various things, which tap into my experience over the years as a scientist and as a pharmaceutical industry executive.

- TB: You have been involved in neuropsychopharmacology for a long time. When did you attend the first meeting of the ACNP?
- LI: I think in the 1970's. I was invited to one of the catecholamine sessions, but I wasn't a member until the mid 1980's. Since then I've been a fairly regular attendee. I find it very beneficial to hear what's going on in the field. It's one of the best places for finding out what's going on.
- TB: You mentioned that you had been working with your wife, who's a psychologist.
- LI: Yes, Susan joined the Merck labs shortly after I moved there and she headed a substantial group of behavioral pharmacology scientists for about nine years and left to take a Chair of Psychology at Oxford, which is where she is now.
- TB: Didn't you write a book with her?
- LI: Yes, in the 1970's. Susan wrote most of this short textbook on behavioral pharmacology, which we felt there was a need for at the time.
- TB: It was a very successful book.
- LI: Yes, as textbooks go. More recently, with my cannabis interest, I've written a book on *The Science of Marijuana*, also for Oxford University Press, which I enjoyed doing. It was an attempt to bring a neutral scientific analysis of the evidence, pro and con, to a general well educated but not a scientific readership. That book did quite well, going into paperback, and had a 2nd updated edition later.
- TB: When did you publish your first paper?
- LI: 1962.
- TB: Wasn't it on norepinephrine uptake?
- LI: Yes, the very first study we did was repeating some of the work done at NIH in Julie Axelrod's lab. It was on what happens when you inject radiolabelled norepinephrine intravenously into a mouse. When you inject a catecholamine intravenously, after a certain period of time, it will disappear. But that was not actually what was happening. When you inject the radiolabelled norepinephrine in a low dose and follow it over time, a lot of it disappears in the first few minutes but almost half remains in the animal for many hours. What happens is that some the injected NE goes to the liver and gets metabolized rapidly by COMT and monoamine oxidase, but some gets taken up by peripheral sympathetic nerve endings and stays until it gets released and eventually disappears. And this takes hours. We were able to show that epinephrine was somewhat less vulnerable to uptake and retention than NE.
- TB: Where was it published?
- LI: *British Journal of Pharmacology*.
- TB: What was your most recent paper?

- LI: If you count reviews, the one I'm most proud of is a large review on Cannabis. It was published in the journal, *Brain*, a distinguished neurology journal. It is unlike the book I wrote on the subject, a much more detailed academic review.
- TB: What would you think is your most important contribution to the field? You moved in your research from uptake mechanisms to Alzheimer's disease.
- LI: I think my contributions to schizophrenia were, at the time, quite important, but rapidly superseded by more important events. In the neuropeptide field, I'm pleased to have been one of the pioneers of the field, who kept with it for many years. Tomas Hökfelt and I, now sit down together and remember we stayed with this for thirty years and we're finally seeing some results from it. So, that's incredible. We can't claim to be the ones that produced all the results, but we were there in a pioneering field, popularizing the idea. That was important.
- TB: What would you like to see happen in the future in the field?
- LI: I would like to see a better way of conducting clinical studies in Alzheimer's disease, which, I think is urgently needed. It's very gratifying to see the enormous basic research and pharmaceutical company effort in this area, not just treating the symptom but the illness itself, understanding the molecular and genetic basis. We've made really big advances, but I think clinicians will admit they're still very poorly equipped to identify the right patients to treat at the right time. If we find a new drug that interferes with the process of Alzheimer's disease, we need to identify patients in an early stage of their disease. By the time you get clinical symptoms, you've probably lost a significant amount of brain tissue and there's no pharmacologist in the world, who's going to put that back. The challenge in this aspect of psychopharmacology is to find better ways of looking into the human brain, seeing how to visualize the amyloid, which is beginning to happen, having better diagnostic imaging and neuropsychological tests.
- TB: Is there anything else we should have on the record?
- LI: I'm delighted to see, in the field of schizophrenia, we finally, in the year 2002, are beginning to see the pay off from the human genome project. We're beginning to see the first real insights into the genetic basis of psychiatric illness. Schizophrenia may be one of the first and that's tremendously exciting. It's a whole new era of fresh targets and pharmacology.
- TB: I think we should conclude this interview on that note. Thank you very much.
- LI: It was my pleasure, thank you.

MURRAY E. JARVIK

**Interviewed by Thomas A. Ban
Acapulco, Mexico, December 14, 1999**

TB: We are at the thirty-eighth Annual Meeting of the American College of Neuropsychopharmacology in Mexico at the Acapulco Princess. It is December 14, 1999, and I will be interviewing Dr. Murray E. Jarvik* for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Can we start from the very beginning? If you could just tell us when and where you were born, grew up, say something about your early interest, education and we can move on from there.

MJ: I was born June 1, 1923 in New York City at the Flower Hospital on 5th Avenue, and I lived in New York until I was twenty-one. My family owned a small house in the Bronx and we lived there until the Depression. My father became ill during the depression which was not a good time so we lost our house because we couldn't keep up the payments. I come from a small family, just my Mother, father, brother and me, and my father became sick about 1935, had a heart attack and died. He was fifty-one years old and I was eleven. We had no source of income and had to go on welfare, what was then called relief, and we were very poor. The house was taken over by the bank and we spent the next couple of years moving from apartment to apartment, taking advantage of what was colorfully known as 'concession', where they would let you live free for a couple of months, just to get tenants. This was during the depths of the depression.

TB: We are in the mid-1930s?

MJ: In 1935, when a cataclysmic event happened in my life. I got rheumatic fever and some of the worst sequelae, including aortic insufficiency and rather severe heart disease. Somehow I managed to keep going before the days of penicillin, when the only therapy was bed rest. So, two bad events happened very close together in my young life; my father died and I got rheumatic fever. At the same time we also lost our house. Nevertheless, my mother did the best she could and, in 1939, things began to look up for us. That was the beginning of World War II and the depression was beginning to end because the United States was gearing up for the conflict. We moved to Washington Heights where I went to George Washington High School. One of my classmates was Henry Kissinger although I didn't know him particularly well. After high school my mother managed to get work and supported me and my brother. He was ten years older and working in

* Murray E. Jarvik was born in New York, New York in 1923. Jarvik died in 2008.

the Physiology Department at Columbia University. This was on 168th Street in Washington Heights. He, also, was a major support for the family. The next big event that I remember was Pearl Harbor. At the time I was in City College in New York, an excellent college and I remember Franklin Roosevelt's December 7th speech. At the time he delivered it I was in Physics class. I'll never forget that. They were showing us how sound could be converted into light waves. They hooked things up to the radio and we could see the sound converted to light waves, transmitted through a photoelectric cell. What was coming across was President Roosevelt giving his speech. So that's how I heard about the beginning of the war. Because I had rheumatic heart disease I wasn't eligible for the army and stayed in college. I was first a Chemistry major but decided Chemistry wasn't what I was interested in. Psychology was more my interest so I switched majors. I studied under some pretty good psychologists and got a part time teaching assistantship in the psychology department that had a big influence on my career.

TB: When did you graduate?

MJ: I graduated from City College in 1944, and since I wanted to go out to the wonderful west coast, I wrote letters to colleges in California. Sure enough, there was an opening at UCLA; they needed a teaching assistant in Experimental Psychology. I didn't have any real training, but I did have a Bachelor's degree and they offered me the position. My salary was \$750 a year. That seemed like a fortune so I went from New York to the west coast. I remember the long train trip, and the wonders of Los Angeles, compared to New York. In 1945 I started in the Psychology Department at UCLA as a teaching assistant to Dr. Roy Dorcas, who had recently come from Johns Hopkins with Knight Dunlap. It was such a different life, living in Los Angeles. I stayed in a student co-op and made a lot of interesting friends. One of the most interesting was a fellow teaching assistant, named Gordon Tompkins. He was three standard deviations above the rest of the class in his abilities and very smart. So, we got to be friends; Gordon was eighteen and I was twenty-one. He was an only child, his father was a doctor and his mother a pianist. Gordon went on to become an eminent molecular biologist. He went to Berkeley and I followed after I got a teaching assistantship there.

TB: When did this happen?

MJ: This was in 1945 or 1946. There was a lot of intellectual activity at Berkeley but not the radical student activity that occurred years later. I forgot to mention one other thing. When I was living at the student co-op in Los Angeles, I met Leonard Lindey, a roommate who became another friend. There were three of us in one room and we paid \$27 a

month for room and board. I think the co-op still exists; it was a good deal!

TB: So, you made another friend, Leonard.Lindey?

MJ: Leonard was an undergraduate at UCLA; by coincidence, we met again years later. I'll come back to that.

TB: So, you moved from UCLA to Berkeley.

MJ: I was a graduate student now in Psychology interested in Learning and Memory. I worked under Edward C. Tolman and learned how to run rats in mazes. Everybody in the department had to learn this, even if they were studying to become clinical psychologists. I was interested in Philosophy and I'd read a lot of Burke and Russell. There was a philosopher at Berkeley whose course I took. Now I'm 76 years old I can't remember his name; although he was well known. He was teaching probabilistic positivism and that interested me a lot. So, my PhD thesis was on gambling, gambling in rats mind you, and also in humans. My first paper was on *The Gambler's Fallacy*. It was based on the thought that if you toss a coin and it comes up heads three times in a row, you're going to bet it's going to come up tails the next time. That's a fallacy, of course. I did work under another psychologist named Agon Brunswick who became my thesis chairman. Brunswick had come to this country from Vienna. He was actually a Baron. Agon Brunswick was a fascinating teacher with a strong philosophical bent, interested in Probability Learning. I became interested in Probability Learning and, by coincidence, went to work as a research assistant for his wife, Elsa Frankel Brunswick. At the time, there was a big project on Racial Prejudice.

TB: When was this?

MJ: This was in 1946 or 1947. This wasn't long after the Nazi era ended in Europe and there were a lot of very intelligent refugees from Germany and other parts of Nazi occupied Europe at the university. Elsa Brunswick was Jewish, Agon Brunswick wasn't, but he left Germany because of her. It was my good fortune to work for both of them. Then, something else happened in my life, which was unexpected. It shows you how bad things can sometimes turn out to have good fallout. I came in contact with a social worker. I told her I had rheumatic heart disease and she said, "Well, you may be eligible for some kind of support for vocational rehabilitation. We can send you to school. What kind of school would you like to go to?" I said I'd like to go to medical school. Sure enough, in those years, the rules were such that she could get support for me in medical school, at least for tuition. I had not even dreamed I would be able to afford to go to medical school, so this was a wonderful thing.

TB: What year was that?

MJ: This was in 1947. In the meanwhile, I had worked towards my PhD, but hadn't finished. Still, I took advantage of the possibility to go to medical school.

TB: So, you went to medical school. Where?

MJ: University of California, San Francisco. At that time, the first year for both schools, was at Berkeley, so I stayed there. The first day I registered I met Leonard Lindey, who, as I told you before, was one of my roommates at UCLA. We decided to be partners in Anatomy, worked on the same cadaver, and became very good friends over the next four years. During this time, I spent the summers back in the Psychology Department, where I could work on my thesis and do a little research. It was pretty clear to me I was going to specialize in some kind of research, probably related to behavior, even though I was also going to get my MD.

TB: When did you get your MD?

MJ: I got my MD in 1951.

Leonard and I kept in touch off and on all these years and just recently he told me that next year we've got to celebrate our fiftieth anniversary, "It's going to be our fiftieh, 1951 to 2001, the year after next." I said, "Yes, if I'm still alive", and there was some question about that.

TB: What did you do after you finished medical school?

MJ: When I finished medical school I felt I'd like to find out what goes on in the brain; when and how something becomes a memory. The reason for that was I'd been running rats with Dr. Tolman and the other people in the psychology department and all of them were interested in learning and memory. There was controversy at that time about the nature of learning in memory with Tolman having one theory and Clark Hall at Yale having another and, of course, those of us at Berkeley were very biased toward the Tolmanian theory. But all those theories were superficial. This was black box psychology; people didn't know what was going on in the brain. I thought, there must be somebody in the country who, is looking into the brain, and, of course, there was. He was Karl Lashley, professor at Harvard at that time. So I wrote to him and asked if I might have a job with him. And, as luck would have it, he did have a job for a research assistant in Orange Park, Florida at the Yerkes Laboratories, which was a monkey and ape colony. Lashley had a grant from the Navy to do brain operations and see how this would influence learning. He had already established a name for himself doing brain operations in rats and just about the time I met him, he came up with a theory of equipotentiality, which I think has been largely disproven

over the years, but at that time it was considered to be good stuff. So, I moved from Berkeley to Orange Park, Florida.

TB: What year did you move from Berkeley to Orange Park?

MJ: This was in 1951 or 1952. At that time Orange Park, which is a suburb of Jacksonville, was part of the deep-south. There was no institution of higher education in Jacksonville, except the Jacksonville College of Music, which was a small place where Lashley used to go to practice his cello. The Yerkes Laboratory was also out in the country. There must have been a hundred chimpanzees and a large colony of monkeys so I started to do some brain surgery on monkeys with Lashley. But after a short time, I decided I didn't like the sight of blood. It was amazing how Lashley operated. He didn't use any sterile technique and there was no air conditioning in those days. I remember to this day the sweat pouring from his brow into the the wound while he he was operating on a monkey's brain, but the monkeys always seemed to survive anyway. At that time, I got interested in One-Trial Learning. There was a lot of interest in Wisconsin in learning because of Harry Harlow. It took hundreds of trials to train monkeys to do a simple discrimination, but I found if I used colored breads, flavored with capsicum or quinine, they could learn in one trial. Unfortunately, another bad thing happened to me while I was at the Yerkes Laboratory.

TB: What happened?

MJ: There was some land for sale near there. I bought ten acres of land for \$27, and thought I'd put a trailer up and live there, rent free. I did that, but one day I found I was unable to get out of bed. I couldn't move, had a high fever and was alone. I was just lying there and thought, I'm going to die. I can't move. But, after several hours, one of my colleagues noticed that I didn't come to run my monkeys. I ran my monkeys seven days a week and when she noticed I hadn't showed up, she and her husband came out to my trailer and found me. They took me to the hospital.

TB: What did you have?

MJ: I had bulbar polio, and this was before the Salk vaccine. I managed to miss two important things, penicillin for rheumatic fever and the Salk vaccine for polio. In a way, I was lucky, because the polio didn't kill me. It was only bulbar. The rest of my body was OK, but my vocal chords and my swallowing apparatus were partially paralyzed and I couldn't talk for awhile. I recovered, mostly, but I've never recovered fully. I still have trouble talking and I'm only speaking with one vocal chord. Things were so bad that my brother, who was living in Stanford, said you've got to come to Stanford and recuperate here. So I did. I had been at

Yerkes for about a year and a half and it was time to leave. I looked for a new position and found one in New York. Heinz Lucas Tarboro was a physiological psychologist, very much interested in the brain, and he said, "Well, there's a position opening at Mt. Sinai Hospital and maybe we can get you a job there." It was an interesting job, indeed. I went to see Dr. Hoffman, who was the head of psychiatry at that time at Sinai, and he said, "You can become a Fellow in the psychiatry department and work here at Mt. Sinai Hospital; we have a special project we would like to put you on."

TB: What was the project?

MJ: It was the study of a new drug, which they'd just heard about. This was in 1952. The substance was called LSD-25 (lysergic acid.) They told me a little bit about it as well as about Hoffman's work, and I thought, that sounds fascinating, I'd like to work on that. The fellow in charge of the project was named Harold Abramson. He was the one who actually hired me and paid my salary, even though I was stationed at Mt. Sinai Hospital. Harold Abramson was an unusual person. He was a physician, who was really a physical chemist, but also practiced psychoanalysis. I didn't know then how he was able to get money for his research from a wealthy donor, whose name, he told me, was Dr. Geschichter. "Is that really his name?" I asked, and he said, "It is and, we're going to have a meeting with him." Sure enough, Dr. Geschichter from Washington, DC showed up and he said, "Yes, we are going to study this new drug. It has very interesting characteristics and I'm donating this large sum of money, out of which we'll pay your salary. I think it was \$6,000.00 a year, which seemed like a lot of money at the time. So, we set up this project. I remember we were given a suite of rooms in the basement at Mt. Sinai Hospital and we advertised in the Village Voice to get subjects who were willing to take LSD. There were no committees for the protection of "human rights," so we got a lot of people who volunteered, not knowing what they were going to get. I must have had about a hundred subjects on 50, 100, or 150 micrograms of LSD. I remember taking fifty micrograms myself, but I didn't get much of an effect. Some of our subjects did get hallucinations and disturbances of thought and my job was to to examine the changes in psychological functioning the drug produced. I worked with a staff and we produced a lot of papers.

TB: What kind of tests did you use?

MJ: We used a battery of tests which included reaction time

TB: So you used a battery of performance tests.

MJ: Performance tests primarily, and we got a dose-response relationship that was pretty good. LSD really did impair performance. Looking back

what was surprising to us was the small dose, the extreme potency of this substance. By the way, we had no trouble getting LSD. Sandoz was very cooperative. Louie Burcher, a Sandoz representative, used to come with a large valise full of LSD. We didn't have to go through any red tape in those days, which was both good and bad.

TB: What years were you at Mt. Sinai?

MJ: I spent from 1952 to 1955 at Mt. Sinai. The most interesting thing of all happened in 1954.

TB: What happened?

MJ: I met my wife, Lissy Jarvik, who was an intern at Mt. Sinai Hospital. She had wandered into my lab, lost somehow, and we got acquainted. One thing led to another; it was a very lucky thing for me. We were married at the end of 1954. That was just about the time I was ready to leave Mt. Sinai. I got a lead from somebody that there was a new medical school, opening in the Bronx, Albert Einstein College of Medicine. So, I got in touch with the prospective chairman of Pharmacology, Alfred Gilman. He interviewed me and said, "You've had experience working on drugs and behavior. It looks like there's a renewed interest in that. Maybe you'd like to join my new department." I replied, "I certainly would". Gilman was already well known for his book, Goodman, and Gilman, on Pharmacology. So I went to this new school, Albert Einstein, which was part of Yeshiva University, and I was the first one, besides Gilman, in that department. Then he recruited a lot of other people, all of them very good. Gilman was very helpful to me. He told me he was on a council at NIH and suggested I should apply for a grant. He also told me he would help to prepare it. He did and I got the grant. It was just amazing, my first grant. It was \$15,000 a year and out of that, I was able to hire two assistants to set up a monkey laboratory. \$15,000 was like \$150,000 today. That was the beginning of my career in Psychopharmacology. He also did something else, which was very good for me. He said, "There are new drugs coming out for the treatment of schizophrenia. Why don't you look into it and in the next edition of Goodman and Gilman maybe you'd write a chapter on Drugs and Psychiatry"? And I did; I wrote the chapter on Psychopharmacology for the next three editions of Goodman and Gilman which came out every five years. This was the 1960 edition and I was able to recount the amazing advances in Psychopharmacology from 1950 to 1960, a period in which all the new drugs came on the scene, starting with reserpine and chlorpromazine then followed by antidepressants. In 1971 I left Albert Einstein after seventeen years, from 1955 to 1972.

TB: So while you were at Einstein your primary area of research was on the effect of drugs on performance tests?

MJ: That's true. I also did some interesting memory experiments. Remember my friend, Gordon Tompkins? He was by then Chief of the Molecular Biology branch at NIH, and he said, "You're interested in memory. Why don't we look at the role that DNA and RNA might play in it. I'm going to put you in touch with a young psychiatrist, working in my laboratory. His name is Samuel Barondes". Sam did experiments with some new compound, like puromycin and actinomycin. In the meanwhile, I had devised a one-trial learning test for mice. So we gave intracerebral injections of puromycin and actinomycin. Puromycin is a protein synthesis inhibitor and actinomycin is an RNA synthesis inhibitor. We found both of these substances impaired memory. We gave the injections post-trial at different intervals and got retrograde amnesia, which was related to the inhibition of synthesis of both protein and RNA. I was also interested in the effect of electroshock (ECT) on mice. We got a nice curve of retrograde amnesia using ECT, which bore out what had been reported in the clinical literature following ECT. This was my first paper that was published in *Science*.

TB: When was it?

MJ: It must have been around 1962 or 1963. During these years I had a number of foreign fellows who worked in my laboratory. The fellow who worked on retrograde amnesia from electroconvulsive shock was Rudy Kopp from Germany and he was senior author on the paper in *Science*.

TB: What happened to your research with LSD?

MJ: After 1970, I didn't work much with LSD anymore. By this time LSD was becoming something you didn't work with. It had become an underground drug; Sandoz had already pulled it off the market. They weren't even making it, let alone distributing it. It had to be manufactured illicitly. So, I decided it was time I didn't work with LSD anymore; although I was interested in it and still am. It's a fascinating drug and we don't know exactly what its mechanism of action is yet or why it is so potent. But working with LSD played a role in my subsequent career.

TB: What was your subsequent career?

JW: Around 1970 or so, I met a fellow, who also had worked with LSD. His name was Louie J. West, Jolly West, and he was starting a department at UCLA. He was moving there in 1969 and would I be interested in coming? I was very interested, because I was tired of New York and the New York winters. We didn't move permanently in 1970. It was just a sabbatical year I took first. We had to negotiate for a job for Lissy, because Jolly had only offered me a job. At the end of the year, I went back to Albert Einstein and had to tell Gilman I was thinking of leaving. Then, after another year we left for good and went to Los Angeles

where we've been ever since. Jolly managed to get a job at the VA for Lissy. We thought that wasn't so great, but it turned out to be an excellent opportunity for her. At that time the West Los Angeles VA was affiliated with UCLA; it was the premier VA hospital in the United States. Jolly had engineered a split between two branches of VA hospitals; Wadsworth was to become the medical branch, and Brentwood the psychiatric branch. He put one of the members of his own department, Phillip May, in charge of the hospital which was great, because, both Lissy and I were then able to work for Phil. But they didn't have any space for us. West said that they were renovating some buildings. There was an earthquake in Los Angeles in 1971, and one of the buildings had been shaken up so this was the reason for renovating. Anyhow, Jolly said, "We're going to renovate this building and when it's finished, you'll have lab space in it. In the meanwhile, we'll put up some temporary trailers and you can work there". So, they built six trailers and Lissy and I each had two. The others were given to somebody else. This was 1972, and we're still in the trailers. We never moved out although there was a lot of space. Now the trailers are so old they're beginning to fall apart, but we've had a lot of good use out of them. I just remembered another major change in my career that happened around 1970.

TB: What happened?

MJ: I got an invitation from the American Cancer Society. The background to the invitation was that a few years before, Luther Terry, the surgeon general, had issued his first report on the ill effects of smoking. The American Cancer Society knew I had been working on the behavioral effects of drugs, so they asked me whether I would be interested in working on the behavioral effects of nicotine and cigarette smoking? I thought, that sounds like an interesting idea. So, they said, "If you apply for a grant, we'll help you to put it together and see if you get it." Not surprisingly, I got the grant and what I was planning to do was to study cigarette smoking in animals, where you can control things.

TB: What animals did you use?

MJ: What animal was the best for this? Monkeys, I thought. So at Albert Einstein, I set up a monkey laboratory with a cigarette smoking apparatus but it turned out to be a much tougher problem than I thought. People may take to cigarettes very readily, but monkeys don't, nor does any other animal. Still, I managed to force monkeys to inhale smoke in order to get water but they didn't smoke the way humans do. Other people in the world have tried to do the same thing, but so far as I know to date, nobody has got any animal to smoke the way humans smoke cigarettes. There's one exception and that was the thing that

really forced me to continue with this monkey business; when I was at Yerkes Laboratories there was a female chimpanzee, named Alpha, who used to smoke cigarettes. The keepers, every morning when they went around to feed them, would give her a cigarette and she smoked it just like a human being, held it in her hand and puffed deeply and exhaled the smoke. I thought if chimpanzees can do this, monkeys could do it too, but my monkeys never did. I decided there's another primate species that maybe easier to work with and so, I switched to humans. At that time there were plenty of human smokers around. Everybody I knew was smoking. When I was in medical school sixty percent of my classmates smoked but I never did. When I was still at Albert Einstein there was a visit from a Nobel Prize winner to Murdoch Ritchie's laboratory. I've forgotten his name, but he was from Sweden. Both, he and his father were Nobel Laureates. When I told him I was interested in cigarette smoking, and I had smoking monkeys, he said, "Do you know we're interested in smoking in Sweden as well and there's a new gum they're trying out which delivers nicotine"? And, I said, "I'm very interested in that. Could you give me the name of the person who is working on it"? And, he looked it up and gave me the name.

TB: So, this happened when you were still at Albert Einstein?

MJ: Yes. Then when I went to UCLA, I got in touch with Leo Pharmaceuticals. They were making nicotine gum and when I got to meet Dr. Ferno, the inventor of the nicotine gum, I said, "I'd really like to work with this stuff. Could I have some"? And, he said, "We'll have to set something up for you". Actually, it took a couple of years to set it up with the company that was the liaison in the United States to Leo in Sweden. They were able to supply me with samples of nicotine gum. They also gave me a little money to run a clinical trial to see if nicotine gum would be of any help in smoking cessation. I hired a very bright UCLA graduate student, named Nina Schneider, and had her to work on our clinical trials in this area. She did a wonderful job and over the next few years, I guess it must have been around 1974 or 1975, we ran a number of clinical trials for this drug company, the name of which I've forgotten. But the company, before the trials were finished, decided this was not a viable product and gave it up. It was a bad mistake on their part and maybe that's why I can't remember their name. But, Leo in Sweden, of course, never gave it up. They found a new company, Dow Chemicals, and we did some further trials supported by them. We also published our results in which we showed that the gum was certainly better than a placebo in helping people to stop smoking. So, I became very interested in nicotine and that's been a central theme of my work since the beginning of the

1980s. One of the things I was interested in was the way of administering nicotine and I looked into this. I learned there was something called green tobacco sickness, which is a sickness people who pick tobacco get if they handle it with their bare hands. What this told me was that nicotine must be getting through the skin. So, I tried to look into a way of administering nicotine via the skin. I had another post-doctoral fellow working with me, named Jed Rose, and we figured out a skin patch would be a good idea, a nicotine patch. I told Jed if this really works, it might have some commercial value and should be patented. So, we went to the patent office of the University in Berkeley, and when we told them what we have they said, they were interested. Well, it took a long time to get it patented. We started in 1980 and finally got the patent approved in 1990. It took ten years of incredible litigation, going back and forth with administrators in the university. We assigned the patent to the university, but managed to get a pretty good royalty from it. The university had assigned our patent to Ciba-Geigy, which was a big drug firm, and they marketed our skin patch as Habitrol. Then, Ciba-Geigy and Sandoz amalgamated and formed a new company.

TB: Novartis.

MJ: Novartis, exactly. And Novartis decided they weren't going to put it on the market. I never found out exactly why, so that was a big crimp in the royalties. But, it's still being prescribed by prescription. My research interests since the 1980s have been primarily in nicotine; how nicotine works and the tobacco withdrawal syndrome, which is really a nicotine withdrawal syndrome.

TB: How does nicotine work?

MJ: I don't think people know yet exactly how nicotine works but there's a lot of evidence that one of the primary mechanisms is that it releases dopamine from its stores, wherever they are. It releases catecholamines, generally, including epinephrine and norepinephrine, but dopamine seems to be the key neurotransmitter released by nicotine. In some of our recent research, we tried to hone in on this by giving drugs, which either are agonists or antagonists to dopamine. So in recent years we've worked with bromocriptine, which is a dopamine agonist, a drug that behaves like dopamine and we have given bromocriptine to smokers to see how it influences their habit. We have also worked with haloperidol, which is a dopamine blocking drug, to see how that influences smoking. And I've been interested in smoking in schizophrenics. They are smoking a lot; the prevalence of smoking is very high in schizophrenics.

TB: So, you studied the effect of bromocriptine and haloperidol on smoking.

MJ: We did dose-response curves with haloperidol and we found what we expected turned out to be true; haloperidol increased the amount of smoking that people did, as though they were trying to overcome the block of dopamine receptors. We also found that with bromocriptine people smoked less. We've just published a couple of papers on the subject. Our findings support the idea that dopamine is an important intermediary in the action of nicotine. That's not all that nicotine does. It has a complicated cascade of effects.

TB: Did you continue to work in both animals and humans?

MJ: No, only in humans. In fact, I've given up animal work. I gave it up around 1980 or so. It was increasingly difficult for me to work with monkeys. It became very expensive. There were problems with possible diseases and with viruses like Ebola. So, I decided that humans were better to work with. We had a lot of smoking humans at that time in Los Angeles; they're fewer now, but there are still enough people.

And, I might mention one other irony in my life. Since I've been working with smoking, I work with the American Cancer Society. I never smoked a cigarette, but in 1992, I was diagnosed with lung cancer; I had a lung cancer as a non-smoker. It was successfully removed. It was localized, just one small cancer with no metastases and I was followed very thoroughly for the next five years. There was no recurrence, and I'm still around. It's almost 2000 now and my surgeon assures me that I'm cured and I'll accept that. But, it was an irony that I should get lung cancer; whereas, my smoking subjects didn't. I've had other health problems. My rheumatic heart disease, of course, has remained with me all my life; At one point, when I was eighteen years old, I looked up the life expectancy for people with my type of rheumatic heart disease. There was a book by Mae Wilson and on the basis of all the symptoms and signs life expectancy for people like me was thirty-three years. I'm seventy-six years old now, so I guess it didn't work out the way it was supposed to.

TB: Let us try to recapitulate some of your research. You introduced one-trial learning and studied the effects of drugs like puromycin and actomycin on learning and memory?

MJ: Yes.

TB: You are one of the few people still around who worked with Lashley?

MJ: That's true. Lashley was already towards the end of his career when I worked with him. He was an interesting and colorful figure.

TB: Then you did research with LSD?

MJ: That's right.

- TB: You also did research with the new psychotropic drugs while at Albert Einstein and you were the first to write a chapter on them in 1960 in Goodman and Gilman.
- MJ: Right.
- TB: You covered chlorpromazine, reserpine, meprobamate, imipramine and iproniazid in that chapter.
- MJ: That's right.
- TB: The benzodiazepines were just introduced.
- MJ: Meprobamate was the big one at that time.
- TB: Frank Berger's drug.
- MJ: You know, somebody told me Frank Berger is still alive.
- TB: He is very much alive. I talked to him couple of days ago.
- MJ: Is he here?
- TB: No, he's not here.
- MJ: I visited with him around 1960 or so. At the time, he was the richest pharmacologist around.
- TB: I'm sure he would be happy to hear from you.
- MJ: I'll look him up.
- TB: Could you elaborate on some of the drugs you worked with at Einstein?
- MJ: One of them was chlorpromazine, the drug introduced by Lehmann and...
- TB: Hanrahan.
- MJ: Lehmann used it first in North America, if I recall. That was around 1955 or one year before. I remember going to an early CINP conference in Rome in the late 1950s. All of the people involved in the development of these new drugs were there. I remember Madame Curvoisier.
- TB: Madame Curvoisier, the pharmacologist who worked with chlorpromazine.
- MJ: And there must have been people there who worked with reserpine.
- TB: Nate Kline was there.
- MJ: I think, Bein from Ciba was also there.
- TB: You mentioned you worked with chlorpromazine at Einstein. What did you find?
- MJ: It's such a long time ago, but I remember one thing about chlorpromazine was that it was different from the barbiturates. Actually, a friend of mine, who had been working with me, named Conan Kornetsky, developed a continuous performance test which he and I used to differentiate barbiturates from chlorpromazine; barbiturates produced a marked impairment of equilibrium and coordination whereas chlorpromazine didn't. I did some other work, too, in which I found differences. I worked with a neurosurgeon at Albert Einstein named Allen Rothboyd who developed

a method for injecting drugs into the carotid artery of cats and we tried to compare chlorpromazine with barbiturates. When we injected a barbiturate into the carotid artery, we got an immediate hemi-paresis, a stroke so to speak, but when we injected chlorpromazine nothing happened for about half an hour and then, slowly, the animal would start moving toward the side of the injection. Unfortunately, Allen Rothboyd died about ten years after that, but we did publish a paper.

TB: So you also collaborated with Conan Kornetsky on the continuous performance test. Did you work with him in normal subjects and also in schizophrenic patients?

MJ: I didn't do that with him. By that time, Conan was working at NIH.

TB: Then, he moved to Boston.

MJ: Right. We've kept in touch. In fact he organized a sort of old timer's symposium about six months ago and I took part in it in Boston.

TB: You have been in research for 50 years.

MJ: More than fifty.

MJ: Nearly sixty years.

TB: And during those years you published many papers, right?

MJ: I have about three hundred papers.

TB: Three hundred papers. You mentioned the first that was published in Science. Would you like to mention any of the others?

MJ: The paper describing the usefulness and effects of the nicotine patch, which we published around 1984, was an important one, because it helped us get a patent. It's hard for me to pick what stands out; I have three hundred titles running through my mind. I don't think any of them are worth a Nobel Prize. The One-Trial Learning procedure, which I worked out for mice, I consider important, because up until that time nobody had used a one-trial procedure. They'd only used multiple maze learning procedures. The fact you could have one-trial, with a lasting effect, meant you could follow it at different time intervals with treatments and get a precise measure of the temporal events following the learning trial. I think that was the most important thing that I did.

TB: Any other papers you like to mention?

MJ: Being an early investigator of LSD was interesting, because it's a substance which had some wide sociological influences, to put it mildly.

TB: You mentioned you had no problem in getting LSD from Sandoz, and when they stopped, people could get psilocybin.

MJ: Yes, and I did work with psilocybin and also with other hallucinogens such as mescaline.

TB: Did you find any difference between the effects of LSD and mescaline?

- MJ: I don't know that I went into it in enough depth. I did some animal studies with various hallucinogens and there might have been some subtle differences. The major effect in animal studies was impairment of performance. With humans, of course, I always used just retrospective reports.
- TB: You had many people working in your lab.
- MJ: That's true.
- TB: So, you trained quite a number of people.
- MJ: That's correct.
- TB: Would you like to mention some of them?
- MJ: I hate to leave anybody out, but in 1998, last year, a couple of my students or fellows decided to have what they called a Festschrift for me. It really wasn't a Festschrift. It was a party at the Society for Research on Nicotine and Tobacco, which met in New Orleans in March. They tried to gather together all of my students or fellows, but I was very sick and couldn't go to the meeting. They arranged to make a video tape and they showed it there. This was organized by Alan Grids, who is a professor at the University of Texas, and Ian Stolerman, who is at the Maudsley Hospital and both of them worked with me. They also got about ten of my former students and colleagues together, who gave brief talks which were very nice. I was very sick and it looked like I might be dying but I didn't. I fooled them; I'm still around! I hate to mention anyone, because I'm going to leave out somebody I should mention.
- TB: We talked about your papers. Did you write or edit any books?
- MJ: I edited one book on Psychopharmacology.
- TB: Would you like to elaborate?
- MJ: That was around 1975. It was called *Psychopharmacology in the Practice of Medicine*, I think, and I had contributors like Wikler and Jerry Jaffe. About a dozen people wrote some very interesting chapters. But the book is out of print by now, as it should be, because time and science marches on, although some of the chapters by people like Wikler, are useful from a historical point of view.
- TB: When did you become involved with ACNP?
- MJ: In 1961.
- TB: Are you one of the founders?
- MJ: That's right and the same is true of the CINP.
- TB: I think you mentioned you participated in the first CINP congress?
- MJ: It was in Rome in 1958. I remember that we went to see this very controversial Pope.
- TB: He actually gave a very enlightened speech.

MJ: Yes, I remember that. Now he's controversial because he didn't oppose the Nazis like he should have, but there're pros and cons on that.

TB: Any other organization you are involved with?

MJ: The biggest organization I belong to is the American Psychological Association, because I got a PhD in Psychology. So, I've belonged to the American Psychological Association for all these years. Now I'm emeritus I don't pay dues for many of these organizations, which is very nice.

TB: Is there anything we did not cover and you would like to add?

MJ: Just my personal life; I've been very lucky. I've been married to this wonderful woman, Lissy Jarvik, who has been with me through thick and thin. She's also a good scientist and she became a distinguished physician in the VA. And she, of course, became professor of Psychiatry at UCLA. She's with me here and we have a family. We've got two boys, now middle aged men.

TB: You are still active.

MJ: I try, yes.

TB: Thank you very much for sharing all of this information with us.

MJ: Well, thank you.

ERIC R. KANDEL

Interviewed by Huda Akil
Boca Raton, Florida, December 9, 2007

HA: I am Huda Akil and I have the great pleasure of interviewing Dr. Eric Kandel*, Professor of Neuroscience at Columbia University and winner of the 2000 Nobel Prize in Physiology and Medicine. I am holding in my hand the wonderful book of his called *In Search of Memory, the Emergence of a New Science of Mind*, which beautifully intertwines his own personal history and the history of the field. I hope today we can explore some of what's in this book and beyond. So, Eric, tell us about your life.

EK: Well, I am pleased to do that, particularly with you Huda, a friend for many years. I must say I am particularly grateful to you, because we have Leo Bollinger as our president at Columbia University, a wonderful leader, who was tutored by you, and is fascinated with the brain, just as you and I.

HA: That's wonderful. I would like to start at the beginning, with you as a child in Vienna. Tell us how it was then and what propelled you to leave Vienna to come to the United States?

EK: I was born in Vienna on November 7, 1929 to a lower middle class family. My father had a small toy store on the Kirchberggasse and my mother worked there. We had a small apartment in the ninth district and lived a lower middle class average life until March 13, 1938, when Hitler came into Austria, and to my and everyone's astonishment, was treated by the Austrians as a hero, the person who had united the German speaking people. I vividly recall Hitler coming into Vienna. About two hundred thousand people milling in the Heldenplatz, screaming Heil Hitler, as he described Austria as the crown jewel in greater Germany. That night, the enthusiasm turned into enormous hostility against the Jews. Jews were beaten up, some were incarcerated, some were forced to scrub the streets where there was political graffiti, and it was just horrible. Carl Zuckmayer, a famous dramatist who left Germany to escape from Hitler, was in Vienna the night Hitler spoke and described what he had seen that night as the most horrible thing during the twentieth century. It was if hell opened its doors. The next day, while I was walking on the street, a boy I knew came up to me and said, "Kandel, my father told me that I should never speak to you again" In a few weeks all Jewish kids in my school were sent to a special school in the outskirts and I was roughed up in the park. There was a climax to things on November

* Eric R. Kandel was born on November 7, 1929 in Vienna, Austria.

9, 1938, two days after my ninth birthday. I was home with my mother and brother when two people knocked on the door; they were Nazi policeman. They gave us a few minutes to pack and we were told we had to move to the apartment of another Jewish family we didn't know, and stay with them until further notice. So we packed a few things; I left behind the toys that I had for my birthday, including a small blue car that could be remotely controlled, which I loved a great deal. I left everything because I thought we'd be back in a few days. When we returned to our apartment a week later, we found everything of value was gone, including my toys. By then we realized we had to get out of the country. We had a relative in New York, my mother's brother, and he sent us the necessary documents and an affidavit stating he would support us in case my father didn't get a job. So, we left Austria. My grandparents, who were the parents of my uncle who sent us the affidavits came first; my brother and I came next. My grandparents came in February; we came in April, 1939. My parents arrived at the end of August, 1939.

HA: So, you traveled alone with your brother?

EK: Yes.

HA: You were eight years old?

EK: Nine. My brother was fourteen. Two kids by themselves. We took the train and got aboard the ship. My kids recently found, on the internet, the passenger list of the ship we were on. Bruno Bettelheim was on the same ship.

HA: That was an amazing journey. When you got the Nobel Prize somebody should have given you a remote controlled blue car! Some day you may still get one. So, you arrived in New York City and started school. Would you like to tell us about that?

EK: I went to public school PS217. It was a very nice school but I felt uncomfortable because there were many kids with blue eyes and blond hair. I assumed all of them were Christians and would turn on me. We were in a Jewish neighborhood and probably many of those kids were Jewish, but still, I felt uncomfortable. My grandfather, the one who arrived just a few months before us, was a very scholarly orthodox Jew, and wanted me to get a serious Hebrew education. He offered to tutor me in Hebrew, so I could qualify for Yeshiva, a Jewish parochial school, which was near where we lived. I had no interest in Hebrew or getting a religious education but I was interested in getting out of the school I was in. So, he tutored me and after passing my qualifying exam, I went to this parochial school for four years. I went to high school at Erasmus Hall and during those years I became interested in history, particularly in German and Austrian history. I thought to apply to Brooklyn College

after finishing high school because my brother went there but my history teacher, Mr Campagna, suggested Harvard. I didn't know much about Harvard and when I discussed it with my parents they were not enthusiastic because it meant spending more money. So, Mr. Campagna gave me the money. I applied and was admitted to Harvard with a scholarship, and had four fantastic years. I started in a special field, called History and Literature, and wrote my dissertation in my senior year on the attitude of some writers toward national-socialism. In my junior year, I fell in love with a wonderful woman who was the daughter of two Viennese analysts, Ernst and Marianne Kris. The three of them got me interested in psychoanalysis. They told me if I wanted to understand motivation, to what happened to me, I had to understand unconscious mental processes. I had no interest in science in those days and did not take any course in science at College. To be able to apply for admission to medical school I took a chemistry course between my junior and senior year. Based on that one course and my general performance at Harvard, I was accepted to medical school and started at NYU with the idea of becoming a psychoanalyst. But I thought even a psychoanalyst should know something about the brain and since NYU had no single person doing neurobiology I went to Columbia, and spent six months with Harry Grundfest in their neurology department. When I first got there Grundfest asked me what I would like to do, and when I told him that I wanted to study where the ego and super ego were located, he humorously brushed that aside and said, "what a grandiose idea that was." It was Grundfest who pointed out to me that the best way to study the brain was to study one cell at a time. He had me work with a crawfish and taught me how to make and put electrodes into individual cells. So, I started to record from the crawfish brain. I knew that Freud had studied the crawfish. I never enjoyed anything as much as doing experiments so I spent quite a bit of time working with Grundfest and Purpura while in medical school. At the time I graduated there was a physician's draft and Grundfest asked me whether he should nominate me for a fellowship at NIH that would make it possible for me to do research instead of being on active duty. It was a very attractive alternative. Luckily I was accepted by Wade Marshall, the head of the Laboratory of Neurophysiology for a two year rotation. I spent an extra year at NIH because I found the work enjoyable and interesting.

HA: I discovered you did some research while at NIH with LSD. Could you say something about that?

EK: At that time Woolley and Shaw had the idea there was an endogenous compound that caused psychosis in people and that serotonin which

interacted with it was required to keep one sane. We ran various experiments because Woolley and Shaw did most of their experiments on the snail heart and simple invertebrate preparations. They did not even use neural preparations. So we thought it would be interesting to test their “hypothesis.” We were not successful but being involved in that project made me aware one can test psychiatric hypotheses, or at least begin to test them, in animals. It made me appreciate one could begin to test psychiatric ideas in animals. I intuitively knew this was the kind of work I was interested in doing and my greatest good fortune was that I have learned to trust myself.

HA: So, that experience had a great impact on your life. You were at the time in Wade Marshall’s lab. Could you tell us something about him?

EK: Wade Marshall was a person recovering from schizophrenia. By the time I got to his lab he had lost his scientific zeal; he was no longer terribly curious about his own scientific advancement. But, he was a marvelous person, extremely generous and supportive. Anyway, he let me do pretty much what I wanted, but I didn’t have the foggiest notion what to do. So, I began to think what would be interesting from a psychoanalytic point of view that we could do on a single cell level. Brenda Milner had just published her classic work on the involvement of the hippocampus in memory storage, so I thought I would study the hippocampus on the cellular level. In the lab right next door to me, Karl Frank was studying the spinal cord on the single cell level. I knew about microelectrodes and he knew about mammalian systems. When I told him I would be interested in studying the hippocampus he told me that would be very difficult but I should go ahead and he would be ready to help. I started to work on the hippocampus and, soon after I started, Alden Spencer came along. I showed him what I was doing and he developed a very nice dissection of the hippocampus. We began working together, and Alden was the most marvelous human being. He became my closest friend but died of amyotrophic lateral sclerosis in his mid-forties. We succeeded, within several weeks, in getting intracellular recordings from the hippocampus and were thrilled. It was the first cellular recording of the hippocampus; a major accomplishment. After the initial euphoria wore off we asked ourselves, what had we learned about memory, and had to admit we didn’t learn a darn thing. Memory is a complicated process. You have to see how information is transformed as a result of learning, how it’s associated with something else. So, we started to study how information gets into the hippocampus but found it difficult and pretty much decided we would have to abandon the hippocampus and do something else. Then, John Eccles saw our data and invited us to come to Camberra, in

- Australia to work with him on the hippocampus. It was a great honor and we debated for awhile whether we should go, but ultimately decided against it.
- HA: What did you do after the NIH?
- EK: I completed my residency training in psychiatry at the Mass Mental Health Center, and went to France and worked with Ladislav Tauc. It was love at first sight. The cells we saw were gigantic; you could put an electrode into a cell and it would stay there all day long. At home if you recorded for half an hour it was a major achievement. Here you could put an electrode in the cell, record for several hours, go to lunch and come back and it was still there. That made life easier. It takes a long time to set up surgery in vertebrates. Often experiments run late into the night, and Denise made it clear to me that with children this can't go on and I should try to find something more manageable.
- HA: You have not mentioned in this interview Denise as yet. In your book you described how you fell in love and jumped into marriage and she gave you courage to jump into other fields. When did this happen.
- EK: By the time I went to work with Harry Grundfest I'd broken up with Anna Kris and had just met Denise. We had dinner together several times, and I remember telling her how much I enjoyed our dinners and I could see doing it for the rest of my life, but it was unrealistic because neither she or I had any money. I would need to go into private practice if we got married and were going to have a family. She said this was ridiculous; money was of no importance, and the important thing was that I enjoy doing my research. I was frightened to get married, as I had been in three earlier relationships. I wasn't ready for it, but Denise felt very confident we could make a go of it. It was for me, as it is for everybody, a leap of faith ultimately. We've now been married for fifty-one years and it's a privileged relationship. She has influenced me enormously, and in some ways I have influenced her.
- HA: So, let's go back to your research in France.
- EK: As I said before, the cells were large and uniquely identifiable. So, you could call one Huda, another Stanley, and a third Brendan. In every animal of a species, I realized we could work out the neuronal circuits of behavior. I selected a very simple behavior, a withdrawal reflex, like withdrawing a hand from a hot object, and together with a number of colleagues, who included Irving Kupfermann, Vincent Castellucci and Tom Carew, particularly Irving and Tom, I studied this reflex in a simple animal. We were able to show the neural circuits in several simple forms of learning. We could show first, sensitization and habituation. Then later, we showed the neural circuits of classical conditioning.

Recently, Bob Hawkins and Tom Carew have shown the neural circuits of operant conditioning. And with each form of learning there is a short term and a long term memory. It was remarkable to see that a simple reflex, like the withdrawal reflex could be modified. The whole universe of elementary forms of learning was there. Using this reflex we worked out the neuronal circuits of behavior. It turned out to be very simple. In the gill withdrawal reflex a number of sensory neurons pick up from the siphoned skin and make direct connections to the motor neurons that move the gill. We looked at the architecture of that reflex and were struck how invariant it was; the same cells invariably hooked up to the same target cells. At first it seemed paradoxical, how one would get the flexibility of behavior we see from such a fixed wired diagram. Then, we looked at the neural circuit with different forms of learning while the animals were being trained and found that even though the architecture of behavior, the neural circuit, was specified by genetics the strength of synaptic connections was unspecified. And, that's what changes in learning with sensitization. It becomes stronger with sensitization and weaker with habituation. We were now in a position to explore how short term memory converts to long term memory. What we saw was that short term memory involved a functional change but no anatomical change, while long term memory gave rise to the growth of new synaptic connections with sensitization and loss of synaptic connections with habituation.

HA: That's amazing.

EK: After the anatomical work I did with Craig Bailey we looked at the biochemistry. I was very fortunate that one of my friends at the Harvard summer school, where I took the course in chemistry before entering medical school, was a guy called Jimmy Schwartz. He ended up on the NYU faculty the same time that I joined.

HA: When did you get to NYU?

EK: I was a resident at Harvard first, went to France, returned to Harvard as faculty, and then I was recruited to NYU to develop neurobiology. I asked Alden Spencer to join me at NYU and, lo and behold, I meet Jimmy Schwartz. The three of us joined forces to do biochemical research in the nervous system. We looked for the biochemical changes in the brain when you produce learning events and identified serotonin as a critical transmitter for sensitization.

HA: What year was that?

EK: In the mid-seventies. We found learning increased the level of cyclic AMP. We looked at some other second messengers as well but they were not affected. We then took cyclic AMP and injected it into the

- sensory neurons. We found that it could produce sensitization. We collaborated with Paul Greengard who was characterizing cyclic AMP dependent protein kinase in those years. This gave us the first molecular insight into the learning process. Then we were curious how cyclic AMP produces long term effects. Roger Seine was developing labels for cyclic AMP. Using labeled cyclic AMP we could show that with short term training the cyclic AMP dependent protein kinase was only active locally at the synapse, but with repeated training, the catalytic subunit moved into the nucleus and activated the genes. We knew that one of the targets of the cyclic AMP dependent protein kinase in other tissues had been a transcription factor called CREB (cyclic AMP responsive and binding protein). In further research Pramod Dash, in my lab, succeeded in selectively blocking long term memory and Dusan Bartsch succeeded in producing long term facilitation. This brings me to about 1990 to 1992, when the technique of knock-out genes was introduced.
- HA: So, you entered a new phase in your work.
- EK: We began to explore the difference between short term memory and long term memory in mice. Once one turns on the long term process you turn on genes and get to what look like structural changes. Probably CREB is not the only factor involved in long- term memory although it seems a very important one. You learn fear in the molecular CREB. It's critically important. So, at least some of the alphabet is applicable.
- HA: And the principle is general.
- EK: Principles are quite general. This takes us to about 1997 and 1998 when we began to look at age related memory loss in the mouse. Alzheimer's disease does not occur in the mouse, but half of the mice as they age have a hippocampus based memory deficit. When we looked at the hippocampus we saw that cyclic AMP dependent phosphorylation was compromised. Then, we gave rolipram, that boosts cyclic AMP, and found it restored physiology and memory. We did these experiments with Ted Able, and one night at an ACNP meeting when we told this story over dinner to Wally Gilbert, who is a friend of mine, he said, "why don't you guys start a company?" So Wally and I started Memory Pharmaceuticals, which is now a public company, trying like many other companies to develop drugs for age related memory loss in Alzheimer's and for cognitive deficit in depression and schizophrenia.
- HA: Interesting.
- EK: Academics didn't get involved in companies when you and I began, but now many are involved. It's actually quite exciting; it's good for the person and hopefully good for the field as well. It got me using mice as animal models in mental illness.

HA: How did that come about?

EK: We began to look at fear, which involves the amygdala in mouse and man, and found that some strains of knock-out mice show a tremendous enhancement of learned fear. Then, one day, Jack Gorman walked into my office and told me they had become interested in starting a schizophrenia center and looking for fresh ideas. He asked whether I would consider doing something in schizophrenia. Normally, I would not have considered doing anything like that but Conrad Gilliam and Myrna Weisman thought it might be possible to do research with our learned fear project at the center. So I began to interact with them. I don't, by and large, interact with psychiatrists, or at least at that time didn't interact with clinicians. But when I started to I found psychiatry has grown and I enjoyed our interaction. I was very fortunate in recruiting two spectacular post doctoral fellows, Eleanor Simpson and Christoph Kellendonk, and together we have begun to develop animal models for schizophrenia focusing on what we know about memory, looking at cognitive deficits in the prefrontal cortex. We are having a very good time, and may be learning something.

HA: It's a wonderful journey; it's amazing. So, in the time left, I would like to go back to your early history and especially your personal history. You described in your book, what happened after you received the Nobel Prize and were asked to go back to Vienna. I would like you to reflect on that. We understood it was a very difficult period in your life but you came full circle and went back to Vienna with kind of a mission. You want to tell us a little bit about that?

EK: When I heard about the Nobel Prize, which, needless to say, was a marvelous moment, lots of people called. I remember vividly learning about it at 5:30 in the morning a few hours before it became public news. Tom Kessler is a wonderful friend and colleague of mine at Columbia and he came over about 9:00 AM with his kids and his wife and we sat down together. We had a very pleasant breakfast interrupted by phone calls, some from Austria saying how wonderful to have another Austrian Nobel Prize. I straightened them out saying this is not an Austrian Nobel Prize, it is an American Jewish Nobel Prize. So, the President of Austria wrote me a very nice letter and he said, "How can we recognize you?" And, I wrote back, saying, "I really don't need recognition. I have more recognition than I deserve, but I would like to have a symposium at the University of Vienna, of how Austria handled herself during the Nazi era." I got Fritz Stern, the German historian, who is a friend of mine to help me, because I didn't know who would be the best people to invite. We used Germany as an example, because Germany has been

remarkable in the post war period in its transparency and honesty, facing up to what happened. To give you one example; Hubert Markl, who's is head of the Max Planck Institute, demanded an investigation of how the Max Planck contributed to the holocaust, the fact they were collaborating with the Nazis carrying out human experimentation in concentration camps. Nothing like this was happening in Austria. It was completely covered up but in our symposium we uncovered everything and cleared the deck. It made people think about what was done and there is now so much more transparency and interaction with the Jewish community. I had gone back several times before to Austria but I now go back more frequently. I have written a second book. It is on the Vienna School of Medicine and the Origins of Austrian Expressionism. There are three wonderful Austrian painters and I found some evidence they were influenced by Rockitansky of the Vienna School of Medicine who suggested you shouldn't stay on the surface but go deep into the psyche. It was a sort of independent discovery of Freud's unconscious instinctual drive that has fascinated me. I begin my book questioning why I have this fascination with Vienna, with people who did such horrible things to me. It's like a repetition compulsion; a post traumatic stress disorder, in which you try to relive experiences in order to gain some mastery, some understanding of what happened. Our lives, to some degree, are attempts to gain that kind of understanding.

HA: I felt that in reading the book you wanted them to face up to what they did, show the courage to face up and move on. That's how I felt.

EK: Huda, that's a wonderful insight, but I did not have that on my mind. It was completely a fantasy association. Vienna was great in 1900. I was not there, it was before I was born. Vienna was great for people who went to the opera and the museums. My parents were lower middle class; they were not intellectuals. We rarely went to the museum. I did go to the opera occasionally. They did like music. So, it's a fantasy association, but it's somehow important to me. You play a Strauss waltz and I want to dance. Viennese music has such an effect on me. And, I very much would like to see a better Vienna to emerge. I have become quite friendly with President Fischer, the current President of Austria, and a woman by the name Petra Seeger who has done a documentary about me, in which we visited all the places of my childhood. We visited my father's store, the apartment where we lived, and her film is going to be shown in Vienna. I've not seen it yet. Denise and I are going to Vienna for New Year and we will see it then. It hasn't been shown publicly but she did show it to a couple of people who supported the project. She got support from the Sloan Foundation here and from public television

in Germany and Austria. The man from Austria broke down when he saw the film; he was so moved by it and he's not a Jew.

HA: I see.

EK: There is a wonderful book that was written in Vienna, of all places, in 1923, a decade before Hitler came to power, fifteen years before he came into Vienna. The title of the book is *Die Stadt ohne Juden, City without Jews*. In this novel the city fathers get together and decide that the Jews were too influential and grubby and so they got rid of them, and forced all the Jews out. The Jews left and all of a sudden there was a decline in the stock market. The elegant department stores had to close, because ladies were not going to shop there any longer. Women dressed less elegantly because they were no longer competing. Young ladies said, my God, where are those sugar daddies from whom we used to get presents? The city fathers went around town and heard this moaning and groaning about the good old days when we had the Jews here. So, they were forced to ask the Jews to move back. I tell my Austrian friends, I'm still waiting for that invitation. They should try, as Germany has done, and bring Jews back into Austria. Maybe someday they will.

HA: I knew you were Jewish and I knew you were from Vienna, but I had not realized how much antisemitism affected your personal life. It's remarkable that you have maintained this great optimism, this wonderful laugh, this great-spirit in the face of very painful memories. It is impressive how you have sublimated those painful experiences by trying to understand the history of ideas through an interest in psychoanalysis and by trying to understand first memory, and then, fear modulated memory. There is a theme there that seems to be healing.

EK: I agree. I was in analysis and Vienna was not a major issue. It must have been so repressed, somehow. I was dealing in my analysis with more contemporaneous problems, more about my career and things like that. It is an enormous repression. Can you imagine a nine year old kid leaving his parents? I don't remember being scared. It is inconceivable I wasn't frightened. There are horrible things in my unconscious. I have some unpleasant competitive streaks, but somehow my unconscious has guided me. I have become more comfortable with that with aging. Also, I have had a privileged marriage that has just been fantastic for me.

HA: You are also the epitome of mental health. You triumphed over all the adversities experienced in early age. Could you comment on the sources of strength in your life and the joy of the Nobel Prize?

- EK: I am the delusional optimist and one of the reasons I have enjoyed biology is that it is optimistic to an extent that's delusional. I was alive and I presume you were when DNA was discovered. It is amazing how far we have come since 1951. It's absolutely miraculous! I remember going to meetings with physicists, in which they would tap me on the shoulder and say someday this will be a mature discipline. Now people want to enter neuroscience as much as they want to go into physics, maybe more. So, it's a very nice fit between my delusional optimism and the field. Why I have that, I don't know. My father was a very optimistic guy.
- HA: And what about your wife?
- EK: I'm more optimistic than Denise; she is a more realistic person than I am. But, I've been very privileged in my life. Obviously, there have been a lot of disappointments. Science is filled with disappointments, but I've had a lot of wonderful opportunities. I had the opportunity to go to Harvard. The Nobel Prize was such a fortunate event. I feel very privileged and blessed about it. There are so many more people worthy of it. I could list a whole bunch of people here who are deserving the Nobel Prize. So, I feel very privileged to get it with Paul. It was great for the society, great for us, and for psychiatry. It was a fantastic experience. Don't ever turn it down if you are awarded it.
- HA: I'll keep that in mind! And I want to end this interview with your wonderful laugh. Thank you so much. It was fascinating.

ALEXANDER G. KARCZMAR*

Interviewed by Erminio Costa
Boca Raton, Florida, December 8, 2007

EC: I am glad to talk to you in this wonderful location. And to start our conversation let me say that we are friends, for a long, long time.

AK: Sixty years.

EC: And, I remember when I first met you. You predicted that I would have a great career and fortune as a neuroscientist. I am grateful for that.

AK: The little meeting that you allude to took place in our apartment on Lake Shore Drive of Chicago. At that time, in 1957, you were associated with Harold Himwich, a great neuroscientist who proposed, among his other concepts, that the cholinergic system has an important role in the control of the EEG and behavioral arousal. I was right with regard to your fame and fortune.

EC: I don't know as to myself. Now, with regard to you, you were born in Poland; could you give me some details of the first twenty years of your life?

AK: I was born in Warsaw, Poland on the beautiful 9th day of May, 1917. I graduated as a "Primus", with highest honors, from a private high school called, redundantly, "Gymnasium". In Poland one would enter the University's professional or academic curricula without going to College; while the high School program was more ambitious than the high school USA program. Nevertheless, it took longer to graduate at the Warsaw University whether with an AM, a PhD or an MD degree because the earlier years of the Warsaw University studies would be taken up by what would be in the States the College curriculum.

EC: Did you study Latin in your high School?

AK: I studied Latin and Greek, just like you. In fact, at one time I could speak Latin fluently, and that's why later on I could easily learn Italian, as you know. To return to my University studies and to the contemporary situation in Poland, Warsaw University was known at that time as Jozef Pilsudski University. Since the end of the eighteenth century Poland was partitioned between Austria, Russia and Germany; after the defeat of Austria and Germany in the First World War, Polish independence was decreed in 1918 by the allies, led by President Wilson, but Russia did not relinquish its part of Poland, and Jozef Pilsudski fought victoriously against Russia. Independent Poland had first a democratic government and then a dictatorship. This dictatorship, at first tolerant under Pilsudski to religion and to the Jews, became, after Pilsudski's death,

* Alexander Karczmar was born in Warsaw, Poland in 1917.

gradually anti-Semitic. This was contemporary with Hitler's becoming Chancellor in Germany, and in 1937 or 1939 Poland's regime formed an alliance with Hitler's Germany. There was an official economic boycott of Jewish businesses, and some "unofficial" violence. Only a few Jews were admitted to the University because of "numerous clausus," and the Jewish students had to stand up during the lectures, on the left side of the hall.

EC: That's unpleasant!

AK: It's nothing compared to what happened after the Nazi invasion of Poland in 1939. In 1934, I entered the University with a strange curriculum I concocted composed of medicine and biology; I elected not to apply for entrance into the medical curriculum, for reasons too complicated to explain here. After five years of studies and two or three years of what would correspond in the States to graduate work I was ready to graduate but then the Second World War and the Nazi invasion of Poland intervened.

EC: That was in nineteen thirty-nine?

AK: In the fall of nineteen thirty-nine. To be a Jew and a Pole and to escape and survive what happened in Poland and in Europe after nineteen thirty nine, you had to be very fortunate, and I was lucky enough to be on vacation in Switzerland when the War broke out.

EC: And, you never went back?

AK: I couldn't and I shouldn't and I didn't. And it was very lucky that I didn't.

EC: Yes, you were very lucky.

AK: In fact, my father, a businessman, was also not in Poland when the war broke out and ultimately he managed to get, in due time to New York, as did my mother and one of my uncles, while another uncle, a Doctor, succeeded in getting to Mexico City and establishing a successful practice there; still another uncle was, at the time, my father's business affiliate in Rio de Janeiro. So, I went first to London, obtained a visa for Brazil and, after one year in Rio de Janeiro, my American "quota visa" became valid.

EC: One year in Rio! A nice place for a year's residence!

AK: Yes, but these were dreadful times. A world war, concentration camps, massacres, while I resided safely in Rio. I still have a strong feeling of guilt about it. As I mentioned before, my parents and my uncles on my father's side were, luckily, out of Poland when the war broke out, but the rest of my family perished in the concentration camps. In the nineteen twenties and thirties very many Polish Jews and quite a few non-Jewish Poles wished to immigrate to the USA. They were listed in the "quota system" and a certain limited number of Poles could migrate to the

States each year. So, the list was very, very long, but when the war broke out, my quota number came up relatively rapidly, because very few Poles were in a position of availing themselves of their quota. So, I came to New York from Rio, and I immediately enrolled into the graduate program of Columbia University. I obtained a Master's degree in the Department of Zoology, chaired by Leslie Dunn, a famous geneticist. Other famous geneticists who taught me in the department were Ernest Meyers and Theodore Dobzhansky, who liked speaking Polish to me. James McGregor, a comparative zoologist and sculptor of several models of primitive men, was also my teacher. Following my MA, my thesis advisor in the PhD Program was Selig Hecht, Professor of Biophysics. His research dealt with the retina, he was well known, and still famous, for his discovery of the quantal response of the retina to photons of light. Also, he wrote a popular book on the atom and its structure. He was also a superb and elegant teacher! I still remember the shock I had, during my first year at Columbia, when I saw one could ask a professor, questions after and during the lecture; that was never done at a Polish University.

EC: This was in the nineteen forties?

AK: That was between 1940 and 1947, you calculate very well Mimo. I earned my PhD in 1957. But, my thesis did not deal with biophysics, it dealt with limb regeneration in urodeles.

EC: Very different.

AK: Yes, this shift of mine from biophysics to regeneration is a good example of the zig-zaggy nature of my scientific career; you will see other examples of this jumpiness later on. In this case, the shift occurred when I went for a summer to study in the Woods Hole Marine Laboratory. There, I listened to a lecture by Oscar Schotte, a Professor in the Biology Department in Amherst College in Massachusetts, on the regeneration of amputated limbs of urodele larvae that depended on limb innervations. Dr. Schotte was a student of Hans Spemann, a German embryologist and a Nobelist. During the discussion that followed Schotte's lecture I suggested to him an experiment that would give a clue as to the nature of the factor involved in the nerve dependence of regeneration. Impressed with my suggestion, Schotte, who had a fellowship at his disposal offered me a year's position at Amherst to work on the experiment I suggested. This study resulted in the first two papers of my career published in 1941 in the *Journal of Experimental Zoology*.

After my expedition to Amherst I did not return to Columbia University as there were no funds available to support me. So, I obtained another fellowship, this time with Professor Alexander Sandow in the

Biology Department of New York University. This was another zag in my career as Sandow worked on the skeletal muscle and its latency relaxation (LR). Because of its shape and the name of its discoverer the LR was, referred to popularly as the “Rausche Nase.” I discovered much later that Sir John Eccles with his advisor at the time, Sir Charles Sherrington, co-discovered this phenomenon using a very sensitive lever, but they were not quite sure of their results and did not publish their data. Sandow studied the LR by means of an ingenious piezoelectric lever with a sensitivity of a few micromillimeters and great speed of response; it could measure muscle dynamics such as the LR that lasted only milliseconds. I published with Sandow as well.

Then, Columbia found some funds for me and I became a Teaching Fellow in the Department of Biology, and I could turn, with Hecht’s permission, to my early love, regeneration. When I published my thesis in 1946 in the *Journal of Experimental Zoology*, I proposed that the nerves, irrespective of their type or nature, liberated a trophic substance needed for the regeneration of urodele amputated limbs. I should have stuck to this work which preceded by some fifteen years, the definitive identification of nerve related growth factor by Victor Hamburger and the Nobelist Rita Levi-Montalcini.

EC: What were your feelings when you arrived in the United States?

AK: In some respects, New York is a very European city, and I felt quite at home. As I mentioned, my parents and one of my uncles lived by then in New York. I felt that New York was the place where people of all kinds meet and where everybody is well tolerated and well understood, no matter the accent, personality or skin color; perhaps, in the nineteen forties, this statement might be an exaggeration with regard to the Afro-American population. Then, finally, I became an American citizen and met and married my wife Marion in New York. In fact, obtaining my USA citizenship, the completion of my work on my thesis, and my marriage all occurred in 1946, a memorable and wonderful year for me! So, I was very happy in New York and I felt very much at home. When I accepted a job in Washington, and later when I moved first to Albany and then to Chicago, that was another story and I felt alienated, at least at the beginning of my residence in these cities. Anyway, after I was through with my thesis, David Nachmansohn invited me to join, as postdoctoral fellow, his Columbia University team.

EC: In New York.

AK: In New York, I had at the same time an invitation from Theodore Koppanyi to join his Faculty at Georgetown University.

EC: Georgetown University Medical Center in Washington, DC?

AK: In Washington, DC. Of course, the late David Nachmansohn was a very great scientist. If he did not swerve from his discovery of the enzyme he called choline acetylase, known today as choline acetyl transferase (CAT), to stubbornly pursue his untenable speculation that the acetylcholine system underlies conduction of all nerves, whether sensory, cholinergic or adrenergic he would have become a Nobelist. Many famous scientists, Wolf Dettbarn, Sy Ehrenpreis, Ernest Schoffeniels, and, more recently the great Jean-Pierre Changeux, at this time the Director of the Molecular Biology Department at the Institut Pasteur, were postdocs in Nachmansohn's laboratory. Nachmansohn's interest in me was motivated perhaps by my curriculum and grades, but I think his main reason was that he was a good friend and a great admirer of my advisor, Selig Hecht. Anyway, I became, during my interview with Nachmansohn, not very happy with his personality. This was subsequently a bone of contention between my friend Changeux and myself, since Changeux admired and liked Nachmansohn very much, not only on a scientific but also on a personal basis; he published recently a very laudatory biography of Nachmansohn.

So, I accepted a faculty position in Theodore Koppanyi's Department of Pharmacology at Georgetown University Medical School and I moved from New York to Washington. There I pursued my work on regeneration and, in 1946, I applied successfully for NIH support. This was the very beginning of the existence of the extramural research program at NIH; I have had many NIH grants since then. I was awarded an NIH grant just two years ago, so it seems the history of my NIH support is one of the longest. Immediately upon my arrival, Koppanyi launched me on the studies of autonomic ganglionic cholinergic transmission and, from that time on, I stayed almost exclusively with the cholinergic nervous system. We worked on the ganglionic nicotinic transmission which Koppanyi and I evaluated with anticholinesterases, including physostigmine and organophosphorus (OP) agents, and cholinergic agonists and antagonists. This led to the novel concept of direct action of anticholinesterases, both with regard to their facilitatory as well as blocking effects on nicotinic stimulation of the ganglia, and with regard to their potentiation with small doses and blocking with large doses of the nicotinic effects of acetylcholine. We postulated that these direct effects were due to the direct actions of anticholinesterases on ganglionic nicotinic receptors, these actions being independent of their enzymic effects. We also studied the role of blood cholinesterases, which remains enigmatic even today. We proposed that the enzymes we referred to as "trans-

port” cholinesterases served to protect the organism from endogenous choline esters.

‘One day, as Koppanyi saw me working with urodele larvae and when he discussed this work with me, we realized that these animals, which obtain oxygen as they swim underwater via their skin, may also absorb drugs through the skin. So we studied what we called the “overt” behavior of the urodele larvae, particularly under the influence of physostigmine, and we distinguished between what appeared to be an ‘alerting’ effect of small doses of anticholinesterases and convulsive effect of large doses. After seven years with Dr. Koppanyi I moved to the Sterling Winthrop Research Institute in Rensselaer, New York, a suburb of Albany.

EC: But, you liked Washington DC?

AK: After living with Marion for a few months in Washington I began to like Washington very much, until the era of McCarthy that you may remember. During most of my work with Koppanyi, Washington was a very liberal, progressive, cultured city, with parties all over the place, including those given by various embassies, and entry into the parties was quite easy. With the advent of the McCarthy era the interaction ceased and nobody spoke to anybody; everybody was afraid of everybody else.

EC: Especially in Washington, DC.

AK: It was not a very pleasant time in Washington. But, Theodore Koppanyi was a great master and a great pharmacologist. He was also eccentric; Koppanyi stories abound still today. I remember that whichever discovery was mentioned to Koppanyi, he would say that he discovered it first and he would pull up a reprint to prove the point. He was also a very great friend of your ex-boss, Steve Brodie. They were very close.

EC: But they were two different types.

AK: Indeed! They were both eccentric and creative, but Koppanyi was more eccentric than creative, and the reverse was true for Brodie, who was always much more persevering as a scientist.

EC: Both were extremely intelligent, and Brodie was a genius.

AK: Brodie was a genius, who deserved the Nobel Prize but never got it. The great writer and philosopher, Arthur Koestler listed in one of his books Koppanyi as one of the Wunderkinder in his adopted city, Vienna. Koestler was born in Budapest. In Vienna Koppanyi published a number of papers on eye regeneration, with no less a luminary than Paul Weiss. In fact, the gossip was that Koppanyi was to get the Nobel Prize for eye regeneration, except that as he was to demonstrate at a Congress the functional recovery of the amputated eye of a rat, just like Otto Loewi had to demonstrate at a Congress the cholinergic nature of

the vagal transmission. Koppanyi's demonstration was a flop! So, when Koppanyi came to the States in the early nineteen twenties, he abandoned work on regeneration completely. He worked at Cornell University with Hatcher on defecation and other autonomic functions, and then on ganglionic transmission and on barbiturates.

EC: You have a good recollection of the time with Koppanyi?

AK: Yes, because he was such a strange character and so catholic in his tastes. In Georgetown, I developed several friendships that lasted a life time. I met George Koelle, a world-famous "cholinergiker" and the developer of histochemical stains for butyryl and acetyl-cholinesterase, when he came to Georgetown to deliver a lecture. We developed immediately a friendship that lasted till George's death 5 years ago. Bo Holmstedt, subsequently a renowned toxicologist and forensic scientist, worked at the time on a Fellowship with George Koelle at the Philadelphia University Medical College. Bo liked to come to Washington on weekends, because he felt that Washington was very cosmopolitan and cultural; we became close friends and remained so till Bo's death. I said at the time to George, "You know Bo really doesn't like Philadelphia"; George could not get over it, because as a born and bred Philadelphian he loved his City. Anyway, after 7 years with Theodore I received a good offer, money-wise, from Maurice Tainter, Director of the Sterling Winthrop Research Institute. My other inducement for accepting the offer was that several well known scientists, like Al Lands, Froilan Luduena and James Hoppe, worked at the Institute.

EC: How long did you stay there?

AK: Three years. I felt after three years that the corporate and pharmaceutical laboratory life didn't agree with my character. So I moved.

EC: Too many rules?

AK: That's right. And, too much intra-Institute intrigue.

EC: Research, even in a good place in industry, is quite difficult because of the priorities.

AK: If you don't discover a miracle drug for your company your name is mud. Well, I did develop, or help develop a couple of drugs that are still in use. Ambenonium (Mytelase) was developed by Al Lands and me as a treatment for myasthenia gravis. Myordil was, or is used, as an antiarrhythmic drug. Finally, I worked on a benzoquinonium derivative that appeared, in animals, to be an effective mild antipsychotic; unfortunately, the Institute did not, at the time, have the capacity for clinical testing of this drug. In fact, I developed at the Institute a battery of tests for the development of antipsychotics; it included a test in the monkey that I developed on the basis of Charles Darwin's book on

facial expressions of mood in man and monkeys. And, I got the Institute to purchase from Joseph Brady an automated device for quantitating conditioned learning in mice and rats. This was copied by other pharmaceutical companies, as any pharmaceutical company was glad to purchase this equipment as it worked at night, saving the company precious time. Altogether, I did quite well at the Institute; nevertheless, I think that Tainter did not quite approve of me, and, at one time he almost fired me. This happened when I went with Tainter to visit the famous neuroscientist, Karl Pribram, Director of the Institute of Living in Hartford, to seek his opinion of our program. When I explained the program and our tests to Pribram, he said: "I would not compliment these trials with the term 'tests' ", and Tainter got very upset! I would like to stress that I worked out a couple of novel concepts at Sterling-Winthrop I am proud of. I demonstrated that a congener of Ambenonium, an oxamide, exhibited what I referred to as "sensitizing" actions at the neuromyal junction that were receptor-based and not related to any anticholinesterase effect. I published this novel concept simultaneously with Steve Thesleff's description of the reciprocal, "desensitizing" action, also referred to as receptor inactivation. And subsequently, together with John Paul Long, later the Chair of Pharmacology at Iowa Medical College, I demonstrated, in 1955, that muscarinic CNS receptors are structurally identical with the autonomic, peripheral muscarinic receptors. After Eccles' demonstration in 1954 of chemical cholinergic transmission at the spinal cord's Renshaw cell, this was an early evidence for the presence of muscarinic transmission in the CNS.

EC: After three years you went where?

AK: In 1956, I became the Chair of Pharmacology at Loyola University Medical Center. The Department was located in a pre-Chicago fire building that was about the oldest building in Chicago, infested with rats. When I arrived, the Dean of the School, Dr. Sheehan, told me that they were just ready to move to the new building, and I said, "You don't have to reassure me you are going to move to the new building; how can you possibly continue to have a Medical School in this building". But, it took him eight years to fulfill his promise. Chicago was the place where I met you.

EC: We met because Brodie was our mutual friend. Anyway, you were very, very successful as a Chairman of the Department.

AK: You mean, administratively.

EC: Also scientifically. All your staff said you gave them freedom and support with regard to their research.

AK: Before me there was no Department of Pharmacology at Loyola University Medical Center (LUMC). The late Thomas Ivo Oester, who became chair of a department in the late nineteen forties, for not being able to do much for his Department which, before him, was alternatively moribund and non existent since it was established around 1910 (my history of the Department is available in the Archives of the Library of the Loyola University), as he was very busy heading a laboratory specializing in the saliva test for race horses, and being Associate Chief of Staff for Research at the Hines VA Hospital.

When I arrived at LUMC I applied for a training grant to NIH and the late Lou Goodman, chair of the pertinent Study Group said in his evaluation of my application that Karczmar is a good man who is trying to revitalize a defunct department. Parenthetically, I got the grant, as well as the first of many NIH, NSF and Department of Defense grants for the cholinergic studies. The training grant helped me to recruit two good researchers and excellent teachers, Alex Friedman and Joe Davis to the Department. Alex was a pioneer of the studies of circadian rhythms, and Joe, who started as a NIH awardee in ontology, found his own corner when he discovered a new organ, the testicular capsule, and defined its autonomic control. They were also very gifted teachers. And then, slowly but surely, the Department grew in reputation and attracted young scientists who were well known then and even more so subsequently. This was a very international team! It included Kyozo (Kyo) Koketsu, a co-author with Eccles and Fatt of the Nobel-prize winning paper on the cholinergic transmission at the Renshaw cell; Syogoro Nishi who was a Rockefeller Fellow when he joined my Department; Alan North, a student of Hans Kosterlitz, the pioneer of the endorphins studies at Aberdeen, Scotland; Bob Jacobs, a graduate of the University of Wisconsin and a specialist in neuromyal transmission; Les Blaber, a student of Bill Bowman of London University, world-known for his neuromyal studies; more recently, Stan Lawrence, a well-known psychopharmacologist, and Luke van de Kar, a Berkeley post-doc in the area, believe it or not, of serotonin transmission. John Eccles became an Adjunct Professor in the Department in sixties. He participated in our seminars and advised our graduate students. Another Adjunct Professor was the late Guy Everett of Abbott laboratories, the discoverer of tremorine and its parkinsonian-like effects. We had distinguished foreign fellows, such as Vladimir Skok from Kiev, Gordon Lees of Aberdeen and Vincenzo (Enzo) Longo of Rome, and we collaborated with members of other Departments of LUMC and of the Hines VA Hospital. My VA associates included Volia Liberson, an famous

physiatrist, EEG expert and neuropsychopharmacologist, who was a student of Pavlov; Alfred Kahn, a student of addictions and Joseph Bernsohn, a neurochemist and specialist in tranquilizer research. At LUMC, I collaborated with Abe Rosenberg, the Chair of Biochemistry. I should also mention my Senior Assistants, Gizela Kindel and Lionell Barnes who worked with me for twenty years and participated in all kinds of studies. So, we had a very successful Department, focusing on neurosciences and neuropsychopharmacology. With the help of LUMC and the Illinois Department of Health we managed to establish, as part of the Pharmacology Department, the Institute for Drugs, Mind and Behavior.

EC: Where you studied cholinergic mechanisms.

AK: Mostly. All my scientific life I was in love with cholinergic mechanisms, and I am quite chauvinistic when it comes to cholinergic. At this meeting of ACNP I am upset because all I hear is about dopaminergic, serotonergic, GABA-ergic and peptidergic phenomena, and nobody mentions the cholinergic system. Fortunately, we have now regular meetings of a cholinergicsociety, the International Symposia on Cholinergic Mechanisms (ISCMs), as well as Symposia on cholinesterases (ChEs) and on Alzheimer Disease (AD), led by such luminaries as Mirko Brzin and Elsa Reiner in the case of ChE Symposia and, in the case of AD, my successor at LUMC, Israel Hanin. The ISCMs were initiated by Edith Heilbronn, a German born famous Swedish scientist, who felt in the nineteen sixties as I do today, that the cholinergic system is neglected. We have had, by now, twelve ISCMs, and the thirteenth ISCM will take place in Brazil.

EC: I believe I attended one or two of them.

AK: You attended the Florence ISCM, and, in fact, you insisted that the organization provided a limousine to drive you from the airport to the site of the meetings, which we happily did. You presented your pioneering method to measure acetylcholine turnover and evidence about the effect of functional states on turnover. You felt, quite rightly, that acetylcholine turnover is more important as a marker of functions and behaviors with cholinergic correlates than acetylcholine levels.

To return to the Department of Pharmacology at LUMC, when Kyo and Syogoro returned to Japan to become the president of Kurume University and the Chair of Physiology at Kurume, respectively, we continued our collaboration on ganglionic, neuromyal and central transmission, and several Kurume postdoctorals, including Yoko Ohta, K. Akasu and K. Kaibara, joined us for a year each to help us with this work. Together, the LUMC-Kurume team established receptor sites at the autonomic B and C neurons, and enteric and parasympathetic ganglia;

and we defined at these sites the fast nicotinic and the slow muscarinic potential, and the extra-slow peptidergic and the inhibitory potentials. This work resulted in a book, *Autonomic and Enteric Ganglia*, published by Plenum Press in 1986. Independently, we followed my earlier work on receptor modulation which would be today defined as an allosteric conformational change, and we described NaF, studied earlier by Edith Heilbronn, as a reactivator of organophosphorus anticholinesterases-inhibited acetylcholinesterase, a potent sensitizer of cholinergic transmission, both centrally and peripherally.

I also continued behavioral work, with the association of the late Charles Scudder, my very brilliant graduate student. With him, Volia Liberson and Enzo Longo, with whom I worked previously in Rome where I was a Guggenheim Fellow at the Istituto Superiore di Sanita, we defined cholinergic EEG and behavioral arousal, and demonstrated the cholinergic nature of REM sleep. Volia and I also demonstrated the cholinergic "cure" of "obsessive animal behavior," using the "no goal" paradigm. With Charles Scudder and my assistant Gizela Kindel we developed an automated multilever two-way conditioned learning device for the study of learning in mice, and a big enclave into which we released all kinds of genera of mice, to study ethological, "normal," mouse behavior. George Koelle called this enclave model, "the mouse city".

EC: You had games for the mice!

AK: Yes. And, George, alluding to the politics of Chicago, said that at one time I discovered that the elections in the "mouse city" were rigged; so I closed "the mouse city". Well actually, Charles and I did not close "the mouse city". In "the "mouse city" we could quantitate every ethological behavior, such as exploration, maternal protection of the pups, three or more types of aggression, predatory, consumatory and territorial, social behaviors, such as grooming, etc. We studied the effects of drugs, cholinergic and non-cholinergic, on all those behaviors as well as the relation in the various genera of mice between these behaviors on the one hand and genetic and transmitter characteristics on the other. We linked the cholinergic activation, cholinergic neurotransmitter profile and certain sites within the cholinergic pathways in the brain to learning and aggression. Altogether, this work led me to define the role of the cholinergic system, in animals and humans, as the facilitator of "realistic" cognition of the outside world. Thus, the cholinergic system is necessary for the realistic interaction between an organism and the environment. I called the pertinent cholinergic syndrome, Cholinergic Alert Non-Mobile Behavior (CANMB).

EC: You were right, because the brain has a central master director, the cholinergic system, especially in the case of the limbic system, the brain stem, and the hypothalamus.

AG: Thank you. Yes, hypothalamus, the hormones and the cyclic hormonal rhythms, with the reciprocal interaction between these rhythms and the cholinergic system are functionally and behaviorally most important, particularly for sexual behavior and thermocontrol. The important question here is, how does the cholinergic turnover change when progesterone, testosterone and estrogen levels go up and down during the diurnal, seasonal and sexual cycles, and vice versa. We provided a few answers to this question, but it's for future investigations to fully clarify the matters. I am quite proud of positing the concept of the CANMB. I wrote a number of review papers on the role of the cholinergic system and of CANMB in counterbalancing schizophrenia in the human and animal models of schizoid behavior. I know that you and Sandro Guidotti stress the role of the GABAergic system in schizophrenia, but perhaps there is an interaction between these two transmitter systems in the generation of schizoid behavior.

EC: Altogether, your Department specialized in neurobiology.

AK: Yes, neurobiology, rather than neurosciences. But, we formed, within the Department, the Institute for Mind, Drugs and Behavior devoted mainly to neurosciences. My late, talented friend, Charles Scudder, served as the Associate Director of the Institute.

Also, we studied cholinergic ontogeny and ontogenetic and morphogenetic effects of cholinergic agents and anticholinesterases. With Joe Bernsohn, we showed that anticholinesterases cause a shift in the ontogeny of isozymes of cholinesterases, which is important with regard to the effect of anticholinesterase treatment of pregnant mice on post-natal behavior, such as aggression, of the offspring. I continued these studies after resigning from my chairmanship, as the Senior Fullbright Fellow at Bill McGuire's Institute in Sydney, Australia. With Bill, the discoverer of the human thalidomide ontogenetic malformation, we investigated the ontogenetic effects of administration of organophosphorus (OP) agents to pregnant rhesus monkeys. This is a matter of great importance in Australia, in view of the energetic, agricultural use of OP agents as pesticides in Australia. Altogether, this work confirmed my earlier concepts of a direct morphogenetic action of cholinergic drugs that is initiated in the embryo before the onset of neurogenesis, and of the trophic and morphogenetic role of the cholinergic system during development. So, the cholinergic system is important for both mor-

phogenesis and the control of interaction between neurogenesis and ontogenesis of functions and behaviors.

EC: Also, it is very important to investigate how during development these interactions are orchestrated. Central neurogenesis is fundamental in being the master of this interactive concert.

AK: You're right. This interaction concerned early students of the cholinergic system, including David Nachmansohn, Zenon Bacq and Charles Sawyer. They were interested in neurogenesis and phylogenesis of the cholinergic system in several species and their relation to function, such as motility. Their studies were carried out prior to the demonstration of central cholinergic transmission in the nineteen fifties. Eccles, Sawyer, Bacq and Nachmansohn felt that the presence of a strict relation between cholinergic ontogenesis, neurogenesis and ontogenesis of function, would demonstrate the chemical, cholinergic nature, of neurotransmission. Today we know that presence of the cholinergic system in an embryo is very precocious with respect to neurogenesis and the development of function!

EC: Nachmansohn's greatness lies in his discovery of choline acetyl transferase.

AK: Yes; we mentioned this fact already. He also described acetylcholinesterase as one of the most rapid, if not the most rapid, enzyme in existence. Then, he pioneered the studies of acetyl CoA; as we mentioned before, he should have got the Nobel Prize for this and his other work, but unfortunately he stuck to his idea of the role of the cholinergic system in conduction of all cholinergic and non-cholinergic axons, and worked for years trying to prove this speculation. This was indeed bizarre, and I feel, and I was told, this endeavor lost him the Nobel Prize.

EC: He was really denying progress.

AK: He was very stubborn. Let me tell you an anecdote which is pertinent. Nachmansohn participated in a 1959 Symposium in Rio de Janeiro and during a break, he went to the beach where he fell asleep in his chair. So, Eccles and others started pushing Nachmansohn in his chair into the sea. Nachmansohn wakes up in the middle of this activity, sees himself deep in the water, and says: "You can kill me but you cannot kill the theory".

EC: Much can be said about him, but he was a very intelligent and creative person, more intelligent than many people around him. He held in close control his laboratory, and made his associates work hard to provide evidence for his speculation, whether they believed in it or not. He was always thinking about the brain as a whole that obeys the same physi-

cal and chemical laws whatever the site or type of neurons, axons and dendrites.

AK: As I alluded to before, he left behind him a number of very able men. Speaking of Ehrenpreis, at the same Rio Symposium I mentioned, he described a cholinergic receptor of the electric organ of Torpedo, as did, somewhat differently, Ada Hasson with Carlos Chagas, the son of Carlos Chagas of Chagas Disease. Before their studies, for many years, our idea of the receptor was abstract, because it was based on structure-activity relationship (the SAR) of compounds that exhibited affinity for a given receptor, and not on any direct description of their nature. No one really envisaged the receptor as a chemical molecule.

EC: That was true not only for cholinergic but for all transmitters!

AK: Quite right, and Bob Furchgott, who earned a Nobel for his SAR studies opined that we will never get a chemical image of a receptor or obtain a transmitter molecule! So, when at this Rio de Janeiro meeting, Chagas, Hasson and Ehrenpreis spoke of isolation and purification of a receptor, in this case, a cholinergic, nicotinic receptor, we were all flabbergasted! It transpired later that both Chagas with Hasson and Ehrenpreis got their receptor wrong. Jean-Pierre Changeux, Nachmansohn's postdoc as I already mentioned, who was personally very fond of Nachmansohn, liked to stress that Nachmansohn did not appear as an associate of Ehrenpreis, at Ehrenpreis's Rio presentation, because Nachmansohn did not believe in Ehrenpreis' results. Changeux did not want his idol to be accused of being wrong on this matter!

We studied, with Joe Bernsohn, Gizela Kindel and Abe Rosenberg the metabolism of acetylcholine during development and aging. Under your influence at that time, we also studied the acetylcholine turnover, because we followed your concept that transmitter turnover levels are more important in diagnosis of behavior than transmitter levels. We showed that with the decrease of the pool of acetylcholine synthesis in old mice, there is a compensatory increase in incorporation of choline in the synthetic pool of acetylcholine, and in acetylcholine turnover.

Since the nineteen sixties I have had a chance to review our different studies in a number of Journals, after my retirement from the Department Chair at LUMC. I did not do much experimental work later, but I continued with my review work; I published several of my reviews in Journals where you served as the Editor. I also organized several Symposia, participated in meetings, including the ISCMs and ACNP, and I was busy working on my book, *Exploring the Vertebrate Central Cholinergic Nervous System*. The book serves as a maxi- review of our past work as well.

EC: When did it come out?

AK: In 2007, this year. This is essentially a one-author work, although out of its eleven chapters three are collaborative. I sense that in regard to its scope, it is a unique opus. It stresses the history of the cholinergic system, and it proceeds from shamans and hunters, and prehistoric use of cholinergic medicinal plants to the current status of CNS cholinergic research. It took me eight to nine years to put it together. There are many multicolored photographs in it, including three-dimensional and dynamic illustrations of cholinergic receptors and cholinesterases, schemes concerning acetylcholine synthesis, and designs linking cholinergic pathways with specific functions and behaviors. You don't need this book to be immortalized, but there is a color photograph of Dr. Erminio Costa, Dr. Gian-Carlo Pepeu of Florence and his wife, the doctress Ileana, Dr. Israel Hanin, a prominent cholinergic researcher and discoverer of a chemical assay for acetylcholine and my successor as the Chair of the LUMC, Department of Pharmacology and his late wife, Leda. There are many other photographs of the present and past great cholinergic researchers, from Otto Loewi and Henry Dale to Mona Soreq and Rita Levi-Montalcini. So, this is quite a book, if I say so!

EC: Writing this book required so much of your stamina, effort, and emotions. How could you write this without emotion, living again through all your own research and that of your friends?

AK: Well, it's true. I'm ninety years old, so I am a full-fledged participant in the great story of continuously ongoing cholinergic research. Fortunately, there are many questions not answered as yet, that might be answered in the future.

EC: Who is the publisher?

AK: Springer, New York.

EC: This is just out and the great Victor Whittaker is author of the Foreword.

AK: Just out, just out.

EC: This is a beautiful book.

AK: Very beautifully edited. It has a color photograph of a Himalayan peak symbolically representing the fact that, unlike the Roman Empire which rose and then fell, the studies of the cholinergic system rise but never fall.

EC: How many years did you spend at the LUMC?

AK: I was Chairman for thirty years. To be a Chairman of a Department of Pharmacology for thirty years means you are crazy. I retired as the chair about twenty years ago, but I continue serving as a consultant to the Veterans Administration and the Defense Department of the United States of America.

EC: Have you been in Georgetown recently?

AK: No, not recently.

EC: Georgetown used to be a beautiful Washington area where people could play, but, now, it is a city. There is a rule that Georgetown University students have to live in Georgetown.

AK: Georgetown University is a beautiful university because there is a big campus, and within it there is a shady, wooded valley separating the University from the Medical School. One could walk or jog from the University to the Medical School. Within the valley, there is a cemetery with the old tombs of Jesuits fathers, members of the University. But, you are right; Georgetown is now a City. You know this very well, as you served for so many years as the Director of the Fidia-Georgetown Institute.

EC: I think the Medical School is still controlled by the Jesuits.

AK: This reminds me of a point I would like to stress with regard to Loyola Medical Center. When I entered the Department, the school was controlled by the Jesuits but now, the LUMC is an independent entity. During my time the Jesuits and the President of LUMC controlled it fiscally and administratively. They were, and are, very tolerant. Among some Jews who served as Departmental chairs or Professors at LUMC, I'll not deny I was rather strange or eccentric in my behavior; I think the Jesuits were more tolerant than any other university would have been, of my, shall we say, eccentricity?. Jesuits are wise people; they are an old and sophisticated organization, devoted to learning. Jesuits know all about human vagaries, and they accepted me the way I was.

EC: From all the time that you spent at Loyola University, what do you remember? What are the strongest memories, from your professional and the human viewpoint?

AK: On its 100 year anniversary, in 1969, Loyola University instituted a great celebration.

EC: So, the Chicago LU was inaugurated in eighteen sixty nine?

AG: Right. I was invited by the Chancellor, Very Reverend James Maguire, and his Council to prepare, as a part of the celebration, a symposium that would be appropriate in its themes with the Jesuit ideals of unity between knowledge and religion. All the costs of the symposium, including the travel of the participants and their honoraria, were covered by the LU. Jointly with Eccles, who, as I already said, was an Adjunct Professor in my Department we organized a symposium entitled *Brain and Human Behavior*, the proceedings of which were published by Springer Verlag of Berlin in 1972. At the symposium, we had philosophers like Steve Tulmin of Brandeis University and Ernan McMullin of McGill

University who discussed the mind and the brain from the philosophical and epistemological viewpoint. Then, there were psychologists, such as the famous Jean Piaget of Geneva University and notable neuroscientists, including Holger Hyden of the University of Goteborg, Eduardo de Robertis of the University of Buenos Aires, Seymour Kety of NIH and Boston General Hospital, Michel Jouvett of the University of Lyons, Igor Beritashvili (Beritoff) of the University of Tbilisi and Sam Barnett of Australian National University. The Symposium was unique because three of its participants were Nobel Prize winners: Danielle Bovet, John Eccles and Ragnar Granit. They were sitting on the same bench and didn't bite each other! And many other cholinergikers were present.

EC: This was one of the greatest scientific gatherings that ever occurred in an American school.

AK: You're the one to know; you organized a great Symposium for the inauguration of the Fidia Institute. Also, I was very proud, professionally speaking, to establish a great department. I should stress that throughout my tenure, we had an outstanding body of graduate students; a long-standing NIH Graduate Training grant was instrumental in this. Our graduate students worked with us, published with us, and many of them became my close friends, such as Nae Dun, Chair of Pharmacology at Temple University, Sam Speciale of NIH, Luke Konopka, Chief of the Neurosciences Laboratory at Hines VA Hospital, and Joel Gallagher and his wife, Pat Shinnick-Gallagher, both Professors at Galveston University Medical Center.

EC: Let's go a bit further in your life. You had a number of people working with you. In whom did you most imprint your way of thinking?

AK: There are a number of great guys who came out of our laboratories. It's very difficult to say who is best. Nae Dun, is an extremely able neuroscientist, both in terms of neurotransmitters and molecular activity of enzymes on the one hand and function on the other. He likes to use, after me, Jewish-Polish expressions, such as "Schnook". I think he learned from me the art of grantsmanship...Experimentally, I may have taught him to ask big questions rather than stick to what an advanced technique may deliver, and also, to be skeptical. His favorite statement is; "how come"? Another graduate student of mine, Charles Scudder, whom I already mentioned, accepted a faculty position after his graduation and became a close friend of Marion and myself. He was most eccentric and at one time he tinted his hair purple-red, to the great discomfit of his colleagues on the faculty. He also had a pet monkey. He bought an old mansion on West Adams Street in Chicago, in the middle of the black ghetto, because he needed a big house

to install the baroque furniture he purchased when the old Balaban Cinema palaces went on liquidation sale. To top all this, he was a professional level harp player who was invited to join the Chicago Orchestra. I am not kidding! Fortunately for me, he preferred to stay with science. He had some original ideas about unity of the universe and published the results of some experiments designed to prove his speculations. He retired early, as he wished to be in full strength to be able to build, with a couple of friends, a mansion he designed himself, in the wilderness of Georgia. Then, a tragedy struck, when he was killed by a couple of marauders. Then there were Kyo Koketsu and Syogoro Nishi. Of course, when Kyo joined us he was a mature scientist. He worked earlier with Eccles and subsequently he has had his own laboratory at the University of Illinois, but we soon became close friends and collaborators. Similarly Syogoro came to me as a Rockefeller Fellow and in our laboratories he worked originally with Kyo, but, when Kyo left to become the President of Kurume University we became close, as friends and collaborators. The three of us published a number of papers and reviews and were the co-editors of the book on *Autonomic and Enteric Ganglia*, which I already mentioned. Syogoro and Kyo taught me to be patient carrying out experiments. They developed a very delicate synaptic in vitro frog preparation that took a whole day to work out. Whenever there was any sign of damage or bleeding during the dissection they would stop and wait and wait and wait till everything returned to order, and they would start recording after most of us had left for the evening. This patience, this delicacy of touch, this persistence, always astonished me. It may be impossible for a European or an American, for me and possibly for you, to achieve that degree of patience. We're too temperamental!

EC: One person that was capable of this was Floyd Bloom. I never saw someone so persistent.

AK: Floyd Bloom is a good example. There is another stunning preparation that Kyo and Syogoro developed; the bullfrog lung assay for measurement of acetylcholine concentrations. Now we have all kinds of chemical methods for the measurement of acetylcholine, such as the gas chromatography-mass-spectroscopy technique established by my successor in the Department, Israel Hanin, and the chemoluminescence method, even more sensitive, developed by Maurice Israel and Yves Dunant. But the bullfrog lung assay was more sensitive than all our chemical methods. I think it was sensitive to ten to minus twenty-one milligrams.

EC: It all depends on the volume of the bath in which you put the assay organ.

AK: I guess you're right! I shared with Syogoro and Kyo their interest in Japanese culture, in Shintoism, Buddhism and art. Minako Nishi was an exquisite koto player and we spent many evenings listening to her playing original Japanese music. Then there was Alan North, whom I mentioned before. Besides being a great neuroscientist he was a great climber; he climbed in Scotland and the Alps, and he also was a participant in an English expedition to the Himalayas, where he froze a couple of his toes which had to be amputated. We shared the mountaineering interest, although my climbing was miniscule compared to Alan's. And Alan was, and is, very sophisticated and worldly. Marion, Alan and his first wife Valerie established a good and jolly social relationship.

EC: Where is Alan North now?

AK: He is Vice President for Research at Birmingham University in the UK. After leaving us, he became Chief of the Institute in Portland Oregon, and then he was a section chief of Glaxo Drug Company in Geneva. He left me to get better money, but I love him anyway!

I have an interest that I did not share with my students or associates. This interest concerns the study of the "self," and I don't mean cognition.

EC: Do you differentiate between cognition and the subject the Romans referred to when they said; "Learn about yourself"?

AK: It is the "self" or the "I" I am talking about, the Greek term, not necessarily the Latin term. Cognition concerns learning and memory, and, perhaps, perception. Cognition is a behavior, just as aggression or addiction. Cognition and other behaviors can be explained quite well in neuroscientific terms. The brain sites, circuits, transmitter pathways and transmitters involved, all the physical and chemical phenomena pertinent to these behaviors, are well defined. But the "self" is not cognition; the self is the feeling of "I". You have no doubt that you are you, Mimi, and I have no doubt that I am I! Yet, what is the "self"? Since the days of Heracleitus, Democritus and Cartesius this problem occupied many minds, both scientists and philosophers. We can classify them as reductionists or dualists. The reductionists or monists think that, just like behaviors, the "I" can be reduced to physics and chemistry, and to the material brain, and the dualists opine that the brain phenomena and the "I" are two separate entities. Today, when we know so much about the brain and behaviors, this topic is discussed with more sophistication than ever before. This is a very popular subject today, and the Churchlands, Changeauxs, Smythies, the Nobelists Crick and Edelman, Llinas and many others deal with it vehemently. Many of them consider

cognition as consciousness, and consciousness as similar or identical with the “self.” They do not offer clear differentiating definitions as to the “self” versus consciousness. They attribute the “self” and other mental phenomena such as cognition or aggression to the functioning of the cortex and/or other parts of the brain. But, many philosophers, who are concerned with these matters say the “self” is an epiphenomenon, although they hate to be called epiphenomenalists. For instance, the great American philosopher, John Searle, claims the “self” is a characteristic of the central nervous system, like digestion is a characteristic of the intestine. That’s exactly the metaphor he uses.

EC: Oh, my God!

AK: Oh, my God is right. John Searle is a renowned and respected philosopher, but this doesn’t make any sense. I agree that digestion is a product of the action of intestinal enzymes and juices, but the “self” does not, to me, result from neuronal and transmitter phenomena that we can describe.

EC: But, the product remains as the important phenomenon: the intestine produces shit and the brain produces the “self”!

AK: Yes, but the question is how do they manufacture their products? The Sherringtonian Society I am a member of, instituted by Sherrington’s student Jack Eccles, is concerned with this problem. The great Charles Sherrington in his book *Man on His Nature* described what the “self” is compared to consciousness. He was a theist, and therefore a dualist, as was that other theist, his student Sir John Eccles. At any rate, the Sherringtonian Society is very much interested in solving that conundrum. The problem is complex, and I’m simplistic describing it here. I cannot do it otherwise in this short interview. As a scientist I am of course a reductionist, but I also sense we do not have, as yet, all the data needed to “reduce” the problem. In the Introduction I wrote for the book, *The Brain and Human Behavior* I say we are a hundred years too early to answer the question, what is the “self”? Since that book was published some forty years ago, we still have sixty years to go to solve the problem in reductionist terms. I opine that the current approaches of “reductionists” even when more sophisticated than Searle’s are still unsatisfying and premature. Thus, Changeux in his recent book that bears a challenging title, *The Physiology of Truth* describes states of consciousness clearly, impressively and neuroscientifically, but his relating these states to the “self” suffers from the same sins I ascribed earlier to modern reductionists or monists. A specific, Eureka-kind speculation is needed to breach the gap between consciousness and other behaviors on the one hand, and the “self” or the “I” on the other. A brave and fascinating

attempt was made by the very great English physicist, Roger Penrose, who solved, with Hawking, the mystery of the “Black Holes”. First, he stresses that the function of the neuron is, basically and fundamentally, quantal in nature like any other biological, physical or chemical phenomena. Then, to state his speculation simplistically, he posits that “the self”, and he defines “the self” very clearly, emerges when the synaptic phenomena transfer from quantal to macro molecular level during the phenomenon of so-called “Objective Reduction”. It may be chuzbah, even for as a great scientist as Roger, to leap from physics to biology and neurosciences. Fortunately the distinguished neuroscientist Nancy Wolfe at the University of California, has proposed that certain cortical neurons that contain microtubule-associated proteins (MAP-2) are activated muscarinically and this generates quantal phenomena, including Objective Reduction with emergence of the “self”.

EC: It is easy to insert this proposal into brain function. They need to do this.

AG: Yes, in order to perform the mental jump needed to explain the “self”. Yet, as in the case of many other explanations of the “self”, the Penrose and Woelf speculation, when described in full becomes counter-intuitive; it lacks parsimony and becomes “big.” It lacks simplicity

EC: Parvo sed mihi apto.

AK: Parvus, but not easy to achieve!

EC: Transluminial.

AK: I agree with you, Mimo. Many philosophers and logicians, such as Frege, Wittgenstein and Carnap, as well as the mathematician Goedel, would claim that this lack of parsimony in our current proposals for the nature of the “self” reflects a poor semantic basis for the proposals which are “nonsensical”, as Carnap would state. I describe this point at length in my recent publications. This may be due to the fact we do not, at this time, have full cognizance of the physical and chemical world; we still do not have a single equation, sought by Einstein that defines gravity, quantal mechanics and space. Till such understanding is available, a valid proposal as to the nature of “I” cannot be posited. Perhaps we need knowledge of many more than our four dimensions to understand the world, as suggested in the “strings” theory.

EC: Let me ask a question that is more personal. How do you plan to spend the next year of your life?

AK: Only one year?

EC: No, the next five, ten.

AK: I have several programs. First, I will continue being engaged in the International Symposia on Cholinergic Mechanisms as I am the Chair for

the International Advisory Board. Then, I will be active as a member of the Sherringtonian Society and work with other members of the Society on the matter of “I”. Finally I have a program of a very personal nature. This has to do with my notion that I am immature spiritually, and I would like to become more of a Buddhist.

EC: You are a Buddhist a bit already.

AK: I am a Jew by genetics and tradition, but primarily I’m a pseudo Buddhist. I would like to relax, to live by the day, to have more feeling I live in the moment. I am secular rather than spiritual; I would like to show more relaxed compassion, contrary to selfishness. I would like to have more enlightenment versus ego.

EC: Would you like to go to some Monastery in Asia?

AK: We went with Marion to the Himalayas and I found it’s much easier to meditate in front of a Himalayan peak than in front of the Palace Hotel in Miami or the Trump Tower in Chicago. Of course, there is much of Buddhism I cannot accept, such as the idea of reincarnation.

EC: You think the spirituality of Buddhism is very difficult to learn, but this is the life ingredient you need?

AK: You put it very well.

EC: But if you go back to science you find a way to transcend secularism.

AK: That’s why I am a scientist. I look for the “truth”, including the physiological truth of cognition and of the “self”; this “truth” is very difficult to understand, but it is a spiritual “truth” in many respects.

EC: But, what is it you can’t understand? What is the truth? You have to guess whether it’s truth or not?

AK: The question of what is the truth is very difficult; the answer has been sought for millennia.

EC: What is the “truth”? The truth is what you can’t understand.

AK: That is a very good proposition. Perhaps the “truth” is something we cannot as yet understand.

EC: There is something we cannot understand, but that is a goal. Now we are becoming a little too much, like philosophers.

AK: You can never be too much of a philosopher. It’s very useful!

EC: We should be, for instance, more cognizant of Buddhism. I didn’t read much about the Buddhist religion. Since you consider yourself a little bit of a Buddhist, what did you read?

AK: Buddhism is a philosophy of life, not a religion. I read the books of Dalai Lama, Sogyal Rinpoche and D.L. Suzuki, as well as essays of Arthur Koestler. Some of Dalai Lama’s books are the easiest introduction to Buddhism.

EC: When you went to the Himalayas, did you visit with Buddhist monks?

AK: Well, I don't speak their language, and the many sages that came from India to us sometimes get a bit too Talmudic, they rationalize too much. It's not so easy to exchange real information, because, as we say, "If you can explain it, then it's not Zen". Perhaps the same is valid for "truth", if you can explain it, it isn't truth, it's something else. I also have to mention that one of the good reasons why in the past I followed many directions, and now I turn in the Buddhist direction, is because I am married to Marion, whom you know well. Marion is an ordained guru, her Buddhist name is Evening Light, which is a very beautiful name, and she taught me a lot as she made my sixty-one years of married life very happy. And Buddhism, as a philosophy of life, is very compatible with a happy marriage, particularly when one spouse is very difficult.

EC: Are you a very difficult man?

AK: Yes, I think so.

EC: Nature gives you a break, as you get old.

AK: Yes, getting old, one begins to be a bit milder.

EC: Now, you are ninety?

AK: Ninety and a half, to be quite precise.

EC: In your case, this is nothing!

AK: Thank you very much. Does that do it? Are we through with each other?

EC: Well, I am eighty-four and I don't know if I'll get to ninety. You have obtained that target with success, because you are in control of your mental and physical qualities, and in control also of your personal relations.

AK: You are very kind. As I said in the beginning, to be a Jew and to be born in Poland, you've got to be lucky to survive to be ninety. You have to be lucky, but you also have to be a bit spiritual.

EC: The more you become old, the more you can identify with infinity.

AK: Now, we are really getting philosophical. Thank you very much, Mimo.

JOSEPH KNOLL

Interviewed by Thomas A. Ban
Budapest, Hungary, January 23, 2002

TB: This will be an interview with Professor Joseph Knoll* for the Archives of the American College of Neuropsychopharmacology. We are at the Department of Pharmacology and Pharmacotherapy of Semmelweis University in Budapest. It is January 23, 2002. I am Thomas Ban. Let's start from the beginning. Please tell us when and where you were born and say something about your early interests and education.

JK: I was born on the 30th of May 1925 in Kassa, a city in northern Hungary, now Kosice in Slovakia, but my parents moved to Budapest when I was three weeks old and where I have lived since. As a matter of fact I had seen Kassa only 40 years later. As a child, we lived in the outskirts of Budapest, called Kispest which translates in English as Little Budapest. As a teenager I had to travel a distance by streetcar to high school that was located in the center of the city. In Hungary we have eight years of high school, called gymnasium, after four years of grade school. I was lucky to be admitted to the Jewish Gymnasium. It was an excellent school, where I learned a lot. From my very early childhood, I wanted to be a physician. I can't tell you why; there was no physician before in our family.

TB: When did you graduate from high school?

JK: I graduated in 1943. It was a very difficult year. Hungary was an ally of Nazi Germany, and as a Jewish family we suffered a lot. Although I was at the top of my class in the gymnasium I was not admitted to medical school because I was Jewish. So, I had to take a job instead of going to the university. Then, in March 1944 the German army occupied Hungary. Shortly after, my family, as all Jewish families, was moved into houses marked by the yellow Star of David.

TB: Did you have any siblings or was it just your Mother, father and yourself?

JK: I also had a brother who was two years older. But, soon after the German occupation he was called for service in the special division of the army for Jews called "munkaszolgálat" that translates literally as "labor service." Before he left home we agreed I would take care of our parents if anything happens. We were prepared for the worst.

TB: So, you stayed with your parents.

JK: Shortly after my brother left I was also called for service, but in May when I learned from the news that all the Jews from the suburb where my parents lived would be "deported," and taken to a concentration

* Joseph Knoll was born in Kassa, Hungary in 1925.

camp, I deserted from the army and joined my parents in Kispest. I felt they were too old to be left alone and I wanted to be with them. So, I managed to be transported with my parents to Auschwitz. But we were not left together for long. As soon as we arrived at our destination we were separated immediately; and they were sent to the gas chambers and killed. There is no way to convey my feelings to anyone who has not lived through that. I was left there alone. For days I was in a daze; I was kept alive by the poems I knew by heart.

TB: You were kept alive by the poems you knew by heart?

JK: It was my Mother who introduced me to poetry. I like books, and by the time I finished high school, I knew by heart about 200 poems. I kept on reciting those poems I knew, and used to recite as a child to fall asleep. But this time I kept reciting them over and over again to keep in contact with humanity, for not losing faith.

TB: When did you arrive in Auschwitz?

JK: I arrived in Auschwitz in June and was barely there for three weeks when I was almost killed. Everyday a few of us had to carry the dinner, usually a dirty vegetable soup, from the kitchen in large wooden containers, to the outside where the other inmates were waiting for the food. The chief of the kitchen, a huge two meters tall sadistic Lithuanian SS, was standing at the door of the kitchen, and, while counting the containers, he struck the back of the man carrying the container who just passed. He knew that those of us who were already weakened by starvation would fall or spill the soup. Those of us who fell or spilled, he dragged to the kitchen and beat to death or until losing consciousness. This is what happened to me and I would have died if Jaksa Wegner had not saved my life.

TB: Who is Jaksa Wegner?

JK: He was another inmate from Kispest; a very strong man, a former boxing champion. He was the leader of a group of inmates working in the Lager's bread and food store for drawing rations. He found me unconscious in the kitchen, carried me to our barracks or "Lager," as they used to call it, and arranged to have me in his group. We had to work hard in the store, but we could eat as much as we wanted.

TB: Did you work in his group all through the time you were in Auschwitz?

JK: No. One morning the commanding officer was looking for an inmate who spoke German.

I spoke German with my Mother at home and Yiddish with my father. I was fluent in German so he picked me to become his servant. He treated me well; I think he really liked me. I remember I always got a taste from the cookies and pastries his wife sent him.

TB: How long were you in Auschwitz?

JK: From June to September. When I was taken from Auschwitz to Berlin I was in good physical condition; I weighed 78kg. Compared to some of the Polish prisoners I was not in Auschwitz for very long. But, it was long enough to see the flames and the fumes of the gas chambers that worked all the time at full capacity, where thousands of Hungarian Jews and others were killed and cremated.

TB: You were transported from Auschwitz to Berlin.

JK: To Berlin first and then to Ohrdruf. I remember that in Ohrdruf I was beaten up and left tied up for 24 hours in the freezing cold for stealing potatoes to curb my hunger. By the time I was untied my hands and feet were frozen.

TB: Were you liberated in Ohrdruf?

JK: No, I was liberated in Dachau. From Ohrdruf we were transported to Buchenwald. When we arrived and were marching towards the Lager I heard guns and people around me were falling to the ground. We did not stop and kept on moving towards the main gate but only a few of us made it. Everyone who turned back to see what was happening was shot, but I will never know what happened. From Buchenwald I was immediately transported to Dachau. It took 21 days to get from Buchenwald to Dachau and only a few of us survived. We were on the train that was called the "Dachau death-train" without any food or water. I was one of the few survivors and weighed 37 kg when we arrived. I was fully conscious but unable to move. The day after our arrival at Dachau on April 29, 1945, our "Lager" was liberated by American soldiers. Most of them were black. Each of us was given a loaf of bread and a can of meat; thousands died after eating the first food from being starved for weeks. It took me several weeks to get back my strength and learn to walk again. Since my English was fairly good I became a clerk in Captain Schlenker's office, who was very helpful to me. He even offered to get me a scholarship in the medical school at Zurich. I turned it down because I firmly believed my brother was alive and I wanted to return to Budapest to meet him. Although Captain Schlenker warned me of the slim chance of my brother's survival, I still decided to return. Unfortunately, he was right, I lost my brother as well as my parents

TB: When did you arrive in Budapest?

JK: On September 8, 1945 and I soon learned from my family only an aunt survived with a niece, who was to later become my wife. I was alone and had to rebuild my life. I wanted to enter medical school immediately, but it was too late to register. So, I applied and was admitted to the Műegyetem, the Technical University in Budapest, where they

trained engineers. After the first semester, in February 1946, I managed to transfer to medical school. In the summer of 1946 I was given the opportunity to take the courses and examinations from the first semester I had missed. I graduated from medical school in 1951, *summa cum laude*. I wanted to become a neurologist or a psychiatrist, but I also thought I should get some research experience before becoming a specialist. As a good student, I was one of the best in my class, I had no difficulty in getting a job as a demonstrator in a basic science department while still a student. I was very impressed with the famous scientist Géza Mansfeld our professor of physiology, and my intention was to apply for a job in his department. But he became seriously ill and passed away. In February 1949 I took my final examination in pharmacology and Professor Béla Issekutz, our professor asked whether I would like to work in his department. I was happy to have this opportunity and agreed. It was important that the Hungarian Academy of Sciences was reorganized just about the time this happened so I was able to get a stipend from the Academy to live on.

TB: So, you joined the Department of Pharmacology in February 1949.

JK: And I have never left the department since. At the time it was still on the second floor of the old building in the medical school. I fell in love with my work, and did not become a clinician. But, I always kept in close contact with the clinical faculty of the university. I loved my work so much I even gave up chess to spend all my time in research.

TB: So, you were playing chess in your free time.

JK: I loved to play chess and was on the chess teams of the Jewish Gymnasium and the University but I gave up playing because it distracted me from work.

TB: What was your first project in the department?

JK: I was studying cholinesterase, the enzyme involved in the metabolism of acetylcholine. My research dealt with morphine and cholinesterase. I studied the synergism between morphine and prostigmine, a cholinesterase inhibitor. By the time I graduated from medical school I had seven papers published on this topic.

TB: What was your next project?

JK: In about 1951 I started the project I was to become engaged in for the rest of my life. It is concerned with the physiological basis of life, the brain and its self.

TB: How did you get involved in CNS pharmacology?

JK: I never worked in any other field. I entered pharmacology when neuropsychopharmacology began and it became the center of my interest. I was a member of the team in Hungary that was involved in studying

chlorpromazine, imipramine, and desipramine; it was in the early 1960s that I developed deprenyl.

TB: Before moving to the 1960s could you tell us something about your research in the 1950s?

JK: When I started to work in the 1950s I had to find a method that would link CNS physiology and pharmacology. I became interested in the “activating system” of the brain. In the early 1960s experimental tools specifically influencing the operation of the catecholaminergic and serotonergic systems in the brainstem were developed and I thought they might provide a key to understanding the operation of the brain. I became especially interested in what is responsible for what we call drive.

TB: You used the term “activating system.” Were you referring to Moruzzi and Magoun’s “reticular activating system”?

JK: Let me give you a simple example of what I mean when I refer to an “activating system” in the brain. A rabbit is eating cabbage in a relaxed manner and an eagle comes with lightening speed to capture the rabbit. The rabbit, to survive, has a split second to change the activation process in the brain. In that split second, it must change from a relaxed situation to maximum activity, to use all its capacities to escape. I’m referring to the system that makes it possible for the rabbit to escape. There is a mechanism, I call the “enhancer mechanism” responsible for this activation, in which endogenous monoaminergic substances, such as noradrenaline, dopamine and serotonin are released. I have been interested in the regulation of “enhancer mechanisms” and in developing substances involved in that. From the different agents that have an effect on enhancer regulation, so far only β -phenylethylamine, (PEA), and tryptamine have been analyzed. I developed drugs for enhancer regulation. In the early 1960s I had found deprenyl, a synthetic phenylethylamine derived enhancer, and in the late 1990s, I developed (-)-BPAP, essentially a tryptamine derived selective and highly potent enhancer substance.

TB: You mentioned you did research with some of the newly introduced psychotropic drugs in the 1950s but did not say what you did.

JK: When chlorpromazine was introduced in the mid-1950s I developed two tests for the differentiation between classical sedative-hypnotic drugs and the new tranquilizers. One was based on a jumping reaction, and the other on hunger motility. We found using these tests that the new tranquilizers selectively blocked the conditioned reflex, whereas the old “hypnosedatives” blocked both unconditioned and conditioned reflexes. I presented my findings in a paper at the first CINP congress in Rome. Do you remember that congress?

- TB: I know of that congress from my activities on the CINP's history committee. It was held in 1958, about a year after the CINP was founded. Emilio Trabucchi, the professor of pharmacology in Milan, organized it.
- JK: Daniel Bovet, one of the founders of the CINP, invited me to participate in that congress. It was my first trip to the West.
- TB: So, you were invited to participate in that congress by Daniel Bovet, the Nobel Laureate?
- JK: Yes. He was President of the first CINP Congress and had won the Nobel Prize in 1957. Bovet was interested in my research on the "active focus." He recognized its importance; later on we became friends and collaborated in research projects. I used to send my assistants to spend some time in his laboratory in Rome.
- TB: So, Bovet was interested in your research in the "active focus." When you say, "active focus," could you tell us what you are referring to?
- JK: I refer to a special form of excitation in a particular group of neurons that provides the basis of an acquired drive. I developed, in the 1950s, a rat model to follow changes in the brain during the acquisition of a drive from the start of training until it becomes manifest.
- TB: Didn't you write this up in your first book?
- JK: Yes, I did, with the title, *The Theory of Active Reflexes: An Analysis of Some Fundamental Mechanisms of Higher Nervous Activity*. It was published in 1969 jointly by the Publishing House of the Hungarian Academy of Sciences in Budapest, and the Hafner Publishing Company in New York.
- TB: Could you elaborate on your theory summarized in this monograph?
- JK: According to my theory, the appearance of the mammalian brain with its ability to acquire drives ensured the development of social life and ultimately led to the evolution of human society. This most sophisticated form of organized life on earth is still in the trial and error phase of its development. It seeks to outgrow the myths-directed era of its history, and arrive at its final state, a rationally organized human society. Furthermore, in the mammalian brain capable of acquiring drives, untrained Group 1 cortical neurons possess the potential to change their functional state in response to practice, training, or experience in three consecutive stages, getting involved either in an extinguishable conditioned reflex (ECR,) in case of Group 2 neurons, in an inextinguishable conditioned reflex (ICR,) in case of Group 3 neurons, or in an acquired drive, in case of Group 4 neurons. The activity of the cortical neurons belonging to Group 3 and 4 is inseparable from conscious perception. At any moment of life 'self' is the sum of those cortical neurons that have already changed their functional significance and belong to

Group 3 or 4. In the early period of my work I wanted to show by EEG that there is a difference between an extinguishable and inextinguishable conditioned reflex, but our laboratory was poorly equipped in the early 1950s. It's a very long story.

TB: Tell us the story.

JK: The story began with my interest in drives.

TB: What is your definition of a drive?

JK: In behavioral studies "drive" is the force that activates the mammalian organism. There are innate drives of a limited number in the service of indispensable, vital goals. The analysis of innate-drive-dependent functions, such as maintenance of homeostasis, fight for survival, feeding, sexuality, progeny-care, etc., constitutes the main body of literature on behavioral physiology and endocrinology. Though innate drives are primarily based on sub-cortical regulations, none of the goals can be reached without the participation of the cortical neurons. Exclusively innate drives keep the majority of the mammalian species alive.

TB: What about acquired drives?

JK: The capability to acquire an irrepressible urge for a goal, which is not necessary for survival of the individual or species, represents the most sophisticated function of the telencephalon. Though the development of an acquired drive always originates in one way or another in an innate drive, this relation becomes later unrecognizable. Humans are the only living beings on earth whose life is predominantly based on acquired drives. To a certain extent, a minority of the mammalian species: the monkey, dog, horse, dolphin and rat possesses this endowment, which, under natural conditions, remains unexploited. Nevertheless, humans obviously discovered thousands of years ago, probably through a kind of serendipity, that the behavior of such animals can be modified by proper training, and this started the development of the domestication of various species. The ambition to be in a permanent state of activity is a natural endowment of the human brain, which acquires drives with utmost ease. In goal-seeking behavior, which is the essence of life, the nature of the drive determines the goal and determines the fixation of millions of chains of inextinguishable conditioned reflexes, the 'knowledge' needed to reach the goal. The mechanism is simple, always the same, but the drives and the goals determined by them are immensely different. Thus, the essence of my theory is that an immortal poem is created by essentially the same mechanism as a pair of shoes. Since the basic mechanism operates also in animals capable to acquire drives, I studied it from the early 1950s in the rat and summarized my findings and conclusions in my first monograph. The acquisition of proper drives

in the most sensitive developmental period of life, from weaning until sexual maturity, will thereafter be the determinant for the lifelong basic activity of the individual. It is obvious that since the fate of most individuals is still governed by the position in the society into which they are born, only a minority is lucky enough to acquire professional drives in full harmony with natural endowments. The majority forms, under coercion, work-related drives that will ensure the place of the individual in society. Conformity between one's innate abilities and acquired work-related drives is of key importance for lifelong equilibrium. However, not only the desire to be permanently active is a natural endowment of the human brain, but there also is a need for a new challenge to one's drives in due time. Even the most satisfying professional drive becomes boring after its permanent, continuous use and there is a need to continue to keep the brain in a satisfyingly active state. Inexhaustible forms of supplementary activities serve this aim. Absolute dominance of a fully satisfying professional drive and the acquisition of well-chosen supplementary drives are the conditions for a harmonious, well balanced life. Lack of full satisfaction in one's acquired professional and supplementary drives generates an urge to flee from frustration and seek salvation in smoking, alcohol, drugs, and so on.

TB: How did you study acquired drives in animals?

JK: In the early 1950s we developed a method to show the development of an acquired drive, a "glass-cylinder-seeking drive," in the brains of rats that was stronger than the animal's innate drives. It was based on an unconditioned avoidance reflex, escape from a hot plate to the sound of a bell that played the role of a high priority conditioned stimulus. The cylinder was open at the bottom and on the top, and the animals were trained to search for the glass-cylinder, manage to get into the glass-cylinder through an opening in the side and jump to the upper rim. In properly trained rats, the acquired cylinder-seeking drive was so strong that it suppressed innate drives. When such a rat was deprived of food for 48 hours and then was offered food within the usual setup, that included the glass-cylinder, it looked for the glass-cylinder and left the food untouched at the sound of the conditioned signal. Similarly, when a receptive female was offered to a glass-cylinder trained male rat, the male looked for the glass-cylinder at the sound of the bell and neglected the receptive female. With the employment of this method it became obvious to me that cortical neurons have the innate potential to acquire a drive. With the help of our training method the rat activated a group of cortical neurons that kept the animal active until the goal, the upper rim of the glass-cylinder, was reached. The essence of both,

innate and acquired drives is a selective activation of a special population of subcortical neurons, that I refer to as an active focus in the case of innate drives, and of a special population of cortical neurons, in case of acquired drives.

TB: Did you succeed in developing acquired drives in all animals?

JK: The faculty for acquiring a drive is uncommon in the animal kingdom. It was shown by Berta Knoll in the late 1950s that the mouse, a rodent closely related to the rat, was unable to acquire the glass-cylinder-seeking drive. She has found that, in striking contrast to the rat, the mouse was unable even to fix the inextinguishable form of the conditioned avoidance response, the functional stage that preceded the acquisition of the glass-cylinder-seeking drive in the rat. It seems that the appearance of mammals with the ability to acquire drives was the last step in the development of the mammalian brain. Vertebrates can be divided into three groups according to the mode of operation of their brain. One, a large group, which includes the majority of vertebrates, operates with innate drives only. Another, a small group, which includes some vertebrates, has an ability to acquire drives. And, the third group which includes only one vertebrate, *Homo Sapiens*, operates almost exclusively on the basis of acquired drives. Thus, the appearance of the mammalian brain with an ability to acquire drives ensured the development of social life and ultimately led to the evolution of human society. This most sophisticated form of organized life on earth is still in the trial- and- error phase of its development. It seeks to outgrow the myths-directed era of its history and arrive to its final state, the rationally directed human society.

TB: Coming back to your earlier remark, how did you record the corresponding EEG activity to an extinguishable- and an inextinguishable conditioned reflex?

JK: My coworker Károly Kelemen spent half a year in Rome in Bovet's laboratory and finished the work showing the difference between the short lasting EEG activation to an extinguishable conditioned reflex, and the prolonged EEG activation to an inextinguishable conditioned reflex. The paper co-authored by Kelemen, Longo, Knoll and Bovet was published in 1961.

TB: How did Bovet learn about your work?

JK: I published about six papers on my findings by 1956. Bovet read some of those papers and became interested in the research I was doing. At that time, Hungary was a communist country. We had the rats but no sophisticated machinery, not even EEG. We could only do the EEG studies in a laboratory like Longo's in Rome that was properly equipped.

- TB: Vincenzo Longo, one of Bovet's collaborators?
- JK: Yes. He is a very nice man; a good friend of mine. I have not heard of him for a long time. He has probably retired by now.
- TB: He retired from the Institute but still works as a consultant.
- JK: Longo understood very well what we were doing, and he had the necessary EEG technology to show the expected functional difference between an extinguishable and an inextinguishable conditioned reflex.
- TB: Did you yourself do any work on the neurophysiological and molecular level?
- JK: I didn't at the time but now I do, and measure, for example, the enhancer effect of drugs on noradrenaline release from the locus coeruleus, dopamine release from the substantia nigra, tuberculum olfactorium and striatum, and serotonin release from the raphe.
- TB: So, by the 1960s you became interested in the enhancer mechanism and enhancer regulation by drugs?
- JK: I was interested in understanding the physiological characteristics of an acquired drive. It was only later, in the course of my research with deprenyl, that I ultimately recognized the operation of an enhancer regulation in the brainstem. This finding initiated the working hypothesis that the enhancer regulation operates also in the cortical neurons and determines ultimately the learning capacity of the individual.
- TB: Could you elaborate on that?
- JK: According to this approach the naïve cortical neuron, which is born with the ability to perceive one of the senses, color, light, pain, sound, smell, taste, or touch, also has the ability to synthesize its own specific enhancer substance. PEA and tryptamine or their long-acting synthetic analogues, deprenyl and BPAP respectively, enhance the activity of the enhancer-sensitive brainstem neurons; the natural cortical enhancer substances act similarly on the proper cortical neurons. Since this working hypothesis was an outgrowth of deprenyl research, it would be more expedient to come back to this approach after discussing the deprenyl story in more detail.
- TB: I see. According to your present view deprenyl is a synthetic, phenylethylamine derived enhancer?
- JK: Yes. Deprenyl, the therapeutic agent now in use, is the minus isomer of phenylisopropyl-methylpropargylamine, a close relative to methamphetamine, thus a derivative of PEA. Long-acting PEA derivatives, like amphetamine and methamphetamine, release catecholamines from intraneuronal stores, as their parent substance, and produce aimless hyperactivity and inhibit goal directed activity of innate and acquired drives.

- TB: Does that mean that by releasing catecholamines these substances instead of enhancing, are inhibiting innate and acquired drives?
- JK: Amphetamine and methamphetamine are of course enhancer substances but their releasing effect completely covers up the enhancer effect of these amines, which were classified as the prototype of indirectly acting sympathomimetics. I am not going into details but I was interested in that. In 1960 I developed, with a good friend of mine, Zoltán Mészáros, the director of research at Chinoin, a Hungarian drug company, a new family of analgesics. When I told my friend I would be interested in finding someone working with amphetamines he brought me together with Zoltán Ecsery, one of the leading chemists at Chinoin. At the time iproniazid and monoamine oxidase inhibitors in general were at the center of interest as experimental tools because of their antidepressant effect. I worked with iproniazid as soon as it became available and I had the feeling that maybe somehow we have to combine amphetamine-like effects and MAO inhibition. So we started work on that. As I was hoping, Zoltán Ecsery presented me with a series of about 60 compounds and I selected, as the best candidate for development, the compound we now call deprenyl. At that time it was E-250. I selected it because I was fascinated by the finding that E-250, in contrast to the other monoamine oxidase inhibitors known at the time, did not potentiate the blood pressure increasing effect of amphetamine by releasing norepinephrine from stores in noradrenergic terminals. In fact when I gave E-250 it inhibited amphetamine's blood pressure increasing effect. That was new to me. It showed me we had something new.
- TB: To what did you attribute the uniqueness of E-250?
- JK: In 1963 a large number of clinical reports, demonstrating the occurrence of dangerous hypertensive attacks in patients treated with MAO inhibitors were published. In accordance with Blackwell's suggestion, the metabolism of tyramine was inhibited by the MAO inhibitors and therefore cheese and other foods containing tyramine provoked the hypertensive episodes in patients treated with MAO inhibitors. This 'cheese effect' restricted the clinical use of MAO inhibitors. We analyzed the peculiar behavior of E-250 and as I expected, the studies revealed it did not potentiate the effect of tyramine but inhibited it. This was first demonstrated in a study performed on cats, and on the isolated vas deferens of rats which was published in 1968. We proposed in this study to use deprenyl as an MAO inhibitor free of the cheese effect.
- TB: How did you know that it applied also to humans?
- JK: In 1965, after we found that deprenyl in contrast to other MAO inhibitors, inhibited the tyramine releasing effect of amphetamine, the psychiatrist

Ervin Varga, who worked in the Psychiatric Clinic of our university, checked it out for me. He administered deprenyl and tyramine to normal volunteers and found that deprenyl did not potentiate the effect of the tyramine. But he did not publish his results. As a matter of fact the validity of my proposal that deprenyl is an MAO inhibitor free of the cheese effect was demonstrated in humans by my good friend Merton Sandler and his coworkers in London in 1978.

TB: When did you publish first on E-250?

JK: The first paper appeared in Hungarian in 1964 and the English version in 1965. The paper was co-authored by my collaborators at the time; Ecsery, Kelemen, Nievel and Berta Knoll. Then, in 1968, I published a second important paper on E-250 that was co-authored by Vizi and Somogyi, my other collaborators in this project. As I mentioned, it was in this second paper that we noted that the hypertensive reaction seen in some MAO-inhibitor-treated patients after cheese consumption is absent with deprenyl. We suggested that deprenyl, an MAO inhibitor without the cheese effect, might be highly valuable for human therapy. But no one cared. Unfortunately even the leaders at Chinoïn did not dare to develop further E-250 because of its MAO inhibiting property.

TB: Didn't you already have in the title of your first paper that E-250 is a psychic energizer?

JK: We did. Actually the first clinical trial with racemic deprenyl in depression was done by Ervin Varga, my childhood-friend, my schoolmate in gymnasium and class-mate at the university. The preliminary results were presented at a Conference in Budapest in 1965. The study was extended and was published by Varga and Tringer in 1967. The first clinical trial with the minus isomer, the drug now in use, was published by Tringer, Haits and Varga in 1971. In spite of their favorable findings the possibility of introducing deprenyl as an antidepressant remained unexploited for many years after.

TB: One wonders why. Am I correct we are before the time you discovered that E-250 is a selective MAO-B inhibitor?

JK: Yes, we are. Varga and Tringer published their first in extenso paper in 1967, and we discovered E-250's selective B type monoamine oxidase inhibiting effect in 1970.

TB: Could you elaborate on that discovery?

JK: In 1968, the same year our second paper was published, Johnston reported on a substance to be named clorgyline that preferentially inhibited the deamination of serotonin. He proposed the existence of two forms of the monoamine oxidase enzyme, a type A enzyme that is selectively inhibited by clorgyline, and a type B enzyme that is relatively

insensitive to clorgyline. Thus, a selective MAO-B inhibitor was a missing pharmacological tool for further research. Because of the peculiar behavior of deprenyl I expected my substance might be the missing link. It was about two years after that, in 1970, that we were lucky to prove that deprenyl selectively inhibits the enzyme that was insensitive to clorgyline. Since János Nievel, who was responsible for the biochemical techniques in my laboratory, did not return from the study-tour I organized for him in London, where he spent a year in 1965, a young medical doctor, trained in biochemistry, Kálmán Magyar joined in deprenyl-research. I published our finding that deprenyl is the selective inhibitor of MAO-B with Kálmán Magyar in 1972. This paper became a citation classic ten years later, in 1982.

TB: So, the paper was published about two years after the discovery.

JK: Yes. This paper was an in extenso publication of my lecture presented in the first international MAO meeting in Cagliari, Sardinia, in 1971. I first presented evidence at that meeting that deprenyl is a selective type B monoamine oxidase inhibitor. Then I presented a lecture about the pharmacological effect of selective MAO inhibitors in 1975 at the Ciba Foundation Symposium in London, with title, *Monoamine Oxidase and its Inhibition*.

TB: Would it be correct to say that after you discovered deprenyl is a selective inhibitor of the type B monoamine oxidase your interest shifted to this particular effect of the drug?

JK: For several years the selective MAO-B inhibitory effect was at the center of our interest. It was the selective MAO-B inhibitory effect of the compound that led to the first clinical application of deprenyl.

TB: What was the first clinical application of deprenyl?

JK: In the light of the serious side effects of levodopa in Parkinson's disease Birkmayer and Hornykiewicz tried to achieve a levodopa sparing effect by the combined administration of levodopa with a MAO inhibitor. As such combinations frequently elicited hypertensive attacks they were soon compelled to terminate this line of research. After we found deprenyl is a unique MAO inhibitor that does not potentiate the catecholamine-releasing effect of indirectly acting amines and thus free of the cheese effect my claim was corroborated on human volunteers by Sandler and his group in London. The results of that study came to the knowledge of Birkmayer before it was published, so he finally dared to combine levodopa with deprenyl in the treatment of Parkinson's disease. The trial was successful. The levodopa-sparing effect was achieved with deprenyl in parkinsonian patients without any hypertensive

reaction. His report triggered a development that led to the world-wide use of deprenyl in Parkinson's disease.

TB: When did this happen?

JK: The Birkmayer paper which triggered this development was published in the *Lancet* in 1977.

TB: Deprenyl is still extensively used in the treatment of Parkinson's disease.

JK: Today, the most evaluated effect of the drug is its ability to slow the progress of Parkinson's disease by retarding the rate of functional deterioration of the nigrostriatal dopaminergic neurons. It is obvious now that this effect is unrelated to the MAO-B inhibitory potency of deprenyl.

TB: So, your research on the type B monoamine oxidase inhibiting effect of deprenyl has paid off in the treatment of Parkinson's disease?

JK: Yes. The real progress in the clinical history of deprenyl was the establishment of the indication to use it in *de novo* parkinsonism. This was the conclusion of the famous DATATOP study in the USA performed between 1989 and 1993. This indication was further supported by important multicenter studies between 1991 and 1999 in France, Finland, Norway and Denmark. The authors of the DATATOP study expected deprenyl to be efficient in their trial because of its MAO-B inhibitory effect. Their hypothesis was that the activity of MAO and the formation of free radicals predispose patients to nigral degeneration and contribute to the emergence and progression of Parkinson's disease. In accord with their working hypothesis, they expected the combination of deprenyl, the MAO inhibitor, with tocopherol, an antioxidant, would slow the clinical progression of the disease because MAO activity and the formation of oxygen radicals contribute to the pathogenesis of nigral degeneration. They selected patients with early untreated Parkinson's disease and measured delay of the onset of disability necessitating levodopa therapy. When the DATATOP study started I already knew from my studies that only deprenyl would be efficient because of its peculiar stimulatory effect on the catecholaminergic system, which tocopherol was devoid of. Nevertheless, at the time I was only at the beginning of fully understanding the enhancer mechanism, but more and more experimental evidence accumulated in favour of the concept that deprenyl induced activation of the catecholaminergic neurons is unrelated to its MAO-B inhibitory activity.

TB: What is the evidence that deprenyl's enhancer effect is unrelated to MAO-B inhibition?

JK: With the development of 1-phenyl-2-propylaminopentane, (PPAP), the deprenyl analogue free of MAO-B inhibiting property, we furnished direct evidence that the enhanced dopaminergic activity following

administration of deprenyl was unrelated to the inhibition of MAO-B. I published this paper in 1992; my coworkers in the study were Berta Knoll, Zoltán Török, the chemist, who synthesized the compounds, Julia Timár and Yasar Sevil. Because PPAP, like deprenyl, inhibited the uptake of tyramine in isolated smooth muscle tests, we first assumed that the drug-induced enhanced dopaminergic activity was due to an uptake inhibiting effect. Further studies revealed that this interpretation was false. The availability of HPLC to measure catecholamines and serotonin in physiological quantities allowed a new approach. The thorough analysis of the dose-dependent effect of deprenyl on the release of catecholamines and serotonin from isolated, discrete rat brain regions, dopamine from the striatum, substantia nigra and tuberculum olfactorium, noradrenaline from the locus coeruleus, and serotonin from the raphè, pointed to enhancer regulation in the mesencephalic neurons. Ildiko Miklya, a young talented pharmacist was my coworker in these studies which demand much hard work. We treated rats with five different doses of deprenyl, between 0.01 and 0.25 mg/kg, once daily for 21 days, isolated the discrete rat brain regions 24 hours after the last injection and measured the biogenic amines released during a 20 minutes period from the freshly isolated tissue samples. The amount of dopamine released from the substantia nigra and tuberculum olfactorium clarified that the dopaminergic neurons worked on a significantly higher activity level even in rats treated with the lowest, 0.01 mg/kg, dose of deprenyl. As this small dose of deprenyl leaves the MAO-B activity and the uptake of amines practically unchanged, this study was the first unequivocal demonstration of the operation of a hitherto unknown enhancer mechanism in dopaminergic neurons stimulated by deprenyl in very low doses. We published this work first with Ildiko Miklya in 1994. This work was of crucial importance for the further development of enhancers. Further studies clarified the operation of an enhancer regulation in the catecholaminergic neurons in the brainstem and proved that PEA is a natural enhancer substance. Since PEA, in higher concentrations, is a highly effective releaser of catecholamines from their intraneuronal stores, this effect covered up completely the enhancer effect of the endogenous amine, which was classified as the prototype of the indirectly acting sympathomimetics. Amphetamine and methamphetamine are PEA derivatives with a long-lasting effect which share with their parent compound its catecholamine releasing property. Deprenyl was the first PEA, methamphetamine derivative that maintained the enhancer effect of its parent compounds but lost completely the catecholamine releasing property. This peculiar change in

the pharmacological spectrum of the PEA-derivative ultimately enabled the discovery of enhancer regulation, since the enhancer effect of deprenyl was not covered up by the release of catecholamines from their intraneuronal stores. In the light of this knowledge we realized that clinicians who used deprenyl in the belief that the therapeutic benefits observed in patients treated with this drug were due to the selective inhibition of MAO-B in the brain, were mistaken from the very beginning. It is clear by now that besides the levodopa-sparing effect of deprenyl due to its MAO-B inhibiting property, the clinical benefits are due to the enhancer effect of the drug.

TB: I see. We keep on talking about “enhancer regulation.” Could you tell us what the term “enhancer regulation” means?

JK: I define enhancer regulation as the existence of enhancer-sensitive neurons capable of changing their excitability and working on a higher activity level in a split second, due to endogenous enhancer substances. Of these substances, PEA and tryptamine are currently being experimentally analyzed, and their synthetic analogues, deprenyl and BPAP are the specific experimental tools for studying enhancer regulation in the brainstem.

TB: Where are those enhancer-sensitive neurons located in the brain?

JK: We usually refer to mesencephalic enhancer regulation because even if enhancer sensitive neurons also exist outside the mesencephalon, the mesencephalic dopaminergic neurons are of key importance in enhancer regulation. These most rapidly aging neurons of the brain are primarily responsible for the progressive age related decline of behavioral performances.

TB: Did you say that the mesencephalic dopaminergic neurons are the most rapidly aging neurons?

JK: According to our present knowledge the nigrostriatal dopaminergic neurons are. The dopamine content of the human caudate nucleus decreases steeply at the rate of about 13 percent per decade over age forty-five. We know that symptoms of Parkinson’s disease appear if the dopamine content of the caudate nucleus sinks below 30 percent of the normal level. The age related decline of the nigrostriatal dopaminergic brain mechanisms play a significant role in the decline of performance with passing time. Safe and effective prophylactic medications are needed to slow these changes. I suggested the use of deprenyl for this purpose after we found that treating rats with 0.25 mg/kg of deprenyl three times a week, prolonged their life significantly. It was my lecture at the Strategy in Drug Research, the 2nd IUPAC-IUPHAR Symposium held in Noordwijkerhout, The Netherlands, in 1981 when I

first presented this new strategy. The lecture was published in the volume of this symposium in 1982. We also revealed that deprenyl-treated rats lived not only longer than placebo-treated rats, but also that males maintained their ability to ejaculate for a significantly longer period and remained better performers in the shuttle box than saline treated pairs. With my coworker János Dallo we followed through decades the sexual performance of male rats and found that a daily dose of 0.25 mg/kg deprenyl slowed significantly the age-related decline of this function. In one of this series we worked with 90 male CFY rats and treated half of the group with saline and half with deprenyl from the 25th week of age until they loss their ability to ejaculate. The saline-treated rats reached this stage at an average of 112 weeks, whereas the deprenyl-treated rats reached it at an average of 150 weeks. That deprenyl is capable of slowing the rate of functional deterioration of the nigrostriatal dopaminergic neurons was shown not only in rats but also in patients with early, untreated Parkinson' disease. Age related deterioration of the striatal machinery is a continuum and any short segment of it is sufficient to measure the rate of decline in the presence or absence of deprenyl. Tetud and Langston were the first to publish in *Science* in 1989 that deprenyl delays the need for levodopa therapy. In their study, the average time that elapsed before levodopa was needed was 312.1 days for patients in the placebo group and 548.9 days for patients in the deprenyl group. This was clear proof that deprenyl, which enhances the activity of the surviving dopaminergic neurons, kept these neurons at a higher activity level for a longer duration of time. Today the most evaluated effect of the drug is its ability to slow the rate of the functional deterioration of the nigrostriatal dopaminergic neurons in patients with early, untreated Parkinson's disease, and thus to slow the progress of the disease. The indication to use deprenyl in de novo Parkinsonian patients was established in the USA by the Parkinson Study Group and corroborated by a French Study Group in 1991, a Finnish Study Group in 1992 and a Norwegian-Danish Study Group in 1999.

TB: Let us get back to PEA for a second. You refer to it as a natural enhancer substance. Now, PEA is usually classified as an indirectly acting sympathomimetic drug.

JK: As we discussed already, since PEA, in higher concentration, is a highly effective releaser of catecholamines from intraneuronal stores, this effect covered up completely the enhancer effect of the endogenous amine. Deprenyl was the first PEA derivative that maintained the enhancer effect of the parent compound but lost completely the catecholamine releasing property. It was this peculiar change in the

pharmacological profile of a PEA-derivative that ultimately enabled the discovery of enhancer regulation in the catecholaminergic neurons in the brainstem, since the enhancer effect of deprenyl was not covered up by the release of catecholamines from their intraneuronal stores.

TB: You mentioned that not only PEA but also tryptamine is a natural enhancer substance.

JK: It was in 1994 I first published that tryptamine is an endogenous enhancer. It is a natural enhancer like PEA, but not a releaser. The discovery opened the way for a structure-activity relationship study aiming to synthesize a new family of enhancer compounds structurally unrelated to PEA and the amphetamines. It was on the basis of the results of that study that benzofuran-propylaminopentane, BPAP, was selected as a tryptamine-derived synthetic mesencephalic enhancer. Because I couldn't get the work done in Hungary, I found a small Japanese private company, Fujimoto, to develop it. Professor Yoneda, an excellent chemist, led the group which synthesized about 60 compounds and I selected the highly potent and selective enhancer, needed for my further work. BPAP was 100 times more potent than deprenyl as an enhancer. My first paper, co-authored by Yoneda, Berta Knoll, Ohde and Miklya was published in the *British Journal of Pharmacology* in 1999. A new world was opened! This substance stimulates, activates, and enhances the activity of noradrenergic, dopaminergic and serotonergic neurons in femto to picomolar concentrations, in a very special manner with a bell shaped curve. This indicates that very specific enhancer receptors exist because otherwise we cannot explain a compound acting in femto to picomolar concentrations. And now something came about which I have to tell you. Towards the end of the last year, they found a gene for a totally independent family of receptors that are activated by PEA and tryptamine, the two endogenous enhancers I described. It was published in the proceedings of the neuroscience meeting of the United States. This might be very important for the future. I think BPAP, the new compound, which is at present a highly specific and highly potent experimental tool for studying the enhancer regulation in the brainstem, might also become very important clinically as an antidepressant, an anti-Parkinson drug, an anti-Alzheimer's agent, and also a safe and effective compound to slow the age-related decline of the catecholaminergic system in the brainstem, thus prolonging life span.

TB: What you are saying is that enhancers might have a broad range of clinical indications.

JK: Absolutely. In my view the only reasonable hope to fight off the two main neurodegenerative diseases, Parkinson's and Alzheimer's, is

prevention. In case of Parkinson's disease there is no doubt that age-related irreversible deterioration of the nigrostriatal dopaminergic neuronal system has already surpassed a critical level and the disease is incurable; prevention remains the only chance for the future to fight off Parkinson's disease. The daily administration, from sexual maturity until death, of a small dose of a synthetic enhancer substance acting on the dopaminergic neurons in the brainstem suggests a proper and safe method for this aim. In case of Alzheimer's disease the only reasonable hope to fight off the disease is to keep the cortical and hippocampal neurons at a higher activity level as long as possible by the prophylactic administration of a proper enhancer substance. It is remarkable in this regard that BPAP protected cultured rat hippocampal neurons from the deleterious effect of β -amyloid₂₅₋₃₅ fragments in as a low as 10^{-15} M concentration.

TB: What about your longevity studies demonstrating that deprenyl treatment extended significantly the lifespan of rats?

JK: We performed two longevity studies in rats, the results of which were published in 1988 and 1994. If you compare the average life expectancy in 1900 to the average life expectancy in 2000 in developed countries, there was at least, a 25 year extension. Average life expectancy at birth increased from 55 years to 80 years. Why? The reason is that many people died earlier before the introduction of immunization, before the development of antibiotics, lack of hygiene and many other factors. But, regardless of life expectancy each species of animal has a natural life span that cannot be exceeded. You remember that according to the Old Testament Moses lived 120 years. This is by chance in accord with the human Technical Life Span (TLS_h), which is in fact about 115 to 120 years. It did not change from 1900 until 2000. Why? Because we had no knowledge about what regulates it. What I'm proposing is that the age-related decline in the enhancer regulation of the catecholaminergic system in the brainstem is of key importance to natural life span and to slow this process by the preventive administration of a proper synthetic enhancer will extend lifespan. As I summarized the physiological and pharmacological evidence in an invited paper, *Memories of my 45 Years in Research in Pharmacology and Toxicology*, in 1994, there can be little doubt that the maximum level of activation of the CNS via the catecholaminergic system, decreases progressively with aging. The blackout, natural death, of the integrative work of the CNS, signaled by the disappearance of EEG, occurs when the catecholaminergic system's ability to activate the higher brain centers sinks below a critical threshold and the CNS can no longer be activated to the required

extent. This would explain why a common infection, a broken leg, or any other challenge that is easily surmountable in young age, while the catecholaminergic machinery is working at full capacity, may cause death in old age. My hypothesis is that the quality and duration of life rests on the inborn efficiency of the catecholaminergic brain machinery. A high performing longer-living individual has a more active, more slowly deteriorating catecholaminergic system, than its low performing peer; a better brain engine allows better performance and a longer life span. We demonstrated in rat experiments that the age-related decline of the catecholaminergic system in the brain stem which starts immediately after sexual maturity was reached, plays a key role in the natural aging of the brain and the rate of decline can be slowed by the life-long daily administration of 0.25 mg/kg deprenyl. Deprenyl-treated rats lived significantly longer and maintained their sexual potency and learning ability for a significantly longer duration than their saline-treated peers. Thus, it is feasible to transform a lower performing, shorter living rat into a better-performing, longer-living one. It follows that the duration of life beyond the “technical” life span, with a yet unpredictable upper limit, must be possible in all mammals, including the human species, by keeping the catecholaminergic system in optimal operation with the administration of a very small daily amount of a proper enhancer substance.

TB: Was deprenyl the first substance in the literature shown to prolong life span?

JK: Deprenyl was the first compound described in the literature that by curbing the age-related deterioration of the nigrostriatal dopaminergic neurons in the brainstem, prolonged the lifespan in the rat significantly, so that in some rats it exceeded the technical lifespan. I presented these findings in two papers published in *Mechanisms of Ageing and Development*: The title of one of the papers, published in 1985 was, *The Facilitation of Dopaminergic Activity in the Ageing Brain by (-)-Deprenyl: A Proposal for a Strategy to Improve the Quality of Life in Senescence*. The title of the other paper, published in 1988, was, *The Striatal Dopamine Dependency of Lifespan in Male Rats: Longevity Study with (-)-Deprenyl*. After publishing our first longevity study with my coworkers Janos Dallo and Tran Ty Yen in 1989, I became interested to see whether the highest performing rats selected from a huge population live significantly longer than their lowest performing peers and whether deprenyl treatment would evenly extend the lifespan of both groups. Thus my second study lasted over four years, published with my coworkers Tran Ty Yen and Ildiko Miklya in 1994, had 1600

male, healthy rats from a special strain. We tested their sexual activity by bringing them together with receptive females in four consecutive weekly mating tests. On the basis of their sexual performance we separated the lowest and highest performing individuals. The selection from such a huge population was extremely tiring, boring work. Then, we measured the learning performance of the selected two groups of rats in five-day training in the shuttle box. We found that the sexually high performing rats were significantly better learners than their sexually low performing peers. In the four year study we also found the low performing rats lived 134 weeks, while their high performing peers lived 151 weeks. In both low and high performing rats, deprenyl, an enhancer of the release of catecholamines in the brain, significantly increased sexual performance and longevity. The lifetime of deprenyl-treated low performing rats increased from 134 to 152 weeks, and of high performing rats from 151 to 185 weeks. The increases in longevity were statistically highly significant. So the enhancer increased sex, learning ability and duration of life. This applies also to man. In Hungary, for example, millions die at age 62 or 63 now but if you compare that with the age of the members of the academy you will see that their average age at the time of death is 81.5 years. What I'm saying is that a man who works, who is active, lives longer than a passive one. I work a lot although I am now retired. I could just look at television. So people ask me why are you going at 8:00 in the morning to your laboratory and coming home at 6:00 in the evening and then you work until 2:00 a.m. on your papers at home. Are you crazy? I'm not crazy. The conclusion of my lifework is that the longer you keep your brain at maximum activity, the longer and better you live. What I'm saying is that what we have shown in the rats, applies also to humans. I'm 77 now. In the 20th century we have seen a highly significant increase in average life expectancy. By enhancer regulation we should be able to prolong life span further, and sometimes in the future surpass significantly the TLS_n . Enhancer regulation is the key to life and death.

- TB: Would it be legitimate to hypothesize that if one would get a bunch of 30 years old guys, measure their sexual activity and, if it is high, predict they would live longer?
- JK: Man is complicated. It is optimal for the human brain to work under the influence of an acquired drive which is in harmony with ones natural endowments. It is reasonable to assume that for a human being the optimal condition is to be in a state in which a group of cortical neurons are permanently maintained by their specific enhancer substance at the highest level of excitability. The essence of this mechanism is

detectable even in animals capable of acquiring drives. An acquired drive in the brain of a dog is coupled with the animal's extreme joy in exercising the acquired goal-seeking activity and the animal spares no effort to reach that goal. Humans know from experience they prefer to be in an active state that is pleasant, amusing, that makes them happier and more satisfied than to be in a vigilant leisure state. It is natural for humans in possession of a proper work-related drive that their preferred activity never makes them tired. Creative minds demonstrate this physiological endowment of the human brain most convincingly. Mozart wrote once to his father that to compose music is a rest for him and the inability to do so immediately tires him. Millions and millions in possession of a proper work related drives could have written this letter.

TB: Where do you measure enhancer effects in the brain?

JK: Since catecholaminergic and serotonergic neurons are enhancer sensitive neurons and we demonstrated that PEA and tryptamine are natural enhancer substances acting on these neurons, their long-acting analogues, deprenyl and BPAP, are the proper experimental tools to study enhancer regulation in the brainstem neurons. In contrast to deprenyl that is an enhancer of the catecholaminergic neurons and almost ineffective on the serotonergic system, BPAP is a highly potent enhancer of the serotonergic neurons too. As a matter of fact BPAP is at present the most selective and potent experimental tool to investigate enhancer regulation in the catecholaminergic and serotonergic neurons in the brainstem. I just finished a paper, co-authored by Ildiko Miklya and Berta Knoll, which I am sending to *Life Sciences*, analyzing in more detail that a bi-modal, bell-shaped concentration effect curve is characteristic to the enhancer effect of both deprenyl and BPAP. BPAP acted, for example, on the isolated locus coeruleus of rats in a manner where we found a peak-effect at $[10^{-13}]$ M concentration and a second peak at $[10^{-6}]$ M concentration. It is obvious that the specific enhancer effect is the physiologically relevant one. Interestingly, at $[10^{-10}]$ M concentration we were unable to detect the enhancer effect. We measured also the BPAP-induced enhancement of noradrenaline release from the locus coeruleus 30 minutes after the subcutaneous administration of a single dose of BPAP and found the same characteristic dose-dependency of enhancer effect. For example, the most effective dose of BPAP, 0.0005 mg/kg increased the release of noradrenaline from 4.7 nM/g in controls, to 15.4 nM/g, but a 100 times higher, 0.05 mg/kg dose of BPAP, did not change it.

TB: This is a very strange, unusual form of dose-dependency, isn't it?

JK: It is. But, it seems to me that this peculiar form of dose-dependency is of high physiological significance. It allows giving a reasonable explanation for the substantial individual differences found in behavioral performances. Since an optimum concentration of the enhancer substances was needed for the optimum performance, I postulate that the substantial individual differences found in behavioral performances are due to the peculiar dose-dependency of the still unknown natural cortical enhancer substances. This approach grants us new perspective on the results of our two longitudinal studies on rats. As an example, let me analyze our second longitudinal study on rats from this perspective. This study was performed between 1990 and 1994. As I mentioned earlier we started working with a random population of 28-week old male rats and tested their sexual performance once a week. Rats representing the two extremes in performance were selected for the study; ones that did not display a single intromission during the four consecutive weekly-mating tests used for selection, and ones which showed full scale sexual activity with mounting, intromission, ejaculation, in each of the four tests. Out of 1600 sexually inexperienced 28-week-old Wistar-Logan male rats that met a receptive female once a week for four consecutive weeks, 94 did not display a single intromission during the selection period and 99 displayed at least one ejaculation in each of the four tests. The former were taken for the sexually lowest performing (LP) rats and the latter for the highest performing (HP) ones. Considering the unique dose-related effect of an enhancer substance, it is reasonable to assume that out of the 1600 rats the 99 HP rats produced their endogenous enhancer substances at the peak of the bell-shaped concentration/effect curve, while the 94 LP rats produced them at the least active part of the curve; and the production of the overwhelming majority of the population, 1407 rats, would fall between the two extremes.

TB: Are enhancer substances neuroprotective agents?

JK: It is obvious that an enhancer substance acts as a neuroprotective agent on enhancer-sensitive neurons. To illustrate it, let us analyze our first study on the neuroprotective effect of BPAP on cultured rat hippocampal cells. To elicit cell death the cultured hippocampal neurons were treated with β -amyloid₂₅₋₃₅ fragment. BPAP exerted its enhancer effect in its characteristic bipolar manner with bell shaped concentration-effect curves. The peak effect was reached at 10^{-14} M in the low femto/picomolar concentration range and at the high 10^{-8} M concentration. Because of the neurotoxic effect of β -amyloid₂₅₋₃₅, no more than 20 per cent of the cells, obviously the high performing cells, survived this

attack. As BPAP significantly enhanced the performance of the neurons in the culture, in the presence of the optimum concentration, i.e., 10^{-14}M of BPAP, about 70 percent of the cells survived. We published these findings in 1999. We also published that BPAP enhanced the activity of the catecholaminergic and serotonergic neurons in isolated discrete midbrain regions in exactly the same bipolar manner and in the same concentration range. The studies with BPAP performed on noradrenergic, dopaminergic, serotonergic and hippocampal neurons proved unequivocally the operation of a highly specific, complex form of enhancer regulation in sub-cortical neurons. This is very much in keeping with the ascription of a commanding role to midbrain neurons in goal seeking behavior.

TB: So, there is a highly specific form of enhancer regulation in sub-cortical neurons.

JK: The sub-cortical system is the place of the innate drives in the service of the limited number of vital goals, sexual activity, feeding, nurturing. But, as I told you, humans are the only living beings on earth whose life is predominantly based on acquired drives.

TB: Didn't you test the effect of your enhancer substances on cultured cortical neurons?

JK: The first study of the enhancer effect on cultured cortical neurons was performed with BPAP on a primary culture of rat cerebral cortex. It was done by the Japanese and showed that BPAP significantly protected cortical neurons against serum-free-condition induced cell death in the high concentration range. However, in striking contrast to the finding on cultured rat hippocampal neurons, BPAP did not exert an enhancer effect on the cultured rat cortical neurons in the femto/picomolar concentration range.

TB: So, BPAP in the low concentration range has no effect on cortical neurons.

JK: The reason for this finding is now clear. BPAP acts on the enhancer-sensitive sub-cortical neurons, but it is ineffective on cortical neurons.

TB: What is the experimental evidence for your statement that BPAP has no effect on cortical neurons?

JK: To test a compound's ability to enhance the acquisition of a conditioned avoidance reflex (CAR) in the shuttle box, it is necessary to select proper training conditions. In the case in which the rat was trained with 100 trials per day, the acquisition of CARs reached an 80% level. To demonstrate the highly significant enhancer effect of BPAP on sub-cortical catecholaminergic neurons in vivo, we trained the rat with 100 trials per day, blocked the acquisition of CARs by pretreating the rats

with tetrabenazine, and restored the learning ability with the simultaneous administration of BPAP. Learning is a cortical function. In the series of experiments aiming to test the effect of BPAP on cortical neurons we trained the rats with 20 trials per day in order to have a chance to detect the drug-induced improvement in the learning ability realized via the direct stimulation of cortical neurons. The percentage of CARs in rats trained with 100 trials per day was 77% on the 5th day of training. In contrast, it was only 8.5% in rats trained with 20 trials per day. Thus, in case BPAP had possessed a specific enhancer effect on cortical neurons, we could detect it easily in the form of a significant, dose-dependent increase in the percentage of CARs in rats trained with 20 trials per day. Because of the bell-shaped concentration effect curve, characteristic of the enhancer effect of BPAP, we used 10 doses of the compound, ranging from 0.000001 to 10 mg/kg, to clarify the effect of BPAP on the cortical neurons. None of the applied doses of BPAP was capable of changing the learning performance of rats in the shuttle box. Thus, in accord with the findings on cultured rat cortical neurons, the *in vivo* experiments confirmed that BPAP, the presently known most potent enhancer of the sub-cortical catecholaminergic neurons, is devoid of a specific enhancer effect on cortical neurons.

TB: I see. You say that BPAP activates the cortical neurons only via enhancement of the catecholaminergic system in the brainstem?

JK: Exactly. And now I'm coming back to my unexplained working hypothesis, catalyzed by the discovery of the enhancer regulation in the brainstem, that learning is a cortical enhancer-regulation-dependent function. My concept is that learning only needs the concurrent operation of functionally different groups of cortical neurons under proper conditions. In vertebrates, learning, the modification of behavior through practice by training or experience, is the main physiological function of the cortex. Modification of behavior rests on the inborn ability of cortical neurons to get acquainted with each other through training, learning to influence each other's function, and cooperate thereafter according to need. The mechanism of this important process is still unknown. The discovery of enhancer regulation offers the following interpretation of learning. Each member of a population of naïve, Group 1 cortical neurons, born to perceive a specific quality of stimuli originating outside or inside the body, synthesize the same enhancer substance. It is also supplied with enhancer receptors to which this enhancer substance is the highly specific ligand. The stimulation of the neurons with their enhancer substance leads to enhanced excitability. On the other hand, each cortical neuron is able to activate under proper conditions,

by training, an enhancer receptor to any of the cortical enhancer substances. Thus, neuron A is born with its specific enhancer receptor ER_A and with the ability to synthesize its own enhancer substance ES_A . Neuron B is born with ER_B and synthesizes ES_B , and so on. Whenever a cortical neuron gets excited, its specific enhancer substance is synthesized in an increased amount, and its sensitivity toward other enhancer substances is significantly increased. When neuron A and B are simultaneously stimulated, both are continuously bombarded with a higher amount of the enhancer substance of the other neuron and at the same time also sensitized to activate a receptor to the alien enhancer substance. As a consequence, the concurrent stimulation of neurons A and B time after time in training, ultimately leads to the fixation of a new functional constellation. Neuron A acquires sensitivity toward ES_B , and neuron B acquires sensitivity toward ES_A . Thus, learning means that a neuron acquires the ability to respond to originally alien stimuli. As a consequence of this change we experience the training induced modification of behavior.

TB: Am I correct that your neuronal inferences are based primarily on behavioral findings?

JK: Using the shuttle box technique, there is a reasonable possibility of testing the validity of this concept on rats. The shuttle box is a simple and useful setup for following the development of a two-way CAR. The box is divided inside by a barrier with a small gate. The rat is trained to cross the barrier to a flashing light, the conditioned stimulus (CS). If the rat fails to do so, the animal is punished with an electric footshock, the unconditioned stimulus (US). The rat is trained to respond to the CS with 100 trials per day. One trial consists of a 15 seconds intertrial interval, followed by a flashing light for 15 seconds that overlaps with a footshock for 5 seconds. The rat learns to avoid punishment, acquires the CAR, and escapes in response to the flashing light within 10 seconds. This is automatically counted. According to present views, the rat, driven by fear, tries to prevent punishment and learns by trial and error to escape in due time. The efficiency of learning is thought to be proportional to the number of the successful crossings in response to flash light within 10 seconds. According to our new concept the efficiency of learning depends on the repeated simultaneous operation of functionally different populations of cortical neurons. In light of this approach we need to weigh carefully the series of events in the cortex during the training procedure. The concept predicts that development of a stable CAR in the shuttle box signifies the acquisition of a special cooperation between the groups of cortical neurons born to perceive

the US footshock and the CS flashing light. Nevertheless, other groups of cortical neurons, stimulated for example by the setup as a whole, are also involved in the special modification of the rat's behavior. In the course of training numerous groups of cortical neurons, A, B, C, born to perceive special information only, are synchronously active and influence each other. Furthermore, each group of neurons has a chance to develop sensitivity toward each of the enhancer substances belonging to the simultaneously activated groups of neurons. Thus, during the training procedure a network of co-operating groups of cortical neurons develops, which operates thereafter as an entity. The training-induced cooperation between the groups of neurons can be transient in nature, such as a chain of extinguishable conditioned reflexes (ECRs) or a chain of inextinguishable conditioned reflexes (ICRs), or to the development of the most sophisticated form of excitatory state in a group of cortical neurons, an 'active focus' that will operate thereafter as an acquired drive. However complicated the cooperation developed between different group of neurons during training may be, it is their common feature that they work thereafter as an integral whole, and this entity can be activated via a few decisive groups of neurons. Thus, my approach is that the modification of behavior of the rats trained in the shuttle box depends on the synchronous activation of different groups of cortical neurons in the brain for a proper period of time.

TB: I see. Could you say something about how these behavioral findings were influenced by drugs with known pharmacological actions?

JK: Treatment of rats with 1 mg/kg tetrabenazine, which blocks selectively and reversibly the reuptake of the catecholaminergic transmitters into their intraneuronal stores, depletes noradrenaline and dopamine from the end organs of the catecholaminergic neurons in the brain stem. Since the operation of the catecholaminergic brain engine is the condition sine qua non for the trial and error mechanism, the success in reaching a goal, the acquisition of a CAR in the shuttle box, cannot be detected in tetrabenazine-treated rats because of the blockade of the animal's ability to cross the barrier. Nevertheless, the activation of cortical neurons via the unconditioned and conditioned stimulus remains unchanged in tetrabenazine-treated rats. These experiments are now in progress; let me mention my first results. I treated rats with tetrabenazine which blocks the catecholaminergic engine of the brain without acting on cortical neurons. I am using a strain of rats with exceptionally low learning capacity and work with females which are lower performers in the shuttle box than their male peers. I am testing the rats daily in the shuttle box from Monday until Friday with 100 trials daily.

One group is treated subcutaneously with saline the other group with 1 mg/kg tetrabenazine. The saline-treated rats developed a stable conditioned avoidance reflex. Because we work with a dull strain of rats, on the first day of training, the flashing light, the conditioned stimulus was only an average of 10% effective in eliciting escape to the other part of the compartment within 10 seconds. On the 5th day of training 79% of the rats escaped in response to the flashing light. However, even on the 5th day of training less than 5% of the tetrabenazine-treated rats escaped in response to the flashing light. After the 5-day-training period both the saline-and tetrabenazine-treated rats had a rest on Saturday and Sunday. This resting period is enough for the complete elimination of tetrabenazine. On Monday we tested again the animals and found that 81% of the saline-treated rats and 65% of the rats treated with tetrabenazine during the training period, escaped in response to the flashing light. You remember that only 10% of saline-treated rats of this dull strain escaped on the 1st day of training in response to the flashing light. Now, despite of the fact that the tetrabenazine-treated group of rats did not show any sign of the acquisition of a CAR during the 5-day training, in fact they fixed the CAR in their cortex since after the elimination of tetrabenazine 65% of the rats escaped in response to the flashing light. This finding is in accord with the concept that learning needs only the concurrent operation of functionally different groups of cortical neurons under the proper condition.

TB: The results of this experiment are really thought provoking and seem to be supporting your working hypothesis that learning might be an enhancer-dependent cortical function. But be that as it may, it will for sure initiate much work in this new direction. What about the recent finding that BPAP exerts an enhancer effect also on neuroglial cells?

JK: Neuroglial cells play an important physiological role in the brain and modulate the function of neurons in a complex manner, but they do not participate in the realization of drive-dependent, goal-seeking behavior. Our Japanese collaborators used astrocytes in their research and measured the rate of synthesis of three neurotrophic factors, the nerve growth factor (NGF), the brain-derived neurotrophic factor (BDNF) and the glial cell line-derived neurotrophic factor (GDNF). They found that BPAP increased significantly the synthesis of neurotrophic factors in the micromolar concentration range, but we found in a series of experiments, now in progress, that BPAP is ineffective on glial cells in the low from femto to picomolar concentration range. Thus, the specific form of enhancer regulation is not detectable in the glial cells. These findings support the view that the specific form of enhancer regulation stimulated

- by BPAP in the extremely low concentration range is the behaviorally important form, whereas the enhancer effect of BPAP in the micromolar concentration range is insignificant in behavioral terms. Nevertheless the finding that BPAP induced enhancement in the synthesis of neurotrophic factors in the micromolecular concentration range is a remarkable pharmacological effect that deserves further analysis in the future.
- TB: Am I correct that you have done all your research in the Department of Pharmacology at Semmelweis University in Budapest?
- JK: Yes. I started my career in the department as a medical student in February 1949 and I never left during my lifetime.
- TB: Since the time you published your first book on *The Theory of Active Reflexes* more than 30 years have passed.
- JK: As a matter of fact by the end of 1953 I already developed and studied in detail the technique to analyze in rats the acquired drive and my theory, that I summarized in this monograph, was basically ready 16 years earlier. I needed thereafter 30 years to get to the core of the acquired drives and realize that the root of the matter is enhancer regulation in the brainstem and the cortex. As we already discussed, enhancer-sensitive neurons in the brainstem and in the cortex are in my view capable of changing their excitability and working according to the need on a higher activity level in a split second. I have already started to summarize my neurochemical concept of innate and acquired drives in a new monograph.
- TB: You mentioned earlier that the antidepressant effect of deprenyl was shown but not fully explored. Could you elaborate on that?
- JK: It was Varga who first described the antidepressant effect of deprenyl in 1965 and published with his coworkers two more papers in 1967 and 1971 extending their results. Then, later in the 1980s, Mann and Gershon, Mendlewicz and Youdim, Quitkin and his associates, and McGarth and his collaborators provided substantiation that deprenyl is an antidepressant. Unfortunately no big drug company picked it up and deprenyl was never registered as an antidepressant. It might happen in the future and BPAP is also from this aspect a promising compound.
- TB: Do you think that enhancer substances have antidepressant effects? The diagnosis of major depression refers to a clinically and pharmacologically very heterogeneous population.
- JK: BPAP, which is a selective enhancer substance, stimulates the catecholaminergic and serotonergic neurons in the brainstem via a previously unknown mechanism. Because it is a highly potent compound there is good reason to believe it will be used sometime in the future as a valuable antidepressant.

- TB: Regardless what happens with BPAP and enhancer regulation, you developed deprenyl, the first MAO-B inhibitor and this alone is a major contribution to the field of neuropsychopharmacology. Was this research followed up? Are there any other MAO-B inhibitors?
- JK: There are, but none of them is comparable to deprenyl in its effect in Parkinson's disease.
- TB: When did you start with the development of BPAP?
- JK: It started in the early 1990s.
- TB: How did you get the idea to develop BPAP?
- JK: I wanted to develop a selective enhancer substance which is unrelated to phenylethylamines and is devoid of MAO inhibiting properties. I firmly hope that in the long run BPAP will convince the scientific community that enhancer regulation in the brain is a mechanism of key importance and drugs which stimulate selectively this mechanism are of significant therapeutic value.
- TB: Is there any relationship between your anti-aging drugs and the late Giurgea's nootropics?
- JK: Nootropics have nothing to do with enhancer regulation. Since we have the specific method for measuring quantitatively the enhancer effect of a compound on the locus coeruleus, striatum, substantia nigra, tuberculum olfactorium and raphe, we recently tested piracetam in a wide dose range on these isolated discrete rat brain regions. We found this prototype of nootropics, Giurgea's original substance, is devoid of an enhancer effect.
- TB: Could we switch to more personal matters in your life. You told us you joined the department of pharmacology after your third year in medical school.
- JK: I started to work in February in 1949 as a student and graduated from medical school in 1951.
- TB: Tell us about the Department of Pharmacology at Semmelweis University. Isn't it one of the oldest pharmacology departments in the world?
- JK: Since the first pharmacology department in the world was founded in 1849 in Dorpat Germany, now Tartu in Estonia, and our department was founded in 1872, it is really one of the oldest. Its first chairman was Kalman Balogh. He was followed by Arpad Bokay, Zoltan Vamossy, and by my predecessor, Bela Issekutz. I succeeded Issekutz in 1962. I was the fifth chairman of the department. I retired from my chair in 1993, after 31 years. But I remained fully active as a member of the Hungarian Academy of Sciences and continued with my research. I was chairman of the department longer than any of my predecessors.

- TB: So, you are an active member of the Hungarian Academy of Sciences.
- JK: Yes. Each of my predecessors was a member of the Academy and I have continued in that tradition. I became a corresponding member of the Hungarian Academy of Sciences in 1970 when I was 45 years old, and a full member in 1979. In 1970 I was the youngest member of the Medical Class of our Academy and now I'm one of the oldest.
- TB: I remember the celebration of your 60th birthday by the Academy.
- JK: In 1985 I received the National Prize, the highest honor given for scientific achievement in Hungary. The birthday celebrations at the Academy and in the Institute, were touchy events. I was honored with a Festschrift, *Neuropharmacology 85*, edited by Károly Kelemen, Kálmán Magyar and Szilveszter Vizi, published by the Hungarian Academy of Sciences. It included 49 papers by distinguished scientists from all over the world: I was honored also on my 75th birthday with a Festschrift, *Milestones in Monoamine Oxidase Research: Discovery of (-)-Deprenyl*." This one was edited by Kálmán Magyar and Szilveszter Vizi, and published by Medicina Publishing House, in Budapest.
- TB: What about your relation to foreign Academies and Universities?
- JK: I was honored in 1974 to become a member of the Leopoldina Academy of Natural Sciences, one of the eldest academies in the world. In 1984 I became honorary doctor of the Medical Academy of Magdeburg and in 1989 I was honored with a honorary doctorate by the Bologna University at the occasion of its 900th year anniversary. Since the University of Bologna was the first university in the world, I feel this honor a privilege. In 1990 I was elected Honorary Fellow of the Royal Society of Medicine, London, and in 1995 I became a foreign corresponding member of the Polish Academy of Art and Science.
- TB: Have you been active in professional societies?
- JK: Traditionally, pharmacologists everywhere in the world were members of their national physiological societies which were, in turn, members of the IUPS. The rapid development of pharmacology made it clear by the end of the 1950s that time was ripe for the creation of independent national pharmacological societies and the IUPHAR. But it was neither on the national level nor on the international level easy to break with tradition. In 1958 I started, in Hungary, the fight to attain our independence and we succeeded to establish, in 1962, the Hungarian Pharmacological Society; I was the first executive secretary and after Bela Issekutz, the second president. Since 1983 I have been Honorary President of the Society for Life. IUPHAR was established in 1965; I was member of the Executive Board from 1982 until 1984 as councilor and from 1984 until 1987 as First Vice President. I was elected, in 1980,

an honorary member of the Pharmacological Society of Poland, in 1985 of the Czechoslovakian and Bulgarian Pharmacological Societies, and in 1986, of the Austrian Parkinson Society. I was honored in 1999 with the Award for Distinguished Service in European Pharmacology, and in 2001 with the Award for Outstanding Contribution to Anti-Ageing Medicine.

TB: Would you like to mention people you trained?

JK: I'll mention just those who worked with me through decades; Károly Kelemen, Berta Knoll, János Dallo, Kálmán Magyar, Szilveszter Vizi, Zsuzsanna Füst, Tamás Friedman, Klára Gyires, Huba Kalász, Valeria Kecskeméti, Julia Timár, Zsuzsa Gyarmati, and Ildiko Miklya.

TB: Is there anything else you would like to mention?

JK: You can see two-large leather bound volumes on my bookshelf. I received those on my 50th birthday in 1975 from my co-workers. Reprints from our numerous publications during my first 13 years as head of the department are bound in them. One would need at least 10 such volumes to include a reprint of all our publications from the 31 years I was chairman of the department.

TB: And you are still fully active.

JK: I am fully active in research, but I retired from my administrative positions. Zsuzsanna Füst, one of my pupils, is now head of the department.

TB: Besides being chairman of the department of pharmacology did you have any other administrative position?

JK: I was, from 1964 until 1970, the Vice President of the University responsible for research, and I was Vice President of the Medical Class of the Hungarian Academy of Sciences from 1967 until 1976. After that, apart from the Hungarian Pharmacological Society and IUPHAR, I never accepted any administrative position.

TB: What would you consider your most important contribution?

JK: From a practical point of view, the discovery of enhancer regulation and the development of synthetic enhancer substances, and from a theoretical view, the discovery that with the evolution of brains capable of acquiring drives, species appeared whose members could manipulate each other's behavior and act in concert. This was the sine qua non for the evolution of social living, a form of life that enabled the species to surpass, qualitatively, the performance of any individual.

TB: On this note we should conclude this interview with Professor Joseph Knoll. Thank you for your contributions to neuropsychopharmacology and for sharing this information with us.

JK: I feel honored by having this interview. Thank you very much.

IRWIN J. KOPIN

**Interviewed by Thomas A Ban
Acapulco, Mexico, December 12, 1999**

TB: We are at the Acapulco Princess Hotel in Mexico. It is December 12, 1999. I will be interviewing Dr. Irwin Kopin* for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Let's just start from the very beginning. Where are you from?

IK: I was born in New York.

TB: Where were you brought up?

IK: My first memories are of the Bronx and we used to go away during the summer to Long Island. We had a small place in Rockaway on the beach where I learned to swim. Swimming has been part of my life. My wife says that there are four S's in my life: swimming, science, stamps and spouse, and she says, the most important better be spouse. In any case, science started a long time ago. When I was about nine years old, I got a chemistry set, and this is why my wife married me; the connection you'll see in a minute. I played with the chemistry set and told my father, when I was about ten or eleven years old, that I wanted to be a chemist when I grew up. He responded: "You'll never be a chemist unless you know how to make a mirror." Well, my father had a factory that made mirrors. He was in the "mirror business" and I was intrigued by the idea that you could make a mirror with chemicals. I went to the public library and read up on making mirrors. I found out that forming a mirror is a test for the identification of aldehyde. You take a silver nitrate solution and add ammonia to it. At first, you get a precipitate. Then the precipitate dissolves. When a reducing agent, such as an aldehyde, is added, you get a mirror. I tried what I read and got a black precipitate with a little silver streak of a mirror along the side. If you see that streak, you know silver has been deposited and that's the way you make a mirror. Well, I showed this test tube with the black precipitate and the silver streak to my father and he said, "Do you think I could sell that for a mirror"? And, even I, an eleven year old, knew that you could never sell this black thing with a little silver streak as a mirror! So, I went back to the books and read some more. This was over years. By the time I was fourteen, I had learned a good deal more chemistry. I went to the Bronx High School of Science and during that period I persisted and tried to make a mirror about thirty different ways. I wrote to the Department of Commerce and asked, "How do you make a mirror?" They sent me a brochure that listed about a hundred ways of making a mirror. Over

* Irwin J. Kopin was born in New York, New York in 1929.

the years, before and after receiving the brochure, I tried about sixty of them. They would all give the black precipitate and a little bit of silver streak. My father said, "At this rate you'll never be a chemist. But at least you should have a trade." I was about sixteen at the time and was allowed to work. On weekends he took me to the factory and I learned how to drill holes in glass. At that time they used a tungsten carbide drill with water dripping on it to keep it cool and prevent glass powder from being inhaled. If you pressed too hard, the glass broke. If you didn't press hard enough, you could sit there all day and wouldn't get a hole. After a while, it took about seven days, my father said I had "the touch." I could drill one hundred and eighty holes an hour in the glass, but I hated to do it. I didn't know what to do during the boring task. I used to skip lunch so I could go home early. When I told my father how I felt, he replied, "Well, you'll have to learn how to make a mirror." So, one day, I went up to the person who was in charge of silvering glass to make mirrors and told him about my experience. He said, "You have to wash the glass! Grease or a little bit of dirt, act as a nidus for the black precipitate. You have to clean the glass thoroughly!" So he taught me how to clean glassware. First, use sodium hydroxide solution, then use distilled water to wash that out, then scrub with red cuprous oxide, then wash with more distilled water. Only after this do you add the silver nitrate solution. When I did this at home I was able to bring a beautiful silver finger, like the inside of a thermos bottle, like a Dewar flask, to show my father, who said, "Now you can go to college!" So, that was my entry to college. I went to City College for two years with the idea I would do something in chemistry. At about that time, however, I decided, I wanted to go to medical school. In those years, it was very difficult to get into medical school from City College so I had to transfer to a different college.

TB: What year was that?

IK: It was in 1948. About that time my father wanted to bring my aunt to the United States who had been in a concentration camp, the only one of my father's five siblings who survived the Holocaust. She was unable to get a visa to enter the United States, but Canada was more receptive. So, my father arranged for her to go to Montreal and settle there. I was an only child and he knew I needed to get out of the house and go off to college. But he didn't want me to be alone, cold and hungry in a strange city without any relatives. So he convinced me to go, with my good friend, Rubin Bressler, to McGill University in Montreal. Rube and I are friends since second year high school and went to City College together. So that's how I got to McGill. In the organic chemistry course

at McGill, Rube Bressler and I were lab partners. There were girls taking the same course and in one of the laboratory exercises we had to make an aldehyde and test for its presence. Although we had done everything together, when it came time to testing for the aldehyde, I said, "Rube, you must step aside. I will do this". Of course, I cleaned the glassware thoroughly and got this beautiful silver finger of a test tube. We brought this to the instructor and he'd never seen one like it. He was used to seeing the black precipitate with a silver streak on the side of the tube. When we gave him our test tube, he put it on exhibit in front of the class. The girl I was dating, Rita, was so impressed she finally agreed to marry me! That was my first introduction of how important it is to wash glassware; the details of laboratory work were impressed on me very early. Years later, Julie Axelrod, with whom I worked at NIH, claimed he used to get his best ideas washing glassware. His laboratory work was mainly enzymology and it was important to have clean glass. If I had known that when I was younger, I would have been able to convince my father earlier that I was college material. But, it was a very useful experience. At McGill, Rube and I majored in Biochemistry. Professor David L. Thompson, who was Chairman of the Department of Biochemistry, was a wonderful inspiring lecturer. He used to come to class with a small card and taught us everything from Nutrition to advanced Protein Physical Chemistry. Professors Orville Denstedt, Murray Saffran and Joshua H. Quastel constituted a great group of biochemists. After graduating from the Honors Course in Biochemistry, I went to McGill's Medical School. It was a very good school, and it was there I first found out there could be a rational approach to drug treatment of psychiatric disorders. Professor Heinz Lehmann was a gem of a teacher. He could bring a patient into the room with a group of about fifteen of us. He would introduce the patient, and he tell us to examine him or her. We were to watch the patient's behavior and discuss later what we saw. I can still remember, vividly, after over fifty years, many of the patients. To show us mania, in 1953, before drug treatment had been introduced, Heinz Lehmann brought in a female patient for us to examine. She was unable to remain still. She danced around the room, flirting from one student to the next saying, "Oh, what a beautiful tie you have! Oh, my, look at your jacket! It's gorgeous. Your shoes are so polished," We were all laughing with her, not at her; we enjoyed her presence. When she left, Dr. Lehmann said, "This is mania. This is a pure manic patient. You feel happy with the patient, you enjoy the patient". Of course, when she did what she was doing in class, for twenty-four hours a day, it became anything but enjoyable to her husband. Nevertheless, that is the feeling mania

induces. Another time he brought in someone who was depressed. The patient told us that he committed an unpardonable sin and we all felt the depression the patient experienced. The hebephrenic schizophrenic patient he showed us had received a PhD at McGill in biochemistry before he became sick. One day he was found wandering around in the nude on a mountain behind McGill. When he entered the room, he said, “Ah, ha, what a wonderful idea, what a happy, happy day.” He spoke nonsense in a high tone, although he was a big guy and we expected he would have a deep voice. Professor Lehmann explained this was typical of hebephrenic schizophrenia. The patient is silly. Unlike the manic patient, you find the patient uncomfortably laughable. Another time he brought in a person who came well dressed in a jacket and tie with the daily newspaper under his arm. He sat down comfortably and when we interviewed him we found absolutely nothing wrong with him. He was oriented in time and place. He knew current events. He seemed aware of everything. We finally asked the patient why he was in the hospital. Then, he explained, “Well, you know, these people don’t understand me. My wife had this X-ray machine, and she keeps looking into my brain and telling me things to do. It became impossible, and because of that, I had to kill her”. Dr. Lehmann said, “This is an example of the island of abnormality in the mind of a paranoid schizophrenic”. He warned us, “Don’t turn your back on a paranoid schizophrenic. You’ll have a nice conversation with him and, suddenly, he’ll pick up the ash tray and hit you over the head with it”. This was Heinz Lehmann, only he could carry this off. I don’t know where he found these typical patients. I’ve never seen them again. The patients I encountered always had mixed, unclear diagnoses but he had these rare, “typical” patients from the large population at Verdun Protestant Hospital, which was the McGill teaching hospital for psychiatry. There was another psychiatric hospital that was closer to the Medical School, the Allan Memorial Institute, which was up on the hill. There I saw shock treatments given to schizophrenics, but we never really got the same feel for the disease that Heinz Lehmann was able to impart.

TB: What did you do after graduation from McGill?

IK: I took my internship and residency at Boston City Hospital. At that time, in the U.S., there was the “Berry Plan”. If you enlisted in the Army during Medical School, they allowed you to take your residency and, then, you went into the Army after you completed your training. Entry into the Army was postponed. Since I went to McGill in Canada I had not been part of the Berry Plan. My draft board wrote to me in March 1957, that I would be drafted into the Army unless I enlisted by July1. I decided

I would enlist but would finish my internship and my second year of residency and then go into the Army. But the Army told me I couldn't enlist until September. At that time I had a wife and two children, having married at the end of my first year in medical school. I was very lucky to have a supportive wife. Our first child was born in Montreal during my last year of medical school and the second child was born during my internship in Boston. We had these two babies and I couldn't afford not to have a job for three months. So, I decided I would call the Navy, but the Navy gave me the same story, as did the Air Force. Then, I heard about the US Public Health Service. They were accepting enlistments on the 30th of June. So, I decided I would apply. I was accepted and received a letter saying I was assigned to the Tuberculosis Research Section because of my "background in mathematics". I had been a good mathematician in college. I won a prize at CCNY (College of the City of New York) for "Pure and Applied Calculus" and when I graduated from McGill, I had won the Hiram Mills Gold Medal in Biological Science along with Honors in Biochemistry. I thought they had assigned me to a real research project. But I soon found out this assignment was all statistics. At that time, I was caring for patients and I didn't want to lose my touch so I went to Washington and explained, "I'm delighted I'm with the US Public Health Service; however, I would like to be in a hospital where I see patients". The personnel department was very accommodating, "Well, there are two jobs open in this new hospital on the outskirts of town called Bethesda and there's a new clinical center". I'd been at the old Boston City Hospital and when I walked into the beautiful new marble hallway of the Clinical Center at the NIH I thought, "I would take a job sweeping floors here". It was a gorgeous place. I was interviewed by two groups of people. One was in the Dental Institute. They were studying dental agenesis in patients with albinism. The other was a study of schizophrenics at NIMH. They wanted a physician to take care of the normal controls and a very select group of schizophrenic patients. That job was in the Clinical Center, whereas the other involved living in a trailer in a south portion of Maryland. It was June and very hot. The trailer had no air conditioning so the choice was an easy one, "I'll be in the Clinical Center". So, by accident, I choose to work with the project on schizophrenia.

TB: What was your task in the project?

IK: My first task was to go to the mental hospitals and examine the patients to determine whether they were appropriate for admission to the schizophrenia project. Seymour Kety helped in designing this project. He wanted to find out whether or not there was a familial tendency in

schizophrenia and whether there was a biological difference between schizophrenics that had a strong family history and those that didn't. My job was to make sure the schizophrenics were healthy except for their psychiatric disorder. So, I examined them and made sure they didn't have any Parkinsonian symptoms from their drugs, liver disease, etc. We brought into NIH fourteen schizophrenic patients; seven of whom had a family history. Some families were loaded with the illness with one parent, an uncle, a cousin, three or four people in the family blatantly schizophrenic. The others had absolutely no history of schizophrenia. Four hundred man-hours went into the examination of these patients to select them. It took about three months but after that I would go on ward rounds, which took about fifteen minutes in the morning, and I had free time all day. At that time, serotonin had just been found in brain. So, I wanted to find out whether or not serotonin had anything to do with brain function in schizophrenia. I went to Marion Keyes, who was head of the Section on Biochemistry in Seymour Kety's laboratory, and told her I wanted to look at spinal fluid for 5-hydroxy-indole-acetic acid, 5-HIAA, the metabolite of serotonin. Paper chromatography was at that time the method for detecting such a substance and I proposed looking for 5-HIAA in spinal fluid using paper chromatography. To do this, Dr. Keyes told me, I had to get rid of the salts first and then do paper chromatography to find if 5-HIAA was present. She also told me, "I'm writing a book on allergic encephalomyelitis, so I'm not using my bench. Feel free to use it". I went to the library to find out how to remove salts from spinal fluid, and made a large desalting apparatus with mercury bubbling up. It was one of those complex glass things; it reminded me of a cartoon I once saw, where ladies are cleaning the laboratory and inspecting a huge complex glass apparatus with a boiling solution. One cleaning lady says to the other, "I don't know what they use it for, but I use it for making coffee". Well, that's what this thing looked like, but it worked. I was able to get the desalting apparatus to function and was already doing lumbar punctures on the schizophrenic patients to be sure they didn't have syphilis so I froze some of the spinal fluid to try to detect 5-HIAA in it.

TB: Are we in the late 1950s?

IK: This was in 1957, shortly after serotonin was discovered in brain by Park Shore. About the same time, in 1957, it was decided to have a conference on catecholamines at NIH. The reason was that catecholamines had become very important. Ulf von Euler had, in the early 1950's, discovered norepinephrine was the neurotransmitter of the sympathetic nervous system and a great deal of research followed his discovery, seeking the

role of catecholamines in disease states. Also, there was an hypothesis that adrenochrome, derived from the oxidation of epinephrine, might cause schizophrenia. The adrenochrome hypothesis was based on anecdotes that, during World War II, when outdated adrenaline, which had become pink from formation of adrenochrome, was injected into people they became psychotic. The hypothesis that catecholamines might be involved in causing schizophrenia was sufficiently important it had to be investigated. Seymour Kety, who was Chief of the Laboratory of Clinical Science, had spawned interest in biological factors in mental disorders. He is regarded by many of us as the father of Biological Psychiatry. We were encouraged to investigate various biological factors related to brain function and psychiatry. Kety encouraged Julie Axelrod to follow his interests in catecholamine metabolism and I was encouraged to examine tryptophan and serotonin metabolism.

Zeller had described that after giving a tryptophan load orally to schizophrenics and normal subjects, the increase in the urinary concentration of 5-HIAA was significantly lower in schizophrenic patients than in normal volunteers. Seymour suggested that, perhaps, since I was involved in measuring 5-HIAA anyway, I should look at this problem. So we loaded the patients and controls with tryptophan and collected their urines. Well, schizophrenics aren't very cooperative and the conscientious nurses would follow the schizophrenics around the ward to make sure they got a complete urine collection. To encourage them to urinate, patients were urged to drink a lot of water. As a result, the concentration of 5-HIAA in the two to three liters of urine collected from schizophrenics was low compared to that in the one liter of urine that came from normal controls. Zeller had reported concentrations and not the absolute amount. Well, his findings of lower concentrations were confirmed; we obtained the same results that he reported. Yet, although the concentrations were low, the total amount of HIAA excreted was the same for the schizophrenic and normal subjects.

About that time, Julie Axelrod had become deeply involved in the study of O-methylation as the route of epinephrine metabolism. This was an interesting story, because Julie, who was an expert biochemical pharmacologist and had for many years, worked with Bernard Brodie, just recently obtained his PhD, but was already a Section Chief in Kety's Laboratory. Julie attended the Federation meetings in 1957 in Atlantic City, where Armstrong described vanillylmandelic acid, VMA, in urine as a product of epinephrine in patients with pheochromocytoma. Since, on the basis of earlier experiments with ^{14}C -labelled epinephrine reported by Schayer, it was generally believed that epinephrine was deaminated,

Armstrong proposed that epinephrine was deaminated and then O-methylated to form VMA. But Julie thought this might not be the order of events and had the novel idea that maybe O-methylation was first and more important than deamination. It was fortunate that Julie's laboratory was just down the hall from Julio Cantoni's lab. Cantoni had previously discovered S-adenosylmethionine (SAME), the methyl donor for such methylation. So Julie got some S-adenosylmethionine from Cantoni's lab, used it to incubate epinephrine with a homogenate of liver and found a new spot on chromatography. But he could not prove that this spot was O-methylated epinephrine. It's stained like a phenol and it seemed by its extraction properties to be an amine, but to prove that it was an O-methylated product he had to have the authentic compound. Julie phoned Bernardt Witkop, who was head of the Laboratory of Chemistry at another institute, NIDDK, and asked if he could synthesize the hypothetical O-methylated product of epinephrine. The Visiting Scientist Program at NIH was just initiated, and Bernardt assigned the task to Shiro Sanoh, the first Japanese Visiting Scientist to come to NIH. Shiro synthesized metanephrine for Julie in three days and by chromatography they showed that it had the same retention, R_f value, and had the same staining characteristics as the substance formed from epinephrine and SAME in the liver homogenate. They published this in *Science*. Julie showed that formation of metanephrine was important; but he could not find any adrenochrome formation from adrenaline in animals.

Kety organized a group of us to present reviews in a symposium on newly emerging findings in biological psychiatry. Lou Sokoloff, Seymour Kety, Julie Axelrod, Elwood LaBrosse and I presented summaries about various biological aspects of mental disease, and also about some of the pitfalls of studies in biological research in psychiatry. Much of this was about the mistakes that had been made. An example was one based on the use of paper chromatography, a popular technique at the time. Based on urine samples from patients and normal subjects subjected to chromatography there were reports of a spot that always showed up in urine from schizophrenics, but didn't appear in the urine of the normal subjects. LaBrosse was studying at the time schizophrenics and had normal controls, most of whom were volunteer Mennonites. These normal Mennonite men came to NIH to be volunteers in medical research, instead of serving in the armed forces, because they didn't believe in violence or war. Kety had arranged to have fourteen schizophrenics and fourteen normal controls in the study. All of the normal subjects were Mennonites except one, and he was a little bit peculiar.

When their urine was compared to that of the schizophrenics there was a clear difference in the samples. The urine of all of the schizophrenics except of one, who had no family history of schizophrenia and who was a little bit different than the others, produced a specific spot on chromatography. Only one of the normal subjects had the spot and he was not a Mennonite. He was also an older fellow, a little bit different from the other control subjects. After searching to find out the nature of the "schizophrenia spot" in the urine, they found it was caffeic acid, a constituent of coffee. The young Mennonites didn't drink coffee and they didn't smoke, but the older fellow, who was a little different, drank coffee. All the schizophrenics drank coffee, lots of it, but the one patient who was a little bit different, avoided it. So, it was the "coffee spot" that was different. Elwood LaBrosse was the person who was responsible for this work. This was a good example of the errors and pitfalls that were being made in schizophrenia research in early years.

Another important development was the introduction of reserpine, which was initiated by a pharmacologist from India, who went to various drug companies with evidence that a folk medicine, *Rauwolfia* alkaloid, calmed animals and excited patients. Finally, Ciba picked it up and isolated reserpine, which turned out to be a useful drug and was brought to market. Park Shore, in Brodie's laboratory, showed that reserpine depletes brain serotonin and noradrenaline. When reserpine came into use to treat hypertension, it was found that it sometimes caused depression. The hypothesis that depression was related to the depletion of brain norepinephrine was partially based on this finding.

Julie Axelrod had been working with catecholamine metabolism and disposition in those years. He used to sit in an open laboratory. His desk was in the laboratory with a sink right next to the seating area and his workbench next to that, with a blackboard behind the desk. On that blackboard had been written all of the questions, all of the formulas and all the outlines of the experiments being planned.

Seymour Kety had introduced radioactive adrenaline and noradrenaline into the laboratory. Seymour made an arrangement with New England Nuclear Company to make radioactive noradrenaline so that we could follow it through the body. He did this for clinical purposes. Julie used it to study the metabolism and disposition of these amines. I remember the time when George Hertting, a pharmacologist from Vienna came to the NIH, and Julie and I were standing around discussing some findings. Julie said, "You know, after we inject ^3H -adrenaline intravenously into animals, we find half of it is retained in the tissue". He had done this research in intact animals in the mouse, and in cats.

A large fraction of ^3H -adrenaline remained in the heart and Julie said, “It seems that adrenaline goes to where noradrenaline is and maybe there’s something special about this. Maybe uptake is important in some way”. George Hertting, listening to the conversation, recalled that after denervation, after cutting sympathetic nerves, they degenerate and the tissue becomes supersensitive to adrenaline. So, he said, “If the nerves are where ^3H -adrenaline remains, that won’t happen on the side where the nerves degenerate”. Hence, George and I removed the right superior cervical ganglion from cats and waited for a week for the nerves to degenerate. We then injected ^3H -noradrenaline and an hour later removed the tissues from the nictitating membranes and salivary glands on both sides. We found the tissues on the side from which the superior cervical ganglion had been removed didn’t take up the ^3H -noradrenaline whereas the tissues on the intact side did. The basis of supersensitivity became apparent. Since there was no uptake on the side where the superior cervical ganglion was removed, uptake was perceived as the mechanism for inactivation.

At that time there was a disagreement about whether O-methylation or deamination was the important mechanism for inactivation of noradrenaline. A Belgian pharmacologist, Zacq, had found that pyrogallol, a catechol, slightly potentiated the actions of adrenaline, whereas inhibition of monoamine oxidase had almost no effect. Of course, we now know that it is uptake that is the mechanism of inactivation of catecholamines released from the nerves. But, the fate of injected adrenaline is somewhat different. The question was whether O-methylation or deamination was important? I had suggested we use double radioactive labeling to find this out. It required the labeling of metanephrine with ^{14}C , which we could make with radioactive S-adenosylmethionine. We used this ^{14}C -metanephrine simultaneously with tritiated adrenaline. I did the experiment in patients, and together with Julie I started to study the metabolism of catecholamines in rats. From the ratio of tritium to carbon in the urinary metanephrine, it became clear that O-methylation was the predominant route of metabolism of the administered catecholamine in rats and in humans. Yet, inhibition of O-methylation didn’t potentiate the effects of nerve stimulation. George and Julie showed that cocaine, which was known to potentiate the effects of sympathetic nerve stimulation, prevented the accumulation of injected ^3H -noradrenaline in tissues. The concept that neuronal reuptake is important for the inactivation of a neurotransmitter stemmed from that early work, done around 1959, and published in 1960 and 1961.

During the studies of urinary ^3H -catecholamine metabolites, a new metabolite had appeared in the urine of rats. It was neither VMA nor metanephrine. The metabolite could not be obtained from $\text{N-}^{14}\text{CH}_3$ -labeled metanephrine, but did form after administration of the side chain labeled ^3H -catecholamines. It turned out to be 3-hydroxy-4-hydroxyphenylglycol (MHPG). In rats, MHPG was the major urinary catecholamine metabolite. In humans, MHPG is also excreted in urine, but VMA is the major urinary metabolite. At that time, we thought that this was a species difference in the metabolism of the intermediate aldehyde metabolite, but this was not the case.

TB: What year was MHPG identified?

IK: In July 1960, I went off to complete my residency in internal medicine and returned to NIH after one year. Seymour Kety had left NIH by then to become Chairman of the Department of Psychiatry at Hopkins. Seymour invited me to go to Hopkins with a joint appointment in the Departments of Medicine and Psychiatry, but in order to “pay back” NIH for the period of time they allowed me to take my residency, I had to remain at NIH for at least one more year. While I continued doing research on noradrenaline, another compound, melatonin, became of interest.

Melatonin, which is 5-methoxy-N-acetyl of serotonin was discovered by Aaron Lerner at Yale. He presented a seminar on melatonin at NIH, and suggested that the substance was metabolized to 5-HIAA. Lerner thought that after the N-acetyl and the methyl groups are removed from melatonin, the resulting serotonin is converted to 5-HIAA, a metabolite of serotonin. I had been working with double labels at the time and suggested to Julie that we label the whole molecule of melatonin. We labeled the O-methyl group with carbon and the acetyl group with tritium. If Lerner was right, we should not find any radioactive compounds related to indoles in the urine. If we would find radioactive compounds related to indoles, we had the capability to determine whether one or both ends of the administered melatonin remained intact. Michael Pare, a psychiatrist from England, joined us at that time and participated in this project. It turned out that the ratio of carbon, that labeled the O-methyl group, and tritium, that labeled the acetyl group, was identical in the urine to the ratio in the melatonin that was injected. Clearly, there was no deamination or deacetylation. When we gave large amounts of unlabeled melatonin, paper chromatography of the urine sprayed with Ehrlich’s reagent, which stains indoles, showed a sky blue spot. We found that the same type of spot was present in the urine of a woman that Aaron Lerner sent us, who had been given large doses of melatonin

to treat her melanoma. Of course, it didn't help melanoma, but we had the urine and she had this sky blue spot, also. Well, I didn't know much about that type of chemistry, but NIH is a wonderful place, because there's an expert in almost any field. Among them, was an expert in the field of indoles, Evan Horning. I took the material to him, and he recognized, from the shy-blue color reaction with Ehrlich's reagent, that it was a 6-hydroxy-indole. Thus, 6-hydroxymelatonin, and 6-hydroxymelatonin sulphate were found to be the major metabolites of melatonin.

It was about this time, that, Dick Wurtman joined the laboratory. There were also a number of other young scientists coming in from all over the world. George Hertting had already been there. Leslie Iversen and Jacques Glowinsky came to the NIH to work in Julie's lab, and these people became the founders of a major portion of the biochemical aspects of pharmacology, particularly in the nervous system. Many of the stars in neuropharmacology, particularly in the amine area, grew up in the laboratory that was established by Seymour Kety. Seymour, after one year at Hopkins, decided that Hopkins was not for him. He told a story, that when he first went to his new office at Hopkins and sat down in the chair of the department, the chair broke. He claimed he felt this was an indication he might not last. After a year, he decided to return to NIH; when he came back he told me I should stay. He wanted me not to go to Hopkins. So I agreed to stay. At that time, I had the good fortune of being able to hire a wonderful technician. Edna Gordon was a woman who had worked with Jarvis on phenylketonuria in New York. After she had married and had a child, she left work for about eight or ten years. But at this point in time she was ready to return to the laboratory. When I went home and told my wife, Rita, about this woman whom I had interviewed, she said, "You should hire her, because that's the type of person who would have gone on to get a PhD." And she was right. Edna Gordon was a gem. She did all of the work I couldn't do with the precision that she brought. She taught me how to keep notebooks. She kept all of the data, beautifully organized. Also, a normal volunteer, Dale Horst, a Mennonite, started to work in the laboratory. Dale was bored on the ward where he worked and offered to help out in the lab. After a while, Dale decided that he had some interest in biology. He left NIH, went back to school and majored in biology. After receiving his degree he applied to NIH, looking for a position as a technician. I gave him a job in the laboratory. As part of the research I was doing, I had learned how to inject the tail vein of mice and rats to get urine flowing so we could get clean samples. I asked Dale to learn how to do this and explained it would not be easy to do initially, it would take time

to get the hang of it, so he must be very patient. After explaining all of this and how to put the needle underneath the skin in the tail where the vein can be seen, he easily did it the first time he tried! He had done it beautifully; much better than I would have. He then constructed a rack, so we had eighteen animals with intravenous infusions of fluid going in their veins while their urine was collected. It seemed as if the fluid input were connected to the penis, because as fast as the fluid was infused, the rats began to urinate at almost the same rate. We were able to get half-hour urine samples from these animals and could study the kinetics of the excretion of metabolites of the labeled catecholamines we injected. We started to study the effects of drugs on the excretion of the products of ^3H -catecholamines. We could distinguish which were the immediate metabolites in the urine excreted in the first hour. They were mostly O-methylated. After several hours however, the major metabolites were deaminated metabolites. After tyramine was administered there was a large increase in sympathetic responses, and the urine contained increased amounts of O-methylated products. But after reserpine administration, which depleted catecholamines from their stores and interfered with sympathetic function, we found marked increases in the deaminated metabolites in the urine. That led us to the conclusion that the reserpine-induced depletion of amines is accomplished by interference with their storage. If the catecholamine is released into an active form outside the nerve it is O-methylated. But O-methylation is relatively unimportant for inactivation of most of the released amines, because most of the amines are inactivated by reuptake.

TB: When did you become a section chief at NIH?

IK: By 1963 I had become a Section Chief. There were a series of outstanding postdoctoral fellows who came to work with Julie Axelrod and me during the next decade. I already mentioned Leslie Iversen, Jacques Glowinski and Dick Wurtman by name. Others included Ross Baldessarini, Sol Snyder, Dick Wurtman, Jose Mussachio, Joe Fischer, Saul Schanberg, Joe Schildkraut, Goran Sedvall, Lou Lemberger, Tom Chase, George Breese, Richard Kvetansky, Perry Molinoff and Dick Weinshilboum all of whom later made their mark as outstanding investigators and leaders in academia and the pharmaceutical industry.

This was the time of the Korean War and there was a draft to serve in the military. Those who joined the US Public Health Service could satisfy their military obligation by serving at NIH, rather than go to Korea. This was a popular option and, at one year, I had six young physicians, each of whom were first in their class in medical school, apply to come to our Laboratory as a Research Associate. They would serve for two

years and we had star applicants. One of them was Joe Schildkraut, a young psychiatrist who joined me in 1966 after having extensive discussions with Seymour Kety. Together, building on the earlier observation that reserpine sometimes induced depression, they gathered the evidence which supported the hypothesis that catecholamine depletion was the basis of depression. Goran Sedvall, another psychiatrist who joined our laboratory, subsequently became Chair of the Department of Psychiatry at the Karolinska Institute. Joe Schildkraut, became a professor of psychiatry in Boston. Ross Baldessarini, then a young medical student at Hopkins was referred to our lab by Dr. Kety who phoned me, saying, "This fellow is very bright. Why don't you take him as a summer student"? At that time, we were interested in S-adenosyl methionine and we were employing the double label technique again, using melatonin as the product. Melatonin could be separated from both the added ^{14}C -methyl-labeled S-adenosyl methionine, and from ^3H -N-acetyl serotonin. The added ^{14}C -methyl-labeled S-adenosyl methionine was diluted by the tissue S-adenosyl methionine and enzymatically converted to melatonin. From the ratio of the carbon/ to tritium we could calculate how much endogenous S-adenosyl methionine had been in the tissue. This was the project that Ross did over the summer of 1963 and we published it first as an assay for S-adenosyl methionine. Several years later, Ross came back to our laboratory as a Research Associate. Seymour Kety by that time had returned to NIH and I had become a Section Chief. Catecholamines had become important, not only in psychiatry, but to all those who studied the sympathetic nervous system. Hence future neurologists, anesthesiologists, and internists, came through our laboratory at one time or another. Mike Roizen, who became Chairman of the Department of Anesthesiology at the University of Chicago, had his first experience with catecholamines in our Laboratory. In the late 1960's we started to study the release of noradrenaline and related compounds from the sympathetic nerve endings. Joe Fischer, a surgeon, in our Laboartory, became expert at perfusing cat spleens with intact sympathetic nerves. This was a very useful means of studying amine release when nerves were stimulated. The people that came to our laboratory and left who have had a major impact on developments in the drug industry as well as in academia, included Perry Molinoff, Steve Paul, Gus Watanabe and Bill Potter. Because of the responses of the sympathetic nervous system in emergencies, we became interested in stress. Stress elicits responses in the sympathetic nervous system and the adrenal medulla. Richard Kvetnansky, from Bratislava, came as a visiting scientist, and, brought a model for studying "immobilization stress" in

rats that he'd been working with in Bratislava. But in Bratislava, they didn't have the techniques that we had to examine catecholamines. We started to study the effects of stress on the adrenal medulla and on the sympathetic nervous system, and particularly enzyme induction. Goran Sedvall had developed a technique for stimulating, in a rat, the sympathetic nerves in the neck on one side of the head, so we could compare changes in the two sides. Using DOPA labeled with one isotope and tyrosine labeled with a different isotope, he was able to show that conversion of tyrosine to DOPA was the rate-limiting step in norepinephrine synthesis and that this conversion was enhanced by nerve stimulation. DOPA was easily converted to noradrenaline, but if you stimulated the nerve, more tyrosine was converted to noradrenaline; so the carbon/tritium ratio in the salivary gland was increased on the side the nerve had been stimulated. This was the first indication that sympathetic nerve stimulation increases tyrosine hydroxylase activity. We subsequently found that DHPG (di-hydroxy-phenylethylene-glycol) is the major initial metabolite of noradrenaline and is converted by O-methylation to MHPG in the tissues. The MHPG enters the blood stream and is converted in the liver to VMA, which is the product that is excreted and can be measured in the urine in humans. We could then use blood levels of MHPG as a basis for studying sympathetic activity in humans in many studies. Graham Eisenhofer, Dave Goldstein and I continued to develop much of the MHPG story.

TB: Are we now in the mid 1960's?

IK: We're spanning the mid 1960's. We conducted a series of studies on false transmitters in the early 1970s. The concept of false transmitters began with the introduction of α -methyldopa. When α -methyldopa was given, α -methylnoradrenaline was formed and largely replaced norepinephrine. α -Methyldopa is used as an anti-hypertensive agent, because the α -methylnoradrenaline formed doesn't stimulate the α -receptor and norepinephrine is more active at β -receptors, which causes vasodilation. In the brain, after α -methyldopa administration, α -methyldopamine and α -methylnorepinephrine are formed.

TB: You have made major contributions in setting the neuroscience foundation of neuropsychopharmacology. Am I correct that you were the recipient twice of the prestigious Anna Monica Award?

IK: Yes, once with Joe Schildkraut, and once alone, for the MHPG story. Joe led a group of us that won the first Anna Monica Award for work that led to the concept of noradrenaline being involved in depression. Later on, when the MHPG story developed, almost ten years later, I won the Anna Monica Award. Our research clarified the important role

MHPG plays as an index of sympathetic activity and as a means for using plasma MHPG and CSF-MHPG to evaluate norpinephrine metabolism in brain. Many people contributed to these studies, and I was lucky to have been singled out for the award. At the time MHPG was a central area of our research.

TB: Tell us about some of the other young people you didn't mention as yet, who spent time in your laboratory.

IK: We had a number of young physicians who began their research careers in our laboratory. One of them, Steve Silberstein, joined us to study tissue cultures. He's currently a neurologist, and is studying headache. Another one was Justin Zivin, who was doing research with us on stroke and trauma, promulgating the idea that catecholamines have an important role in development of pathological changes after spinal cord injury. People like Silberstein and Zivin got their early training with us and, then branched off into their own areas of research. It's given me great pleasure to see how they developed and continued to do research using the conceptual framework they learned in our Laboratory for their investigations, as, in Walter Cannon's words, "the way of an investigator." I learned from Julie and from Seymour how to think and how to manage a laboratory, and I see the things I learned I've been able to pass on to them, like to my children.

TB: Isn't your son a molecular biologist?

IK: My son started as a gastroenterologist, but has evolved into a molecular biologist. As part of the requirement to participate in research to obtain Boards in gastroenterology, he learned to clone a gene. He was new to this area but became good at it so I learn a lot about molecular genetics from him! We live now in a new world of research and I've had the good fortune of bridging the time when we knew little about the molecule, and current times when we know so much about it. In this new world, information comes faster than we can possibly digest it. We need computers to keep track of everything that's going on; it's difficult to see how we managed before 1965, when we didn't have Medline. In the 1980's you would have to have gray hairs to remember what happened before Medline, and this is the time I bridged.

TB: Weren't you involved in the 1-methyl-4-phenyl-1,2,3,6-tetrahydro pyridine (MPTP) story?

IK: There was a turning pointing in my research in the late 1970's. In 1978, I got a call from a neurologist, who said that he had a very peculiar type of patient, a twenty-four year old boy, who appeared to suddenly develop catatonic schizophrenia. His mother found him in his room, lying in bed in his feces, unable to move, and took him to the local

hospital. The boy grew up in the shadow of NIH, he was taken to the local Suburban Hospital where, after diagnosing his disorder as typical catatonic schizophrenia, they sent him to a mental hospital. During the next month or two, he became more rigid and they called in a neurologist. The neurologist recognized that the boy appeared to have severe Parkinson's disease rather than catatonic schizophrenia. When he was treated with L-DOPA, lo and behold, he suddenly loosened up and said, "What have you guys been doing to me?" About four hours after he got the L-DOPA, he was back into his prior state. They had given him ammonia to smell, trying to get a response, but he was unable to move. Later he said, "I just couldn't carry out any actions". So, they had started to treat him with L-DOPA. The neurologist asked if I was interested in studying this young man and I said, "He sounds fascinating, bring him to NIH." After he was admitted, Dr. Davis, a young NIMH psychiatrist found out the patient was abusing drugs and to increase their effectiveness he started to take Demerol with cocaine. He felt this was a marvelous mixture, but had a great deal of difficulty in getting Demerol. He was a bright young man and went to the library where he found there were other compounds like Demerol he could synthesize himself. So, he set up a laboratory in his basement to synthesize a derivative of an isomer of Demerol in which the carbon and the oxygen atoms were reversed on the molecule. He had all the equipment for doing this, and when he tried the compound he synthesized, he thought it was wonderful. He obtained the crystalline compound and was taking about twenty-five milligrams of it at a time. He decided, during one summer, that the amounts he was preparing were too small, so he tried to make a big batch. While preparing a big batch he realized he would lose a lot of the compound if he recrystallized it so he took some of the uncrystallized material. After two doses, he suddenly developed the syndrome for which he was hospitalized. This was the first case of MPTP toxicity. Sandy Markey, who joined our laboratory to head the mass-spectroscopic facility, went to the patient's house to try to get some of the substance the patient had made, but his mother had cleaned up her son's laboratory and threw out most of the stuff. The only thing left was one desiccator. That desiccator had a little bit of the powder left in it, that Sandy was able to analyze by mass-spectroscopy and found it contained MPTP along with two other compounds. We thought that we should publish this interesting case, but it was very difficult to get it into print. Finally, we did succeed. About a year or two after this, in California, there was an outbreak of Parkinsonism among drug addicts and Bill Langston traced down the compound that had been used and sent it to Sandy Markey, who found

that it was MPTP. At the time we had tried this compound in rats, guinea pigs and rabbits, with little effect. However, it did cause a Parkinsonian syndrome in monkeys, and the MPTP story started a new era in neurology. As you know, DOPA had been suggested as a potential treatment for parkinsonism after dopamine had been discovered by Carlsson in the late 1950's, and, in the early 1960's, Hornykiewicz reported that dopamine was depleted in the brain of Parkinsonian patients. Early attempts at using DOPA in the treatment of Parkinson's disease failed because of its side effects, but in the late 1960's, George Cotzias was brave enough to give the large doses of DOPA that were needed and proved its efficacy in alleviating the symptoms of Parkinson's disease. Soon after, the side effects of DOPA, which were largely due to formation of dopamine outside the brain, were found to be preventable by the use of peripheral DOPA decarboxylase inhibitors. Gus Watanabe studied the effects of DOPA after the administration of peripheral decarboxylase inhibitors on the vascular system and later became vice president of Eli Lilly. Tom Chase was also with us as a Fellow in those years. He had been studying the release of compounds from brain slices with electrical stimulation. Later Tom was promoted to Section Chief at the Institute. Subsequently, he became scientific director of the Neurology Institute and, in 1983, I succeeded him.

TB: Any further developments in the MPTP story?

IK: After the MPTP story became well known, I received a telephone call from Denmark about a young chemist who had suddenly developed Parkinson's disease several years earlier. He had been working in the drug industry and made a large batch of MPTP used as an intermediate in the synthesis and manufacture of some drugs. After re-crystallizing it, he spread it out on paper with his hands to dry it. Although he went home sick that day, he did the same thing a week later. He got sick again, but never returned to work, because he developed severe Parkinsonism. I traveled to Denmark and, after confirming the diagnosis, I asked him to come to NIH with Dr. Pakkenberg, his neurologist. At NIH, this brave patient agreed to be taken off L-DOPA and Dr. Pakkenberg noted the patient's Parkinson's disease became as severe as it was ten years earlier at the time he started medication. Ten years of treatment with L-DOPA had not affected the severity of his Parkinson's disease and he was still responding to his medication without developing dyskinesia that is often a problem after long term treatment.

In parallel, Stan Burns, who had been studying the effects of MPTP in monkeys, developed the first animal model of Parkinson's disease. This was followed a short while later by Kris Bankiewicz with whom we

were able to produce a hemiparkinsonian animal. We could make half the brain Parkinsonian by infusing MPTP in one carotid artery. Like rats that had received 6-hydroxydopamine into one side of the brain, the monkey circled towards the affected side. An affected animal would be able to reach for food with his hand on the opposite side and he was very smart. If you offered him two pieces of food, he wouldn't reach with two hands. He would take the first piece and put it in his mouth and, then, reach for the second piece with the unaffected hand, whereas before MPTP, they would reach with both hands. It was clear that he wasn't able to use the hand on the affected side. We could measure the circling effect, as it had been done in rodents made hemi-Parkinsonian with the administration of 6-hydroxydopamine for studying dopaminergic systems. The MPTP treated hemiparkinsonian monkey became a useful tool for studying treatments of Parkinsonism. Kris moved on to study the effects of fetal tissue implants, but US government policy prevented NIH scientists from using fetal human tissue implants. In fact, they frowned on use of fetal tissue in research of any type at that time. Private funds allowed such research outside of NIH. Later the same animal model of Parkinson's disease was used to study the effects of transfer genes into the brain of animals, whether it be rats or monkeys.

We continued to study stress in our laboratory, another area of research that has been highly productive. The sympathetic nervous system, of course, controls blood pressure. In our studies of patients with orthostatic hypotension, many years ago, Mike Ziegler and I found that patients could be divided into two groups. One group had central nervous system disease, with their sympathetic nervous system essentially intact. They had normal plasma catecholamines at rest, but when they stood up they didn't have the normal elevation of plasma catecholamines. These patients had multiple system atrophies in their brain. In the other group of patients, the central nervous system was intact, but the sympathetic nerves were almost absent. This group had peripheral autonomic neuropathy, with absolutely no symptoms of central nervous system disease. Their orthostatic hypotension was associated with abnormally low plasma catecholamines as well as failure to increase the plasma catecholamine levels when standing. These patients have a better prognosis because only their sympathetic nervous system has failed.

We had been studying false transmitters and one of the early false transmitters that interested us was labeled with fluorine, fluorodopamine. I anticipated it would be useful for imaging the sympathetic nervous system. If fluorodopamine is injected intravenously, it is taken

up into sympathetic nerves where it can be converted to fluoronorepinephrine. I thought that if ^{18}F labeled fluorodopamine is used, we could detect it in the peripheral sympathetic nervous system and determine its distribution by PET scanning. We saw some patients with Parkinson's disease who developed orthostatic hypotension that was attributed to the accumulation of dopamine instead of noradrenaline in their sympathetic nerves after being given high doses of L-DOPA. Dave Goldstein showed these patients had degeneration of their peripheral sympathetic nerves, which could be demonstrated using ^{18}F -fluorodopamine and PET scanning of the heart. This was a new observation we published in the *New England Journal of Medicine*. Later, it was amply confirmed. Dave Goldstein was doing the PET studies in humans; it took about ten years to develop his method from the time that we used fluorodopamine accumulation in tissues to label noradrenergic nerves in animals. The work to develop the method began with "Mike" Chiueh with unlabelled fluorodopamine. Graham Eisenhofer followed it up using ^{18}F -fluorodopamine made from the excess of ^{18}F -fluoro-dopa that was being prepared for imaging dopaminergic neurons in the brain. We did the same experiment we had done many years before, using unilateral sympathetic denervation. In a dog, we removed the superior cervical ganglion on one side, gave ^{18}F -fluoro-dopamine, and used PET imaging to examine effects on the accumulation and retention of the ^{18}F -fluorodopamine. We found that the denervated side didn't have any radioactivity, whereas the salivary gland on the intact innervated side did. We repeated this experiment in humans and found we could not visualize, with ^{18}F -fluoro-dopamine, sympathetic nerves in the hearts of patients with orthostatic hypotension with primary autonomic failure. The other group of patients with orthostatic hypotension, suffering from multiple system atrophy, appeared to have intact cardiac sympathetic innervations but they couldn't appropriately activate their sympathetic nervous system because of central nervous system disorder. These patients sometimes have Parkinsonian symptoms. So it appears we have a spectrum of patients who display Parkinsonian features with orthostatic hypotension as their primary symptom. Many patients with Parkinson's disease have orthostatic hypotension; although originally it was thought that was secondary to L-DOPA, it has become evident it is due to degeneration of the sympathetic nerves in the heart and probably elsewhere. Both internists and neurologists were interested in orthostatic hypotension, so several have come through the lab who've been interested in such studies. One of the first was Ron Polinsky, a neurologist who has gone on to a career with drug companies. Another

was Dave Goldstein who was to become a leading figure in this area of research. Over the years, I've been fortunate in having people with broad expertise join our laboratory. They benefited from the excitement about science that pervades the NIH. To repeat, Leslie Iversen, Jacques Glowinsky, Sol Snyder, Dick Wurtman, and Perry Molinoff all spent their early years in the Laboratory of Clinical Science with Kety, Axelrod and me. In psychiatry, Joe Coyle, Steve Bunney, his brother, Biff Bunney, Mike Ebert, Fred Goodwin and Dennis Murphy, as well as others, began as young post-docs in our laboratory. Dick Weinshilboum, who went to the Mayo Clinic, started his work on the genetics of different enzymes with studies of S-catechol-O-methyltransferase in our laboratory. Dave Dunner, Walter Kaye and Bill Potter also came through the lab. Martha Weinstock, who is chairman of Pharmacology at Hadassah, came to work with us as a visiting scientist. So did Giora Feuerstein, originally from Israel, who stayed here in the pharmaceutical industry, Joe Fisher, who was a surgeon, and is now chairman of the Department of Surgery. He and Ross Baldessarini carried out studies of S-adenosylmethionine to try and explain the deficits in hepatic encephalopathy. Joe, as a surgeon, made portal vein shunts in animals, and studied the effects of this on methylating processes in brain. The people that came through the NIH are a source of pride and we keep track of their progress and accomplishments. They're "family."

The NIH has been very good to me and it's given me a great deal of pleasure over the years to have worked and been taught by such stellar people. I'm grateful to the teaching of people like Heinz Lehmann, who, when I was a medical student at McGill, introduced me to psychiatry, and of Seymour Kety and Julie Axelrod, my supervisors and collaborators, as well as the many young post-docs that came through our Laboratory. I also benefited from several outstanding technicians, like Edna Gordon and Virginia Wiese. These are people who spent thirty or forty years working with me, ensuring the quality of our studies. Edna Gordon, unfortunately, has died. Virginia Wise is retired. She lives near NIH and I see her every once in a while, and some of my secretaries have been with me for twenty years. Virginia has visited scientists that spent time at NIH, like George Hertting in Vienna. They have been friends for over forty years. There is a unique perspective in seeing the carryover from the old pharmacology to the new molecular genetics and looking ahead to see that molecular genetics is not going to be the total answer. It's going to raise more questions than we can answer and the pendulum is going to swing back towards the intact animal research, the polymorphisms, the genomics, the informatics that we have now.

The future direction of the College is going to be fun to follow. Many of the people I've mentioned are members of the ACNP and some are foreign corresponding members. There are also those who are in other professional organizations, such as in neurology, anesthesiology, internal medicine, and some who are working in drug companies. All these people contributed immensely to the intellectual environment of NIH and have had a major impact their disciplines in the United States and abroad. It's been such a great pleasure to work with them, and many friends that I've made at ACNP. I am a Past President of ACNP, so I keep going to the Past Presidents luncheons. I have also continued for many years as Treasurer.

TB: When did you become a member of ACNP?

IK: In 1968, Sid Udenfriend and Seymour Kety urged me to join this group. It was very fortunate for me that I did.

TB: When did you become president?

IK: In 1992. The theme that year was to put the "Neuro" back into Neuropsychopharmacology. As president, I tried to do that. It may have been premature, but I think that it is also the theme of the current president, Steve Paul. Steve is another Laboratory of Clinical Science (LCS), alumnus, as was his predecessor at Eli Lilly, Gus Watanabe.

TB: All of them were in the LCS?

IK: Yes, all of them. They've grown up. They are analogous to children and grandchildren, if you like. They have expanded beyond the areas we've been studying, whether it was depression or Parkinson's disease or orthostatic hypotension. But there remains some overlap with the main theme being brain function, not only psychiatry, but for neurology, anesthesiology, internal medicine, etc. For example, Alzheimer's disease is being studied in many Institutes; by the Institute of Aging, by the Neurology Institute, by the NIMH. No one institute can claim it's the only one to study the brain. The Child Health Institute has a tremendous influence on what's becoming neuroscience and neuroscience encompasses so many disciplines. This is being recognized more and more widely.

TB: You have been in research in neuroscience since the 1950s, the time of paper-chromatography and the discovery of monoamines in the brain.

IK: Yes. I've seen the field develop and it's been a real privilege to work with the people who had so much impact.

TB: Are you still involved in the training of young researchers?

IK: Yes, I'm still involved. I'm officially retired, but a Scientist Emeritus at NIH, so I have my office and, most importantly, parking space. Although I do not have a lab bench, I still have discussions with post-docs and I'm

- able to bounce ideas around or have people come to me and use me as a sort of memory. Having the gray hair, I am supposed to remember what happened a long time ago.
- TB: Your bibliography reflects the development of neuropsychopharmacology.
- IK: Well, partially, yes. I've published over seven hundred papers, and that's largely due to the people who worked in the lab. I had these talented people that came through that really spark your interest and keep your enthusiasm going.
- TB: But it was you who trained them.
- IK: It's mutual. They trained me; I trained them. When they come to a new lab, they bring new ways of thinking. They raise problems and the solving of these problems is a joint effort. I like to interact, draw out and be drawn out. It's never a one-way street.
- TB: Your research had a great impact on psychiatry but you're not a psychiatrist.
- IK: Neither was Seymour Kety. The Laboratory of Clinical Science, which he started and I inherited, trying to carry on the tradition, was a founder of biological psychiatry based on what has now become the discipline of neuroscience. Kety's lab probably trained half the people who were in on the beginning of biological psychiatry in this country. The people we trained continued to train others and we're now on the second and third generations of people who are trained by them. But, it all stems from Seymour, who got the Lasker Award for his lifetime contributions. He started as a physiologist and developed the first method for measuring cerebral blood flow, for which he became famous. Then Lou Sokoloff, who was initially interested in psychiatry, and Seymour exchanged ideas, and, then changed their courses of research interest. Lou went on to become more of the physiologist and developed the deoxyglucose method that is now used for imaging brain blood flow with PET scanning, whereas Seymour picked up the psychiatry and he's considered by many to be the father of biological psychiatry in this country.
- TB: You have made, in addition to your research, a major contribution by training many of the people who became leaders in the field. It's a most important contribution.
- IK: The most important contributions were made by the people that came through the lab and what they've done afterwards. It's been a pleasure and a source of great satisfaction to me. I've worked with melatonin, with MPTP, with false transmitters, with brain imaging and with heart imaging. All of these things are relatively minor compared to the people that have come through and have gone on to do research, both

at the clinical and the basic level, and the impact they've had on the drug industry, on thinking in the field, on the whole of neuroscience and on neuropharmacology. That is what I consider my greatest source of satisfaction.

TB: You should feel very pleased with the results. Look at the changes that have taken place in the field and not just in the United States.

IK: Yes, Marta Weinstock in Israel, Sedvall in Sweden, Glowinski in Paris, Hertting in Freyburg...they are all over the world. There's also Corsini, who is now in Pisa. Many of these people became heads of departments, and they send their young people to NIH. There must be over a hundred who've come at various times and spent up to two or three years with us.

TB: During the years have you been affiliated with any university?

IK: Just with local universities. I have an appointment as an Adjunct Professor at Georgetown and at the Armed Forces Medical School across the street from NIH and I lectured at four minority colleges when I was president of the ACNP. I also had the good fortune to attend many international meetings and catecholamine conferences that have been held every few years to bring things up to date. I was at all the International Catecholamine Symposia held every few years throughout the world. Dave Goldstein was President of the one held in California in 1996. It included a wide variety of interests, from very basic neuroscience to the clinical studies of cardiovascular disease, pain, neurologic disorders, psychiatry and everything in between.

TB: Didn't the people who worked at the LCS organize a gathering at one of these conferences and have a Festschrift in your honor?

IK: That was the Eighth International Catecholamine Symposium at the Asilomar Conference Center. Many of my old post-docs contributed to the Festschrift in my honor. It brought back old memories such as the work I did with Sophia Zukowska, who is professor now at Georgetown. She first came to our laboratory about 25 years ago. I first met her in Bratislava at a meeting on Stress organized by Richard Kvetnansky. When she presented her work at the meeting, she expressed interest in coming to NIH. She stayed with us for three or four years. In fact, she and Dave Goldstein did the work on monoamine uptake. When Dave came to me with an idea for trying to find out what the concentration of noradrenaline is at the synapse he suggested the administration of tyramine. For a number of reasons that couldn't be done, but that started me thinking. We compared the effects on blood pressure of stimulating the spinal cord of a pithed rat with the effects of infused noradrenaline. This was done by comparing the pressor response curves

to the plasma noradrenaline levels in relation to blood pressure. We found that you have to raise plasma catecholamines to much higher levels with exogenous norepinephrine that the levels in plasma attained with an equivalent pressure response elicited by stimulating the spinal sympathetic outflow. The reason for this is that there is uptake in between the plasma and the synapse. But the reuptake is the same whether the norepinephrine is coming out or going in. So the concentration that you obtain during stimulating the nerve is less than is at the synapse, but when you give it exogenously the concentration in the blood is higher than at the synapse; the synaptic concentration is in between. So, by comparing the log of the plasma catecholamine-blood pressure response curves, the concentration in the synapse is halfway between; the logarithmic mean of the concentrations at any given pressor level. To prove that this was the case, we gave desipramine and the curves moved closer together because the uptake was blocked. The exogenous catecholamine gets more effective the less the endogenous NE is removed and the curves move together towards the synaptic concentration. That's another story that has been applied clinically to study patients with orthostatic hypotension.

TB: Your research embraced a wide range of different areas. You were involved first with research in schizophrenia, or even before with research on making a mirror. That was probably crucial.

IK: It may well have been. I sometimes think my father was very wise in the way he stimulated me.

TB: Obviously you are a dedicated teacher.

IK: Everything is taught earlier now than before. When my son went to high school, they also told him how to test for aldehyde by making a mirror, but they also told him to clean the glass. I guess I've told this story so often that everybody now knows you had to clean the glassware to get a good mirror. He was thrilled because he had reproduced what I had done at about his age.

TB: Is there anything we left out and you would like to add?

IK: No. It's been such a privilege to be a member of this college, to be part of the NIH and to have lived during this marvelous transition. In the future even greater contributions will be coming from molecular biology to provide a better understanding of brain function, that will lead to better treatments of neurological and psychiatric disorders. Thank you very much.

TB: Thank you very much for sharing this information with us, and, for contributing to the training of many of the participants at this meeting.

IK: Well, it was just being there at the right time and it was, as I said, a privilege and a pleasure.

TB: You were the right man at the right place at the right time.

IK: Thank you.

HARBANS LAL

**Interviewed by Elizabeth Bromley
Waikoloa, Hawaii, December 12, 2005**

EB: This will be an interview with Harbans Lal.* It is December 12, 2005. I'm Elizabeth Bromley. Can you tell us your name and where you're from?

HL: I am Harbans Lal and I'm living in the Ft. Worth area in Texas. I retired from the University of North Texas Health Science Center at Ft. Worth where I was appointed Chair of the Department of Pharmacology in 1980. I retired in 2000. I wanted to retire earlier, but my children said, Dad, you must work into the next millennium.

EB: So, you got in how many months?

HL: About four months in this millennium. But, that is amazing, in my opinion. I remember when I was a graduate student at the University of Chicago, we used to talk about the New Millennium, but we never really thought we'd be living in it. It was far away and it's amazing not only that I was living, but I was working in that millennium. We're living and working for longer periods. So, I'm really pleased to be part of this New Millennium.

EB: Where were you born?

HL: In 1931 in a town called Habib Koite Azara, in the Haripur district of the Hazara region of Pakistan. My father, Dr. Harbans Lal was physician, but he died in early 1940. He dabbled in politics, was mayor of the town and somewhat pro British. At that time, the British were in India. Some people did not like that and wanted to throw them out but my father supported various developmental programs instituted by the British. He was very influential and could not be defeated in an election. Then the politicians had him assassinated through food poisoning when the family was away. When my mother and siblings went to the hills for the summer father stayed behind for his patients. During this period he had his food catered from a local restaurant which provided the opportunity for his opponents to poison him.

EB: What year was he killed?

HL: It was in 1940. I was only nine years old and I'm the oldest child in the family meaning I became the head of the family at that young age. So, my Mother decided she would not let her children go into politics. To her, that was dirty work and not for us. My Mother had us educated and kept us away from political activities. The Country was partitioned when I was finishing high school. In India the high school examination was statewide and held at the designated examination center.

* Harbans Lal was born in Habib Koite Azara (Haripur, Hazara,) Pakistan in 1931.

However, civil war broke out in our area when I was ready to take the examination and non-Muslim minorities were not safe. It became very unsafe to travel to the examination center. There were fires, arson and murders. Most of my non-Muslim classmates decided not to take the exam and stay home for safety. School was essentially closed, but it was announced that if somebody wanted to take the exam, the military would provide escort service and protect students during the exam. As a result four of us minority students took the exam. I recall that a Muslim student brought a gun, perhaps to intimidate us non-Muslim students, or perhaps to keep the exam supervisor at bay. Taking the examination turned out to be a blessing. Soon after the country was partitioned, we were forced to migrate hundreds of miles away where we could not be certified for college admission; others who were deprived of the examination opportunity had to go through another year of high school before college.

I lost my father, a physician, so my mother was determined we should become physicians. I could, however, not be admitted because medical school had started before I could complete my admission requirements. I was asked to wait another year which I could not do because I did not have financial resources. In India, there were no temporary jobs to sustain someone in the interim. In desperation I considered alternatives; admission to Pharmacy School was available. So I went to the college of pharmacy which was located in the medical school facility with the same faculty. I almost did not realize I was not studying medicine. I took classes with medical students for the first two years. In the third year, the medical students began clinics and the pharmacy students started training in hospital pharmacy.

EB: Did you like science?

HL: In the College of Pharmacy I started liking pharmacology; it was one of the majors and I decided to undertake doctoral training.

EB: This must have been the early or mid-1950's?

HL: It was in 1952. In India, at that time a graduate program in pharmacology was available only to physicians. Pharmacology was not open for non-physicians, so I enquired was there any way I could pursue pharmacology? Someone informed me it could be done in Western countries. So, I applied and was accepted by the University of Munich. Its appeal was the low cost of living since I did not have money to go to any other University. Then I went to see a banker friend to seek guidance as he had been to Germany and the USA. He questioned my choice of Germany since I did not know the language and was offered no financial assistance by the university. I was expected to work at

restaurants to support my education. My friend told me I should go to the USA because that was the country of opportunities and I could get a pre-doctoral fellowship to support my education. At first I did not comprehend the logic of pursuing education in the most expensive country as I had little money, but I had confidence in my friend's advice. He also promised me if I was unable to support myself in the USA he would provide a grant from his family foundation.

EB: Now, who was this?

HL: This was a friend of mine, Sardar Mohan Singh, who was the managing director of a major state bank, the Bank of Patiala.

EB: A family friend?

HL: Yes. So, he pushed me to come to the United States. Of course, I never needed his money. I found a part time job at the University of Kansas during the first semester followed by a research assistantship in the following semesters. After receiving a Master of Science degree in Pharmacology and Toxicology, I was admitted to the Pharmacology graduate program at the University of Chicago with full financial support.

EB: Was this someone who was a mentor of yours? Did he believe in your potential?

HL: Yes, he was very much interested in furthering my education.

EB: Why was that?

HL: He was interested in youth who showed potential for higher education with a leadership desire to help others. Later he visited the USA and I thanked him for his offer of help at a time of need. But I was very proud to inform him I did not need any financial support; my fellowship took care of my needs. Friends like him were many in my life and each was crucial for my growth to the next level of accomplishment.

EB: Did you have intellectual mentors growing up? Did you know what you wanted to study?

HL: I did not have intellectual mentors but my Mother was a stimulus to undertake medical sciences for higher education. I had lost my physician father when I was only nine, I was the oldest sibling and I had to take care of the family. We went through terrible times; no earning member in the family, forced to leave our birth home and infra-structure on account of civil war and population exchanges. My Mother was a strong woman who became a widow at the age of 27. She did not lose heart, she stood by us and her parents helped us by keeping us with them during the migration processes. We were also people of faith and believed in the divine hand behind what was happening to us. I marched on and had a successful life at every step.

EB: So, you came to the University of Chicago?

HL: I came to the University of Chicago after I finished a master's degree at the University of Kansas. I planned to go back to India to work there.

EB: Your undergraduate work was in India?

HL: I finished the bachelor's degree in pharmacy in India. And after I completed the Masters of Science degree in Kansas, I wondered about further specialization so that I could do something innovative and progressive in India. I didn't want to be an ordinary professional. In those days, nuclear medicine was being talked about. Isotopes were being invented for medical research. So, I looked around and found that the University of Chicago was a pioneer in using isotope technology in medical research. And pharmacology department was the promoter of this new tool. I called the Chairman of the Department of Pharmacology, at the University of Chicago and told him I was a student planning to go back to India to work and wanted to take the isotope technology in medicine with me so I would like to pursue graduate work with him. As a result, he invited me to visit the department. I took an overnight bus from Lawrence, Kansas to Chicago, as I didn't have money for train or air transportation and stayed at the YMCA. After I visited the Department Dr. Lloyd Roth, the Chairman, accepted me as his graduate student and offered me a research fellowship. He asked me about my travel expenses and was surprised I could only afford overnight bus fare. He reimbursed me for my fare and expenses at the YMCA and said, if you would have told me, you could have come by more comfortable transportation. A few months later, I arrived at the University of Chicago as a graduate student. The University of Chicago was a pioneer in applying nuclear technology in research; the first Geiger counter was built there and the first scintillation counter was placed at the University of Chicago's Pharmacology Department for field testing. Scintillation counters were scarce and experimental. The manufacturer, Packard Instruments, put one in our department to provide data to help in further development. In the beginning the scintillation counter was not accessible to students, only to research scholars. Those were very primitive but expensive instruments. To measure radioactivity each tissue sample had to be dissolved in special scintillation fluids and counted manually along with bottles containing only the scintillation fluids to determine background levels. One had to spend long hours with the equipment to complete any experimental reading. I struggled but learned to determine drug concentrations in tissue using isotopes. Today's students are deprived of this learning because of automation.

EB: You helped build the machine?

- HL: I helped in the sense that I reported the faults and shortcomings I experienced. There were a number of modifications done; the scintillation fluid and counting techniques were improved to increase efficiency and specificity.
- EB: What year was this?
- HL: I started in 1958.
- EB: And, who was it that you worked with?
- HL: Dr. Lloyd Roth who worked at the US Atomic Energy Agency on contract at the Nuclear Laboratory off campus. My professor worked with Dr. Hassalback to perfect the technology of labeling drugs with radioactive isotopes. He had an MD and a PhD in chemistry. He pioneered work on the entry and distribution of drugs in the brain. He was the first to label drugs; the drugs he labeled first included meprobamate, urea, barbiturates, acetazolamide and Dilantin. I was the first to study the cellular distribution of radio-labeled meprobamate in the mouse, rat and cat at a cellular level in the brain without brain homogenization. When I arrived at the UC Dr. Roth and Dr. Barlow were using brain slices to study drug distribution; I established whole body autoradiography in the department. The technique was just developed in Sweden, a technique I inaugurated with the help of Dr. Ake Hangren, a Swedish pharmacologist who was visiting our laboratory.
- EB: Why were you interested in that?
- HL: I was always interested in the brain and the mind.
- EB: In the mind?
- HL: In the mind. I did not know anything about mind, but I did think that it was in the brain somewhere and, consequently, one should study the brain. I was going to research the brain, how external chemicals entered the brain and how the brain was protected from poisonous chemicals.
- EB: Do you know why you were interested in the mind-brain connection?
- HL: I was interested when I was a child and I was interested in it as an adult. I'm still interested in it. When you are educated you look at things in a different way than the layman does you want to ask why things happen.
- EB: To what religion does your family belong to?
- HL: Sikh. We're the smallest religion that started in India five centuries ago. There are about twenty-five million Sikhs in the world; there may be about half a million in North America. So, I told my mentor I'd like to study neuroscience with the help of radioactive isotopes. He outlined the research path for me. I was to study a psychoactive drug which affected the brain, trace it in the brain to learn how it entered and where it was distributed, and then how it impacted the structures and how that translated into behavioral changes. Labeling the drug molecule with an

isotope would help trace it. I loved that proposal and began studying how a drug overcomes hurdles to enter the brain, travels to its site of action, and then modifies the structure it is attracted to. When I joined the laboratory several others were engaged in similar research. My co-advisor Dr. Charles Barlow was studying the role of water spaces in the brain and their role in drug distribution. He tagged urea with isotopes for his studies. Dr. Roth asked me if I would study meprobamate and pentobarbital along with urea. I said yes, but I told him I wanted to first study pentobarbital's biologically more stable analogue, barbitol. Barbitol is not metabolized much in the body relative to pentobarbital which is far less stable. I thought this would also keep me busy until radioactive meprobamate became available. Dr. Roth was working on making meprobamate radioactive.

EB: Was meprobamate commercially available at the time you were studying it?

HL: It was commercially available but not in the radioactive form. It had just come on the market and was designated as a tranquilizer. I began to study radio-labeled barbiturates. We soon found there was binding to certain proteins in the brain that prevented its free movement. It was, thus, considered to be a dirty, unsuitable drug for studying parameters of drug distribution and the study was abandoned. Similar was the fate of Dilantin (diphenylhydantoin,) an anti-epileptic drug, as it was highly bound to brain structures. Well, in retrospect, ten years later, we realized we were overlooking a discovery. A binding site would be an indication of receptors being present for that molecule. At that time brain receptors were believed to be present only for endogenous chemicals such as neurotransmitters. A neuroreceptor for an exogenous chemical was unheard of. It was later on, with the discovery of morphine receptors, that the idea of drug receptors was entertained so we had missed credit for that discovery. To study receptor binding by the help of radioactive drugs was not conceived back then. You only predicted receptor activity from the physiological changes resulting from neurotransmitter release in the synapse. I have an interesting story to tell here. I applied for a post doctoral position to work with Dr. B. B. Brodie at the National Institute of Health. I had a lot of respect for him and his work on brain receptors for norepinephrine. I wrote to inquire if I could study the isotope labeled norepinephrine for its receptor binding and release properties in the brain. He replied that he would be happy to accept me in his laboratory but he did not understand why I would need to use labeled norepinephrine. He advised me to give up the idea as I could better study norepinephrine

release through methods utilizing fluorescence assays. He did not expect at the time that he would be changing over to radio-isotope technology in the future and his colleagues would win the Nobel Prize for using those advances. On the other hand, we in Chicago rejected drugs with properties of special attraction to brain components as a nuisance, when the studies were actually pointing to the discovery of drug receptor sites. Who would have thought in those days that exogenously synthesized drugs could have brain receptor sites. The brain receptors were thought to bind only to endogenous neurotransmitters. Then, in my research, meprobamate was to bind with brain membrane proteins, and so did pentobarbital. We found that first by using brain slices. Since meprobamate was labeled with tritium it could be localized with high definition. Thus, I ventured to develop methodology of cellular localization. I succeeded and produced the first cellular localization of meprobamate binding sites in the brain.

EB: What kind of animals did you work with?

HL: I worked with mice, rats, cats and monkeys. I started with kittens as they do not have a fully developed blood brain barrier. We studied developmental aspects of the blood brain barrier.

EB: And, you were interested in watching how things moved through the brain?

HL: First, from blood to the brain through a barrier; then, interacting with the outside surface of the brain cells before penetrating into the cell. For cellular localization we had to use tritium for labeling. In this technique a compound is exposed to high activity of radioactive tritium gas and as a result many chemical bonds are broken and others are labeled with radioactivity. So, we ended up with tritiated meprobamate in a mixture with numerous known and unknown metabolites that were also labeled and difficult to distinguish from each other only on account of radioactivity. If this mixture is used for study and radioactivity is measured one would not know if it came from meprobamate or any one of the metabolites. Such a study would be useless. Since the chemists in the department failed to purify meprobamate free of all labeled breakdown products, I began reading chemistry books to figure out a solution. Suddenly, something lit up in my brain. It occurred to me that I could employ a living animal to purify the drug. I injected the tritiated mixture into a rat, then collected the urine and isolated meprobamate from the urine. It worked and every one celebrated. I published this as a new method of purifying tritiated chemical compounds.

EB: Was there a thought that some of the metabolites might have activity, as well?

HL: Yes, but we were studying the brain distribution of meprobamate. Drs. Heller and Harvey in the same laboratory were studying the pharmacology and toxicology of meprobamate. That's how I started and finished my pharmacology at the University of Chicago in 1962.

EB: At this time, did you have a sense of what your overall objective was, or were you still thinking about going back to India?

HL: I was still entertaining the idea of going back to India and, hopefully, set up research labs to continue my work there. My professors in the department were supportive of my objectives except that my major professor wanted me to acquire competency in an additional research area before I would return. He suggested post doctoral training in neurophysiology. Meanwhile, I received a call from the Illinois Institute of Technology (IIT) asking me if I would work for the US Department of Defense to study biological warfare agents such as tetanus toxin, botulinum toxin, and other chemicals which paralyze the nervous system. The objective was to develop detection methods and antidotes. They heard I had expertise in detecting very small quantities of compounds. The Institute negotiated with the Defense Department a high salary and a promise of a fast track to obtain USA citizenship. The research was highly classified and needed high level security clearance and I could not be considered until I was a USA citizen. This was an attractive offer so I gave up the idea of going back to India and accepted the position while my professor was on summer holiday. I had not defended my PhD. thesis yet.

EB: How did you feel about the project?

HL: I felt I would be a pioneer to study biological warfare agents which affect the nervous system; they paralyzed it. I was not for killing people but I also knew that wars were inevitable. I asked myself, could one develop methods of safe warfare so nations could win without killing people. So, I joined others in the search for biological warfare agents which do not kill, but immobilize armies temporarily, so the USA could win. I assumed if you could expose the enemy to something through water, food, air or shooting from with special guns, so they become physically disabled or mentally disoriented in a reversible manner, a war might be won without bloodshed. For this purpose a new class of drugs was invented, called "incapacitating agents".

EB: Was it in your mind this would really be an opportunity to make a contribution in terms of changing warfare rules?

HL: Yes, I thought I could make a big contribution. The incapacitating agents may be used on armies, on hijackers, and on wild animals to temporarily subdue them.

- EB: And, it was so compelling you decided to stay and not go back to India?
- HL: Yes, I liked that job and I liked working on those possibilities, even though I had to work for the army. I was working for a purpose which would have saved lives without preventing war.
- EB: How did that work go?
- HL: I learned a lot and made discoveries for the army but they could not be disclosed to the public. My lab had many active chemicals available including LSD. Although it was done many years ago, the research still remains unknown. We worked with animals but accidental exposure to humans did occur occasionally and we learned about the clinical consequences of ingesting such a compound as well as drugs which were potent antidotes.
- EB: So you set up your own lab and started to do work that sounds very different.
- HL: Yes, it was different. I was doing pharmacology but very unusual pharmacology. When still working there I was offered a tenured position as Associate Professor at the University of Kansas, which I could not refuse. It was only three years after I was awarded my PhD and my classmates were still doing post-doctoral work. I considered the offer a great recognition of my scientific contributions and I accepted it.
- EB: How long were you at the D.O.D. job?
- HL: They hired me in 1961, a year before I finished my thesis, and I was there almost five years. At the University of Kansas I continued some of the Army contract work that was in the public domain.
- EB: Can I ask you a little bit about that work and its impact? I'm struck on what drew you to it, to make war more safe.
- HL: And protect your population if anyone uses those weapons.
- EB: Now we think about biological warfare in such a different way.
- HL: There is a lot of progress in chemical detection. If armies or terrorists groups use biological warfare agents in water or air, as is the case now, the methodologies to detect such chemicals will become important. There are chemical detection methods available but they are effective only if one knows the structure of the chemical being spread. My emphasis was to use biological systems which detect a biological change in the body rather than a chemical structure. The reason is that we cannot know which chemical was deployed. For chemical detection, you have to know the chemistry of the substance. You have to have a standard and you have to know the identity of the chemical employed. In biological detection systems you observe biological or clinical changes. You go directly to assay the biological effect which the toxin produces.

After I joined the University I changed my field to investigate drugs for substance abuse, Alzheimer's disease, depression, schizophrenia and aging. In academia, I was one of the first researchers to use haloperidol in research. At a CINP meeting I met Dr. Paul Janssen. We knew each other before through correspondence. Dr. Paul Janssen had discovered haloperidol and encouraged me to use the drug as a research tool, which I did extensively. There was a time when my friends thought haloperidol was named Haldol, after my name. Of course, that is far from the truth but people thought so because of my lead in research with that drug.

EB: Your work with LSD or other work you had done in drug abuse was what interested him?

HL: Drug abuse work, I started with morphine and its effect on the brain.

EB: At Kansas?

HL: There at Kansas. And, from Kansas, I moved to the University of Rhode Island. At Kansas, I stayed only two years, because my wife did not like life in a small community. She was born in Berlin and grew up in Chicago. So, I accepted an offer in Rhode Island, which was the best of both worlds, close to New York and Boston but home still in the small community of Rhode Island.

EB: And, you met your wife when you were in graduate school in Chicago?

HL: Yes.

EB: You got married then?

HL: In Chicago. She was working in the UC hospital, as a laboratory technologist.

EB: She had her own career then?

HL: Yes, when I was a student. After I got a job, she stopped working and raised three beautiful children. When I went to Rhode Island I got in touch with Paul Janssen in Belgium to visit him so that I could begin to know his research colleagues. He invited me to spend my sabbatical there. That resulted in my spending fifteen months in Beerse, Belgium where Paul Janssen invited me to set up drug abuse research laboratories. He had a challenge at hand. He was developing psychopharmacological and anti-diarrheal drugs that resembled narcotic drugs in structure. Law and order agencies suspected they might become drugs of abuse, sold on the street. So they were hindering the development of these structures as drugs for other conditions. Dr. Janssen had heard of my work which measured introceptive stimuli, meaning internal cues produced by drugs, in contrast to any external cue from the drug being injected. My trained animals could reliably indicate if the test drug produced internal cues like drugs of comparison. Should a drug not

produce any cue resembling those produced by a drug of abuse, it would be highly unlikely that people would abuse that drug. Or, if a test drug produced internal cues opposite to those produced by drugs of abuse, the subjects would reject that drug as aversive. Dr. Janssen provided unlimited facilities to generate reliable data that were acceptable by the FDA and corresponding agencies in Europe. We succeeded in our mission. I enjoyed my stay in Europe and my collaborative work with European investigators. I was invited to Beerse again to celebrate the 25th anniversary of my research contributions. They set up an exhibition of the publications from my work there.

EB: You were in Rhode Island when you went to do work in Belgium?

HL: I was a tenured professor in Rhode Island and visited Europe as a visiting scientist. I did work with addiction and addictive drugs in Rhode Island and continued to do so after moving to Texas. One aspect I remained continuously interested in at Texas, where I moved after Rhode Island, was to measure mental or subjective effects of drug withdrawal. In animals and in humans, the cold turkey part of withdrawal from drugs of abuse is well known. In "cold turkey" withdrawal very objective signs occur soon and wear off in a short time. However, the psychological effects of withdrawal begin early but continue for days and months and are considered responsible for relapses to abuse even after long drug free periods. In objective terms, these effects include aggressive behaviors, insomnia, violence and high anxiety. I began to study them along with the ability of environmental cues to elicit them. These effects were well known in humans but not studied in animals as we did not have models to measure either a pleasant or reinforcing effect or aversive effects. I chose to go into that area. NIH bought my ideas and supported my research continuously. In addition, there was support from industry. I found that in rats, after recovery from acute withdrawal, a protracted phase followed which included intensive aggression and anxiogenic internal cues. I developed objective methods of measuring aggression and anxiogenic internal cues in those animals. I tested environmental cues associated with those effects. They were known as conditioned or conditional stimuli in psychological terms.

EB: You saw it first in the animals?

HL: The first time I noticed this was when rats undergoing withdrawal were housed in group cages and they were nearly killing each other.

EB: When was it you started to ask human subjects about this and think about what it might look like in people, that kind of syndrome?

HL: I had a friend, Dr. John Karkalas, who was Chief of a psychiatric hospital in Rhode Island. He gave me a research appointment there so I could

observe mentally ill patients, including those who were drug addicts, undergoing treatments. In the hospital, in collaboration with others, I developed drug withdrawal rating scales for humans and tested some drugs for effectiveness in blocking the withdrawal syndrome. It was there I observed withdrawal anxiety in the addicts. I wanted to measure similar effects in animals but there was no animal model available to measure anxiety. This led me to look for animal models of anxiety where anxiogenic interceptive or internal stimuli that controlled animal behavior could be measured objectively. I was presenting a seminar on interceptive stimuli produced by narcotic drugs. At the end I mentioned that I was looking for an anxiogenic drug so that I may train rats to recognize anxiogenic cues or stimuli. A woman neuropsychologist contacted me and told me that pentylenetetrazol (PTZ) would be such a drug. She had observed her patients expressing high anxiety when given PTZ to precipitate certain EEG changes to study epilepsy. When she was doing research in epilepsy, she employed various drugs to cause the epilepsy like EEG. PTZ was one of the drugs. When she administered PTZ to humans, the volunteer subjects began to drop out of the study. They withdrew their consent. When she followed up she discovered they could not take the intense anxiety they experienced. Meprobamate blocked the EEG and anxiogenic effects of PTZ. It pleased me to no end. I was studying in my laboratory the internal cues produced by PTZ to screen antiepileptic drugs. This was a thesis project of my graduate student, Gary Sherman. Antiepileptic drugs failed to antagonize PTZ stimuli except those in the anxiolytic class. It was making no sense and we had to publish those data on that account. Now it began to make sense. I went back to the lab and trained more rats to discriminate PTZ cues and further develop the PTZ cues to investigate the biology and pharmacology of anxiety. Simply described, I trained rats to press a lever to obtain food in Skinner boxes. Then I injected rats with PTZ and put them in the test box with two levers. If the rat had PTZ in the body, the rat was trained to press one bar to get food. If the rat pressed the alternate bar no food was delivered. On another day, rats were injected with saline and required to learn to press the alternate bar to get food and not the drug appropriate bar. Gradually, the rats learnt to discriminate the internal cue produced by PTZ as different, than those produced by a placebo injection or injection of drugs from a different pharmacological class. Of course, the training and testing protocols required random designs as usual. So every day, either PTZ or saline was injected and the rat was placed in the Skinner box. When a trained rat selected a particular lever it was based upon whether the

rat recognized the internal stimulus as a drug stimulus or a placebo stimulus. It takes about a month to train the rats. Then, I could take these animals, make them heroin dependent and, during withdrawal, test them for anxiety placing them in the test boxes. If they pressed the PTZ bar after a saline injection they were indicating that they perceived the PTZ cue even when they were not injected with PTZ. It was concluded that heroin withdrawal produced a PTZ like stimulus which was anxiety like. Joined by many collaborators in Rhode Island, Fort Worth and Europe, I extensively studied PTZ, a GABA- A receptor antagonist and prototypical anxiogenic drug. First I developed it as the animal model of anxiety and then extensively utilized this and similar animal models in the study of anxiety producing internal and external cues and their treatments. Typically rats were trained to discriminate the interoceptive stimulus generated by systemic administration of PTZ. PTZ produces a reliable discriminative stimulus which is largely mediated by the GABA-A receptor. Several classes of compounds could modulate the PTZ discriminative stimulus including drugs purported to have anxiogenic properties, such as β -carboline carboxylic acid (BCCM) and FG 7142 (N-methyl-9Hpyrido[5,4]indole-3 carboxamide,) 5-HT_{1A} and 5-HT₃ agonists, NMDA, glycine, and L-type calcium channel ligands. If one subjected the rats to aggressive defeat in a home cage intruder test, following injection of saline, it resulted in a significant proportion of them generalizing to the PTZ discriminative stimulus. Spontaneous PTZ-lever responding was also discovered in trained rats during withdrawal from compounds with an effect on the GABA-receptor, such as chlordiazepoxide, diazepam, ethanol, morphine, nicotine, cocaine, haloperidol and phencyclidine. This effect was largely mediated by the GABA-A receptor, which suggested that anxiety might be part of a generalized withdrawal syndrome across drug classes. Infusion of midazolam bilaterally into the amygdale antagonized, in a dose-dependent manner, discrimination of the interoceptive stimulus generated by systemic treatment with FG 7142, which itself generalized to the PTZ cue. Furthermore, infusion of the GABA agonist, muscimol, bilaterally into the amygdale antagonized the PTZ discriminate stimulus in a dose-dependent manner. There are also important hormonal influences of PTZ. Corticosterone plays some role in mediation of its anxiogenic effects. There is a marked sex difference in response to the discriminative stimulus effects of PTZ, and estrogens appear to protect against its anxiogenic effects. A particular observation worth noting was the fact that by PTZ discrimination, I could observe quantitative symptoms of protracted withdrawal from drugs. Drug addicts are known to go back to the old

habits even after a successful treatment of cold turkey or immediate signs of withdrawal. The reason suspected was the withdrawal anxiety and the conditional stimuli produced by the drugs. These effects lingered on for a long time after the past abuse of a drug, thus producing a protracted withdrawal syndrome.

EB: How long does it take to resolve?

HL: Protracted symptoms of drug withdrawal could be measured for weeks and months depending upon the level of dependence. My animal model facilitated this study. This was a very exciting time for me; I had a laboratory method by which I could ask an animal a question that could be answered as yes or no without using human language even when the question was about the inner feelings of the animal. Of course I do not imply that animals have inner feelings that we can measure for sure. But interoceptive stimuli come to approximate them as closely as the objective measure may imply. We ask a patient; "How do you feel?" The answer may be, I feel very anxious. Animals cannot answer like that but they emit behaviors that are controlled by the central effects of drugs known to produce subjective effects in humans. From those we deduce the answer. I trained animals with nearly two dozen different drugs, which produce different states. Then I thought if I had a drug which causes schizophrenia I could train the animal to select a bar appropriate to the schizophrenia producing drug bar, once he knows it is a schizophrenia bar. I could produce animal models of hallucination, epilepsy or anything that produces specific interoceptive effects. One is not successful in every case, because drugs are not available to produce those states reliably. But if anybody discovers a drug which produces a mental state reliably, one could train animals to recognize it.

This line of research led me to other uses of drug discrimination methodology. I had a request to bioassay artificial sweeteners in laboratory animals to discover new sweeteners before they could be given to human subjects. I trained rats to discriminate very small concentrations of sweeteners. I was very disappointed in the beginning because I found that the sweetener aspartame, that was a peptide, was not recognized by a rat. I discovered later that the rat tongue did not have peptide taste receptors. They could detect any other sweetener except those with peptide based structures. Peptides which are sweet to humans are not sweet to animals. It took a long time, but we did discover that through animal studies. Others then reported through electrophysiological studies that the rat was a very peculiar animal as its taste receptors could not detect peptides though they detect every other sweetener.

EB: This is the first kind of animal model that you had built?

- HL: Yes, I did it for testing sweeteners and subjective stimuli produced by drugs, disease and lifestyles.
- EB: It's reminding me what you said about building a safer war, providing the means for war to be less risky, so it's a safer way to test new compounds because you can assess the mental state of animals rather than giving dangerous compounds to people; is that what you are talking about?
- HL: You may say that and my discrimination method could evaluate new chemicals that produce mind distorting effects. However I did not test those in my research. Developing biological war agents that are safe and discovering drugs against addiction, heart diseases and mental illness remain two different fields. But discovery is always exciting, no matter in which medical branch.

My research on biological warfare agents was limited as I could not do human work. These compounds had to be tested in humans. Further, Army research had to commit funds. But at least that research had potential for making this world safe.

When I visited Beerse, Belgium, colleagues of Dr. Janssen were using drug induced catalepsy as a preliminary screening tool for anti-schizophrenic drugs. The potential drugs were further tested in EEG studies and studies using brain self stimulation. I encouraged them to add drug induced stimuli as their screening methodology. Developing animal models for medical research was close to my heart.

In Rhode Island, I developed an interest in aging research. In collaboration with Dr. Kalidas Nandy of Boston University, I established a colony of mice for longevity study starting with calorie restriction and then studying drugs which increased longevity and reduced accumulation of lipofuscin in brain. Calorie restriction, Vitamin E and piracetam were found to reduce lipofuscin accumulation. I continued ageing research at the UNT Health Science Center at Fort Worth where I was appointed Chairman of the Department of Pharmacology and Neuroscience in 1980. This work was continuously supported by the National Institute of Ageing during my tenure in Texas and was continued by my colleagues under the leadership of Professor Mike Forster who started with me as a post-doc and was promoted to full professor before I retired. I began my research with brain reactive antibodies. One of the hypotheses was that neuronal tissue during long term wear and tear began to produce antibodies that were injurious to brain cells. The injuries thus produced may be responsible for brain damage resulting in loss of memory and other brain functions. I tested the hypothesis and combined it with calorie restriction; my research succeeded in attracting support from the National Institute of Ageing. The antibodies can be demonstrated in

blood and brain particularly during senility. Before retiring, in my last research, and my last publications were in the area of substance abuse in aging, as altered by calorie restriction. Before I left we were defining the effects of caloric restrictions and the mechanism of oxidative damage during ageing that was prevented by caloric restriction or caloric optimization. My last publications have been in those areas. We touched the area of genetic manipulation because caloric restriction showed widespread effects not specific to certain organ systems.

EB: What are you like as a lab manager?

HL: I enjoyed working with people. I worked side by side with close to a hundred colleagues who co-authored my papers. They included faculty members, visiting scientists, post-docs, graduate students and technicians. I spent long hours in the lab for most of my life except for the last few years when I stopped handling the animals. In the last years I spent more time playing with the data and writing. I helped develop software for research. The first software to automate programming of Skinner boxes was developed in my laboratory by two colleagues. As a matter of fact, we earned money on the software copyright.

EB: Where do your ideas come from?

HL: From what is going on in the lab. Close observation of behaviors in humans, experimental animals, tissue analysis and new data; all of them provided ideas. Some ideas also came from patients. Let me give some illustrations; When I was at the University of Chicago, I was counting radioactivity in tissue samples using a Geiger counter. In one experiment, the Geiger counter was showing contamination repeatedly in spite of my utmost care. Decontamination was a long, expensive and painful process. The contamination did not happen with the other students. I felt that either I was clumsy, which I was not, or there was something new. I then discovered with certain tissue samples containing urea-C14, the enzyme urease would break the urea and produce radioactive carbon dioxide that evaporated to condense on the electrodes in the Geiger counter. Through this accident I discovered the presence of urease in certain tissues. One example was the presence of urease in mammary glands, which was never reported before, and was not suspected to occur. Further, a new method of studying the distribution of enzymes in the body through whole body auto-radiography was developed. This was an accidental discovery through contamination of a Geiger counter. Some of the ideas for ageing research came via study of radiation damage to the brain that I was studying for the Defense Department. The radiation produced aging like changes and also produced free oxygen radicals.

EB: Most of your funding has been from NIH?

HL: Mostly NIH. I began with money from the Departments of Defense, Army and Air Force. I needed lots of money to keep my laboratory going. The State of Texas was generous with funds in those days which attracted me to that State, leaving behind beautiful Rhode Island. I was also funded by the pharmaceutical industry.

EB: From companies?

HL: From companies and from government. Even the Vietnam War was a factor. The Army was bothered by the fact that soldiers in Vietnam were being infected with malaria, caused mosquitoes. Available mosquito repellents had to be sprayed frequently. I developed an idea to look for a mosquito repellent that could be ingested orally to provide protection. If successful, one could extend the research to develop perfumes to be taken internally in order to impart long term fragrance to the skin. The US Army bought my idea and awarded a research contract to me. There was nothing out there on how to go about it. I began with feeding the known mosquito repellents to mice to test their efficacy in reducing mosquito bites. I soon realized that there was no animal bioassay available to evaluate mosquito repellents. I began placing a mouse in a closed chamber containing a known number of mosquitoes and then counted those mosquitoes that bit the mouse. Since only the female mosquitoes bite, I had to separate mosquitoes by gender through eye examination. All of this was a very tedious and labor intensive process. That led me to develop mechanical ways of separating female mosquitoes. In addition, I found that mosquitoes were after adenosine compounds such as adenosine mono phosphate in blood. So I could inject the radioactive adenosine compound and assay mosquitoes for radioactivity. Thus a bioassay was engineered where female mosquitoes were obtained and bioassayed for blood ingestion through the skin of living animals. That animal bioassay was capable of testing the effectiveness of oral mosquito repellents as well as oral products to be used to enhance physical attraction.

EB: You've done a lot of work that's very practical. This work has a lot of practical implications and applications. How do you think scientists should be sure things they discover are used appropriately?

HL: There are a few problems and one is in the discovery part. In my opinion, probability of discovery is higher when you go to unknown areas, an area that accidents can expose, because a lot of discoveries come through accidents in the lab or in humans. By accident I do not mean injury or death but something unseen or unexpected happening during the conduction of laboratory experiments. Most accidents in research

are ignored as nuisance and we do not teach new researchers to pay attention to every unusual thing happening in the laboratory. Actually one must be open to accidental observations. Then, the second point is, that if an accidental discovery is made, the scientist must be alert to its application in human life. Usually researchers sit on a discovery and publish papers, but fail to realize its application to benefit humanity. We must teach graduate students this aspect so they think of every new observation as an opportunity to obtain a patent and promote its utility for human benefit.

EB: Having patents is more accepted in academia now than when you started, I imagine?

HL: When it became difficult to obtain research funds, our academic institutions did become aware of this new source. They are developing a cadre of people who can go to researchers and dig into their daily observations to discover patentable findings.

EB: How did you learn that? Why do you think that way?

HL: It was inherited. Then my major professor in Kansas encouraged it. A close friend in the field of education, Dr. Ogden Lindsey, also encouraged me. Early on I also became interested in the biography of those scientists who made major discoveries. I was intrigued by the life of Dr. Hans Selye. I followed up the accidents that occurred in the lives of Nobel Laureates. Their Nobel Prize winning discoveries usually came from unusual and unexpected observations in the laboratory. To make those observations, one must be present in the laboratory and then have a curious eye. Then there are other approaches. Prof. Burns of England told me, before he passed away, that he read old papers published 30-40 years ago in the *Journal of Pharmacology and Experimental Therapeutics* and said "I don't believe it." Then he conducted experiments on the things he did not believe and found new and exciting things. Today, we discourage students from finding something unusual or different by saying that he or she should follow the protocol in the thesis proposal.

EB: So, you learned from the history of science?

HL: More accurately from the history of discoveries in science. I read about people who made discoveries by reading their life patterns and daily behaviors. From their stories I learnt that the best way of training graduate students in research is like you teach driving, by sitting next to the learner and pointing out opportunities for questioning the usual and accepting the unusual. You cannot teach a person how to drive by sending him into a room and giving him a manual. Professors should sit by the side of graduate students and post-docs in the laboratory. I do

not like the idea of providing faculty offices away from research laboratories. By the way, I taught a graduate course both in Rhode Island and Texas on Strategies to Scientific Discoveries. Such courses used to be popular in psychology curricula.

EB: You miss something in that?

HL: And, the final thing, I think we should educate people about scientists and their contributions to science. Many scientists ended up doing something different than they started on account of their keen eyes at observing the unusual.

EB: Educate the public about that. You ended up doing something different than you planned. You didn't become a physician. You didn't go back to India. Do you have regrets?

HL: No, I'm very pleased and grateful. I'm very pleased with my life. There are so many hardships and accidents that contributed to my maturity and progress. I wish there were twice as many. I am pleased my colleagues, my supervisors, people who hired me, appreciated my habits.

At an ACNP meeting a long time ago in Maui, I organized a symposium to report my research on the effectiveness of clonidine in drug abuse. Well, nobody ever thought a drug for hypertension would be useful in drug abuse. The ACNP appreciated my seminar proposal. They accepted it and we had a symposium. Similarly, I organized a symposium on The Brain Reactive Antibodies in Aging which was a new idea at the time. At a Neuroscience Society meeting in Miami a symposium of my work on animal models of anxiety was held to recognize my research. The professional community appreciated me a lot. I am pleased, flattered and very thankful.

EB: Do you have a sense of what's exciting for the future?

HL: I stay partial to brain sciences. Brain science is in a primitive stage and accidental discovery potentials are greatest because it is still a black box. So, we will accidentally discover many more things in brain sciences than anywhere else. In my estimation there is a great opportunity to make discoveries that impact learning, intelligence, Alzheimer's disease, senility, schizophrenia, Parkinsonism and other brain degenerative diseases.

EB: Are there things you don't like about doing in brain science?

HL: No, I like brain research both at the molecular level and at the level of behavior. Aging and Alzheimer's are my favorite subjects of interest because I am 75 and the probability of a diagnosis of Alzheimer's is increasing with age. Brain science is just beginning and the brain is a very mysterious organ. What we will learn from brain sciences will impact on many places in the body. I recognized faculty involved in eye

research as brain scientists because the retina is an extension of the brain.

EB: It sounds like those ideas are very useful to people.

HL: Although I am happy with the coverage of science in the lay press such as *The New York Times*, *Wall Street Journal* and *Dallas Morning News*, I would like to see more coverage and more space for science in the news media to arouse awareness among people about the contribution of scientists and academicians to human welfare. I often write to legislators for additional funds for neuroscience.

EB: Have you ever seen science distorted, as some people complain?

HL: No, I am of the opinion there will be less distortion if the coverage is increased. But, if you hide something, or are more cautious, public appreciation will be limited. Every magazine has an art and sport section but not a science section. It is encouraging that newspapers are slowly moving in that direction. Our *Fort Worth Journal* has a weekly column on science or medicine. *The New York Times* has a science section.

EB: Why do you think some don't have a science section?

HL: Probably the newspapers think there's not enough readership. I think they should write more in a common language and attract an audience. If they write more, people would be interested to read more. Our national associations should help science reporters. The Rockefeller Foundation had a task force I was a member of; it promoted reporting on religion. There should be similar programs from our national organizations such as ACNP, FASEB, ASPET and the Society of Neuroscience, to assist news reporters in this task. Grant programs should be created to help promote journalism in science.

EB: I don't have any other questions for you. Are there important things we haven't talked about?

HL: No, except if I have a chance to put a word in that I think the ACNP is an excellent organization. It contributed positively to my life and the life of many scientists. There is a drawback also. It is not open to many scientists. It is difficult to become a member and then it is not affordable to attend meetings, it is a high cost meeting. Those without large grant support are unable to afford to attend. I know that ACNP has been trying to permit added categories of associate members. Still, it is not enough and it is difficult to get a level of funding to afford to attend.

EB: Sure.

HL: I think scientists should live a life, at least the public part of their life, which reflects their concern for public health. If you go to the poster sessions of professional associations including the ACNP, you see

unlimited alcohol being served. Poster sessions are an opportunity to discuss science. It has been proven that after you have a few drinks, you're not in your right mind to discuss science and you're not social. I wrote the ACNP Council and they cut down on hard liquor at my request but unlimited wine and beer still continue to flow. If the outside world comes to know that scientists and clinicians who spend public funds to attend meetings, the purpose of which is to disseminate new research on drug abuse, schizophrenia and brain degeneration and are offered liquor by the organization every evening, it will be a demonstration of a disconnect.

EB: That's a disconnection, between the work you do and how you live your life. It's not helpful.

HL: Fortunately, the outside world doesn't know that.

EB: They should know more about what scientists are doing.

HL: And discourage serving alcohol at scientific functions.

EB: You're right. Scientists are not trained to recognize a connection between the biomedical questions they study and how they conduct their lives, or make impact on the world they live in.

HL: Thank you very much.

EB: Thank you.

SALOMON Z. LANGER

**Interviewed by William E. Bunney, Jr
Scottsdale, Arizona, December 8, 2008**

WB: I'm Dr. William Bunney. I'm from the University of California, Irvine. This is the Annual Meeting of the ACNP, 2008. We are in Scottsdale, Arizona and I will be interviewing Dr. Salomon Langer.* Tell me where you were born and something about your background.

SL: I was born in Buenos Aires, Argentina many years ago and my family came from Poland. In fact, they immigrated to Argentina in the early 1930s and this is how they were saved from the Holocaust during the Second World War. I went to school in Argentina and graduated as a medical doctor. After my internship I came to the United States on a Rockefeller Fellowship and got my post-doctoral training in pharmacology at Harvard with Ullrich Trendelenburg for four years, to be followed by two years in Cambridge, England with Marthe Vogt. That explains, to a large extent, my early interests in autonomic pharmacology, transmitter release and in drugs acting on these systems.

WB: Do you want to tell me a little more about your mentors?

SL: I was very fortunate to do my doctoral thesis in Argentina under Dr. Bernardo Houssay, who won the Nobel Prize for Physiology and Medicine in 1946. My biggest chance was when I hit the jackpot with Ullrich Trendelenburg at Harvard. I was the only post-doc, so I had him full-time for the first year and it was so much fun and enjoyment I stayed for nearly four years. By the end of my stay at Harvard my main interest was working on norepinephrine release, and this is why I went for two years to Cambridge, UK to become familiar with the appropriate laboratory techniques used in this research. Having Marthe Vogt, a well established and famous pharmacologist, as my tutor was another jackpot and I'm extremely satisfied and happy that my training happened this way.

WB: You really had an incredible experience, in terms of your training and mentors. Can you tell me what was psychopharmacology like at that point in time?

SL: Most of my studies on norepinephrine release were carried out on peripheral tissues. At that time I was beginning to cross the blood brain barrier and became interested in the CNS. I knew full well it was extremely complicated but nevertheless made up of many similar units as in the peripheral nervous system.

WB: What years were these?

* Salomon Z. Langer was born in Buenos Aires, Argentina in 1936.

SL: This was in 1969; the period at Harvard was 1963-1967 and Cambridge, England was 1967-1969. It was then that the idea of regulation of norepinephrine release developed and I moved back to Argentina for seven years. I started the Institute of Pharmacological Research at the University of Buenos Aires and published the first papers on presynaptic receptors and their role in the regulation of neurotransmitter release, in that case norepinephrine.

WB: Who were some of the scientists that had a major impact on you?

SL: In addition to the mentors I named before, I must mention Julie Axelrod, and I had the privilege of meeting, Sir Henry Dale while I was in England, J. H. Burn and many of the pharmacologists at Oxford, which maintained a superb department of pharmacology. At Cambridge I worked with Leslie Iversen for one day a week.

WB: When he was with Merck?

SL: No, this was before that, at Cambridge University between 1967 and 1968.

WB: That was long before Merck.

SL: Yes, absolutely. So, these were the scientists that influenced me but, in addition, I must mention Norman Weiner; while I was at Harvard we did some work together.

WB: And, with Julie Axelrod, what interactions did you have?

SL: Julie visited our research laboratories in Buenos Aires in the early seventies and subsequently when I worked at Wellcome, UK, I received a Guggenheim Fellowship and spent time at NIH with him.

WB: When was that?

SL: That was in 1976.

WB: I was still there at the time. Were there other scientists you were interacting with that were critical?

SL: I must mention Jim Black and John Vane. Jim Black, because he was pioneering the classification of sub-types of receptors when I discovered the α_1 and α_2 receptor sub-types. It seemed unusual to me that an alpha receptor agonist would inhibit release of norepinephrine which acts on the same postsynaptic alpha receptors producing vasoconstriction. By carefully categorizing these alpha receptors, it turned out there were two different sub-types. In 1974, it was the first description there were α_1 , α_2 subtypes based on physiological evidence and the relative order of potencies of agonists and antagonists. It took about twenty years more for these receptor subtypes to be cloned, expressed and characterized by molecular methodology that confirmed α_1 and α_2 receptor subtypes were completely different classes of receptors with different second messengers and additional subtypes, namely α_1 , α_{1a} , α_{1b} and α_{1d} , and for α_{2a} , α_{2b} , and α_{2c} subtypes.

WB: So, your initial papers were really landmark publications.

SL: In fact, the 1972 paper on Presynaptic Receptors was chosen by the British Pharmacological Society, as one of the 35 most important published by the *British Journal of Pharmacology* during the past century.

WB: Fantastic!

SL: Yes.

WB: What were the early drugs you worked on?

SL: Of course, they were acting on α_1 and α_2 receptors as agonists or antagonists. There were not enough α_2 subtype drugs early in the game except for clonidine and yohimbine and they were not sufficiently selective. On the other hand, α_1 agonists like phenylephrine and antagonist drugs like prazosin were quite selective for α_1 subtypes. Thanks to those drugs, I could characterize the two sub-types of receptors. Then we asked whether norepinephrine release was modulated by presynaptic receptors and if that phenomenon could be observed for other transmitters as well. It turned out that in the central nervous system, dopamine release like norepinephrine release was equally modulated presynaptically. For dopamine the presynaptic receptors are of the D_2 and D_3 sub-type and we moved on to serotonin and acetylcholine which also possessed presynaptic modulation of release. The receptors were specific 5HT_{1D} for serotonin and M_2 for acetylcholine. These were called auto-receptors because they were activated by the transmitter released from the same neuron. In other words, the transmitter release was not acting only presynaptically on specific receptors to activate or inhibit the postsynaptic neuron, but it was acting also presynaptically to modulate the release of the transmitter according to the information generated in the synaptic cleft by the concentration of the released transmitter.

WB: So, it set up a model paradigm for the whole field.

SL: Exactly. Subsequently, it was discovered that GABA and glutamate have also presynaptic, receptor-mediated control of transmitter release. Therefore it appeared that presynaptic modulation of transmitter release is a general phenomenon whereby nature possesses a regulatory mechanism for fine tuning the release of most transmitters, mediated through presynaptic receptors. Of course, the presynaptic receptors are different from the receptors located postsynaptically and this offered new opportunities for drug discovery.

WB: The physiological knowledge about chemicals led to the discovery of drugs. What were some of the drugs you discovered and worked on?

SL: In France, during the 23 years I spent at Synthelabo, the drugs that reached the market are the important ones; many compounds advanced only part of the way and then were abandoned for different reasons.

WB: Yes.

SL: But, I would like to single out aripiprazole which is an antipsychotic because it has a partial agonist effect on the presynaptic dopamine autoreceptor. Of course, this is not the only effect of aripiprazole because it blocks postsynaptic dopamine receptors and it acts on 5HT receptor subtypes as well. The advantage of aripiprazole is that it does not increase plasma prolactin, because it is a partial agonist on presynaptic dopamine autoreceptors, while prolactin levels are substantially increased with most anti-psychotic drugs. Another example is mirtazepine, an antidepressant that blocks adrenergic α_2 receptors in the central nervous system and that increases the release of norepinephrine. It is also known to increase serotonin release, because serotonin nerve terminals possess α_2 receptors that inhibit serotonin release and when you block them with mirtazepine the release of serotonin is enhanced. Therefore, blocking α_2 adrenoceptors in the CNS increases both norepinephrine and serotonin concentrations in the brain, and it is widely accepted that in depression there is a deficit in both noradrenergic and serotonergic transmission.

Another example, to stay with drugs that reached the market, involves compounds for the treatment of migraine. These are sumatriptan and its analogs that are effective because they stimulate 5HT_{1D} receptors located presynaptically; when stimulated by agonists it inhibits the release of substance P and CGRP, which are important in inflammation and pain. Of course, sumatriptan and its analogs also stimulate 5HT_{1D} receptors in vascular smooth muscle and so both presynaptic and postsynaptic components contribute to the anti-migraine effect of these drugs which are used extensively.

WB: So, your preclinical work on presynaptic receptor had a broad effect but also a major impact on the whole field of partial agonists and on the modulation of other neurotransmitters.

SL: Yes.

WB: What was your specific role in some of the drugs that reached the market?

SL: In some cases I was involved as a consultant in the drug discovery projects. In other cases these events developed spontaneously in competitive pharmaceutical industries because the existing publications pointed to opportunities in drug discovery.

WB: Based on your pre-clinical work?

- SL: Based on information that was published, and because it seemed reasonable to assume that such strategies would yield novel compounds with useful therapeutic properties, and hopefully, with fewer side effects because the pharmacological responses of pre-synaptic drugs are gradual and moderate while an effect originating post-synaptically may be of greater biological significance. Although, this is a speculative statement it is likely that side effects of presynaptically acting drugs may be fewer or less severe than those from drugs acting at the level of the classical postsynaptic receptors.
- WB: In your basic, pre-clinical work, were there novel technologies you developed necessary to do the work you describe?
- SL: The technology of transmitter release from peripheral organs was quite straight forward and almost classic, particularly transmitter release from the perfused spleen and the heart. I developed special techniques for the cat's nictitating membrane, which required innovation and it became, a very useful preparation. In the CNS, you have to work with slices of different brain regions, all with presynaptic receptor modulation of transmitter release so you have to choose the areas of the brain rich in the transmitter you are targeting; in the striatum or putamen for dopamine; the occipital cortex for norepinephrine and the frontal cortex for serotonin. It all boils down to having a very richly innervated area of the brain as a model. But, then, you have to compare your findings to other areas of the brain and make sure that the interaction you are describing is present in areas relevant to a particular disease and to drug therapy. So, it requires patient work that involves several brain regions.
- WB: If you had to list your major discoveries what would they be?
- SL: I would definitely single out the discovery of presynaptic receptors. We made our first report in the early 1970s and then the subclassification of the alpha receptors into α_1 and α_2 subtypes in 1974. In 1976, the concept of co-transmission, namely, that one neuron may release more than one transmitter. That was done in 1976, and carefully demonstrated with both in vitro and in vivo physiological and pharmacological methodology for ATP and norepinephrine. The concept of co-transmission has grown and it does, indeed, exist in the central nervous system in addition to the periphery. We still need to learn more about it, but it is relevant to the regulation of neurons and their communication with each other by more than one transmitter. There is always a main transmitter and the secondary co-transmitter may have an effect only at certain frequencies of nerve stimulation.
- WB: Who else was in your field making major contributions?

SL: In the area of co-transmission, it is essential to mention Geoffrey Burnstock from University College in England, who, at the same time, proposed the concept of co-transmission in a highly quoted article in 1976. In presynaptic receptors I would like to mention Klaus Starke from Germany, who not only started publishing on the subject in the early 1970s, but continued working for three decades on presynaptic receptors in the peripheral and in the central nervous system. As far as receptor subtypes are concerned, the finding of subclasses of alpha-1 and alpha-2 adrenoreceptors I reported in 1974 was important because it happened at the time when alpha adrenergic receptors were universally believed to be of a single category. This finding triggered interest in exploring for subclasses and subtypes in other receptor systems. That was long before the development of molecular biology and the possibility to clone and express receptor subtypes and carefully characterize many of them, which offered new targets for original drug discovery by finding selective agonists, partial agonists or antagonists.

WB: It is hard to estimate how many years it will take to look for drugs that have specific receptor subtype action.

SL: Absolutely. This became, in most rational drug discovery strategies, a powerful tool and remains a very important approach.

WB: How did you balance your research, administration and industry consultations with your other activities?

SL: It is very time consuming to have the number one responsibility for research and development for a large pharmaceutical firm, which was Synthelabo in France. Today it is Sanofi-Aventis, number three worldwide, even bigger now because of different mergers since I left in 1999. There are administrative duties, there are political issues and there is the science. And, unless you leave the top priority for science, you risk getting involved in and paralyzed by administration and politics. The only way for me to survive was to make science a total priority, to stay very close to the lab and to minimize or delegate other activities to allow for the survival of creative research.

WB: I see.

SL: Even minimizing administration it is almost an impossible task to stay up to date with everything that happens in science and navigate towards originality and innovation that address unmet medical needs. For instance, in depression, there are two unmet medical needs. One is the latency period, which is three to four weeks before the improvement in clinical depression is significant, while side effects appear within 24 hours of drug administration. Shortening the latency period may keep researchers and psychiatrists interested in drug discovery. The other

issue in depression is drug-resistance; although we have drugs that are superior to placebo, there are still about 40% of non-responders to the first antidepressant. When you have a non-responder after four to six weeks of treatment, you have a difficult problem; to decide on adding a second drug or replacing the first drug and waiting again.

WB: Tell me more about your experience with the industry.

SL: I was fortunate and very successful, and that is why I stayed 23 years with the same company.

WB: You had an important position.

SL: Yes, I was fortunate because when I joined Synthelabo in 1977 they were small, number 81 worldwide, but very keen on growing and developing into an internationally competitive pharmaceutical company. Today Sanofi-Aventis is number three, worldwide.

WB: What was your position?

SL: I was Director of Biology when I joined and ended up as President of Research and Development.

WB: This covered all fields?

SL: Including chemistry, biology, toxicology, and clinical pharmacology.

WB: So, this involved very heavy administrative responsibility?

SL: Yes, but I delegated by choosing people whom I could trust and were competent. But you cannot delegate too much and so there is a degree of pressure. During this period I had the freedom to recruit, expand and take decisions that made the company competitive internationally and five drugs were discovered, developed and marketed. Today, they are best sellers like zolpidem which is a sleep inducer called Ambien in the USA, to only mention one. It is the best selling hypnotic drug, worldwide. In Europe it is called Stilnox.

WB: Two major compounds.

SL: One compound: Zolpidem, with two commercial names: Ambien and Stilnox.

WB: They are still used today?

SL: Yes, and this is true for other drugs from this period. So, I must say, that this was a highly stimulating experience. The many years I spent in universities before joining industry were useful to the extent that I developed and worked on research projects relevant to transmitters, receptors and receptor subtypes that offered appropriate targets for novel drug discovery. Working in industry provided an opportunity to add a strong input from medicinal chemistry and the necessary organization to develop and advance candidate compounds which was very fulfilling.

Since I retired from that position, I have two small companies that synthesize compounds in projects of drug discovery for the central

nervous system; they are in the early stage, mainly in medicinal chemistry and preclinical evaluation.

WB: Tell us about those two companies.

SL: One is based in Stockholm with the Karolinska Institute and we have a patent on the use of the central α_2 receptor antagonist idazoxan for treatment of drug resistant depression, particularly non-responders to serotonin uptake inhibitors.

WB: In what Phase of development is that?

SL: Phase II, clinical studies; at the level of proving its efficacy in non-responders to serotonin uptake inhibitors.

WB: What is the name of this company?

SL: Alpha 2 Pharmaceutica AB. AB stands for a registered company in Sweden. The second company is based in Tel Aviv and also linked to drug discovery in the central nervous system. We have two projects, one on anti-depressants and the second on sleep inducers with the aim of discovering the successor to Zolpidem, which has been a great success but its patent life ended two years ago so it has been replaced with slow release Zolpidem. Considering the success of Zolpidem, there is still room for improvement with a similar compound in the treatment of insomnia.

WB: Where are those two new drugs at this point?

SL: Still at the preclinical level. We are not even sure whether we have chosen the best candidate, so we are still synthesizing analogs in those chemical series.

WB: How do you manage these two companies. You also have a place in London as I remember?

SL: We live half in London and the other half in Tel Aviv which allows me to be in close touch with the scientists who work in the Israeli company, Euthymia, Ltd. In Sweden, my partner is also a member of the ACNP, Torgny Svensson, professor of Pharmacology at the Karolinska.

WB: You've known him for many years?

SL: Yes, many, many years.

WB: When did you become a member of the ACNP?

SL: In 1984.

WB: Who were the key people in the ACNP at the time you joined?

SL: One is talking to me right now and another was Solomon Snyder, for whom I have a lot of admiration. Of course, Menek Goldstein, who I knew for many years but unfortunately is no longer with us, and Arvid Carlsson who has been an inspiration for my work in this field and to whom I feel indebted for advice throughout those many years.

WB: I think he has a company also in this area.

- SL: Yes, but for dopamine.
- WB: But, the concept is similar?
- SL: Presynaptic modulation. Arvid is very supportive and has always recognized the significance of my discovery of presynaptic receptors.
- WB: Why were these people key for you?
- SL: They were inspirational because of their creative research. Also, I was coming every year to the ACNP meetings which were stimulating and motivational events, because they allowed me to listen to excellent science and to present as well. Also to discuss informally, with plenty of time, many issues relevant to ongoing research and future projects.
- WB: Were you ever on any of the ACNP committees?
- SL: As I was a foreign member, I wasn't involved in committees.
- WB: Was there any impact of ACNP on your work?
- SL: I presented my work at the ACNP on several occasions and one was the first Earl Usdin memorial lecture many years ago.
- WB: I recruited him to Irvine before he died, for about 5 years. Are you happy with the way things have turned out for you?
- SL: Yes, I am. First of all, I was lucky to have chosen promising and interesting problems in my research and to have benefited from excellent guidance and mentors in my career, including the privilege of working with Ulli Trendelenburg at Harvard and Marthe Vogt in Cambridge.
- WB: It's not by chance you picked those people.
- SL: When I was with the Rockefeller Foundation they sent me to visit Yale and Harvard and both accepted me, so I had to make a choice and it ended up being Harvard, but Yale would have been superb as well. I had access to great places for training, experience and guidance which had a tremendous impact on the rest of my career.
- WB: Where do you think things are going in the next five years?
- SL: I could make predictions and probably be wrong, because it is very hard to predict the future; however, I think there are a number of psychiatric diseases where improvement of existing therapy is desirable and possible. I have mentioned two unmet needs in depression and I think progress may be made in the coming 5 to 10 years. Regarding difficulties in clinical responsiveness to the cognitive deficit and the negative aspects of schizophrenia, new antipsychotics may improve efficacy. Neurological and psychiatric diseases are likely to benefit from novel therapies but it is difficult to reverse the process of neurological degenerative diseases although it is not impossible and it would represent a major breakthrough if in Parkinson's and Alzheimer's disease it became possible to reduce the progress of the diseases. Of course that is a very tall order and it may take a long time. Also, genetics is having an impact

on neurobiology and although this is not reflected yet in specific gene therapy, that time will come and it may be sooner than expected.

WB: Are there any other areas you would like to cover that I haven't asked about?

SL: It only remains to add among the people from the ACNP that were influential in my career George Aghajanian, from very early on, was interested in my work and himself characterized the somatodendritic autoreceptors pharmacologically in the mid 1970s; it is always a source of stimulation and motivation to discuss science with him.

WB: Any other things you want to comment on?

SL: I would like to say in closing that although there are areas in drug discovery that could be improved, drug discovery is becoming a very expensive because of the technology, and because there is no place for "me too" drugs, so the only type of medication to incorporate into the market is a new drug that is effective for unmet medical needs or has superiority over available drugs in treatment of a disease. Therefore, although the price of drugs may be a very sensitive issue, drug discovery would benefit from a longer patent life to provide an enhanced return on investment in research, without punishing the public that has to buy these drugs at the pharmacy. I'm not against generics, but innovation and drug discovery need to be supported and encouraged.

WB: I find that a very interesting suggestion. I've been interviewing Dr. Sal Langer, one of the giants in neuropsychopharmacology, and I'd like to thank you very much.

SL: Thank you very much for your time, your dedication and our long lasting friendship, which I appreciate very much.

WB: I enjoy very much our friendship too.

STEVEN MARC PAUL

**Interviewed by Thomas A. Ban
Waikoloa, Hawaii, December 12, 2001**

TB: This will be an interview with Dr. Steven Paul* for the archives of the American College of Neuropsychopharmacology. We are at the 40th anniversary of the College in Hawaii. It is December 12, 2001. I am Thomas Ban. I think we should start at the very beginning if you could tell us when and where were you born and something about your education?

SP: I was born in Chicago, Illinois on November 2, 1950, so I am just 51 years of age. I grew up on the south side in a suburb of Chicago 25-30 miles south of the city. My family was born and raised in Chicago and I went to grade school and high school in a town called Flossmoor, south of the city. I struggled a bit in high school but was very interested in playing rock and roll music. I played drums in a band every weekend. During my junior and senior years of high school, I started to get interested in science and took advanced placement biology. I'm not sure how I got into it frankly, because I was a pretty average student. I did well in that course; it's interesting how teachers play a very influential role in your life. I also worked in the office of a pediatrician. His name was Dr. Sullivan and I also worked with a Dr. Goldberg, my family pediatrician, who took me under his wing. I did urinalyses, eye tests and a bunch of different things in the office. It was a lot of fun and I even sutured a few lacerations. He took me on rounds at the hospital and for a high school kid that was pretty impressive. I went to my high school college counselor and I said I wanted to be a doctor and he replied we're going to have to figure out a way to get you into college. So I went to Tulane University in New Orleans and it was an interesting experience because I had never been in that part of the country, I didn't even know where New Orleans was. I became a pre-med at one of those southern undergraduate colleges. You were at Vanderbilt, so you know Tulane and Vanderbilt are very similar. I decided I to study hard and become a doctor. So, like all overachieving pre-meds, I worked hard and got very good grades and applied to medical school after only two years of undergrad. I got into Tulane Medical School and a couple of others, but I elected to stay at Tulane. I went thinking I was going to be a surgeon and took Gross Anatomy the summer before I went to medical school so I could be a teaching assistant in my first year of medical school. That was a horrendous experience. Having to work day and night in

* Steven Marc Paul was born in Chicago, Illinois in 1950.

the anatomy lab in New Orleans in the summer was just too much. I decided that was probably not the route to go but I connected with a very unusual psychiatrist. You probably know him, Bob Heath.

TB: I do.

SP: Bob was an extremely dynamic, charismatic person. He was a student of Rado at Columbia, a psychoanalyst, although he was more of a surgical type. He worked on the Greystone project, one of the early programs to look at subcortical regions of the brain and their functions. These were the years people didn't know exactly what each brain region did. I spent time following Bob around; it was unusual for a young student to be interested in the brain. I went to the operating room with him while the neurosurgeon he was working with was putting depth electrodes in various brain regions. It was fascinating and amazing; nobody will ever do those experiments again. Bob would interview these patients just like we're sitting in a room now, and up on a screen would be the EEG of the amygdala, the hippocampus, the cortex and, when you invoked certain emotions during the interview, you'd see the amygdala go zoom, zoom, zoom, just like that. Of course, Bob had lots of theories about what brain functions were subserved by the different regions. He was a very energetic and passionate guy. He approached science very much like a physician. He didn't really test any hypotheses. He knew the right answer. He knew the cause of schizophrenia and it didn't matter what the data said, he knew. But he had an enormous impact. He was very charismatic guy, a tall handsome man all the women loved, who had five kids, a big house and a big farm; just a fascinating character. We could spend an hour talking about Bob Heath stories. He was incredible, one of the youngest chairmen of psychiatry in the country, about 30 years old, when came from New York to New Orleans and got involved with Huey Long and all the other funny stuff in New Orleans. Some great Walker Percy books were written about Bob's kind of character. So he really got me excited about the brain. I met another person you know well from down there, Don Gallant, he and I became very good friends.

TB: I know Don, of course.

SP: Don was a wonderful mentor. I often regret not telling Don how good a teacher he was. He cared about his students, cared about them deeply and had an enormous impact. The two of them were very different in terms of style and what they provided, but both were extraordinarily impactful on my career. That was a very important formative period and I knew when I was a first year medical student I was going to go into psychiatry and neuroscience. I met another student with whom I became very

good friend as a freshman. She was the oldest student in the class who came to medical school at 38 or 39 years of age and I was the youngest in the class. She worked with Arnie Mandell in California and before that with Jonas Salk, she was Salk's technician. She was also good friends with Julie Axelrod. And she told me, you know Steve, if you want to be a scientist, you should go work with Julie Axelrod. Well she had me go work with Arnie Mandell for a summer or two. So I went to La Jolla and followed Arnie Mandell around. He was a wonderful, energetic, mentor and I don't think I've ever met anybody quite as bright as Arnie Mandell, with an incredible, incredible mind. In the few months I was there, I did some research. We looked for this enzyme, N-acetyltransferase in the brain and N-acetylate serotonin which I think to this day is an important enzyme, even if not as well studied as many of the other enzymes. And we published some work just from the few months of work I did there. I spent a really impactful summer in Julie Axelrod's lab at NIH that was unbelievable. Julie had just won the Nobel Prize and I had the bench right next to his desk. Joe Coyle was there and Roland Ciaronella was in the lab. Just a remarkable group of people and all of Julie's boys would go to lunch every day with him and that was very exciting. I knew then I was going to come back to NIH, but I had to finish medical school. In my senior year I bumped into Danny Friedman. Danny came to New Orleans and we had lunch at Antoine's. He recruited me to be a resident at the University of Chicago. I graduated early from medical school, did six months of neurology internship at Charity Hospital in New Orleans, and then went to the University of Chicago as a psychiatry resident. We had a small class. Bob Freedman who is in Colorado, was in the class and a bunch of very good people. It was a very exciting department in those days. Herb Meltzer was there and Heinz Kohut, the analyst, Bob Schuster and many others. A tremendous department Danny had pulled together, a small but extraordinarily fine department. I worked with Danny in the lab and a couple of other of his people including Angelos Halaris and Herb Meltzer. We worked on some deaminating enzymes that were responsive to LSD and Herb and I, in that one year, published five or six papers. I also worked with him on effects of neuroleptics; we looked at prolactin levels at the Illinois State Psychiatric Institute where Herb was, although he was affiliated with the Department of Psychiatry at the University as well. I spent a wonderful, wonderful year there and became very close to Danny Friedman. He was sort of my psychiatric father. I had such wonderful mentors, Bob Heath, Don Gallant and Danny Friedman. Then I went to Julie Axelrod's lab but, if I ever needed advice on anything, I would

call Danny. I was in Axelrod's lab for a couple of years and worked on two projects. The first was on the metabolism of estrogen and the formation of catecholestrogens. These are dihydroxy catechol derivatives of estrogen, the result of P450 enzymes that were thought to be only present in the liver, but we showed the brain also had a P450 enzyme that metabolized estrogen to catecholestrogens. That was the project I worked with Julie and we showed that metabolic pathway the first time. Then I started work, while still in Julie's lab, on GABA receptors. After two great years in the Axelrod laboratory I went over to Fred Goodwin's lab and finished my clinical training so I could become Board certified in psychiatry. I also began my independent research career working in Fred Goodwin's branch.

TB: Are we in the late 1970s?

SP: Right. I got a little lab, a couple of modules in Building 10, a couple of floors above Julie's lab. I became involved in some clinical but mainly basic research. That lab grew and grew until Fred became the Scientific Director of NIMH intramural program and I became a lab chief with Candace Pert and John Tallman. They were independent investigators who had their own sections, while I had mine. I continued to work on three or four different projects defining the role of GABA receptors and the mechanisms of action of benzodiazepines. The three really noteworthy contributions I made with my collaborators in those years was that we pinned down that benzodiazepines worked through the GABA receptor systems, that barbiturates, particularly the anesthetic barbiturates, worked through this GABA system, and provided very good evidence that ethyl alcohol produced much of its sedative and anxiolytic effects, through the GABA-A receptor. We developed some microsac preparations to demonstrate this and found some imidazo benzodiazepines could block the effects of alcohol. We had a couple of very highly visible papers. Finally, one of the contributions I'm most proud of is that we described some metabolites of progesterone, allopregnanolone as well as one of the minero-corticoids, and showed that these steroid hormones, instead of interacting with the classic nuclear steroid hormone receptors, interact with a GABA receptor. We called these neuroactive steroids which have become a very interesting area of research. These steroids can be made in the brain de novo or progesterone can get into the brain from its peripheral sources. In animals, there is a significant amount of progesterone made by the adrenal gland, and after entering the brain when metabolized it produces these sedative, hypnotic, antianxiety steroids. We described this in a *Science* paper in 1986, and it became one of the more highly cited papers of my career. One of the

exciting things that happened about a year ago was that, based on the citation count of the ISI, in the last 20 years, I was one of the top 50 most cited neuroscientists. This is a very exclusive group of people; Sol Snyder, Arvid Carlsson and Paul Greengard are among them. So, I was very pleased.

TB: Can we go back to clarify the chronology of events. You became lab chief in the mid-1980s.

SP: Right.

TB: And you were a very active chief and did several important projects.

SP: Yes, a couple of very interesting things which are relatively unknown about my career, but something I'm proud of, is that I had a clinical and a preclinical program. We did clinical research in schizophrenia. I worked with a number of very good clinical investigators at NIMH. We started imaging studies, tried to image the benzodiazepine receptor and also, using cerebral blood flow techniques, to look at the effects of benzodiazepine receptor agonists and antagonists. We did a lot of in vivo imaging in animals to set the stage for these studies. We studied the patients both in the affective disorders arena and in schizophrenia. So it was an extraordinarily broad research program I led. In retrospect, I probably worked on too many problems but it was fun. I have an attention deficit disorder when it comes to science!

TB: This was around the time the receptor assays came about, right?

SP: Exactly. So we used those assays and discovered a number of new receptors for the dopamine transporter. We did studies on the binding of tricyclic antidepressants to the serotonin transporter, and Sal Langer published a wonderful paper in *Nature* showing *An Imipramine Receptor in the Brain*. We found, Sol would hopefully verify this, that imipramine could be labeled with tritium and bound to the serotonin transporter.

TB: It seems that we skipped some of your early contributions. The first paper of yours I read was with Don Gallant.

SP: We did some work with Don on a couple of things. I did a review article with him on the cardiotoxic effects of tricyclic antidepressants and Don was a very scholarly person, so we published that in a book. We studied some schizophrenic patients and gave them Deanol which supposedly was a cholinergic type drug in the brain. Bob and I published a paper together on trying to map pathways from the cerebellar vestigial nucleus to the forebrain. He had some notions about the cerebellum, and today I think some of his ideas have turned out to be pretty correct.

TB: Didn't you do some work also in immunology?

SP: We did some immune work too. I got back into that at NIMH, looking for immunological stigmata in schizophrenics, and we found some interesting things. We never could quite pin down whether they were related to schizophrenia but we did publish some nice papers on that.

TB: Let's get back to the work at NIMH you were talking about.

SP: One of the other things I did at NIMH which was unusual and maybe a result of the times and salaries wasa I started to see patients. If you look at my career, you'd say this is a guy who has principally done research, but for a good 15 years, I had a fairly significant practice of psychiatry. I had a home office, and saw patients virtually every Saturday, Tuesday and Thursday evenings. These were principally depressed patients but I also had a few schizophrenic and bipolar patients I saw in combined psychotherapy and pharmacotherapy. In those days, Washington was populated principally by very good analysts but not very good or comfortable prescribing medications, like lithium, neuroleptics or antidepressants. This was before the SSRI's were even introduced, so a lot of tricyclics and monoaminoxidase inhibitors were used. I practiced a bit with Fred Goodwin and saw a bunch of VIP's from time to time. In fact, Nate Kline sent me a bunch of patients. Way back I worked on some folks in sort of consultation with Frank Ayd. So this goes back quite a few years but I learned about clinical psychiatry from practicing it, being out there and confronted with problems year in and year out, day in and day out. I was a good clinician.

TB: I suppose this was in the 1980s.

SP: It was. I was a lab chief from 1984 to 1988 and it was probably one of the better periods of my career. I won, in one of those years, the Efron Award from the ACNP, one of the better awards I received. We had just published all the alcohol work, the neurosteroid work, the imipramine binding and serotonin transporter work. A lot of that came out at that time. We were labeling imipramine binding sites on platelets and studying patients so we had a paper in the archives around then. I had some tremendous postdoctoral fellows. One great thing about being at NIH was the number of young, bright people you could attract to your laboratory. It was extraordinary, and I was blessed to have maybe 50, 60, 70, or 80 postdocs come through my lab. Many of them are doing very well right now; they are professors, chairpersons of various departments of psychiatry or pharmacology in this country and throughout the world. So things went pretty well. Then, in about 1988 or so Fred Goodwin left and became director of ADAMHA. Herb Pardes had departed from being NIMH Director and Lew Judd came. When Lew Judd was the NIMH Director, I was fortunate to have been appointed Scientific

Director of NIMH. That was an interesting and challenging job. I was now the director of the program I entered in 1976 as a postdoctoral fellow in Axelrod's lab and Irv Kopin was our lab chief. And this was the program that Seymour Kety built back in the 1950's. Seymour Kety was, in my view, one of the great psychiatric scientists of our time. Seymour came back from Boston to the intramural program in his 70s while I was Scientific Director. He had a little office, and came in while he was working on his Danish adoption studies. We had eight, nine or ten members of the National Academy of Science, and we had Lou Sokoloff, who won the Lasker Award for developing the deoxyglucose brain imaging technique. Didn't you, around the 1980s, do some work with SSRI's?

TB: We did.

SP: We did a lot of work labeling serotonin transporters and showing that was where the SSRI's worked. So 1988-89 was kind of a tumultuous time at NIMH. We were trying to make some changes, to introduce a peer review system, and for me as an administrative person it was pretty stressful. For a lot of my friends and colleagues, the Bob Posts, the Phil Golds, the Dave Pickars, and the Danny Weinbergers of the world, really good people, this was stressful, trying to introduce a peer review system and to raise the bar on the quality of science. The blessing of being in the intramural program of NIMH is that you are not reviewed. You are free to do things without having to write research grants and tell people what you're going to do. That's a wonderful thing, but it comes with some liabilities.

TB: Would you like to mention a few of those who were in your program?

SP: They were extraordinary people. In the clinical program we had Dennis Murphy, Judy Rappaport, Bob Post and Danny Weinberger.

TB: Could you say something about them?

SP: Judy is probably the premiere child psychopharmacologist and psychiatrist in the world. Bob does wonderful work on kindling and bipolar disorder. He helped to introduce the anticonvulsants as treatments for bipolar disorder. Tom Ware is a very thoughtful, very bright circadian rhythm person. Richard Wyatt, Danny Weinberger and Joel Kleinman all worked on schizophrenia. Pickar was in my group and Trey Sunderland did a lot of great things in aging. David Rubinow did work on premenstrual syndrome, whatever they call it now. It was an extraordinary group of scientists. Without a doubt it was the premiere clinical program. Preclinically, in the basic neuroscience laboratories, they were also wonderful people. Julie was still very active. Lou Sokoloff, I've mentioned; Julio Cantoni and Seymour Kaufman were there. We had a

fellow that you probably know, Howard Nash, a great geneticist. Mike Brownstein was there. We had a great systems neuroscience program with Mort Mishkin, Bob Desimone and Leslie Ungerlieder. This was a very fine program.

TB: It looks like a comprehensive program. Did you have a central theme you focused on?

SP: That's an interesting question. We really didn't do that. I inherited a program it sort of evolved the way it did in terms of the players. We never had a vision of where we wanted to go and, to be honest with you, as grateful as I was to have ended up in that program, my one frustration was that I couldn't figure out a way to make it greater and to continue to make it grow. One of the issues is how do you do that? I think they are starting to do some really good things now. Dennis Charney has joined the intramural program at NIMH, but I don't know if we ever quite recreated what Seymour Kety did. Now, of course, it's different. When Seymour was there, there was nobody to start with. He set it up de novo, had all this space and everybody came.

TB: How did it start? Could you say something about that?

SP: I hope you have Seymour Kety's tape. I hope you got him before he died, because he was an extraordinary figure. Seymour has told this story, and I don't know if I can do it justice. In those early days the intramural program of NIMH and the intramural program of NINDS, the neurologists, were one entity. It was a wonderful program. There was a bunch of very good people, and it was a great place. It's still a fine place, but it was always a frustration to me that I couldn't make it better. I was 38 years old when I became Scientific Director. That's pretty young to have all this.

TB: Were you the youngest Scientific Director of the program ever?

SP: I'm sure I was. I don't know how old Seymour was, but certainly of recent times, I was the youngest.

TB: Seymour Kety was probably older than you when he became director.

SP: He was at Penn for awhile before and at different places. I did that job for five years and enjoyed it. Frankly, I never thought I would leave NIMH. I thought I would probably be carted off in a box one day from my laboratory but in a rather uncertain career move, I visited Lilly. They asked if I wanted to oversee their neuroscience research program. Lilly introduced Prozac in 1987 so this was in 1992. Prozac had been a very successful drug. They had a few other interesting drugs, and were investing heavily in neuroscience research and psychiatry which was a bit unusual for a Midwestern pharmaceutical company who made its reputation primarily in insulin for diabetes and antibiotics for infectious

diseases. So I went there and probably shocked a few people in making that career move. It was the end of 1992 that I announced I would resign my position as Scientific Director and move to Lilly and I did so in March 1993. I was very fortunate. The people at Lilly were very good people, had a fine program in neuroscience and still have to this day. We're probably one of the most competitive, if not the most competitive, company. We were just about to launch olanzapine, Zyprexa. I did that job for about three years and then was asked to oversee all the different therapeutic area research programs, including infectious diseases and oncology.

TB: Everything, not just psychotropics?

SP: Yes, and I recruited my successor, Chris Fibiger from Vancouver, who is now the Vice President of Neuroscience. Many of the vice presidents in the other areas I also recruited. I continue to this day to have a laboratory and my own postdocs and technicians.

TB: What are you working on in your laboratory?

SP: I have been working on Alzheimer's disease for the past five years and that is going very, very well. I am pleased with the work. We've been trying to figure out the genetics of neurological disorders. It's incredible what's happened in the last ten years; there are some really important genes! For a symposium this week, we invited Peter St. George-Hyslop from Toronto, a fantastic scientist, who discovered two of the early onset presenile genes. But I've been working on a more common gene called apolipoprotein E, particularly the E4 allele, which is associated with risk for Alzheimer's disease; if you have one copy of this gene from either your mom or your dad, you have a threefold greater risk of getting the disease. If you have two, one from your mom and one from your dad, so you're an E4 homozygote, you have a ten to twelve-fold greater chance and you get it early. So 50% of people who'll get Alzheimer's disease are E4 homozygotes at age 65 and 90% by age 85. So this is a very important gene for increasing your risk for Alzheimer's disease, relative to the more common E3 allele. The question is how does it do it; so we've done most of our research in transgenic animals. We've genetically engineered animals to express these different genes and have found they facilitate amyloid deposition. So that's been a big project.

TB: Any other important projects?

SP: The other big project we've been working on that is very exciting, is on this whole notion of being able to vaccinate against Alzheimer's Disease. I don't know if you've heard this story, to vaccinate against the A- β peptide that forms amyloid in your brain. It's a small 40 to 42 amino

acid peptide that deposits in the brain of patients who have Alzheimer's disease and forms plaque. This is what Alzheimer, who was a psychiatrist, first described in 1907. These are plaques he saw and they consist mostly of an aggregated fibrillar form of this peptide. What we and others have found is that antibodies can be raised to the peptide and even though these don't get into the brain very much, they can reduce the deposition of the peptide in forming amyloid plaques in transgenic mice. So this is a wonderful opportunity to test the amyloid hypothesis of Alzheimer's disease.

TB: Are the brains Alzheimer worked with preserved?

SP: I don't know the answer to that. Alzheimer was an interesting fellow. And here's a funny coincidence; Lilly bought Alzheimer's house!

TB: In Munich?

SP: It's not in Munich. It's a modest size home. When we bought it, fixed up everything and dedicated it, there was his microscope. So I have a picture of me looking into Alzheimer's microscope. It's in his house, not the Alzheimer Museum.

TB: So, there's an Alzheimer Museum too?

SP: At the hospital. During the dedication I had lunch with one of his daughters.

TB: That's very interesting.

SP: Yes. I think it's his youngest daughter. Alzheimer didn't live to be very old, I think he was a smoker or something. Anyway, I've been working on Alzheimer's disease which, in this country, is considered a neurological disorder. Interestingly enough, in Germany, it's still a "psychiatric" disorder and psychiatrists usually take care of it. In the US, it's mostly neurologists, geriatricians and some psychiatrists.

TB: You moved in your research from receptors to genetics?

SP: Absolutely, genetics, exactly! When I was at NIMH, before I left, I started a project in collaboration with Ed Ginns, a genetic epidemiologist, studying the genetics of manic depressive illness, in the old order of Amish in Lancaster. Now this is an interesting story. In 1987 there was this wonderful paper published in *Nature* purporting to claim there was a genetic locus on chromosome 11, 11p15 on the short arm that contained a gene for manic depressive illness in the Amish. This was published by Janice Eglin. There was a very famous geneticist named David Houseman. Probably for a year or two it was probably the most exciting and interesting finding in psychiatry. In that region of the genome, there were two interesting genes. One is the gene for tyrosine hydroxylase which, as you know, is a gene that makes catecholamines and the other is for tryptophan hydroxylase which makes serotonin.

So Ed Ginns and I thought these must be the genes for manic depressive disease. So we first cloned tyrosine hydroxylase and compared it in some Amish folks that had manic depressive illness and couldn't find any difference. This was a very curious finding, so we ended up repeating the linkage findings. One of the interesting things about doing genetic studies with DNA, is you can study the exact same subjects repeatedly. In the years we were measuring urinary catecholamines you could never get those patients again. They were gone, and you certainly couldn't study them at the same time. But for genetic studies, I take your DNA, I take your lymphocytes and I transform them. I make lymphoblasts, and store them. I can grow them and they are a continuous source of DNA. So all of this DNA was stored in a repository in Camden, New Jersey, and you could order it. So we ordered the DNA from these subjects and repeated the linkage analysis. To make a long story short, we didn't get the same results. So we published another paper in 1989, *Failure to Confirm*, and this was a very interesting because the group that originally published this consisted of extraordinarily competent, honest, good scientists. So I approached the group and I said let's work this out together. We ended up publishing a paper in *Nature* with the original authors of the other paper. To this day, people think we were the ones who wrote the original paper. The sample Janice Eglin worked with was phenomenal. She's got families, pedigrees, seven, eight, nine offspring, three or four of which had manic depressive illness. Fantastic! We began to collaborate with Janice and to this day, we still do some work. It's been a little less intense since I've gone to Lilly, although I'm starting with the new genetic techniques, the SNP genotyping, the single nucleotide polymorphism gene typing, to sequence the human genome. Now that we have all these genes, we can go into regions we think are important and find the genes one by one. We had a paper that came out two or three years ago, in *PNAS*, which Seymour Kety sent it in for us because he was a member of the National Academy. What we did in this paper was we looked at the Amish and carried out what's called a linkage analysis where we put genetic markers, spaced throughout the genome, to see if there were markers that seemed to be segregating with the transmission of bipolar disorder in the subjects. If there's a marker that seems to be linked with the illness, you can say a gene might reside there. Then we did an interesting thing. We flipped the linkage analysis around statistically and asked whether or not there was any relationship to being mentally well in these pedigrees. In other words, was the absence of affective disorder linked to any marker and sure enough, we found a region on 4p15, where there's evidence, not

unequivocal, but some evidence for a gene that conferred mental wellness. It was a protective locus. What's interesting about that is, remember the apo E gene I told you about, well it comes in three flavors, E4, E3 and E2. E3 is the most common variant, present in about 85% of the population. About 15% has one E4 gene that makes you three times more likely to have Alzheimer's disease. If you have two, that's ten times. Well it turns out that the E2 gene is protective. So if you inherit one E2 gene, you have a 50% lower risk of getting Alzheimer's disease and if you get one 4 from mom and one 2 from dad, the bad effect of the 4 is blocked by the good effect of the 2. You see where I'm going?

TB: Yes.

SP: So this concept that we have alleles, forms of genes that can confer disease or disease protection, is the concept we're seeing more and more now for all the complex traits we're interested in. Is that going to be interactional? You get an interaction and the difference, by the way, between the E4 allele, the E4 gene and the E2 gene, is two amino acids. Just two amino acids makes you go from having a tenfold greater risk to having one-half the risk, so a twentyfold change in the risk for getting Alzheimer's disease. How does that work, that's what we're trying to figure out.

TB: Weren't you also trying in your research to bridge receptorology with molecular genetics, working with cell lines and trying to profile drugs to receptors? Could you talk about that?

SP: That's an exciting area because once the molecular biologists got into receptor biology, the whole field took off. A good example, and this is not so much my own work, but work we've done or capitalized on at Lilly, is that if you take serotonin, and serotonin has 15 separate receptors that have been cloned from different genes, what you can do is take the complementary DNA or cDNA for each of those and you express them separately in a cell line and use the cell line in screening for drugs. You can come up with drugs that are specific for a particular type of serotonin receptor, either one that stimulates or one that blocks it. It has been used for glutamate receptors, dopamine receptors or just pick your set of receptors. It's a wonderful, powerful approach to discovering new drugs.

TB: So that's a kind of receptor screening for new drugs?

SP: Yes, absolutely. Some people call it rational drug design. I don't know what irrational drug design is. But the point is that if you go back to how we discovered imipramine, it was by accident. How did we discover chlorpromazine? It was by accident. It was done by astute, empirical

observations. You modified chlorpromazine and you didn't get an antipsychotic, but you got a mood elevator. Or you're working on antihistaminic compounds and you come up with chlorpromazine, it seems to have antipsychotic effects.

TB: What about MAO inhibitors?

SP: They were discovered almost by accident, looking at the antituberculous MAO inhibitors and they seemed to have mood elevating effects. Didn't Nate Kline make some empirical observations?

TB: And George Crane, and others even before that.

SP: But a generation of psychotropic drugs was created empirically if you also think of John Cade's work in lithium. It was in the 1950's and 60's when these drugs were introduced. So in 50 years we've gone from having no understanding of how the drugs work, before we were able to delineate the neurochemical mechanism of their mode of action. When it was shown that imipramine and amitriptyline block serotonin reuptake, the question was, could that be how these drugs work as antidepressants? Voila, now you come up with the serotonin transport inhibitors. Right?

TB: Right.

SP: And you have this new generation of SSRI's but it's now known that the noradrenaline carrier is important and combining those two, the serotonin and noradrenaline carriers, gives you a better antidepressant. It's also known that it's not necessarily the primary neurotransmitter effect that occurs acutely but it's probably the effects of the second and third messengers in gene expression after you give the drug. So when I give a drug to your brain, it may up-regulate or increase serotonin in your synapse and that's going to cause a change in gene expression; it's probably those genes that are changing the protein products that are penultimately responsible for the drug's effects. Now we can use that information to discover brand new drugs that work better.

TB: How will things go? Do you need better feedback from psychiatry or would this work by itself to generate the development of more selective drugs?

SP: That is a very interesting question because one of the things I think has gone wrong, is we've taken a lot of the empiricism out of psychopharmacology. In my research group at Lilly, the CNS program that Chris Fibiger heads up, they're discovering drugs that work on a whole variety of different receptors, glutamate receptors and serotonin receptors and we have theories of what these drugs are going to do. But until you get them into people and good psychiatrists make observations you don't really know what you've got. We've found, for example, that we bring a

drug into the clinic for this or that disease and find it may not work; but look what else it does. That's what we need more of in psychiatry.

TB: But the current psychiatric nosology works against you because the diagnostic categories are too broad and pharmacologically too heterogeneous.

SP: We're probably getting close to the etiology of Alzheimer's disease because we know what gene produces the disease. We don't have that yet in psychiatric disorders.

TB: I think in Alzheimer's, we might be closer than in other psychiatric disorders but even in Alzheimer's it will probably be better to restrict the concept to the original, and look for the genetics of the early onset disease.

SP: The apo E gene is the late onset gene but there's a point you're making that's important. Even so, when does early Alzheimer's start? There's another syndrome called mild cognitive impairment, MCI, this is the big buzz word. It's a precursor to Alzheimer's, but I think people are depositing amyloid much earlier.

TB: The point I was trying to make was that by separating early onset from late onset disease we might get more homogenous populations.

SP: Well I think that we have a much better understanding of the genetic etiology, pathogenesis and pathophysiology of Alzheimer's disease than we do for schizophrenia or bipolar disorder.

TB: I think that's correct.

SP: In Alzheimer's disease, there are three amyloid precursor protein mutations, Presenilin 1, Presenilin 2 and apo E that have been described. These are actual genes, and we can show their importance in populations. In schizophrenia, we have certain regions of the genome identified but no genes yet. My point is, if you think of the treatments for schizophrenia or for depression to some degree, we're not going to go anywhere unless we get a drug that treats the etiology. The etiology of schizophrenia may have been way back in the second trimester of pregnancy, so you may be dealing with something that you can't treat etiologically in the adult.

TB: Absolutely.

SP: So there's still value in looking at things syndromically and saying, what is depression or cognitive impairment in schizophrenia and can we treat those? The treatment of schizophrenia started out in the 1950's by trying to treat the positive symptoms of psychosis, hallucinations and delusions. Right?

TB: This is what most people say but an early report on treatment by Sol Goldberg, based on the NIMH collaborative study, shows that the

symptoms we refer to today as “negative symptoms” are the ones which responded specifically to antipsychotic phenothiazines.

SP: But the focus in therapy for years and years was can you block the positive symptoms and was that enough? Then people started saying you can only treat these positive symptoms with certain types of drugs but the patients remain impaired. Then we had this concept of negative symptomatology. Actually, who coined the word dementia praecox?

TB: Kraepelin by adopting Morel’s term “démence précoce”.

SP: I’ve got a picture of Alzheimer and Kraepelin sitting in the same room in Munich. So what was Kraepelin picking up on dementia praecox?

TB: First, in 1893, he used it as a diagnosis that accommodated three syndromes: Hecker’s hebephrenia, Kahlbaum’s catatonia, and dementia paranoides, that he himself described.

SP: The point I’m making is that across history, people were picking out different parts of the syndrome we call schizophrenia. Today we think of it as a syndrome whose manifestations may differ from patient to patient.

TB: In the last edition of his textbook Kraepelin himself described 12 different outcomes in patients diagnosed as dementia praecox.

SP: But you know, like Alzheimer’s, like many diseases, you can get different etiologies producing the same phenotype. Like in Hodgkin’s disease, the same gene is producing a different phenotype. Until we find something etiologically that we can put our fingers on in schizophrenia, it’s going to be hard to get the nosology right. You see what I mean. Otherwise, you’re just looking at symptom complexes and making theories which are great, but you’ve got to come back and test them. For the time being, if you have a patient with schizophrenia you may be treating different symptoms in the syndrome, possibly with different drugs or combinations of drugs, like we do with cancer and many other diseases.

TB: Right.

SP: So we’re working on drugs that might help memory disturbance, cognitive disturbance in schizophrenia, or on drugs that might be more effective for negative or positive symptomatology. I think you can approach the problem that way. In fact, if you want to do it properly, there is no other way. For the next ten years of my career, I’m probably getting back to schizophrenia on a new project that involves genetics but I’ll also work on some of these Alzheimer’s disease therapies.

TB: Would you like to say something about the research you intend to do in schizophrenia?

SP: There are some exciting new clues on the genetics of schizophrenia that have to do with stemline mutations in spermatozoa. Another very exciting paper presented a pathway involved in the production of an

amino acid, which Sol Snyder has worked on a lot that seems to be very involved in receptor function. Those are two interesting clues to etiology or, if not etiology, to pathophysiology, although we don't have, at this point, a lot of data to support a hypothesis.

TB: But currently your research is focused on Alzheimer's?

SP: Mostly on Alzheimer's, right.

TB: Do you have any drugs in the making for Alzheimer's?

SP: Yes. In the Alzheimer's area, we've got a drug that I helped discover that was approved just a week ago and will go into the clinic, if all goes well, by December of this coming year.

TB: Any other interesting drugs?

SP: We've got a couple of others too. We're working on neuroprotective strategies for Parkinson's disease. But a lot of my drug discoveries are vicarious through the efforts of the program and we've got many exciting, different types of drug candidates, going into the clinic. Not directly out of my laboratory but out of our whole program at Lilly, and that's exciting to me.

TB: You still seem to keep very close to CNS drugs?

SP: I do, but I have to worry about the other areas too and I enjoy the fundamental breakthroughs going on in cancer, cardiovascular research and infectious diseases. Fortunately, we have very good people who are experts in those areas who I bring together into a group and that's a nice challenge and a great opportunity.

TB: You mentioned a number of people you worked with at NIMH. Would you like to mention a few you trained?

SP: The folks that have come through my lab; some have done very well, a couple at this meeting, Shelly Schwartz who's at Duke, Leslie Morrow who's at the University of North Carolina, Steve Doetsch who's at Georgetown, Howard Gershenfeld at Texas, Aaron Janowsky is in Portland Oregon, Paul Berger is at Cincinnati. I've been very fortunate with the folks who have come through my lab.

TB: It seems you have been very fortunate to work with interesting people. You were lucky with your own mentors.

SP: They were very varied people, they each brought different things to the mix, from a fellow like Bob Heath, to an Arnie Mandell, a Don Gallant, an Danny Friedman, a Julie Axelrod and Fred Goodwin. I've been very fortunate to have worked with some great people.

TB: Would you like to say something about your publications?

SP: Going back in time, I think the alcohol GABA work was good, the neuroactive steroid work, the allopregnanolone work; a lot of papers were good, including the original binding studies with the GABA

benzodiazepine separate complex and the barbiturate work. All those are solid pieces of work. Recently, I'm very proud of the Alzheimer's work we've done, the transgenic mouse model and some of this new work on the antibody over the past couple of years, the antibody to the Amyloid- β peptide. Those are the pieces of work I think are the most important.

TB: What is your last publication?

SP: The last paper I had came out a few weeks ago in the Proceedings of the National Academy of Science, PNAS, demonstrating that a semi-synthetic tetracycline called minocycline has neuroprotective effects, it works in the animal MPTP model of Parkinson's, and not by its antimicrobial properties, but through what we think is a brain anti-inflammatory property. That's a very interesting, provocative paper. We have a couple of others in press or submitted that I'm also pretty excited about. One, in transgenic mouse models, could be used for determining how much amyloid is present in the brain, by measuring how much alpha and beta antibodies are present in the mouse blood.

TB: For your contributions you were the recipient of several awards. Would you like to mention just a few?

SP: The Efron Award of ACNP is a great award I received. The Distinguished Service Medal from the US Public Health Service, the Arthur Fleming Award and the APA's Research Award were all exciting awards. The Max Hamilton Award of the CINP was a nice award, as well as The Bennett Award from the Society of Biological Psychiatry.

TB: When did you become a member of ACNP?

SP: I joined the ACNP in 1982. This really is a fantastic organization. I've come to virtually every meeting for 25 years. I've served on Council twice and served as the President in 1999. That was a great honor. I've served on the Credentials and the Program Committee. So I've been fortunate to do a lot of things for the organization, this College.

TB: Is there anything you would like to add that we have not covered?

SP: I think it's a great College. When I was President, one of the things I wanted to do was figure out a way to keep it intellectually vigorous, to make sure that we were bringing in the young, the brightest people so we continued to evolve and wouldn't become extinct. We've done some good things along that route. I'm very pleased with the quality of the new members and the Fellow promotions. It's a great, great organization.

TB: Just one more question. What are your thoughts about the future of the field and the College?

SP: The field is going to be as good as the science we produce. To comment more on psychiatry because I'm a psychiatrist, we've gone from an era where it was hard to even know anything about nosology, to know anything about disease processes. Clinicians that came into the field were not as interested in applying rigorous scientific methods to understanding what was going on. It may have been such an overwhelming problem, but I think we've made a lot of progress in 50 years and we will continue to apply sound scientific methods to tease out the genetic and the non-genetic factors for diseases. What's the etiology? What's the pathophysiology? What's going on in the brain that causes signs and symptoms of disease and then treatment interventions will occur at the various stages, like all other diseases. Fundamentally, we'll understand the brain that is the most complex organ in the body. But it's not going to be easy to understand soon although we've made extraordinary progress and this College has done a remarkable job as a catalyst.

TB: That's a reasonable note on which to end this interview. Thank you very much.

SP: Thank you, Tom that was fun. Great!

CANDICE B. PERT*

**Interviewed by Leo E. Hollister
Waikoloa, Hawaii, December 1997**

- LH: Candace, can you tell us how you got started in the field?
- CP: In the beginning I wanted a PhD. and I wasn't really sure what it should be in. At Bryn Mawr College, Agu and I had studied psychopharmacology with Larry Stein. I wanted to be in some biological science in order to understand the "black box" of the brain underlying behavior, and through a series of interesting quirks I wound up in Sol Snyder's lab.
- LH: What were the quirks that got you there?
- CP: Oh, things like, I only had Delaware and Hopkins to choose from, because my husband, Agu, would be stationed at Edgewood Arsenal, where they were doing psychopharmacology of their own.
- LH: Oh, that's right, he was in the military.
- CP: He was in the military, the chief of the psychology branch, and I had applied to Johns Hopkins, the Homewood Campus, and at the last minute I heard about Sol Snyder, who was doing the brain and behavior. I sent my graduate application to Joe Brady whom I had met in a seminar at Bryn Mawr. He said, "Send it on to Sol" so Sol called me up and he said, "You're accepted; now apply." I was the first PhD student at Johns Hopkins' pharmacology program; the program was brand new.
- LH: So, you wanted to be a pharmacologist, but not a behavioral pharmacologist.
- CP: Not really. I was married to a behavioral pharmacologist and was extremely interested in it. You know, for years, Agu, and I had been interested in how the brain and behavior go together.
- LH: Agu's degree is in what?
- LH: His degree is in physiological and behavioral psychology from Bryn Mawr. He is a classical behaviorist, so I had his part, but what we really wanted to do, together, was to map the brain. So Sol's lab sounded pretty exciting, and I thought, "Ooh, a PhD in pharmacology, I don't really know what that means, but I'll take it." I didn't realize at the time how incredibly wonderful it would turn out to be.
- LH: You got into a wonderful laboratory in a very creative place and you did get your degree there.
- CP: In 1974, I got my PhD with distinction from Johns Hopkins School of Medicine.
- LH: When I read the title of your PhD thesis, it reminded me of the fact there were a couple of physicists who won Nobel prizes on the basis of their

* Candice B. Pert, was born in New York, New York in 1946.

PhD thesis. I never heard of anybody in biology doing that, but yours was certainly an important PhD thesis.

CP: It was amazing, the title was "The Opiate Receptor, its Demonstration, Distribution and Properties," and, of course, it was a very long shot project. Sol didn't want me to spend time on the project after it didn't work in the first couple of months.

LH: Sol likes to jump around, doesn't he?

CP: It was one of these things, where I fell in love with the project. I had a bread and butter, meat and potatoes project that was going to get me a PhD. And Sol was really only thinking of me. He said, man you've been on this thing for two, now three months. Forget it; you're never going to crack it; you haven't found it and there're papers in the literature that say it doesn't exist. But I kept plugging away. I wrote a book about exactly how it went down called, *Molecules of Emotion: the Science Behind Mind-Body Medicine* that was published in 1998 by Simon and Schuster.

LH: By a strange coincidence, there were two other laboratories, Eric Simon's and Lars Terenius', working on the same problem.

CP: We didn't know a thing about Lars. He published around the same time but he was much more understated and didn't come out and call it the "opiate receptor". Now I had helped Eric. Sol sent him into the lab and Eric said, "My, gosh, you have all these techniques. You have Sol's knowledge; you have Pedro Cuatrecasa's knowledge." Pedro was a famous NIH endocrinologist, who had just found the insulin receptor. So, Sol said, "Learn everything from Pedro". I'd actually been five months in Pedro's lab, so I was putting Pedro's receptor techniques together with Sol's knowledge of the brain.

LH: In 1971, I think it was the INRC meeting in San Francisco, Avram Goldstein gave a paper, called *The Search for the Opiate Receptor*, and he recommended the stereo-specificity approach he had come up with and told of the preliminary data with binding sites. He couldn't distinguish specific from non-specific binding at that time. Many people thought it was due to the fact he didn't have high enough specific activity. Do you think that was the problem?

CP: That was one of the problems, but Avram like the unsung hero, in many ways. In the classic Pert and Synder Science (1973) paper, I wish I had insisted his work be cited right in the introduction, not the discussion only. In the discussion, there was a lot of stuff about where he fell short, which he did. But, he, basically had the idea. He was searching for years and, sure, his specific activity was a technical problem, but there were a lot of other things. He didn't have the rapid filtration technology I had learned from Pedro and several other things. It's hard to

- understand why an experiment doesn't work; there may be a hundred important variables-every one of which has to be perfectly chosen.
- LH: But, you had the insight to think of using the antagonist, rather than the agonist.
- CP: That was indeed a key and it was a really amazing story. Here the ACNP, which has been interweaving in my life for so many years, comes into play. I was chosen as one of the fifty or sixty graduate students from across the country to come to the ACNP summer camp in 1972, at Vanderbilt in Nashville, where all the big famous pharmacologists flew in, and it was very exciting. But, for me, I had been plugging away for months in the lab and it gave me the chance I needed to think. I came there with a huge stack of papers I had gathered that I hadn't had time to read. I'd been so busy doing one failed experiment after the other. And, the one that really helped me crack it was Patton's paper.
- LH: Who's Patton?
- CP: Patton is the famous Chairman of Oxford University's pharmacology department.
- LH: There's another one in Australia with a similar name and I get them confused.
- CP: He had written about a "ping pong" theory. He thought the antagonist must just stick on the receptor. He thought the agonist action is due to the number of repeated pings as it binds while the antagonist competes with the same receptor, but stays stuck there, never pinging on or off. I said "Aha, I need an antagonist, because I want something to stay stuck on the tissue as long as possible while I'm washing away the non-specific binding".
- LH: So, you didn't think that it was more tightly bound?
- CP: Yes, higher affinity and affinity is the ratio of the off rate to the on rate, so the idea that antagonists could stay on much longer seemed perfect. Luckily, Agu had some naloxone because he was using it as a reversal control in his experiments with Tony Yatsch at Edgewood, resulting in the classic "Yatsh and Pert" paper published in 1972, highlighting the PAG. He was mapping the brain sites for opiate analgesia.
- LH: Was it labeled naloxone?
- CP: No, just cold naloxone; I had to get it labeled. When I came back from Nashville, I was all set to get the naloxone but Sol said, "Drop the project; you've spent enough time; you'll never get a PhD." He was only thinking of me, but I persevered; I was just in love with this project and wouldn't give it up. I had read the literature and knew it was there. I didn't care if I hadn't found it yet. I knew if you could just find the right combination of conditions you would get it right. So, I sent Agu's naloxone off, kind

of secretly, to be custom labeled by New England Nuclear. They made it hot and got it back to me; those were the old days, when you got tons of millicuries and purified it yourself. I don't think they let that happen any more, at least not at Georgetown, where I am now. Once I got the new radioactive opiate, the very first experiment, it was unbelievable! Then I got to be a famous graduate student.

LH: That's quite an achievement for a graduate student!

CP: It's being in love with an idea, believing in it, and not giving up.

LH: That's the beauty about the field we're in. You know you can do it. I always feel so sorry for people who think of work as drudgery, when we think of it as fun.

CP: Yeah, we get paid for having fun. We do, we do. It's a great field!

LH: Don't you feel ashamed, being paid for what you enjoy doing so much?

CP: Of course. Once the opiate receptor assay worked, the next person in Sol's lab to crack a receptor was Anne Young who is now the Chairman of Neurology at Harvard. She worked on the bench next to mine.

LH: Who was that?

CP: Anne Buckingham Young, she's now Chairman of Neurology at Harvard; she's not in our field so much, but she went for the glycine receptor and succeeded with the antagonist, strychnine. The same technology that launched the opiate receptor was able to be applied to any neurotransmitter. In Sol's lab, over the next few months, me and my technician were helping to teach the others how to go about it.

LH: Was the dopamine receptor studied in that laboratory?

CP: Ian Creese ran with it and tweaked it to screen for antipsychotics. Because Ian had done a lot of dopamine behavioral work with Susan Iversen, he was able to nail conditions that were "pharmacologically relevant" to screen for anti-psychotic drugs. Once you have the technology and know how to do the filtration it moves on, but every receptor had its special little requirements. Whereas before, receptors had eluded capture for decades, now, within a few months, every student in Sol's lab was working up a different receptor.

LH: Now you're a peptide expert, but in those days you weren't involved in the endorphin story, were you?

CP: There were no endorphins.

LH: That came in 1973, didn't it?

CP: No, 1976. The opiate receptor, our paper in *Science*, Pert and Snyder, was published in 1973, and that touched off the effort to find the brain's own morphine. And, then, when it turned out to be a peptide, everybody went bonkers over it. Peptides are easy; they're wonderful; they're

easily synthesized; they're easily worked with, and, so, there was a big peptide explosion.

LH: Today, you can make any kind of peptide you want.

CP: Absolutely! You could, even back then, but it took a few days. Now, you can order a peptide and it takes longer to ship than it does to make.

LH: You went to the NIMH right after you finished your PhD at Hopkins?

CP: Not quite. I did a one year mini post-doc, with Mike Kuhar, who was a professor in Sol's department. Mike and I developed in vivo receptor autoradiography, the first autoradiography for the opiate receptor. We were injecting the drug into the tail of the animal, the hot labeled drug, and, then, sectioning the brain. It was very tedious, but we got the first real pictures of opiate receptor distribution. Then, when I went on to the NIMH, I refined autoradiography of receptors with my colleague Miles Herkenham. We developed in vitro methodology, which is what's used today. At the NIH, everybody wanted to work with me, because I was Ms. Receptor.

LH: That was the hot ticket then.

CP: That was a hot deal and frankly still is the key to drug design. I had many job offers. Sol was always very generous and smart about placing his students with superb recommendations. Actually, I had twelve job offers. This was 1975 when I took the NIMH offer, because it was pure research. There were no teaching responsibilities, nothing but focused research. When I was hired by Biff Bunney, there were lots of peptides that NIH scientists had with biological activity and they knew there had to be a receptor for them, but before the opiate receptor, they didn't have the technology to go after them. So I was soon collaborating with many labs and over the years identified many new peptide receptors.

LH: Not all receptor agonists are necessarily peptides, are they?

CP: Absolutely not. You mean, drug receptors. But every exogenous drug binds to a receptor meant for an internally produced juice.

LH: That's always puzzled me, how the hell does nature know to make all these receptors for drugs we haven't synthesized? You got any idea? I always felt we needed somebody to come up with a theory like the Japanese fellow did for antibodies, the way he could explain how you could get that diversity of antibodies.

CP: I've given a lot of thought to that and I actually have a theory. I'm publishing my theory in what I hope will be a popular book.

LH: That will be a major contribution. Are you going to publish it as a book, rather than a scientific work?

CP: Correct, but it will be scientifically accurate as well as personal, historical, and hopefully entertaining. It's being published by Scribner in

September. It's called *Molecules of Emotion*. I believe that these internal juices, of which there are now over a hundred within their receptors are the internal homeostatic molecules that give you mood states, and run every physiological system in your body. I think our natural chemicals should keep us pretty on keel and when things go out of whack, then, you need to come in with drugs.

LH: I remember thinking naltrexone was the perfect drug. It does everything you want it to do, but nobody will take it. It is been disappointing as far as having much impact on opiate dependence, and one of the studies we did, a number of years back, was to give it in the same way not only to opiate dependent people but to normal people. Most of them found it unpleasant to take. I did a similar study with naloxone and it makes sense, if the endorphins have any function you can't block their receptor without having an effect. Maybe they're there to make us all happy.

CP: Absolutely.

LH: Instead of the happiness gene, we rely on endorphins.

CP: I think we rely on them a lot and the other peptide ligands too, you know, endorphins get a lot of the spotlight 'cause they're so sexy, but many of the other ninety eight are just as interesting. We just don't have as much good science on them, as on the endorphins. Actually, substance P was the first peptide isolated from the brain. An axiom of pharmacology is now not only, "No drug acts unless it's fixed to a receptor" but also those receptors were made for other things and pharmacologists accidentally discover ways to get in there.

LH: You were involved when Sol founded that company based on searching for drugs by receptor binding techniques.

CP: Nova. No, I wasn't involved. My techniques were involved, but I wasn't. By that time, I had gone on to NIMH and had been there a couple of years.

LH: But, it proved to be very successful, didn't it?

CP: I don't know much about it frankly. Sol and I were once very close, doing some cool science together. But after I started my lab at the NIH and after the Lasker Award controversy, we were not so friendly.

LH: I didn't want to bring it up.

CP: It's okay. I wrote about it in my book and it is pretty much ancient history at this point.

LH: What led you to follow a career looking for peptides as possible therapeutic agents?

CP It was a natural progression from complete immersion in peptide neuropsychopharmacology between 1976 until 1980, when the endorphins and enkephalins were in their heyday. All the big pharma were looking for

a non-addictive opiate and I was going to four or five meetings a year, getting to study enormous amounts of data and learn the principles of peptide modification to make drugs. Knowing that natural ligands are usually peptides was important. Then there was a key paper I published in 1976 in *Science* where Agu and I developed an analog of enkephalin that was very stable. Before that we found that if you drop enkephalin directly into the brain, all analgesia went away in twenty seconds.

LH: It doesn't last very long.

CP: No, it doesn't. We figured it was a rapid enzymatic degradation of enkephalin and I managed to make a substitution of the critical amino acid which preserved the receptor activity, so we really lucked out. We got a peptide that was as potent, as long lasting as morphine. That told me, although even today, people say peptides can't be drugs because they get chewed up too quickly, that's not true. We can use many clever strategies to chemically modify a peptide to achieve stability from degradation or enhanced delivery, or even alter the agonist or antagonist properties.

LH: It would be pretty hard to give them by mouth since all peptides are pretty susceptible to stomach enzymes

CP: I agree with that, but it is possible to make peptides delivered by mouth with the proper protection in a "pill".

LH: You can also give them by inhalation.

CP: Intranasal is very big.

LH: Will they go through the skin?

CP: Sure, nowadays people have all these special creams and transdermal patches.

LH: I would think they'd be too big a molecule to go through the skin.

CP: No, you can get them to go through the skin. One of the peptides we are working with now is being tested for psoriasis.

LH: You apply it via the patch, and it works locally?

CP: Yes, it's inflamed skin.

LH: Hyperplasia, really.

CP: Exactly.

LH: Of course, that kind of skin might be more permeable than regular skin. I've given TRH, which can have some activity, but it's only a tripeptide and that's not long enough to make entry difficult.

CP: Right.

LH: I guess when you get up in the higher numbers they tend to get chewed up.

CP: This is an octapeptide and there is no problem that. There's too much emphasis on switching to non peptide "peptidomimetics" which have a

tendency to toxicities. You can solve the pharmacokinetics and there are ways you can solve the enzyme resistance, so the key is always to have that receptor assay to make sure it still works while you're trying all these modifications.

LH: What's "Neuroprotectin"?

CP: How did you hear that?

LH: That's a big deal these days, to try to find ways to protect the nervous system, both after injury and after stroke.

CP: We were maybe a little ahead of our time. That was a project in my short lived first biotech company which I founded in 1988 to advance a peptide discovery for HIV/AIDS. The neuroprotectin papers we published in the late 1980's were a minor part of that enterprise.

LH: It blocks the cascade of injury?

CP: Exactly; this peptide blocks the excitotoxic effects of glutamate receptor activation. It blocks it quite well actually. We were interested in this as an approach to stroke and head trauma, where the later actions of excitotoxicity are responsible for the bulk of neuronal loss. The idea was that there is a window of opportunity of an hour or so where such a drug could be highly useful, as protection from glutamate toxicities; hence the name, "neuroprotectin".

LH: Interesting, maybe the brain has its own protection?

CP: Yes. The brain has potential for its own protection at times of stress but we had head trauma and stroke as the main commercial interests. You could give this drug, during that critical period after the initial injury, and it's still a good idea. It's a good drug, waiting for the kiss of pecunia! At the moment, there are just too many other things to do, focused on the main project, a receptor-blocking peptide for HIV/AIDS. I've learned it is not enough to do a great experiment, or publish a great paper. If you have the courage of your convictions you need to follow up your discoveries with practical applications. You have to find the people willing to advance millions of dollars to take the drug from the preclinical stage to testing in humans, which, as a pioneer in this endeavor, is not so easy to do. It is not so easy to do those human experiments.

LH: The enthusiasm these days is vastly different from just a few years ago; the idea is that stroke is a treatable disorder. Ever since I was an intern, if someone came in with a stroke you kept your fingers crossed, and that was it. You couldn't do anything specific. But now, with the clot busters, at least in highly selected strokes, it looks like they are pretty good. So the idea of an intervention after the stroke is fully validated. Getting back to Sol, you were not very happy with his 1977 Lasker award?

- CP: No, I wasn't. I was not happy with his Lasker award at all, and I'm not coy. He called me up and invited me to come to the Lasker luncheon. And, I asked, who else is getting the award? And what's the award for? If it had been an award for Sol only, I would have been in the front row cheering, because I really think he made great accomplishments over the years, but then I heard it was Sol and two other men, Hughes and Kosterlitz. To my mind, Hughes had the same relationship to Kosterlitz as I did to Sol. Hughes was the younger guy who actually did the work while Kosterlitz was head of the lab who raised the money and recruited him for the project. I felt it was very unfair, and, the rash gal that I was, even though everyone in the world advised me to just shut up, I publicly complained. The award was for the opiate receptor and endorphins and I couldn't sit quietly by for an award being given to someone else for my thesis work!
- LH: I remember I was talking to Avram Goldstein about that time, too, and he wasn't very happy with the award, either. You know, Avram, in addition to paving the way for the opiate receptor, came up with something he called a pituitary derived opiate peptide, which ultimately turned out to be dynorphine. So he was a pioneer both on the peptide and receptor side.
- CP: Absolutely. There's no doubt about it. But the prize has these rules; the Lasker award, which is the forerunner to the Nobel Prize, can be shared by no more than three people. I turned down Sol's invitation to the Lasker luncheon. Since I declined to show up and my candid letter stating how "I initiated the research and followed it up," appeared in an editorial in *Science*, which created a brouhaha and discussions of me as the first author, the whole feminist issue, and who from Johns Hopkins had submitted the prize nomination. It's not entirely a feminist issue. Women are usually the ones that suffer in these situations but a lot of men do also. It has to do with the scientific hierarchy and who has the skills and stomach and influence for prize seeking. I don't think Avram suffered so much. He has tremendous recognition; he's highly respected; he's had his own institutes over the years, but for me, it was professionally a disaster to think the work I had been so closely identified with was being given a prize that excluded me. It's not as if I had done five or even only fifty percent of it. I was running that whole project in Sol's lab, had first authored many key papers including the first one and had continued productive work in my lab at the NIH.
- LH: Julie Axelrod told me the reason he parted from Brodie was, he did an experiment all by himself and Brodie said we ought to put the names of

everybody in the lab on the paper alphabetically but that B would come first. That's when he decided it was time to part company.

CP: There have always been these little scientific brouhaha's. For me, it was particularly sad, because I adored Sol. I had learned so much from this man about how to do science, hot science, great science. I wanted to do for him in a very nurturing female way, and he had always been extremely kind to me. That was what was so ironic. I mean, I was the first author on all the key papers. He sent me out to all the meetings. He wasn't hiding my light under a bushel or anything, so when it came to this moment of truth, when only three people could win the Lasker, I was soft. My theory is that Sol, since I was always so femininely nice about everything, figured I wouldn't complain, it was easier to cut me out, than to cut out Hughes or Kosterlitz.

LH: When you're tempted by the great prize, I guess it's difficult to sit back and say, look, I've got to share the credit. The only one I can think of that's common knowledge, is the 1954 Nobel Prize for culturing the poliovirus. Enders, the biologist at Harvard who was selected by the committee, heard about it and said, no, you've got to take Weller and Robbins who were graduate students, because they'd done a lot of the work on growth of the polio virus in monkey kidneys.

CP: Right, very interesting.

LH: He insisted they would share the prize, which was the only time I can think of such generosity in face of temptation, like the Devil offering you the world!

CP: For me it was a mad and sad feeling and for years afterwards I was always hoping Sol and I would make up, but finally, I realized there was a hopeless chasm there. I did a lot of personal transformative forgiveness work around this that helped me in my life.

LH: I remember once I had occasion to talk to the guy who was the senior author on the paper about sex and bacteria, for which Joshua Lederberg won the prize. I asked, how does it feel to be the senior author on a paper that wins the Nobel Prize for somebody else? But he wasn't unhappy, he said it helped his career immensely.

CP: Well, this wasn't the Nobel, it was the Lasker, and I just had to express what was in my heart. That December 1978 it is common knowledge the Nobel committee was at a stalemate for the Nobel Prize for Opiate Receptors and Endorphins with several combinations of three scientists, some of which included me. After an unusual pause of many hours, the prize was awarded unexpectedly for a medical scanning device.

LH: Let's talk about peptide T, which I want to understand, including its therapeutic possibilities.

CP: The initial discovery was made at the time I was still Section Chief at the NIMH, with help from many NIH collaborators. It was an example of a style of work that is harder to do now, to bring diverse scientists, in this case neuroscientists, neuropharmacologists, virologists and immunologists into a team to crack a completely new problem. There was no prior research on the topic, which as we defined it, was to identify which part of the virus bound to its receptor, and to then design a peptide inhibitor that blocked virus binding and infection. This work marked a real milestone in my career. For one, it was the most amazing discovery. It had so many seemingly miraculous aspects. First, we derived the structure from one computer assisted data base search; secondly we had enough faith, or in this case NIH funding, to roll the dice and have it made; thirdly the collaborators agreed to study HIV infection when this work was not routine and few labs could do it. To put this in context, at the time there was a lot of politics, including international competition between governments around HIV/AIDS virology, AIDS testing, and creation of AIDS drugs. This was an expanding global pandemic with no treatments, a lot of public fear, and nobody wanted to believe that an AIDS drug could come out of the NIMH. At that time, it was all NIAID and the NCI that were controlling the turf. So, we got just about zero support. In fact, we got active hostility and resistance to even testing our ideas, including editorials in *Science* and *Nature*, as well as many major newspapers. It got so intense that even my bosses at NIMH were taking a lot of heat. So, something I never thought I would do, I left the NIH when I got an offer that would permit me to bring peptide T into clinical trials and bypass battles for fame, glory and ego. By this time Lennart Wetterberg and colleagues at Karolinska had put peptide T into four near terminal men with advanced HIV and reported significant brain and clinical benefits in a 1987 paper in *The Lancet*. The calls for cessation of further clinical testing from NIH and Harvard virologists were revealed, at least to me, as being politically motivated. I got a strong whiff of this truth at the International AIDS Conference, held in Washington DC in 1987. There were five thousand scientists and ten thousand reporters. It was a feeding frenzy and a sharp elbowed affair of jostling for position and pre-eminence that the opiate receptor discovery, as big as that was, never came close to approaching.

LH: So, when you founded your own company, did you get public support?

CP: No, no, no. It was a small start-up with limited seed funding. No one got big offices and fat paychecks. It was lean.

LH: It wasn't a real IPQ, then?

- CP: It didn't get to that stage. The idea was to start little and, when you got something attractive, launch the IPQ or hook up with a Pharma. This venture lasted until 1991, at which point the NIMH had begun to organize a major trial of peptide T for Neuro-AIDS. Ruff and I took faculty positions at Georgetown University Medical School and were eventually able to organize the next business venture which was launched out of that university affiliation.
- LH: Besides the politics, was there any scientific gap that slowed your progress? I mean sometimes discoveries seem "too good to be true".
- CP: Exactly! Unbeknownst to us, by the time my team published the first peptide T paper in 1986 in PNAS, a huge business/NIH/university consortium had spent 3 years and many millions of dollars making 30 twenty amino acid peptides to span the entire envelope protein, called gp120. When none of these peptides tested positive for blocking HIV infectivity, the wrong conclusion was that there was no simple short continuous peptide sequence! Instead a complicated bending and folding of "discontinuous epitopes" was invoked as the binding "site" that persists even today. There were no peptide neuropsychopharmacologists in the consortium and virologists couldn't imagine that peptides can have secondary structures or that they could be chewed up in assays or that assays could be pharmacologically irrelevant. We pharmacologists never assume that an in vitro assay is relevant until we have carefully compared it to excellent parallel in vivo data. But AIDS got a lot of funding really fast and this created a "might makes right" situation; cool science did not prevail.
- LH: Tell me more about peptide T and the therapeutic possibilities. What receptors does it bind to?
- CP: That's a very important question. We had identified in 1986 this short peptide derived from the envelope of HIV that blocked infection, and protected, even reversed, some Neuro-AIDS pathologies in people, but the relevant virus receptors would not be identified for another 10 years, an eternity really. Usually, I get my scientific information from meetings, papers or colleagues. This time, I got faxes of New York Times and Wall Street Journal articles and what happened was, unexpectedly, the AIDS researchers deduced that two chemokine receptors were the receptors for the AIDS virus. This was a really big deal. Up until then, they were saying CD4 was the HIV receptor. It was a bit of a dogma even, although there were clear early signs that some other receptor(s) must be involved. But in 1986, in our PNAS first report, we said peptide T was binding to CD4 based on the prevailing thinking. With these new reports we instantly began to examine the interactions of peptide T with chemokine receptors. We had heard of them because Michael Ruff, my very

close colleague, had been a chemokineologist. He had been studying peptides that controlled the chemotaxis of monocytes. So, in fact, we had done a lot of work together since we started hanging out in 1983, showing that these same receptors in brain are also in the immune cells, and vice versa. We had a lot of papers on this topic, which evolved into “psychoneuroimmunology”, so we were able to get into this work pretty quickly and set up that technology in our lab at Georgetown. Ruff had just come back from the Keystone Symposia chemokine meeting in Colorado, where, unexpectedly, his poster was promoted to be a plenary address. In that talk we showed that peptide T is an extremely potent antagonist at the chemokine CCR5 receptor, the more important of the two as it is the receptor used to infect the body.

LH: So, it blocks it.

CP: Blocks chemokine RS ligands and HIV entry that occurs at that receptor. We came up with this octapeptide that works at picomolar, and lower doses. It seems there are major Neuro-inflammatory complications of AIDS, and some neuropathies that peptide T has shown remarkable efficacy on. The effect of peptide T to block neuro-AIDS likely results from both its ability to block the actions of gp (glycoprotein)120, but perhaps even more, to suppress microglial activation that leads to neuronal loss. As such I think it is obvious that peptide T would have benefits in many other inflammatory diseases, including Alzheimers or arthritis, to cite some significant illnesses with few treatments.

LH: Now, is it possible that this could be done with a human growth hormone that you might turn into a bacterial factory to make these peptides?

CP: Interesting. But the technology for manufacturing peptides is so advanced that Merrifield Solid Phase Synthesis technology seems very good. The drug is potent and such low doses are needed that it's easily administered as a nasal spray, so we hope it can be cost effectively made available in the developing world.

LH: Did you think you were ever going to be a scientist business person?

CP: The business part? I don't have any company now. I'm on the faculty of Georgetown and I'm a scientific advisor to the company that's developing peptide T, but as much as I've had to get involved in business, that's the biggest surprise. I was interested in science, and going for a PhD, interested in basic research. Then, I slowly started to see this work can have treatment benefits; it's not just publishing papers; that you can maybe cure or treat a disease; you can help people; and that's very addictive. But, the business angle, I never thought that I would have to learn some of those ropes to survive.

ALFRED PLETSCHER

Interviewed by Thomas A. Ban
Riehen bei Basel, Switzerland, January 25, 2002

TB: We are in Riehen, in the town of Basel, Switzerland. This will be an interview with Professor Alfred Pletscher* for the Archives of the American College of Neuropsychopharmacology. It is January 25, 2002. I am Thomas Ban. Thank you very much Professor Pletscher for seeing us in your home. I would like to start from the very beginning. If you could tell us when and where you were born and brought up as well as something about your early interests and mentors.

AP: Thank you very much, Professor Ban. I'm really honored that you and Mark came to see me and ask me some questions. I hope that I can answer them. I was born in the far east of Switzerland. It was about three miles off the eastern frontier, close to the river Rhine on the frontier with Austria. I also attended elementary school there. I did my studies in Zurich, Geneva and Rome. I was in Rome for one semester, before the war, from 1938 to 1939. I decided to go there, because everybody went to Germany. We had a relatively flexible curriculum in our universities. We could move for a semester to other universities and many of us went for a semester to Berlin, Germany, or Vienna, Austria, or Rome, Italy. I studied medicine, graduated from medical school, and got my medical degree after I defended my thesis. Then, after practicing for a while, I studied organic chemistry, and again after defending a thesis I got my PhD in organic chemistry.

TB: When did you graduate from medicine?

AP: I got my MD in 1942 and my PhD in 1948.

TB: So, you are a medical doctor and an organic chemist.

AP: Yes. I was always inclined towards biology and I thought I would like to do medical biological studies ought to get an education in chemistry. After completing my studies in organic chemistry I returned to medicine and practiced for four or five years before I was approached by Hoffmann-La Roche and asked whether I would be interested to become their director of biological research.

TB: When was that?

AP: That was at the end of 1954.

TB: Could you elaborate on your early interests?

AP: I was interested in how biological processes work, and how to apply them. Also, I was interested in human relations and I had the idea that with sick people, you could get, perhaps, closer relations.

* Alfred Pletscher was born in Altstaetten, Switzerland in 1917. Pletscher died in 2006.

TB: Did you ever think of pursuing a different career?

AP: No. I wanted to help, to alleviate suffering. And, I liked medical studies, but after I got my degree I had the impression I did not know enough, that I needed to do further studies. I thought of studying organic chemistry because most of our remedies come from biochemistry. I also believed we should not rush into surgery; if a leg is “sick” we should not cut it off. So I became interested in how to prevent illness and the need to know biochemistry to understand biological processes. We were very much behind the United States at that time. The United States, in biology and biochemistry, was far advanced.

TB: We are talking about the early 1950’s?

AP: Yes, after World War II. During the war, America made tremendous progress and we were lagging behind. I was rather idealistic although you could ask, why did then I join the chemical industry, which is not so idealistic. I joined because I thought I would have more possibilities to help sick people than being a general practitioner. If I found a drug, and we found, for instance, Librium (chlordiazepoxide) and Valium (diazepam,) we could then help thousands of people; as an individual physician I could only help a few.

TB: You were frustrated about the state of art of treatment?

AP: Yes, but then I got a letter from Roche who asked me to come. At first, I said no, and half a year later, they asked again. And Ciba also tried to get me, but I felt from my viewpoint Roche was closer to my intentions than Ciba. It was a family owned company and the family created a very good spirit. The management of the commercial department would listen to what we in research said. And that is what I liked. Otherwise, I would not have joined them. Today, I would not join them anymore.

TB: I see. It was a family owned company.

AP: I knew the family very well. I knew the owner, Paul Sacher. He was, more or less, a friend of mine. His wife was a sculptor and he was a famous musician. He supported and created many, many things. He has created a famous Archive of Stravinsky, which is in Basel. So he was very much tied to culture, he had a cultured mind.

TB: Did Roche differ in any other respect from other major Swiss drug companies?

AP: It started as a pharmaceutical company; whereas, all the other ones, Ciba, Sandoz, Geigy developed from the dye industry and pharmaceuticals were not necessarily their priority, whereas Roche’s priority were pharmaceuticals from the beginning. And, at Roche, research, from the very beginning, was important. They had several drugs at the time I joined them.

- TB: Can you tell us about the drugs they had at the time?
- AP: The biggest seller was a sulfa drug. It was a six million dollar business in the United States. Later we got to one billion dollar drugs. They had COX inhibitors and tonics. We had several good drugs marketwise that also made good profits although I didn't care about those things.
- TB: Were the companies that merged into Novartis, like Sandoz, Ciba, and Geigy, still separate at the time you joined Roche?
- AP: They were. Ciba was probably the most famous one, but Roche had a good name.
- TB: Didn't Ciba have reserpine at that time?
- AP: Ciba had reserpine, an adrenergic blocking agent extracted from the root of *Rauwolfia Serpentina*, an Indian plant used as a tranquilizing drug in folk medicine in India. Ciba had extracted the active ingredient, and introduced it in the treatment of hypertension because in animal pharmacological experiments Bein found it lowered blood pressure. Then in the clinic, it was found also to have antipsychotic effects. They used it in schizophrenia and it was called a neuroleptic. At the same time chlorpromazine came and these were the two neuroleptics available at the time.
- TB: What did Sandoz have?
- AP: Hydergine.
- TB: Was Roche interested in developing CNS drugs?
- AP: No. Roche had a CNS drug at the time that came out of serendipity. It was iproniazid, a monoamine oxidase inhibitor and the isopropyl derivative of isoniazid, one of the first successful remedies for tuberculosis. It produced euphoria in some patients that clinicians referred to as an antidepressant effect. It was Nathan Kline, with whom we had contact, who thought it was an antidepressant.
- TB: Was isoniazid a Roche drug?
- AP: No, isoniazid was not developed at Roche, but Roche had a patent for its use.
- TB: What about iproniazid?
- AP: Herbert Fox at Roche synthesized iproniazid in 1951. They wanted to improve the therapeutic effect of isoniazid in tuberculosis.
- TB: So, Roche had two effective drugs for tuberculosis.
- AP: Yes. And it was a serendipitous finding that iproniazid had antidepressant effects because everybody at the time was looking for a better drug than isoniazid in tuberculosis.
- TB: Iproniazid was synthesized just a few years before you joined Roche?
- AP: A couple of years before. As a student I had been a patient treated with iproniazid. That was in 1938, and before that there was no medication.

All you had to do was lie down, be quiet and eat well. Then you either died or survived.

TB: What you are saying reminds me of Thomas Mann's Magic Mountain. There was at the time no treatment for it.

AP: We just had to lie down, and enjoy the mountain air.

TB: So, at the time you joined Roche, they had iproniazid.

AP: There were three drugs in those years, chlorpromazine, reserpine and iproniazid with an effect on psychiatric patients. They didn't call them psychotropic drugs. Nothing was known about the mode of action other than that iproniazid was a monoamine oxidase inhibitor. When I started there were only three neurotransmitters known in the brain acetylcholine, serotonin and norepinephrine. The presence of histamine in the brain was not demonstrated yet.

TB: Norepinephrine was just discovered in those years.

AP: Yes and Von Euler got the Nobel Prize for that. Nothing, or virtually nothing, was known about the transport, storage, and release of neurotransmitters, or about monoamine receptors in those years. There were hypothetical concepts about receptors but no solid physical evidence. All that came much later.

TB: So this was the state of affairs when you joined Roche.

AP: So when I joined Roche I wanted to go to the United States for two reasons. One, they were much more advanced in biochemistry and in order to do my job I thought I would need to adopt what they had. The second reason was that our friends and associates at Nutley, in the US, told us that exciting things were going on in Brodie's laboratory. I decided I would be interested to go there and do some research with him; Severinghaus asked Brodie for a letter of invitation for me and I started in Brodie's laboratory in March 1955. Brodie's closest collaborator, Parkhurst Shore, was a creative and intelligent young man. By the time I arrived they had shown that both reserpine and serotonin, when injected into mice were sedating; they found that both perpetuated the hypnotic effect of hexobarbital. They also found the sedative effect of reserpine and serotonin was antagonized by LSD, lysergic acid diethylamide. Prior to their research Gaddum reported that LSD, a potent hallucinogen, blocked the effect of serotonin on smooth muscle. Brodie and Shore had also shown that reserpine increased the excretion of 5-hydroxyindole acetic acid (5-HIAA), the major metabolite of serotonin formed by oxidative deamination via monoamine oxidase. They suggested that serotonin has a function in the brain and mediates the effect of reserpine. Not many people believed it. So, I decided I would try to find direct proof reserpine depletes serotonin. I was very meticulous

in my research. Serotonin was known to occur in three places in the body; in the intestinal tract, the blood platelets and the brain. By far, the highest amount of serotonin occurred in the gut, especially in the rabbit gut, so we thought the easiest thing, to begin with, would be using that. There was a colorimetric method I had to adapt before I could start with my experiments. After a couple of failures, when there was no color reaction, I found that reserpine releases and depletes serotonin. After we were certain we published our findings in *Science*. Of course we had to show this also happens in the brain. Since the concentration of serotonin is much lower in the brain than in the gut, the colorimetric method I used was not suitable for these experiments. The problem was how to find a method with the necessary sensitivity that would make these experiments possible. Fortunately, in a laboratory close to ours at the NIH, there were two people working, Dr. Bowman and Dr. Sid Udenfriend, who had just created a new instrument, the spectrophotometer. With this instrument the small quantities of serotonin metabolites showed up by activation of the fluorescent spectrum. Use of the new instrument made it possible for us to show that reserpine depletes serotonin in the brain. We could hypothesize that the psychotropic effect of reserpine was a biological effect mediated by an endogenous neurotransmitter.

TB: Wasn't there a correlation between reserpine induced sedation and serotonin levels in the brain?

AP: Yes, it was a correlation between sedation and serotonin levels. It was a crucial experiment.

TB: And, the findings were published?

AP: They were published in 1955 in *Science*.

TB: It was this discovery that opened up the field of neuropsychopharmacology.

AP: Absolutely. It was interesting to see that a psychotropic drug affected an endogenous neurotransmitter.

TB: It has profoundly affected the development of neuroscience. Just a couple of years before these findings were published people argued whether neuronal transmission was predominantly electrical or chemical.

AP: The evidence for chemical transmission grew during the 1950s and interest became focused on monoamines involved in neuronal transmission. There was also another psychotropic drug in those years, iproniazid from Roche in Nutley. Reserpine was tranquilizing and was known, in certain cases, to cause mental depression whereas iproniazid had the opposite effect on mood and behavior. So, I did an experiment on its effect on serotonin in the brain and found that iproniazid antagonized the reserpine induced decrease of serotonin. Reserpine, alone,

might have decreased serotonin but pre-treatment with iproniazid prevented both the decrease of serotonin and the concomitant behavioral changes.

TB: You also showed that reserpine decreased whereas iproniazid increased serotonin.

AP: When I told Professor Kline that reserpine and iproniazid have the opposite effect on mood and serotonin levels he was enthusiastic about my findings and said, "Now I believe we have something."

TB: When you decided to go to work with Brodie did you have in mind that you would do research with iproniazid?

AP: No, I went there to become acquainted with American research in biochemistry. I was always interested in brain research, and I heard there was interesting research going on in his laboratory. While working there I became one of the main actors who found reserpine has a direct effect on serotonin in the brain.

TB: It was your task to show that reserpine depletes serotonin not only in the gut but also in the brain?

AP: I provided direct proof that reserpine depleted serotonin in the hypothalamus.

TB: In addition to Parkhurst Shore and Steve Brodie was there anyone else you collaborated at NIH?

AP: I was working mainly with Park Shore, and, of course, Brodie. We had a tremendous, stimulating environment. We had people around us like Sidney Udenfriend, like Julie Axelrod and I learned a lot from them. And, when I came to the end of my stay, Arvid Carlsson arrived and I got to know him. When I returned to Roche in Basel at the end of the year as Director of Biological Research I had the necessary authority to make the development of psychotropic drugs central in our program. I said that we should look for new psychotropic drugs with all the knowledge we have. We assembled a group of people for that research, found and developed several compounds.

TB: Could you tell us about some of the drugs you developed at Roche?

AP: I wanted to find and develop a reserpine-like substance that would deplete serotonin in the brain. We were lucky to find the benzoquinolizines, a group of drugs that depletes serotonin and produces sedation in animals. In the clinic they had been shown to have a neuroleptic effect, but they could not compete with chlorpromazine. It led to my second paper in *Science*, on the release of hydroxytryptamine by benzoquinolizine derivatives with sedative actions.

TB: And, this was in?

- AP: 1957. It confirmed that certain psychotropic drugs were acting on endogenous substances like serotonin in the brain.
- TB: The recognition that some psychotropic drugs act on endogenous neurotransmitter substances was a breakthrough in itself.
- AP: But it was only slowly that the medical community accepted that.
- TB: In your recollection, who were the ones who recognized it first?
- AP: Nate Kline, really; he was the person who recognized it.
- TB: What about Joel Elkes?
- AP: Elkes was one of them, yes.
- TB: So, after you returned to Basel, you were trying to develop reserpine-like neuroleptics. Were you also interested in developing iproniazid-like antidepressants?
- AP: I was always interested in antidepressants. We started a whole program on monoamine oxidase inhibitors. Some of the drugs that came out of that program probably are still in use. By that time other drug companies became interested in psychotropic drugs and were anxious to see what we did.
- TB: It seems that pharmacologists and the pharmaceutical industry recognized much faster the new perspective opened by psychotropic drugs. Wasn't Fridolin Sulser asking your advice in the late 1950s where he could get experience in the new field? I suppose you knew each other?
- AP: I knew him only when he came to my office and said, Dr. Pletscher, I want to go to America. Where should I go? And I said you would get a great experience in Brodie's laboratory if you are interested in neuropharmacology. That is the place to go to learn about the biochemical action of new drugs.
- TB: So, it was you who suggested Fridolin go to work with Brodie. While working at Roche, weren't you also involved in teaching at the University?
- AP: I always had a connection with the University. I taught pathophysiology in the medical faculty and I was a professor there. But one day the Chairman of Roche told me we were creating a new institute for clinical research in Nutley, New Jersey and they would like me to go there and reorganize research.
- TB: When was that?
- AP: I think in 1957. So I went there and my wife came with me. It was not an easy time. I had to reorganize the whole thing. Nothing was being developed at the time I arrived. When I said, let's look at what we have, I was told there was nothing. Actually they had a substance with the code name Ro 5-0690 (chlordiazepoxide,) but management was not interested in it.

- TB: Was Ro5-0690 the code name of one of Leo Sternbach's benzodiazepines? Wasn't he with Roche in Nutley at the time?
- AP: Sternbach was at Nutley with us. After he left Poland, he worked in Switzerland first as an assistant at the Swiss Federal Institute of Technology in Zurich; then he joined Roche in Basel. Prior to the outbreak of World War II, he moved to the United States and some years later he became Director of Medicinal Chemistry of Roche's research facility in Nutley.
- TB: Did you know him well?
- AP: Yes, he's a friend of mine. He synthesized this chemical substance and nobody knew how it worked biologically. It had a different structure from other drugs. So I thought we should try it. Why not?
- TB: The story one usually hears is that the substance was on the shelf, found during a laboratory clean up, and submitted for pharmacological screening because of the interest of the company in developing chlorpromazine or meprobamate-like psychotropics which were a phenomenal success in those years.
- AP: The management at Nutley was not interested in developing a psychotropic, but regardless the substance was sent for pharmacological screening. Then, one day Lowell Randall, our director of pharmacological research asked me to come to his office. He told me he had a couple of wild, untamed aggressive cats, and about twenty minutes after he gave them Ro5-0690 they became pussycats. But the main thing was the cats were not sleepy. They were tranquilized without losing coordination.
- TB: Am I correct that behavioral changes with Ro5-0690 were similar to what Frank Berger saw with meprobamate?
- AP: Yes, the only difference was that we saw it in cats.
- TB: I wonder whether Randall would have picked it up even without knowing about the pharmacology of meprobamate. But, undoubtedly he was familiar with it. Did you know Frank Berger?
- AP: I met him just one or two times, but we did not discuss much about pharmacology. He was successful with his drug. I was responsible for the whole research program that developed Librium. Sternbach of course was the one who synthesized the drug and Randall did the pharmacology.
- TB: If I understood you correctly, the management did not want it.
- AP: Mr. Hoche, the sales manager told me that there was no market for these drugs.
- TB: But fortunately you succeeded in moving ahead with the substance. Do you remember who, were the first people on the clinical side working with the drug?

- AP: No, I don't.
- TB: Was it Joe Tobin?
- AP: It was not Tobin, he came later.
- TB: Librium promptly became a great commercial success.
- AP: By that time I had returned to Basel.
- TB: When did you return to Basel?
- AP: That was in 1958 or so.
- TB: So, all the research that led to the release of Librium, one of the first blockbuster drugs was done in 1957 and 1958. If I remember well, the first publications appeared in 1959 or 1960.
- AP: Yes. It was amazing.
- TB: It moved very fast. And Librium was soon followed by diazepam, Valium.
- AP: Once we had the experience with Librium, we found developing Valium much easier.
- TB: What was the purpose of developing another benzodiazepine with a similar pharmacological profile to Librium?
- AP: We wanted to have a benzodiazepine that was more potent than Librium. But there are not only scientific but also commercial considerations in drug companies for developing compounds.
- TB: After your return to Basel from Nutley you were appointed Director of Research of Roche International.
- AP: Yes.
- TB: Could you tell us about your activities in the new position?
- AP: I had to organize a more or less new department. We continued our work with the benzoquinolizines and one of the substances, tetrabenzazine we thought to develop into a short acting neuroleptic. It was submitted for clinical trials and showed neuroleptic type activity but it could not compete with the neuroleptics already in clinical use.
- TB: What about benzodiazepines?
- AP: We did further research with Librium, and developed several benzodiazepine derivatives, not only for the treatment of anxiety disorders, but also for insomnia and the control of seizures in epileptics.
- TB: You also had the thioxanthene analogue, chlorprothixene.
- AP: Yes, chlorprothixene was our drug. There were two companies that developed it. In fact, we also had amitriptyline.
- TB: So you were involved in developing anxiolytics, antipsychotics and antidepressants.
- AP: We also had antibacterial agents as part of our profile. It was an important line of research at Roche even if psychotropics were at the center of interest at the time.

TB: I distracted you by asking you about chlorprothixene.

AP: We wanted to know everything about the mechanism of action of the benzodiazepines. Some of this work was focused on their action on the inhibitory neurotransmitter, γ -aminobutyric acid. They have an agonistic action on post-synaptic GABA-ergic mechanisms. As you know specific benzodiazepine receptors, binding sites, have been characterized in several vertebrate species.

TB: I suppose your group collaborated with outside researchers?

AP: We collaborated with Erminio Costa at NIH and with researchers in the department of pharmacology at the University of Basel. And we also collaborated with many other researchers.

TB: You already told us the background to the development of benzoquinolizines, benzodiazepines and iproniazid, but how did you get to developing chlorprothixene?

AP: We had a battery of tests to screen drugs for their possible psychotropic effects and our screen indicated the substance might have neuroleptic effects.

TB: Was it a behavioral pharmacology screen?

AP: Behavioral pharmacology; there was no biochemical pharmacology screen at the time

TB: Was the drug synthesized at Roche?

AP: It was. We got to it by molecular manipulation. We had the patent.

TB: What about amitriptyline. Did you get to it also by molecular manipulation and behavioral screening?

AP: Yes.

TB: In the development of benzodiazepines Leo Sternbach and Lovell Randall played an important role. Is Sternbach still alive?

AP: Yes, he's 94 years old, but he still goes to the office everyday; his wife takes him to his old office.

TB: Where is his office?

AP: In Nutley. He lives in Montclair, New Jersey.

TB: What about Randall?

AP: I lost sight of him. He moved to California. It was Randall who discovered that Ro5-0690 might be an anti-anxiety drug. You could say it was a serendipitous discovery.

TB: Chlordiazepoxide was an immediate success in North America.

AP: Yes.

TB: What about in Europe?

AP: Also. The nurses were stealing it from the hospital pharmacies, in order to try it on their patients. One of our managers told me if the nurses steal we must have a successful drug on the market.

- TB: Is there any other drug related to neuropsychiatry you were involved with we should talk about?
- AP: Are you interested in benserazide?
- TB: Yes, of course.
- AP: It is an extracerebral inhibitor of decarboxylase that enhances the effectiveness of levodopa in the treatment of Parkinson's disease.
- TB: How did you get to it?
- AP: It is a long story.
- TB: Tell us.
- AP: It starts with Arvid Carlsson's discovery that dopamine is a neurotransmitter and not just a mere intermediate in the synthesis of noradrenaline and adrenaline, and Sidney Udenfriend's recognition that DOPA is the biological precursor of dopamine. Dopamine is the decarboxylation product of DOPA.
- TB: Wasn't Udenfriend with Roche at Nutley?
- AP: Yes, he was. The discovery that dopamine occurs in relatively high concentrations in the brain centers responsible for the control of extrapyramidal movements, and Carlsson's findings that DOPA antagonized the reserpine-induced motor depression and decrease of cerebral dopamine, led to the assumption that dopamine was involved in the regulation of extrapyramidal motor activity. This is the background to Ehringer and Hornykiewicz's findings in Vienna that the concentration of dopamine in the striatum of deceased patients with Parkinson's disease is lower than in controls.
- TB: Weren't some findings indicating decreased dopamine in Parkinson's disease reported from Montreal about the same time?
- AP: I think it was a little bit later that Barbeau, Sourkes and Murphy in Montreal reported that in patients with Parkinson's disease the urinary excretion of dopamine was markedly decreased, indicating also a dopamine deficiency.
- TB: I see.
- AP: Since dopamine does not cross the blood brain barrier, whereas L-DOPA does, these findings led to trying L-DOPA in patients with Parkinson's disease by Birkmayer in Vienna and Barbeau in Montreal.
- TB: I remember meeting Barbeau about that time. He passed away a few years later. Both papers were published in the same year.
- AP: It was in 1961. Birkmayer's paper was coauthored by Hornykiewicz and Barbeau's by Sourkes and Murphy. In both papers symptomatic improvement was reported with levodopa in Parkinson's disease. Our contribution to the treatment was adding benserazide to the regimen. The idea

was to improve the effectiveness of treatment by protecting the amino acid from further metabolism and inactivation in extracerebral tissues.

TB: Was benserazide introduced as a combination with levodopa?

AP: Not by Roche but by Pfizer about the same time in the 1960s.

TB: Weren't monoamine oxidase inhibitors also tried by Birkmayer to decrease the dose requirement of levodopa?

AP: You mean levodopa together with a decarboxylase inhibitor and a monoamine oxidase inhibitor?

TB: Yes.

AP: At the time there was no monoamine oxidase B inhibitor available and combining levodopa with a non-selective monoamine oxidase inhibitor caused too many side effects.

TB: When did you step down from your position at Roche?

AP: I was Director of Research Worldwide from 1967 to 1978.

TB: What did you do after you stepped down?

AP: I was asked to create a Department of Clinical Research at the University Hospital in Basel and I did that. The department still exists and it's doing very well. The clinical research building is in the middle of the hospital complex.

TB: So you moved from Roche to the University.

AP: As I told you, I always taught at the University even while I was with Roche.

TB: Could you tell us about your activities in the Department of Clinical Research at the University?

AP: I created first a group that worked in hypertension, then a group that worked in oncology and a group dedicated to brain chemistry, and also some other groups. I was Director of the Institute, but I had a research field of my own.

TB: What was that?

AP: It was my idea of using platelets as a model for the brain, and I was studying in platelets the mechanism of monoamine uptake, storage, etc. Many people still use platelets to screen for monoamine uptake inhibiting drugs. It is especially suitable for studying serotonin uptake which is different from norepinephrine uptake. For the study of norepinephrine uptake the model is not as good. We discovered that serotonin is stored in organelles and showed that reserpine releases serotonin from these organelles. The biochemical work was mainly done with my Italian friends.

TB: When did you start to work with the platelet model?

AP: I started in the early 1960's.

TB: Any other research you would like to talk about?

- AP: We did research in hypertension with β -blockers, and research in immunology related to organ transplants.
- TB: For how long were you director of the Institute at the University?
- AP: For almost 10 years. I retired from my chair in 1988 and became President of the Swiss Academy of Medical Sciences. Prior to that, while I was still with the University, I was President of the National Sciences Foundation. I was also the President from 1981 to 1987 of the Research Council and the Administrative Council of the National Science Foundation.
- TB: Have you kept contact with Roche after you left the Company.
- AP: Yes, I was a consultant for many years. I went to their CNS meetings and remained involved with their clinical research. My successor was a pupil of mine.
- TB: Roche continued the research you started with monoamine oxidase inhibitors?
- AP: Although Zeller was my appointment he discovered iproniazid's monoamine oxidase inhibiting effect before I joined the company. He was working at a University in Chicago at the time when he discovered that iproniazid inhibits monoamine oxidase. He had been involved with monoamine oxidase since the late 1930s. But we did, later on, develop inhibitors of both monoamine oxidase A and monoamine oxidase B enzymes at Roche. I don't know whether we would have entered this area of research if we had not discovered that iproniazid is an antidepressant and without my findings that iproniazid and reserpine had the opposite effect on mood and serotonin levels in the brain. The company ultimately developed a monoamine oxidase A inhibitor for clinical use. Have you heard of it?
- TB: I'm familiar with moclobemide. I think it was introduced in the early 1990s. What happened with the monoamine oxidase B inhibitor line?
- AP: The company was not interested in it.
- TB: During the past 50 years you had numerous publications.
- AP: I published first when I was still at the University, and my last paper on the winding path of the history of antidepressants was published, last December
- TB: 2001.
- AP: Yes. I also reviewed the history of anti-Parkinson drugs. But these last publications are reviews and not reports on our original work.
- TB: During your distinguished career you received many honors and awards, Could you mention a few?
- AP: The first one I got was a Science prize. Then, I got the Marcel Benoist Prize. It is the highest prize in this country given to Swiss scientists. I

was elected honorary doctor and received honors from the University of Basel, Geneva, Rome, Zurich, and several other universities.

TB: You recognized early that progress in treating disease depends on the development of drugs.

AP: This was why I joined the industry; although, I did not necessarily agree with everything industry is doing.

TB: What is your problem with industry?

AP: It's too commercial. All the decisions are made by non-scientists with the involvement of lawyers, commercial people, economists, and the like. All of us are trying to make a contribution to society, and making money should not be the primary objective. Of course, you need money. You have to earn money. That's clear. Without money there's no research. My primary motivation was not profit, but helping people.

TB: You are very idealistic.

AP: But I also have to add I got a good salary at Roche, and I'm thankful for that.

TB: You contributed to helping patients with your new drugs.

AP: It was satisfying I could make a contribution in that way. As I said before, as a practitioner I would have been able to help only a small number of patients.

TB: What would you consider your most important contributions to neuropsychopharmacology?

AP: I would say our contribution to the treatment of Parkinson's disease; introducing the use of platelets as a model of the brain for studying uptake, storage and other processes in the neuron, and of course our demonstration that the effect of some psychotropic drugs is mediated by endogenous neurotransmitters.

AP: You have also contributed by training many people. Is there anything else you would like to mention?

AP: Oh, my family. I have a very happy family. My wife is from Zurich. I think she deserves an award, because I was away from home very often. I am also proud of my children. I have a daughter who is a physiotherapist and a son who is a medical doctor. They helped me out often. I don't know whether I helped them. I also have five grand children.

TB: I heard from somebody that you are a sportsman.

AP: I'm a hiker; I did a little bit of mountain climbing and skiing. I also did marathon runs; I did it several times and I'm proud of that.

TB: What are you doing these days?

AP: There are many things I don't do any longer, but I try to keep up with what's happening in genetics, in molecular engineering, and in the ethi-

cal dimension. I think you have an obligation to work for yourself, but you also have an obligation to contribute to your fellowmen. That's it.

TB: On this note we should conclude this interview with Professor Alfred Pletscher. Thank you very much for sharing this information with us.

AP: Thank you.

PAUL RONALD SANBERG

Interviewed by Matthew J. Wayner
Acapulco, Mexico, December 12, 1999

MW: I am Matthew Wayner and I am interviewing Paul Sanber* for the ANCP History Task Force. I find this to be a pleasurable experience because I've been, to a certain extent, one of Paul's mentors. I nominated him for membership some years ago and also wrote a strong letter in support of his application for fellowship status in the college. It was a strong letter because I believed he deserved it. I wanted him to become a fellow in the College because I knew he had been making significant contributions to the College and would continue to do so. Paul, as I said, it was a pleasure for me to interview you today. You're probably the best and most famous student I ever had. You're certainly reaching for some of the academic and scientific stars, particularly your recent work on nicotine in Tourette's syndrome, and the work you've done on neurotransplantation. I read your recent article in *Nature* on the Sertoli cells. It was a fine contribution and a very elegant piece of research. I would like to start off by asking you to tell us about your educational background, and from there how you got interested in neuropsychopharmacology, neurotransmitters, behavior and then into neurotransplantation.

PS: Thank you for the introduction. I am pleased to be here too and have you as my interviewer. It's interesting that you would ask me to do this; I still feel like a youngster in the field. I was an undergraduate in Toronto and worked with someone who was a major influence on me, Peter Ossenkopp.

MW: I know Peter.

PS: He was a graduate student, at the time, and I was a young undergrad, but he took me under his wings to help him do research. We worked on kindling; it was at the time when kindling had just been discovered in Canada. I was interested in antiepileptic drugs and was doing kindling research to study them. I was very interested in taurine; which is an amino acid thought to be an endogenous antiepileptic. So we looked at taurine's effect on kindling. I was one of these undergrads who wanted to be in the lab all the time, so we were feeding taurine to the rats and I was looking at learning and memory tests, among other things. So, as a young undergrad we published data on the effects of taurine inhibiting learning and memory in the passive avoidance test in the journal *Psychopharmacology*. I would view that as my first neuropsychopharmacology contribution. At that time I knew I wanted to

* Paul Ronald Sanberg was born in Coral Gables, Florida in 1955.

continue working in the field. I loved research. I couldn't get enough of it. So I went to the University of British Columbia in Vancouver to work in the kindling field. On the first day or so, I met another person that influenced me a great deal in neuropsychopharmacology, Dr. Hans Christian Fibiger.

MW: Who's that?

PS: Chris was a young assistant professor at the time. He had done a post-doc fellowship with Drs. Pat and Edith McGeer at UBC and had taken me under his wing. In the hallway he said he'd put me in his lab even though I was originally going to work on kindling with Dr. Wada, who happened to be on sabbatical. Dr. Fibiger gave me a desk with three or four other people in the lab and said "We're gonna start working on kainic acid". It was right at the time when the excitotoxins were starting. The original Joe Coyle paper from Johns Hopkins University and the original McGeer papers in *Nature* had just been published. My research was to do a behavioral analysis of kainic acid lesions.

MW: Where were the lesions?

PS: In the striatum. Loving research and being a dedicated young student we did a lot of work in this area. I ended up finishing my Masters degree there, working both with Chris Fibiger and Eddie McGeer on different aspects of kainic acid. In fact my first presentation at ACNP as in 1977 as a Masters student. Chris Fibiger came here to present our work, and I was an author on it. He was just elected a member when he came to give the presentation. Then I moved on to Australia. I had this strong interest in working on excitotoxicity and models of Huntington's disease, and still had "neuropsychopharm" interests. We were studying a lot of drugs, like haloperidol, amphetamine and apomorphine, looking at the function of the dopaminergic system on behavior in animals. I moved on to graduate school for my PhD at the Australian National University (ANU). Matt, I know you had affiliations with ANU and that was my first time learning about you.

MW: I was at La Trobe University in Melbourne. What year was that?

PS: I was there from 1978 to 1981.

MW: I think our daughter, Lisa, was also studying for her PhD at La Trobe at the same time.

PS: Right. During that time the person that probably influenced me most was Dr. Richard Mark, head of the Department of Behavioral Biology at the ANU. He considered me like a post-doc because I published numerous papers as a Bachelors and Masters student. He decided he would let me do what I wanted. So I continued to work on the striatum and excitotoxicity and then moved on to Johns Hopkins Medical

School to work with Joe Coyle. I consider him a real mentor in my life, someone who helped me a great deal. In fact he still helps me. I saw him today at the meeting and we had a nice talk.

When they asked me “who do you want to do the interview?” I wanted you. You have been a very strong influence on me personally. I met you when I was a Travel Fellow here at the ACNP in 1984, in the second class of Mead Johnson Travel Fellows. I felt honored since I had applied from a relatively small university after I got my first academic position at Ohio University in Athens.

MW: I remember that.

PS: I finally had my own lab but I had gone from being on the fast track at major research universities to a small university. I needed to set up my own space and it was kind of impressive. During job interviews I found that the more prestigious places you go, the less space you get. The less prestigious place you go, the more space you get. I also think, being foreign trained, I didn’t care much about institutional status in the US.

MW: When you went to Ohio University you replaced Robert Almli who moved on to Washington University.

PS: That’s right. So, I came here as a Travel Fellow, and during that time I met you. I had always been impressed by your work; especially through the eyes of Bill Bellingham, and of course I had submitted articles to your journals even as an undergrad. Kindling articles were published in *Physiology and Behavior* in 1976, and one of my very first kainic acid articles was published in *Pharmacology, Biochemistry and Behavior* in 1978. I really thought those journals were very important to my career. So I was in awe with meeting you. You became a good mentor in my life, especially through our talks here at the ACNP. You have sponsored me at various times for various things and I appreciate that.

MW: Were there any novel findings or novel techniques you developed early in your research that you remember? The kainic acid studies were probably right at the beginning.

PS: The first one was the use of excitotoxins to make selective lesions. As an undergraduate I had used electrolytic lesions, like all of us. Then all of a sudden we had a new lesioning tool, which was the excitotoxin kainic acid. I put a lot of effort into that to try to understand it. This is a lesioning tool, especially, in behavioral neuroscience. Some other chemical tools we used were methylaxoymethanol as a mitotic inhibitor to produce a microcortex with Joe Coyle. We also did the early work with Joe on a selective cholinergic toxin, a lesioning tool for the cholinergic system. I also view myself as being fairly inventive with the

DigiScan boxes. When I was in Ohio, I realized I wanted to measure more than one aspect of rodent motor behavior at the same time automatically. Prior to that, I set up equipment to measure rodent behavior in Australia using BRS equipment. The old BRS equipment had shuttle and jiggle boxes and you got one measure out of it. So I thought, is there some way we can get lots of measures simultaneously? In Ohio I became friends with Mr. Kant at Omnitech Electronics in Columbus. He started working on this concept and allowed me to help design the DigiScan locomotor analyzer which allowed you to put an animal in an observation box that had infrared beams in three dimensions. It would give you over twenty different variables of movement. This included where the animal moved, velocity, repetition, rearing, thigmotaxis, etc. I really enjoyed the development of that; it was an important technique because it allowed us to understand the effects of drugs on behavior from a multi-variable point of view. Without that it's hard to delineate between drugs you give any animal when you're measuring only one behavior. When you give, for example, a depressant you decrease motor behavior. Similarly if you give a neuroleptic you may get the same decrease in motor behavior. If you were predicting outcome, you might say those are similar drugs based on simple motor behavior effects, but they're not similar. When these drugs are given to humans, clearly they are different drugs with different effects. We needed multivariate analysis in animal behavior to be able to say that one drug, such as a stimulant, may increase an animal's behavior in a certain way, which is different from another stimulant. This was an area I worked hard to develop an "activity print" for psychoactive drugs. I also started to move into functional recovery which became my next area. I would create lesions and do different things. The idea was how can we use these models to get therapeutic functional recovery. It was important because we need to understand these animals as small patients. For example, if you have an animal model that is hyperactive and you want to bring its activity down by drugs, are you actually influencing the mechanism underlying hyperactivity down? Or are you generally depressing its behavior? We were trying to understand why they showed these deficits, were we developing new therapeutics or just influencing the general level of activity. So, those were theories I needed to develop.

MW: And those were major findings?

PS: Right, those were major ones at the time, bringing computer technology to animal behavior.

MW: You published many comprehensive research reports in this area.

PS: Yes, we had quite a few.

MW: I remember some we published for you.

PS: Yes, many papers were on this topic; studying how drugs affected behavior using an automated computerized multi-variable approach to locomotor activity. My interests continued to move into therapeutics and recovery of function. This led to my research in cell therapy, which is an area I fell in love with in the last ten to twelve years. We've developed many techniques to replace lost cells in the brain or to use cells for delivering molecules to the brain. That is probably another area we made significant findings in.

MW: That was about the time you changed positions, and went from Ohio University to the University of Cincinnati Medical School. That's where you did a lot of work on motor activity analysis related to neurotransmitters and psychoactive compounds, particularly those with motor effects.

PS: Correct.

MW: Then you left to join a biotech company and that's where you started to get more involved in cell transplantation.

PS: Yes.

MW: Can you tell us more about the transitions in your career, starting in Ohio? That represents some significant scientific contributions in your life.

PS: Yes, it was a very interesting time. When I was in Athens, I enjoyed the lifestyle as I had a farm, easy commute and a beautiful University and setting. But, I realized I needed to be back at a medical school to do the kind of research I wanted to develop. So I moved to the University of Cincinnati where I worked in David Garver's group, who is also a member of the ACNP and a significant person in my life. He allowed me to participate in his studies determining physical changes in the brains of schizophrenic patients who were either neuroleptic responders or non-responders. He also allowed me to continue working on transplantation for which I received some nice grants on using fetal tissue transplantation for Huntington's disease. We'd created all these models of diseases using toxins and I had done all this behavioral analysis, so it was a perfect opportunity to study neurotransplantation therapeutics. It eventually got to the point where, in the field of transplantation, biotech companies were starting up. Here was an approach to treat disease by replacing cells and one of the first companies to form was a company now called CytoTherapeutics, Inc. When we started it was called Cellular Transplants, Inc. a spinoff from Brown University in Providence. So we moved to Providence and I became scientific director of the company. It was a very interesting few years, where I learned biotech business, and a whole different perspective related to industrial science. Our focus

was to develop products that could be used and it was at that point I left neuropsychopharmacology research for awhile. I studied things more at the cellular level.

MW: That was about the time we interacted again, in terms of mutual interest. Mine in journals, and you're developing interest in starting a journal.

PS: Absolutely.

MW: Which finally materialized in the new publication, *Cell Transplantation*. What was the first year of publication?

PS: 1991, and it's in its sixth year now. That's an interesting point since I was working with Pergamon Press, which published your journals. I'd asked you for some advice; I thought it was an appropriate time in this new field to have a scholarly journal. You suggested Pergamon Press, we approached them and they went for it. They started the new journal, which is now published by Elsevier.

MW: That's great!

PS: Yes. It's a very interesting field and one that's allowed me to have two diverse areas of research. One is a very cellular therapeutic area which I do not see as different from a lot of neuropsychopharmacology, using cellular approaches to deliver molecules. One we are focusing on now is Sertoli cells as you mentioned at the beginning of the interview. With Dr. Cesar Borlongan we're trying to use these cells that release various trophic anti-inflammatory factors, or various other small molecules we can deliver directly into the brain through transplantation. Thus, we're not having to give a systemic medication which also allows some of the trophic factors, that don't get in through the blood brain barrier, to enter directly. In essence we are using the cell as a drug pump to release localized chemicals. It is a very important direction for the field, especially for neurodegenerative disorders.

MW: Yes, it is.

PS: Even some of the psychiatric disorders, as we see in the posters, are showing more relationships to neuropathology.

MW: Being an innovator in that field must be very satisfying.

PS: It's been very satisfying. It's also a field that's novel enough that it's paid some of the bills. It's allowed me to learn biotech and industry more than I would have. And it's allowed me to help others patent new ideas and set up new biotech companies.

MW: You continue to translate your research into the clinic. For example, the very dramatic effect with the nicotine patches, in boys with Tourette syndrome. How about this new cellular approach for delivering trophic factors or other substances that might be of some benefit? I know you've been working with a neurosurgeon, scrubbing in when he works,

preparing the cells for transplantation surgery and really putting it to the test.

PS: Right. For the archives, it was interesting listening to Dr. Steve Hymans talk today about translational research from basic to clinical. I am really very committed to translational research from seeing something in the lab and then studying it in people. For example, this summer with Dr. Tom Freeman we did our first patients with Huntington's disease using fetal transplantation, and yet it was 1983 when I published the first paper in animals, showing that it might work and it could be used. It was almost fifteen years later that we finally did it in Huntington's disease. It was very satisfying to be in the OR to see the first patient done. Now, as we do Parkinson's patients with transplantation, it's satisfying to move to the clinic. I like the cell transplantation field, but I consider the nicotine field we've been in, also very interesting and more related to neuropsychopharmacology.

MW: I think that the nicotine data you've presented has been dramatic, very important and significant. Would you consider that to be your most important contribution so far?

PS: It's hard to think of yourself when you work as a team, with so many great people. What I've enjoyed and think is important is the translational approach. I remember working with Dr. Don Moss and Dr. Andy Norman when we found our nicotine effect, showing it could potentiate Haldol's behavioral response. Following this I remember walking down the hall to talk to Dr. Brian McConville, head of child psychiatry at Cincinnati. I asked him to try it in some Tourette's patients and it appeared there was actually an effect. And then to take that further and get an RO1 grant from the NIH with Dr. Archie Silver and Dr. Doug Shytle to do a double blind trial on nicotine patches and Tourette's syndrome was stimulating. Furthermore, we now understand the mechanism of action better and can show it's a down regulation of nicotine receptors underlying the effect. We have carried this further into a biotech phase with the nicotine antagonist mecamylamine. I really hope that it leads to some therapeutic relief for kids with Tourette's syndrome. Anecdotally, through the Tourette Association, we have heard of patients that try it with some improvement, since these drugs can be prescribed off label. It's always nice to demonstrate such a journey; the same thing goes with our transplants, working from rat research to human clinical trials.

MW: Being in a medical school setting, where it was easy to interact with people who are interested in more clinical aspects was probably very advantageous in bridging the gap between basic research and clinical potential.

PS: You're right, because being in a psychiatry department as a basic scientist and now in a neurosurgery department, allows me to explore the avenues between basic and clinical research. And I had the time to do it as a scientist. I'm really indebted to Dr. David Cahill, our Chair, for giving me such a unique opportunity. Most clinicians have to see so many patients. They rely on us to help continue some of the research and maintain scholarly interests within the limited research time they have. This is especially the case with the busy neurosurgeons, and they are always willing to consider experimental neurosurgery.

MW: It's very time consuming.

PS: They don't get paid for it. So you have to show them how and get them interested. It's been an enjoyable type of position, I would recommend that for anybody going into the field.

MW: I remember myself many years ago, it's got to be in the late 50's when I was at Syracuse, working with Dr. Sam Atkin, who was a neurosurgeon. A big problem, even then, was trying to do research with a neurosurgeon. We would make plans to do something, for example, we were going to do some recordings on the cerebellum; but we never did get the experiment done because he always had so many emergencies. It's impossible for a good neurosurgeon, who's busy all the time, to get involved in doing research. To have someone like you, who can come in when that rare opportunity develops, is extremely important. It's interesting that some comments were made at the special meeting this afternoon about a different kind of philosophy. Some of these new program projects or center grants are going to require direct interaction between people doing basic research and clinicians; that's going to be very important.

PS: Absolutely. That's the way it has to be.

MW: Truthfully, I think, they can pull it off.

PS: With money being as tight as it is, it has to be that way.

MW: You've been in several important fields. It's difficult, as it has been for me, to determine your most important interest or research contribution; of course, it might still lie ahead.

PS: That's what I'm hoping. I'm hoping I haven't already made my biggest contribution.

MW: It still lies ahead.

PS: It was nice to have this now, after the recent rush in *Nature* of our papers on Sertoli cells. Ten years from now people will be asking why anyone ever thought of doing that, to transplant cells that are trophic factor factories. Will they say it died in the dust?

MW: That's possible.

PS: But, we have other very important cells we are working with and this whole idea of using ex-vivo gene therapy in cell transplantation. Being able not to just put cells in the body, but engineer those cells to release various substances. And to be able to get stable long-term expression of these substances, will be a key thing in the next few years. If we can do that, if we look at this ten years from now, there could be some significant therapeutic cells in clinical trials or even commercially available.

MW: How long were you Director of Research for the biotech company?

PS: A couple of years.

MW: How did you manage to stay in the field? One of the difficulties you were having was trying to resolve the conflict of spending more time in administration and less time in the lab. I imagine what happened was you moved back to academia?

PS: That was true.

MW: You might want to comment on your experiences in administration.

PS: It wasn't the right time. I did not feel comfortable enough with myself to be a full time administrator in a company. Especially in a biotech situation where your venture capitalist investors put fast moving pressure on you and your team. I was learning as I went along. I absolutely missed the creativity, I missed the labs, I missed talking to people about science. When you move to Biotech they say "focus" because you only have one or two products, and you must decide what you're going to do so it can quickly go into the development stage. Designing development experiments is about as boring as you can get in many cases. Once it's set, it's set as per the FDA approval you are seeking. So I missed the creativity and I realized my need to go back to academia. I had a lot of creativity left in me and could develop new ideas, not take a product through rigorous development. I might do that at sometime, but at this point I'm enjoying the life where I'm bridging the academic and industrial worlds. Having been full time in industry allows one to view academia differently. If we have patentable and creative ideas, we can license them out to companies. We can be involved that way and have the best of both worlds. Or even set up a company at your university; that's a great opportunity too.

MW: Are you doing much teaching now? I know in the past you've taught undergraduates and you enjoyed teaching them. But recently, I imagine you haven't been doing much teaching. Do you miss it?

PS: I do and I don't. I miss the undergraduate teaching, and enjoyed the senior undergraduate courses in psychopharmacology, behavioral neuroscience, and some of the graduate courses. I don't miss a lot of the prerequisite courses they want you to do. On the other hand, I am so

busy with other things that giving lectures here and there makes up for the lack of teaching. Finding more money constantly to keep the labs going and your people employed is difficult. In this business, it's hard to sit back and not focus on teaching if you want to teach right and teach well.

MW: That's true. Effective teaching requires a great deal of preparation and there are very few people who can get up before class nowadays, in any biomedical science, and give what would be considered a first rate lecture without extensive preparation. There's just too much literature out there. When I first started teaching you could give a lecture without any notes. You knew the material, you knew what was important, and you could get it across. But now you have that apprehension; what happened yesterday? Are we supposed to really be up to date in this class? That's another aspect of our lives that has changed. So, let me ask, are you happy with the way things turned out in your life and where you are now?

PS: Absolutely, I think I've really been lucky. I've worked with some great people, including yourself. I've worked with good people who helped me along the way, have allowed me to be creative and who appreciated productivity. They have not hindered my growth. Clearly we run into road blocks periodically. But I like the way things have turned out, I like the interactions of academia with industry. It'll be interesting to see in ten, twenty or thirty years how the biotech field and academia are able to relate to each other. Or was this a brief period in history, something isolated?

MW: Are you looking forward to the next ten years?

PS: I'm looking forward to it! I feel I'm fairly young and the ACNP shouldn't be asking me these questions right now. On the other hand twenty years from now...

MW: It might be different?

PS: It could be different and I might be sitting here interviewing someone else. I'll be coming to meetings because I love the ACNP. And it'll be interesting to see what's happening in the field.

MW: I'm sure lots will be happening between now and the next ten years and the ten years following; that's what's interesting about science. It's boundless. Every time you do an experiment, it results in doing another five, ten or fifteen. That is what makes it exciting, the discovery phase. Have you any advice you want to pass on to younger individuals coming into the College?

PS: The College is such a unique place. "College" is the right name for it. It's collegial, although there are times, with my transplantation work,

I feel a little off base. But so many people are interested in different aspects of neuroscience here that it's a nice forum. And I enjoy being a travel fellow alumnus. The fact that there are a few of us who have been travel fellows, became members, became fellows of the College, and have been on committees, is inspiring. To be on the committee that picks travel fellows was a highlight of my ACNP experience. The College makes you feel part of it, makes you feel involved by allowing you opportunities like that. To look at someone like Dr. Charlie Nemeroff, who was a travel fellow before me and became President of the College is great. It's a nice organization and I would encourage anyone to get involved. Especially nowadays with so many more travel fellowships available. Let's hope, in ten or twenty years, there are even more available. The College provides a great opportunity for professional and personal growth.

MW: Well, thank you very much.

PS: Thank you.

ELAINE SANDERS-BUSH*

**Interviewed by Joel Braslow
San Juan, Puerto Rico, December 8, 2003**

JB: I guess we should begin from the beginning. Where are you from and when did you know, initially, what you were going into?

ES: I was born in Kentucky and grew up on a small farm; my parents were poor. Although neither graduated from high school, college was extremely important to my mother and I went to college at her insistence. I planned to be a high school teacher, but when I took my first education course, which was pretty darn boring, I decided that teaching was not for me. I double-majored in biology and chemistry and was beginning to consider an advanced degree. In my junior year, a faculty member from the Department of Pharmacology at Vanderbilt University came to talk to the chemistry majors about graduate studies in pharmacology. I thought pharmacology was fascinating and decided I would go to graduate school. So, I applied to three programs, one in pharmacology at Vanderbilt, and two others, one in physiology and one in biochemistry. I got accepted to all three and decided to go to Vanderbilt, because it had a better reputation.

JB: Your interest in pharmacology, was it primarily motivated by the fact that you took it in college?

ES: No, I had never heard of pharmacology. My interest was sparked by the recruitment visit of the pharmacology faculty member.

JB: What was it that excited you about it?

ES: The blend of biochemistry and physiology; I was good in both and facing a hard choice, so to blend those disciplines seemed ideal. In a sense, that's been an emphasis throughout my career, performing interdisciplinary research where I combine biochemistry and molecular biology with physiology and behavior. I am very interested in cells and how cells function, but I also like to put my research in a broader context of behavior and disease.

JB: What have been the most important kind of studies you've done over the years?

ES: I was trained in drug metabolism, so that was chemistry, and then became fascinated with the new field of psychopharmacology. We had a professor, a young scientist, who was recruited to Vanderbilt to head up the psychopharmacology unit, Fridolin Sulser, and I desperately wanted to work with him because I was so fascinated by the area.

JB: This was when?

* Elaine Sanders - Bush was born in Russellville, Kentucky in 1940.

ES: In 1967 I got my PhD degree, and went to do postdoctoral work with Dr. Sulser. He was at Vanderbilt but his laboratory was off campus at a psychiatric hospital, which has now been closed and bulldozed. But, in those days, it was an ideal environment, with basic and clinical scientists under the same roof, talking to each other.

JB: Was it a state hospital?

ES: Yes, a state mental hospital, Central State Hospital; one building was dedicated to research, the Tennessee Neuropsychiatric Institute. We had a cadre of scientists there who were interested in drugs and psychiatric diseases, i.e., psychopharmacology. It was a very dynamic, exciting environment because of the people who shared common interests and goals. I got married soon after graduation. My husband was a faculty member at Vanderbilt, so I wanted to stay in Nashville, but there were not a lot of opportunities. So, I was fortunate that Dr. Allan Bass, chair of Pharmacology at Vanderbilt, offered me an opportunity to join the faculty.

JB: Was this after graduate school?

ES: Yes, I became an assistant professor in 1969, and my laboratory was off campus at the Tennessee Neuropsychiatric Institute. I stayed there until about 1983. A couple of key people left and the critical mass fell below what was ideal for having this great "collision-coupling" experience. So, I asked to move to the main campus. My research had shifted from presynaptic mechanisms to receptors and postsynaptic mechanisms including intracellular signaling that's one of the major strengths at Vanderbilt. I felt that my research would benefit from being on campus.

JB: Your early work was on?

ES: It focused on psychostimulants, like para-chloroamphetamine and fenfluramine. While I was working as a post-doc with Fridolin Sulser, I discovered the long term action of these drugs on brain serotonin; after a single dose, there was prolonged depletion of serotonin for weeks, which we speculated might be related to neurotoxicity. It was later demonstrated, convincingly, that these drugs were neurotoxic. That was a very novel finding and exciting time; this research was all related to presynaptic mechanisms and basic neurochemistry.

JB: Focus a little on your early work. Were you thinking about studying the mechanism of action of antidepressants at the time? What was your motivation?

ES: No, I don't think I was thinking in the context of antidepressants. I guess I was thinking more in the context of unique properties of halogenated amphetamines and what their mechanism of action was; they interact with dopamine and, there was also some evidence that they might

interact with serotonin. Fridolin Sulser said, "why don't you look at the serotonin system for these psychostimulant drugs that are related to amphetamine and see how they interact with serotonin"? He was primarily working on norepinephrine in those days. So, it was something new for his laboratory. Fridolin was really good at developing young people and thought this project would give me independence and recognition. So, I took the project and made this significant discovery.

JB: What significant discovery?

ES: First of all that they had these long term effects was very surprising and it was novel that a single dose would have such a long term effect.

JB: And, did you have a hypothesis about why?

ES: We tried to define the mechanism. We initially thought the drugs were releasing serotonin, which they did, but then, there was a depletion of serotonin and 5-hydroxyindole acetic acid, as well as a loss of the pre-synaptic serotonin transporter. In those days it wasn't called serotonin transporter but rather, fluoxetine sensitive transport. All of the presynaptic markers of serotonin were markedly reduced, which lead to the hypothesis that these drugs were neurotoxic.

JB: What animal did you use?

ES: Rats, primarily. We did a little work in mice. Mice are much less sensitive to these drugs, so if we had been using mice to start with we wouldn't have made the discovery! What was so fascinating about this work was that there was another drug, fenfluramine, which was clinically used in Europe to reduce appetite. It was a very close analog of p-chloroamphetamine, so we looked at fenfluramine and it also had long term effects. That was kind of shocking because it was being used clinically.

JB: It had been thought these drugs acted for a short period?

ES: A very short period of time, because people had never looked at their duration of action.

JB: What were the implications of that drug having long-term effects?

ES: We worried about neurotoxicity in humans. I mainly stayed away from that issue, which was a big controversy. There was a successful attempt to license a form of fenfluramine in the states for reducing appetite, which ended up being combined with phentermine, Fen-Phen, and later withdrawn from the market. You remember that, don't you?

JB: Yes, I remember that.

ES: The effects of fen-phen that caused its withdrawal were not related to the CNS, but were cardiac valvular defects. But, I always thought I'd never want to take that drug myself or have any of my friends or family take it, because I believed that the biochemical evidence of a long term loss of those presynaptic markers suggested that it was neurotoxic.

JB: Did you continue with other drugs that were being used as appetite suppressants?

ES: We did not; most don't deplete amines like fenfluramine does, so that wasn't the logical thing to do. Then, I shifted over to postsynaptic mechanisms, receptors and intracellular signaling. In about 1978 I was up for the third or fourth renewal of my grant on the halogenated amphetamines, and I had a problem with the renewal. There are good times and there are bad times in any research program. When I wrote the renewal application, it was not the best and most exciting time in my research. The committee that reviewed my grant was not impressed and the grant was not funded. That was the first time this had happened to me, so it was a shock. I thought, maybe I am just re-plowing old ground. Maybe I really need to change. So I changed my focus and started looking at serotonin receptors in about 1979, when radioligand binding was just developed and that research had taken off.

JB: What was the motivation to go into receptors?

ES: In part, it was the disappointment of the grant not being funded, but also the excitement of working on neurotransmitter receptors. When I trained as a student, it was taken on faith that receptors existed. The properties of the drugs were such they suggested there were specific receptors but we didn't have any real evidence. Once we got tools for quantifying and characterizing receptors, it was an exciting time. Since I was interested in serotonin, I decided I should shift over to working on serotonin receptors.

JB: Can you explain more about the shift in focus?

ES: I started first doing simple radioligand binding assays, and found evidence for multiple binding sites but I wasn't confident enough to publish it. In those days, it was spiperone that we used to identify the 5-HT₂ receptor. We had indications that spiperone bound to ³H-5HT binding sites with multiple affinities, which would suggest it's binding to more than one receptor. So, the logical interpretation was there were multiple receptors serotonin was interacting with.

JB: And, that was a new idea at the time in terms of thinking there might be multiple sub-types. And, it hadn't been published before?

ES: No, it hadn't, but I didn't have the confidence to publish it. And, then, Sol Snyder and Steven Peroutka came out with their paper showing there were multiple binding sites for spiperone. Although I was disappointed we were "scooped", it actually made me feel good because we had seen the same thing.

JB: When was this?

- ES: About 1980. So, we shifted from looking at receptor binding to studying intercellular signaling, the second messengers that are formed and downstream signaling cascades.
- JB: It's been a progression in your research from presynaptic to postsynaptic, to intracellular.
- ES: Yes, I have focused on serotonin all of my research career, although the questions and level of analyses have shifted dramatically. It's been a very rich area for study. We did some of the earliest work on signal transduction mechanism for the 5-HT₂ family of receptors, looking at second messengers that were formed and how that was regulated.
- JB: When did you start looking at second messengers and studying them? What tools were available?
- ES: Probably 1982. Adenylate cyclase creating cyclic AMP as the second messenger was well-known in those days, indeed the first and only well-recognized second messenger at that time. There was a paper from Michael Berridge, in Great Britain, showing that serotonin accelerated calcium release in an invertebrate system via a phospholipase C signal transduction pathway. I thought that was fascinating, calcium as a second messenger, and one of my graduate students, Jeffrey Conn, started exploring the possibilities in brain; we were one of the first laboratories to show that calcium was a second messenger for the 5-HT₂ family of serotonin receptors.
- JB: What was it that motivated you to start looking at second messengers as opposed to sticking with the membranes?
- ES: Part of it was the environment at Vanderbilt, where we had scientists who were exploring intracellular second messenger systems, although not in the brain. Earl Sutherland, who won the Nobel Prize for discovering cyclic AMP, was at Vanderbilt and around him, was a tremendous cadre of people that were looking at adenylate cyclase and intracellular signaling in that pathway. So it was the intelligent culture that fostered my interests and the development of a new research focus.
- JB: Was this unique to Vanderbilt?
- ES: It was in those days. Even today we're considered leaders in the field of second messengers and intracellular signaling, because we still have very strong laboratories studying the fundamental processes including kinases and phosphatases and other intracellular signaling mechanisms. If we put together that with the expertise we have in pharmacology, we will learn a lot about how drugs and neurotransmitters produce their effects in neurons.
- JB: Was your work unique at Vanderbilt in a sense of linking, on the one hand, pharmacology and on the other, biochemistry?

ES: Fridolin Sulser had been looking at norepinephrine and adenylate cyclase for several years; while I was his post-doc that was his major focus. But it was all adenylate cyclase and cyclic AMP and not the calcium second signaling cascade. Now there are many more signaling pathways we know, but, phospholipase C/calcium was the second one that was recognized as being important.

JB: And that came from you?

ES: Yes, with regard to serotonin. When you think about serotonin and the drugs that interact with it, understanding the cellular mechanisms is important. Although a lot of my studies in the early days were done in brain tissue, I moved into recombinant cell lines, where we expressed the cloned receptor in a cell and so can study that receptor and its signal transduction in great detail. It was a very attractive molecular tool; the problem is that these recombinant cell studies only tell you the possibilities, not what is actually occurring in brain.

JB: Explain that more, will you?

ES: You're expressing this cloned receptor in a cell line that doesn't normally express the receptor and you assume the mechanisms you are defining in that cell are the same that are going on in a neuron in the brain, but this is merely an assumption. Initially, you're making so many discoveries, you just keep going and going until finally you ask yourself, what does it really mean? In the last decade, I've been challenging the people in my laboratory to start asking, what does it really mean? We know, for example, that hallucogenic drugs interact and activate these signaling cascades; indeed, they activate multiple intracellular signals. Is that really important to their behavioral actions? Now we are trying to devise ways to address that question. It's not easy though. It was a lot easier to do the studies in cells.

JB: Do you see that as a problem in general?

ES: Yes. It's really hard to put it all back together. My advisor as a post-doc, Fridolin Sulser, used to always say, "You can't fix a watch if you don't know how it works". And, that's true. That analogy is true for the brain; you learn all these things about how the signaling cascades work but the question is, how does it all fit together to create brain circuitry and function. Now, we have animals that have been genetically modified to block expression of specific molecules or to over-express specific molecules, so we can begin to examine the role these molecules have in behavior. I have not been enamored of those kinds of studies because you have so many potential complications related to developmental problems. You knock out a gene in utero and the animal grows up in the absence of that protein; this could have major effects on circuitry

- or functions of the brain that are independent of the loss of that receptor in the adult, so that's a complication of these kind of studies. Even so, they have given us some great insights.
- JB: It was ten years ago when you started thinking about how you put it all together. What motivated that thinking?
- ES: That's a good question. I had explored many intracellular signals, including changes in immediate early and late gene expression, defining the sequence of events that produced these changes in isolated artificial systems. But I've always felt the need to relate my research to behavior and disease. You get caught up in the power of this strategy because it's really exciting and you're learning new things. Maybe it's a lull, but all of a sudden you say to yourself, "what does all this really mean"?
- JB: Is there a moment in time you can identify?
- ES: No, I've always had behavioral collaborators and done behavioral studies, but they were a bit ancillary. I liked to think our biochemistry would drive the behavior and the behavior would drive the biochemistry, but it was hard to link intracellular signaling to behavior in the early days. I still do studies on cells in culture, but I am also exploring methods to manipulate intracellular signaling in gene transfer experiments or injecting dominant negative proteins to block a specific step in the signaling cascade to see how this alters behavior.
- JB: Can you explain some of the more important work you have been doing in that context?
- ES: This is still in the developmental phase, but about five years ago, I had a graduate student, Mike Chang, who wanted to take up the challenge of trying to determine whether or not signaling pathways we were defining in artificial recombinant cell lines occurred in cells that naturally expressed serotonin receptors. In collaboration with a peptide chemist, Mike developed tools for blocking different steps in the signaling cascade. The key was to figure out how to get the blocking peptides into native cells since they wouldn't penetrate the cell membrane. So Mike approached this biochemist who had developed peptide conjugates that were membrane permeable and, modifying these techniques, we developed methods for manipulating intracellular signaling in native systems. Then, I began to wonder, could I apply this strategy to the brain, to the whole animal? About this time, retroviral transfer strategies were being developed where the retrovirus infects cells and then expresses the peptide that is linked to it. Early successes had utilized these strategies in primate models of Parkinson's disease. So I thought, maybe we can use viruses to move the blocking peptides into neurons. We cloned the peptide cDNA into a lentiviral construct for microinjection into brain

sites that may be important in the action of hallucinogenic drugs. The goal was to block intracellular signaling at different steps and see which steps are important.

JB: Tell me more about the significance, especially in the context of hallucinogenic drugs.

ES: If we could understand how hallucinogenic drugs alter neuron function to elicit their behavioral effects, that would give us clues about the mechanism of hallucinations in diseases such as schizophrenia and, perhaps, new targets for drug development. I'm interested, in a broader question with regard to hallucinogenic drugs, in defining the circuitry in brain responsible for their profound and unique behavioral effects.

JB: The circuitry in an animal?

ES: Yes. We don't know what the circuitry is and what brain sites are critically important for the action of hallucinogenic drugs. For any psychoactive drug, defining circuitry opens up opportunities for tailoring therapy and reducing side effects. For example, when the shell of the nucleus accumbens was identified as a critically important site for antipsychotic drug effects and scientists started specifically manipulating dopamine receptors and dopamine dynamics in that precise area, much was learned in a very short period of time that reshaped the field. For hallucinogenic drugs we don't yet have a key brain site to focus on. So, I wanted to directly inject the lentiviral constructs into specific brain sites and examine the behavioral consequences.

JB: In the animal, how do you do that?

ES: We model hallucinogens in a behavioral assay called drug discrimination, which is a paradigm where animals, usually rats or mice, are trained to recognize they've been given a drug, using some kind of internal cues. We have no idea what that internal cue is; it's probably not hallucinations but it is brain mediated and specific to the class of hallucinogenic drugs. In my opinion, it's probably the best behavioral paradigm available for hallucinogenic drugs. Again I had an eager graduate student, Efrain Garcia, and we chose a lentiviral expression system, which infects nondividing cells, critical for studies of neurons. Unfortunately, to deliver sufficient peptide, we ran into toxicity problems with the viral preparation so we abandoned that strategy and moved to genetically modified mice for current studies.

JB: Even now, you're very active and pursuing new ideas.

ES: Yes, and in addition to research, I am very active in graduate training. I am Director of the Neuroscience Graduate Program at Vanderbilt. Leading the development of this transinstitutional graduate program for six years is one of my greatest achievements. The non departmentally

- based program has gained national recognition and we have fifty-two PhD students currently in training.
- JB: And, prior to that, graduate students interested in neuroscience were being trained in specific departments?
- ES: Yes, they could take a course in neuroscience, but they were trained in pharmacology or physiology or biochemistry. Our rigorous, focused neuroscience program, changed the landscape of graduate education at Vanderbilt and I'm very proud. I love interacting with students, so that's been another rewarding aspect of my professional life.
- JB: It sounds like your career and your own training modeled this interdisciplinary graduate program.
- ES: Interesting observation. I always try to convince the students, although it's hard because they want to focus right away, to get breadth, be able to think from molecules to behavior, because that's where the future is. I think if our graduates can't use all this information we're learning from molecular biology and put it in the context of the whole animal, they will be missing an amazing opportunity. That's what the future is for neuroscience, and we reemphasize it over and over again to our students, requiring them to take courses that move from molecules to behavior. Graduate school is the last opportunity to get any kind of breath, whatsoever, because once you start your post-doc and you get your own lab, you have to focus, focus, focus...
- JB: Looking back over your career, nearly forty years now, consider this question: What will you be most remembered for?
- ES: I guess it might be the training. That may have the greatest impact, ultimately, on science and health. It's all the young people I've helped train and put out there; they're the ones who are doing great things. We have some stellar trainees, and that's what's really important to me. Of course, research is important, too.
- JB: How big are your honors, in terms of your own scientific discoveries?
- ES: Our early work on the neurotoxicity of the halogenated amphetamines had a major impact in the field as did our early work on signaling and how different serotonin receptors interact with intracellular signaling cascades. We did a lot of permutations of this, such as RNA editing of the serotonin 5HT_{2C} receptor, a novel post-transcriptional modification that alters receptor function that was discovered in my laboratory. Since RNA editing of the 5HT_{2C} receptor is altered in psychiatric diseases and reversed by drug treatment, it is interesting to speculate on the possible ramifications in abnormal human behavior. We're now looking at the single nucleotide polymorphisms identified in humans and how they may

alter receptor signaling. I don't know what will be the most significant; that will be determined by future research.

JB: In view of the dramatic changes over the past forty years what do you think have been the most important changes in neuroscience, in general, and what has been the driving force behind those changes?

ES: This is impossible to answer. Neuroscience was only born within the last forty years. It's gone from nothing to unparalleled importance. There's still so much we don't know and so many more discoveries to be made; it's such an exciting field to be working in. New developments where one can do non-invasive studies of the human brain are very important; current clinical research that links genetics with fMRI, with behavior and with disease is fascinating. It is this blending of different disciplines, and using multiple approaches, that fascinates me and is, in my opinion, the most powerful approach. That's really the future of science.

JB: Do you have a hint as to what accounts for this quite amazing explosion, because your career epitomizes that?

ES: The brain is so complex and difficult to study. It took a long time for the scientific community to begin to think that the brain was tractable enough that we could understand how it functions normally and goes awry in disease. Many people who started in other disciplines have found neuroscience research exciting because there are still so many unknowns. I don't know when I started calling myself a neuroscientist instead of a pharmacologist. Psychopharmacology was the beginning of a dynamic phase of neuroscience research and I feel lucky to have been around near its beginning.

JB: Looking back over your career, who do you think was most influential?

ES: Probably Fridolin Sulser, because he introduced me into the field of psychopharmacology, he was tremendously influential.

JB: Is there anything you'd like to add?

ES: No, thank you.

MERTON SANDLER

Interviewed by David Healy
San Juan, Puerto Rico, December 15, 1998

DH: Today is Tuesday, the 15th of December 1998, and we're at the ACNP annual meeting in Puerto Rico. On behalf of the ACNP, I am interviewing Merton Sandler.* Merton, could we begin with where and when you were born, and then we will move on from there?

MS: We can, but it was an awful long time ago, 1926 in Salford, which used to be a poor relative of Manchester; both have now spectacularly reinvented themselves! Well, there is nothing spectacular about my own birth. I grew up; the only big break was getting a scholarship to Manchester Grammar School, which was the special school in the area and quite well known in the UK.

DH: When you were at school, did you have any feeling for what you would ultimately go on to do? Did you have any awareness of mental illness, biochemistry, anything like that?

MS: The answer is no! I hated school, as a matter of fact. I think I was one of nature's rebels. I hated wearing a school cap and would squash it into my pocket. I was always caught! I hated the discipline and I hated organized sport, but I had to do it. When I avoided it I was duly punished. The amusing thing was, when I came to live in London years later, I was cajoled into becoming chairman of the London section of the school old boys association, the school that I thought I hated so much. That's the way cookies crumble.

DH: When did you actually decide to go into medicine and, why?

MS: I was always going to go into agriculture because I was a keen little environmentalist in those days. I still am. But, at about the age of sixteen, I suddenly thought, I don't know one end of a cow from another. So, I looked around and medicine seemed rather interesting; so medicine it was. I started in 1944, just before the war ended.

DH: That would take you up to 1950, when you qualified?

MS: I qualified in 1949. Next year, I will have been a doctor for fifty years. David can you imagine; it is mind-boggling.

DH: Things would have looked completely different compared with now; drug-wise, you had extremely few treatments. Biochemistry was only just forming as a discipline; neurochemistry wouldn't have been thought of.

MS: My whole career has been shaped by expediency and opportunism and the jobs that were available. I got into this field I suppose I've made a small mark in, completely by accident. I became a soldier for two years,

* Merton Sandler was born in Salford, Lancashire, United Kingdom in 1926.

a national serviceman. Because I'd done a year of pathology training, the Army gave me a small hospital laboratory, but with very few routine duties. So, another doctor-soldier, Michael Pare, who later became a very able psychiatrist, and I teamed up. We started doing things we called research. We were enthusiastic but had no idea of research discipline. Even so, we had a bit of luck and the Lancet published our first two papers.

DH: On what?

MS: Aminoacidurias. The first was called *Starvation Aminoaciduria* and we starved for three days in the process. That was in 1953. We had no hesitation in approaching leaders in the field such as Charles Dent for advice, which they gave freely.

DH: Why did you start to look into this area and why did you begin with amino acids?

MS: I had the crazy idea of developing a new liver function test. I didn't know much organic chemistry, but was fascinated by it. I'd always had chemistry kits as a kid and made bangs and smells and things, I was a bit of a terrorist. The chemical side of things fascinated me. Paper chromatography was brand new and there was time to build equipment for it out of bits and pieces scrounged from the Army Engineers. When I left the Army, I got an intern job at a famous chest hospital, the Brompton. They had brand spanking new chromatography equipment lining the corridors and nobody knew how to work it. It was mouth-watering to see this stuff so I got it going for them! When my internship finished I was offered a research job there. Before the house and research job ended there was another seminal event, as far as my own life was concerned. Two friends and contemporaries at the Brompton, Alan Goble and David Hay, now Sir David Hay and the big boss of cardiology in New Zealand, moved to the National Heart Hospital and started to investigate the very first case of carcinoid syndrome ever seen in England. Remembering my enthusiasms, they came to me and said, biochemically, can you do anything for us? I said I'd have a go because the petals had started to unfold, the biochemical petals. I did a few chromatograms and we were very lucky; I got some nice data showing high concentrations of 5- hydroxytryptamine (5-HT) in the right side of the heart compared with the left. That may be one of the factors in the genesis of right-sided heart disease in carcinoid tumor syndrome. I was fired-up by this finding and became a one-man carcinoid reference laboratory. We are getting close to psychopharmacology, but haven't got there yet.

DH: I know.

- MS: I became a psychopharmacologist very gradually and didn't realize I had become one until ten years after I had done so.
- DH: At that point, what did 5-HT look like to you? I mean, it had been discovered by Erspamer and had been isolated by Page and Rapoport.
- MS: I met Erspamer when he came to London to give a lecture. I hadn't realized how lucky I was, because he wouldn't travel long distances. He gave his lecture in really execrable English but it was nice to meet this great man.
- DH: Was there any feeling then that 5-HT could be involved in mental illness?
- MS: First there was a problem about nomenclature; we called it 5-hydroxytryptamine and the Americans called it serotonin. Gaddum actually called it 'HT' until I had the temerity to remind him that 6-hydroxytryptamine also existed in our brains and that keeps us sane. When Michael Pare and I came out of the Army, I moved to another hospital, the Royal Free, while he got a job as a psychiatrist at St. Bartholomew's Hospital. We teamed up again, because 5-HT emerged as flavour of the month in psychiatry, so we were very happy to oblige and do a few experiments. In the meantime we began to understand 5-HT was inactivated in vivo by monoamineoxidase. Monoaminoxidase inhibitors were claimed by Nathan Kline to be important as antidepressants. The whole field was brand new and Pare and I had lots of leads to follow.
- DH: Who was Gaddum?
- MS: Gaddum started life as a mathematician and later turned to pharmacology. He was a difficult man, difficult to approach; cold and rigorous in his thinking. There was always a barrier, you couldn't become matey with him at all. I finally came across him a little when he was dying and I did a consultancy at Babraham, our major Institute of Animal Science, which Gaddum directed.
- DH: Where he moved to after Edinburgh.
- MS: Yes. He was director for a number of years until, in the early to 1960's he got carcinoma of the stomach. He was a big man with something of a pot belly and an aldermanic look. But now, alas, he had shrunk. He looked like Stan Laurel in Oliver Hardy's trousers. He was still in the lab at seven o'clock in the morning, perusing goldfish gut in a minute chamber looking for substance P, of which he was one of the discoverers some years earlier.
- DH: He used to hang out with Henry Dale, Marthe Vogt and a group of other people. Did you have much contact with this group?
- MS: I remember Henry Dale. I saw him only once when he was chairman of one of those special University of London lectures that were so good. He introduced Rita Levi-Montalcini, who co-discovered Nerve Growth

Factor and won a Nobel Prize, when she came to lecture in London in very broken English. Dale was another forceful and impressive character; he died a few years later. The last I heard of him was at a meeting at the British Pharmacological Society. He was ninety and he couldn't come himself so he sent a video message. Marthe Vogt, I knew very well and she is still alive in 1998.

DH: Yes, she is.

MS: She discovered noradrenaline in the brain and mapped its distribution; that was another very important milestone. These monoamines have really influenced my life; the catecholamines and 5-HT have, to be more precise. Although we did have a long, hard look at the trace amines, but they didn't amount to much in the end. We couldn't find any evidence of a neurotransmitter role; but that is the way things turn out.

DH: Arvid Carlsson describes coming to London in 1960, and meeting a certain amount of resistance to the idea of any clinical role for these substances; but, in essence, these people were physiologists.

MS: You are absolutely right! There was so much resistance to anything that might even faintly have been clinically connected. Perhaps we ought to mention Blaschko at this juncture.

DH: We should.

MS: Blaschko made crucial observations or inspired guesses at every point in the history of the monoamines. Blaschko was there! Even apart from his best studies of monoamineoxidase. Blaschko was a strange chap and would think and then pronounce, with his eyes closed. We would then get a monologue issuing forth, a stream of consciousness. And, there was good stuff in there, if you could bear to listen. But sometimes, it was all rather sleep-provoking! Blaschko, Vogt, Feldberg and many other academics of first rank; these were the people who were kicked out of Germany by the Nazis.

DH: Right.

MS: Jewish, almost to a man, though not Marthe Vogt, obviously. She came from a family of pathologists. Her parents ran a brain institute in the Black Forest where Lenin died of General Paralysis of the Insane.

DH: Yes, right!

MS: They sent Lenin's brain to the two Vogt's, somewhere around 1922 or 1923, and they dissected it.

DH: Lenin's brain hasn't been with his corpse in Red Square all this time?

MS: No, it hasn't!

DH: Right, but there were also people in this group, like John Burns. Do you know him?

DH: J. H. Burns?

MS: I knew him, but not well. He was a great influence on British Pharmacology, a very brusque sort of individual. But he was the scientific father of people like John Vane, who trained under him at Oxford. I believe that Burns started off in London at the School of Pharmacy and then moved to Oxford in his later career. Who else did you mention?

DH: Edith Bulbring.

MS: I knew her, too. She had one of her legs amputated before she finally died, poor old thing. But, they seem to live to a great old age. Feldberg, too, was an amazing influence in Physiology.

DH: Why?

MS: He was a splendid experimentalist and always had a little cigar in his mouth with two inches of ash attached. Sometimes it would drop onto the cat's belly he was poring over. He was treated badly by the animal rights people, in his old age, when he was careless in choosing his assistants! An animal rights evangelist got a job, pretending to be a disciple, and you can write your own scenario! Anyway, Feldberg was a very nice man!

DH: So you had the idea your transmitters might be important for mental illness but the older group couldn't buy the idea fully and it took people like you, who didn't have inhibitions imposed by the field, to pick up the ball and run with it?

MS: I would say you are right. Mike Pare and I, with little learning but a great deal of enthusiasm, did just that. We took up the baton. For instance, we lined up volunteers, about a dozen junior doctors at the Maudsley Hospital and devised an experiment to test Gaddum's hypothesis. We were the first to give 5-hydroxytryptophan (5-HTP), the precursor of 5-HT, intravenously. In those early days, we had to use DL-5-hydroxytryptophan but in retrospect we obviously didn't use enough. Mike and I were not only the first to inject this material into man but we were also the first to use L-Dopa for a similar purpose. We did this together with a psychologist called Brengelmann, not long after the war ended. Brengelmann was a German of rather heel-clicking variety. I was a bit sensitive to Germans just after the war.

Anyway, despite his origins, Brengelmann was terribly good; he had a series of psychological tests which he applied. We gave volunteers LSD, which was all the rage in these days. LSD is an antagonist, as you know, of 5-HT. We thought that if we pretreated our volunteers with a 5-HT precursor we might suppress the schizophrenia-like symptoms one gets with LSD. Strangely enough, after five subjects, it was starting to emerge we'd got it right. We couldn't carry on because the sixth volunteer was a disaster; he had a bad trip on LSD and had to be held down

by half-a-dozen male nurses and tranquilized. He only came back to sanity after about six months, if he ever did. In those days there were no ethical committees to pronounce on our experimental design. They were a later addition. We didn't know we were doing anything wrong and, in those days, it was not uncommon for experimentalists to test new drugs on themselves. On one occasion, for instance, I took 1mg of reserpine intravenously. My nose became blocked and I became mildly psychotic for about a month. We were just following Gaddum's precept to see how far it went. I think our papers, published in the *Journal of Mental Science* in the late 1950's, were a milestone. That journal later changed its name to the *British Journal of Psychiatry*.

DH: At this point, the monoamine oxidase inhibitors started to come on stream and suggested a new hypothesis. Did you look at this, as well?

MS: Indeed we did! Pare and I were unfortunate we didn't have much of an idea how to present our data properly to get the best news coverage! What I believe was a seminal paper was published under the disguise of a clinical trial, *A Trial of Iproniazid in the Treatment of Depressive Illness*. We had a very interesting study design and, as I mentioned before, we also gave 5-HTP and DOPA in the lag period of two to three weeks until the antidepressant took effect. Thus, we tried to shorten the lag period by giving amine precursors, to be decarboxylated to their corresponding monoamine in situ. Although we didn't say it in as many words, the amine hypothesis of depressive illness was implicit in every sentence of the article. It was what we were writing about but we didn't emphasise the information we were imparting and it didn't hit the headlines. Joe Schildkraut scooped that pool seven or eight years later when he wrote a review article talking about the monoamine or norepinephrine hypothesis, as he called it.

DH: Are you sure it was Joe? What about the contributions of John Davis and Biff Bunney, because both articles came out about the same time?

MS: I am talking about the ones that hit the jackpot in Current Contents.

DH: OK.

MS: I am not disputing others were on the right wavelength, too.

DH: Did the 5-HTP that you gave actually help? Did it cause lightening of affect?

MS: No. The single dose we were in a position to give was far too small.

DH: Could your article have been taken to show that the amine lag-period hypothesis couldn't have been right to begin with?

MS: Possibly. I don't think you can say that when you give such a relatively low dose, 25mg of the DL compound which was nothing when everyone

knows how much L-DOPA it takes to have any effect in Parkinson's disease, with or without a peripheral decarboxylase inhibitor.

DH: How did the monoamine story begin to unfold, from your point of view? Iproniazid had been discovered and there was a strong suggestion it was working because it was a monoamineoxidase inhibitor.

MS: I have always been a dedicated reader of the literature. Modesty aside, I would go through the spring edition of *Federal Proceedings*, with its two or three thousand abstracts, as a kind of religious devotion!

DH: You would really go through all of that?

MS: In 1957, there was a pearl in this particular oyster. It was an abstract by Armstrong and Shore. They left out one of the authors names in haste; Macmillan's name should have been on that abstract, too. Anyway, that paper described, for the first time, the major metabolites, the methylated oxidatively deaminated metabolites of the catecholamines, noradrenaline and adrenaline in the urine of patients with pheochromocytoma. You wouldn't believe it, but up to 1957, we had no idea what happened to endogenous or administered noradrenaline and adrenaline. It was the finding in this paper of O-methylated metabolites, and particularly vanilmandelic acid (VMA), that broke the thing wide open. Julie Axelrod was immediately on to the enzyme mechanisms involved, particularly catechol-O-methyltransferase (COMT). And it was partially for this reason he won the Nobel Prize, and quite rightly. We made our own modest contribution to the catecholamine metabolite story then and published the very first clinical assay procedure for VMA. We soon established a corner in this research area. We were quite good at measuring these unexpected metabolites and published the first method for measuring urinary homovanillic acid, the major metabolite of dopamine and were also quickly off the mark with 4-hydroxy-3-methoxyphenylglycol (HMPG). We were very early in the gas chromatographic field which made it so easy to make measurements of trace metabolites. When I first cut my teeth in clinical chemistry, we were measuring sodium by using uranium salts that took a week to get the results! Then flame photometry came along. Things have changed surprisingly since that time. We came along with our gas-chromatographic methods just in time for the L-DOPA revolution. We were thus able to quantify so many of the minor metabolites of L-DOPA, and the major ones too, in Parkinson Disease. Over the years I have followed the monoamines wherever they led. We discovered other unconsidered trifles along the way. Amines started to be implicated in migraine for instance, and research money came from the Wellcome Trust, which was very helpful at that time. The quid pro quo was that we were to investigate the metabolism

of tyramine in the brain. A very nice lady, Edda Hanington who was the Wellcome's Assistant Scientific Secretary claimed that tyramine triggered headache in patients with so-called dietary migraine. Maybe it did and maybe it didn't but it just might in a few affected subjects. Anyway, this was the background to a whole series of investigations that links up with depressive illness. Our tyramine test in depressive illness, which I shall tell you about in a moment, has been a sad disappointment to me and our group. It's too tricky to do routinely in clinical practice although it works and picks out unipolar depressive patients. Somebody should take it up again and try to find the mechanism we never discovered.

DH: What you are saying is, there is a group of people who, with the tyramine test, show one result and others don't.

MS: Yes; the test shows a clear deficit in one particular clinical group of depressed subjects. The metabolism of tyramine is largely carried out by monoamine oxidase (MAO). However, there is an important minor metabolic pathway accounting for about 10 percent of the total, involving sulfate conjugation. We were able to show that in patients with unipolar depression, there was a significant deficit of tyramine conjugation with sulfate after an oral tyramine load.

DH: In all of them, or only certain ones?

MS: In a statistically highly significant number.

DH: In the ones that respond to a particular drug treatment or not?

MH: We had difficulty tying this finding in with drug treatment response. The result hung in the balance. I seriously think there is room for further investigation. It is an expensive test because you have to be meticulous about the precise timing of a series of urine samples. So, there are good reasons this didn't become popular; we hadn't worked up the technology to do the test on a specimen of blood, so that manpower was involved in the urine collection procedure.

DH: You raised the question of tyramine, which in turn raises the cheese effect and the part played by MAO. Can you take me through this and tell me what was your role?

MH: Well, I have written a great deal but I still don't know whether I made any major contribution. My colleagues and I have worked in this area for a long time, even before Johnston, who first described MAO-A and MAO-B pharmacologically in 1968. We ourselves took a wrong track. There were always tantalizing indications that the enzyme MAO had multiple forms and, in fact Youdim and I, in 1967, were able to produce preliminary electrophoretic evidence for such a finding. We published a series of papers pointing to different substrate preferences of the

multiple forms. One of them, for instance, showed a strong preference for dopamine. With hindsight, it seems obvious those findings were artifactual, elegant artifacts true; but it is equally obvious there was a physicochemical basis for their manifestation. Even so they didn't bear much relationship to clinical reality. In the 1960's, there was considerable drug company interest in MAO inhibitors following the success of iproniazid in producing a lightening of affect in some patients with depressive illness. One of these firms, May and Baker, synthesized a pharmaceutical agent called clorgyline and set Johnson, one of their employees, to put it through its paces. Johnston did the work but didn't write it up, because he became ill and died not too long afterwards in a Cambridge mental hospital. Sir Rudolph Peters, the eminent biochemist, who was a consultant for May and Baker, converted Johnson's raw data into a seminal paper, which was published in 1968, in *Biochemical Pharmacology*. Nowadays, every school boy knows that there are two isoenzymes of MAO, A and B, and clorgyline turned out to be a selective inhibitor of MAO-A.

DH: What happened next?

MS: Although clorgyline was a very good lightener of affect, it never got on to the market because there were enough similar drugs already available. The first selective inhibitor of MAO-B was then synthesized and developed by Joseph Knoll and his colleagues. I remember how excited we all were when he first presented his paper at a meeting in the early 1970's in Sardinia when we had an MAO Festschrift for Blaschko's 70th birthday. Mimo Costa and I edited the Proceedings with the enthusiastic collaboration of Ghighi Gessa. We held this meeting in Sardinia, because that was Costa's home island and it became the first psychopharmacology meeting of many. There was this charismatic Hungarian, full of fire and passion, but it was difficult to understand a word that he was saying. To the great interest of all of us, he unveiled the first irreversible MAO-B inhibitor, called deprenyl. Now it's officially called selegiline although deprenyl is still, if unofficially, much more used today. Anyway, this was the only major drug to emerge from behind what was then called the Iron Curtain and Knoll was a great PR man for the Hungarian drug group that synthesized it. To this day he is as full of enthusiasm and fire as he always was. Moussa Youdim visited him in Budapest and obtained a sample of the drug, taking it to Birkmayer in Vienna, suggesting he might like to try it in patients with Parkinson's disease. Now, Birkmayer would try anything on anybody. He was a very interesting character; I don't know if you know anything about him?

DH: Nothing at all.

MS: He was thin, enthusiastic, pipe-sucking and friendly and had been an SS doctor in the late 1930's. When they found out he was partially Jewish, they kicked him out of the SS, which was the making of him.

DH: Right.

MS: Vienna was a very interesting place to be at that time because they have a law there has to be a post-mortem examination in every death. So, brains from Vienna flowed forth to research laboratories of the world. One of Birkmayer's emissaries, five feet tall, arrived at our lab wearing a top coat down to his ankles and a Homburg hat. He was carrying two plastic store bags full of human brains, two in each that he brought through British customs. They didn't stop him!

DH: Gosh.

MS: I will tell you more about the British Customs in a moment.

DH: Right, keep going.

MS: When Moussa Youdim said to Birkmayer, 'Let's try deprenyl in Parkinson's disease', and I heard on the grape vine they were going to try a selective MAO-B inhibitor, my immediate response was how ridiculous, everybody knows that brain dopamine is metabolized by MAO-A, because it was in the literature. We combed the literature once more and it became obvious that the only available information on this point was in the rat. So Vivette Glover and I went quickly to the lab and looked at some human brains. These measurements hadn't been done before in man. Needless to say, we found that dopamine is largely metabolized by MAO-B in man, not by MAO-A! It just shows that man is not a rat. That's one of the few things I have learned in my long life.

DH: It just shows.

MS: So, I was convinced. After the Sardinian meeting, I'd kept in close touch with Joseph Knoll. I called him and said "Can I cadge some deprenyl from you." He said, "Oh yes, as much as you like." So, I flew over to Budapest in what I called my flasher's mac. It was a Macintosh with large pockets. I collected two large polythene bags full of white powder and walked boldly through the British customs. Nobody stopped me and fortunately the sniffer dogs were on holiday. I hate to think what would have happened if I'd been caught.

DH: What do you think would have happened?

MS: I'd probably still be in jail! Anyway, we rapidly put the first deprenyl in England through its clinical paces. I should say this work was in harness with Gerald Stern, my clinical collaborator over many years. We confirmed it worked in Parkinson's disease and wrote a number of papers to this effect. We did have one problem. We told our Committee on

Safety of Medicines what we had done and they said, "You know this is illegal, you are using an illicit drug, brought illegally into the country." Well, they were quite decent about it; they said we wouldn't be prosecuted and we could go ahead and publish. So we did, and more or less lived happily ever after. We discovered a lot of deprenyl's properties; the Hungarians were very appreciative and gave me an honorary doctorate!

DH: The deprenyl story is extremely interesting because it begins to look as if this drug can enhance life, in that it reduces mortality in people who are Parkinsonian. Can you take me through that particular aspect of the deprenyl story as it unfolded?

MS: This is another one of those stories of enthusiasm waning as more data become available. I still think there could be something to it but the data are not as clear cut as they seemed in the very beginning. Knoll's initial experimental findings were quite staggering! His treated rats lived three hundred percent longer than untreated controls, amazing figures. The only thing that I worried about was that he had a Vietnamese collaborator and though I am sure the experiments were done very well, the fact is that they were done in Vietnam and weren't under Knoll's personal control.

DH: Supervision, right.

MS: I don't know; he did do some experiments in his own lab but I think it was the cost of so many rats that threw him. Anyway, there were others who jumped on the bandwagon. There were preliminary clinical impressions suggesting longevity was one of the consequences of deprenyl treatment in Parkinson's disease. Others disagreed. The London group of Neurologists produced data cutting right across that conclusion, suggesting that patients on deprenyl live for a shorter time than those not on deprenyl. So, you pay you money and take your choice!

DH: What about its other actions, which have begun to emerge?

MS: There are fascinating laboratory data. Neuroprotective effects have been claimed....

DH: If that is true, it may herald whole new mechanisms by which psychotropic drugs could work.

MS: The whole business of neurotrophic activity is fizzing at the present. Although, I think of myself, as an archetypal monoamine man and still see monoamines in my dreams, lately I have taken a sideways step and branched out into neurotrophins.

DH: Where did the neurotrophin story begin?

MS: With Rita Levi-Montalcini, who discovered Nerve Growth Factor, (NGF), many years ago, and won a Nobel Prize for it. It's amazing how that

field has blossomed and generated a massive literature. Even so, it's hard to slot into any clinical context, although it's obvious to me that a possible role in depressive illness is just over the horizon. The methods are tricky and difficult and so immunological! You have to be a molecular biologist, for starters. I'm not, as you know. I came along too early for molecular biology, but I have young colleagues who know about these things. With their assistance, I have crept quietly into this new area. I don't look on it as a new area, but rather as a continuation of an old one.

DH: The fact that different areas of research come under intense scrutiny depends, to a substantial extent, on the techniques available for their study. The monoamines, of course, streaked ahead and left the others way behind until recently.

MS: They did.

DH: Was that because, as you imply, you had the techniques or is it an issue of we work on the things we like to work on?

MS: I put it another way, David.

DH: What?

MS: We have been struggling, for forty years, in the conceptual wilderness. I recently wrote a review of one of your challenging books on the history and development of psychopharmacology and put it on record that we have been stuck in a conceptual mindset for forty years. In the 1950's there were so many major discoveries, the tricyclic antidepressants, the monoamineoxidase inhibitors, the neuroleptics, lithium- and, then nothing! The reason is we just didn't have the techniques perhaps; but our thinking was also repetitive. As I see it, we are at last breaking out of the vicious circle. I am thinking specially of the neurotrophins, which you introduced into our discussion a moment ago and, in particular of BDNF, brain-derived neurotrophic factor, which shows signs of being of major importance in explaining the onset and treatment of depressive illness. There are fascinating data stemming from Yale in particular. I am thinking of the group headed by Ron Duman who are responsible for a fascinating hypothesis, pointing to a cascade of events that would explain, incidentally, the lag period in response observed after tricyclic or monoamineoxidase inhibitor administration. This lag period, by analogy is, a sort of gear change in the cascade of events involving cyclic AMP and other important chemical steps until eventually you get to BDNF. Drugs, physical and chemical treatments like electroshock or insulin treatment, all cause a rise in BDNF concentration in animal experiments. Ethically, human data would be hard to obtain. Stress models of depressive illness in animals, on the other hand, bring about

- a decrease in hypothalamic BDNF. It's just too bad that BDNF doesn't cross the blood-brain barrier; we can't think of it yet as a magic bullet.
- DH: To take you back to the 1950's, you were among others working on the first version of the monoamine hypothesis of depression, and one of the useful things observed at that time was that reserpine lowers amine levels and causes people to become depressed. Now, you took reserpine. Can you describe the effects?
- MS: It was one of the most miserable experiences in my whole life. I was depressed, paranoid and aggressive for a month! I couldn't breathe through my nose for a month. It really is a foul drug. I know you have recently been promoting it, David.
- DH: I am not promoting it but I am wondering if it did cause people to become clinically depressed.
- MS: I can tell you from personal experience it does in some people. I only had a small dose, half a milligram, I think, intravenously. A collaborator of mine, recently retired from being one of London's coroners, took two milligrams, intravenously, and had to go to the hospital. He was very, very ill.
- DH: Why did he have to take two milligrams, intravenously?
- MS: We were crazy! We all did this sort of things. It is a grand tradition trying out things on yourself. It's come to a halt now, thank God.
- DH: Do you still think it's important for people working in the drug field to try compounds to appreciate what the issues are?
- MS: I don't know. Our reserpine experiment stemmed from trying to test one of Irv Kopin's hypotheses on compartmentation of catecholamines and that sort of thing. We published a paper or two out of our own discomfort! Ethical committees didn't exist then but we don't do it now. Paul Ehrlich tried everything on himself didn't he? It was a grand tradition.
- DH: You used to go to Russia and you had links with Moscow and St. Petersburg. Can you tell me how this all happened? How were the links developed?
- MS: I will tell you how it all started. There was a biochemical congress in Moscow in 1961, and I got money from the hospital to go to it. They were building the Berlin wall at the time and Brezhnev harangued us from loudspeakers on every lamp post. From my point of view, the Congress was scientifically, a washout! There was only one paper on monoamineoxidase, given by a young Russian called Vladimir Gorkin so I went to hear it. There were about a dozen people in the room but it was very interesting and he and I subsequently became great friends. We were the only people that spoke a similar scientific language. He also spoke very good English. He died recently in Denver. I started to

learn Russian in 1960 from a BBC Russian for Beginners course. I took my young bride, who had also started to learn Russian the previous year to the Moscow Congress. The difference between us is that she is now a simultaneous interpreter in Russian.

DH: All right, good!

MS: This has been one of the spurs that made me go to Russia more often than most people. I have been there perhaps a dozen or more times. We have been lucky enough to obtain grants for joint work with Gorkin's laboratory in Moscow. So we also have young Russians descending on us, from time to time, particularly Alexei Medvedev.

DH: When did you make links with the group in St. Petersburg, with Lapin and Oxenkrug?

MS: It must have been the late 1960s when I first got to know them both. I tried to get Gregory Oxenkrug over to England when I visited them. They had published that paper in *Lancet* in 1968, suggesting that Serotonin was the bees' knees, as far as depression was concerned; it was a very thoughtful paper and it came out of nothing. They had no laboratory facilities to speak of. Scientifically, they were living in the nineteenth century. There were just a few favorite laboratories in the whole Soviet Union that had decent equipment and Lapin's was certainly not one of them!

DH: I had the impression that to do the work they did they must have been reasonably favored?

MS: No, but they were good hardworking and did it on minimal resources. Maybe you should interview Lapin and Oxenkrug sometime. That would be useful because they are quite well known names in the field.

DH: Sure. Did you have to smuggle their articles out?

MS: Yes, we did, some of them, at least.

DH: Could you tell me more about the ways you could help them?

MS: I tried several different ways to get the young Oxenkrug to work in my lab, and they wouldn't let him out. I had to be interviewed by a special "academic committee". They were quite antisemitic at that time, and it didn't help that Oxenkrug was Jewish; Lapin is half Jewish, on his mother's side, but he is properly Jewish as far as Jews are concerned in Russia.

DH: Right.

MS: Eventually Oxenkrug managed to get out to the US and a number of us were helpful to him. We are having dinner tomorrow night; he is eternally grateful and looks on me as his big father. Besides me Irv Kopin, Sam Gershon and Saul Schanberg have been helpful to him. I am very

- pleased because he is a very bright boy and has made it in American psychiatry. He is now a man in his fifties.
- DH: The monoamineoxidase inhibitor story, has it come to an end? What about moclobemide, which was going to be the great hope in that particular field, the reversible MAO-A inhibitor?
- MS: I am sorry to say this but I think nothing of moclobemide. If it works, which it may very well do, it works despite its reversible MAO inhibitory action which is quite weak.
- DH: On that score, have we been slightly misled? Maybe it isn't monoamineoxidase inhibition we're observing?
- MS: I agree with you almost one hundred percent. All drugs are dirty drugs. All drugs have multiple actions. That's what I mean about moclobemide. I am sure it has a perfectly good mechanism of action, maybe because it is a mild antidepressant, but I can't see that effect stemming from monoamineoxidase inhibition, which isn't very powerful, unlike the original group of irreversible inhibitors, which kill the enzymes stone dead.
- DH: Can I take you through the trace amines story because although it's been a minor sideline for you, this is one of the mysterious groups which may in due course emerge from the shadows? What are the trace amines?
- MS: The trace amines are monoamines, very similar to all the other monoamines we have mentioned. The difference is that 5-HT and the catecholamines, including dopamine, all have special receptor uptake and re-uptake mechanisms. The trace amines are present and some are produced in substantial amounts in the body. Take octopamine, for instance, did you know that we excrete in our urine about as much or almost as much p-hydroxymandelic acid, the major metabolite of octopamine, as we excrete 4-hydroxy-3-methoxymandelic acid, VMA, the major metabolite of adrenaline and noradrenaline. If you take a rabbit and give it a monoamineoxidase inhibitor, and this was done thirty years or more ago, tissue concentrations of octopamine rise greatly. There are some species of crustacean where octopamine is a known neurotransmitter with uptake mechanisms and special receptors. There are a whole host of other monoamines, the three tyramines; p-tyramine we talked about briefly, and for a time I thought it might have had something to do with the lightening of affect you get from a MAO inhibitor.
- DH: Right.
- MS: We still don't know but it's still conceivable, especially taking our tyramine test data into account. Then there are tryptamine and phenethylamine.
- DH: They have to be important.

MS: I think they are. Gavin Reynolds and I put forward a phenethylamine hypothesis of schizophrenia in 1976. That's since been dragged from its graveyard by some very respectable genetic teams; they are thinking about it again and measuring phenethylamine, thinking of it as we did, as nature's amphetamine.

DH: Last year, I was interviewing Paul Janssen and this is what he believes in....

MS: Really.

DH: Wasn't it you who put the name "trace amines" to this group of compounds?

MS: Yes, we did. Alan Boulton was the original big enthusiast. He wanted to call them "microamines" and published a letter in the *Lancet*, saying there were a lot of micro amines in the body and they must presumably have a function; they are present in the brain and have a discontinuous location. We know a number of reasons why they should be important. Earl Usdin and I thought we'd try to sort the problem out. We both always liked meetings in the Caribbean, so we set one up and duly published the proceedings. We thought the term, microamines, was unhelpful, because they weren't, so we coined the name, "trace amines".

DH: How do the trace amines link to polyamines?

MS: That is a different ballpark.

DH: You've raised the question of trace amine production in schizophrenics and you, looked at another group you termed aggressive psychopaths, who end up in jail. Take me through this.

MS: The phenylethylamine hypothesis of schizophrenia arose fully armed from a chat I had with a young biologist, Gavin Reynolds, I was interviewing for a job. I gave it to him. He is now Professor of Neuroscience. We had both been thinking along the same lines but hadn't quite put it together; but after the interview, within a week or two, we wrote up our hypothesis for the *Lancet*. If you inject phenethylamine into an experimental animal, nothing much happens, but if the amine injection is preceded by a monoamineoxidase inhibitor a sequence of events follows, similar to that which follows amphetamine administration. I was about to talk about aggressive psychopaths and serendipity. At about this time, I happened to be at one of those interminable dinners at the Royal College of Physicians. I had been seated on the end of a table and the chap, sitting next to me hadn't turned up. The only contact was with a rather morose guy called Field I couldn't draw into conversation. I almost had to sit on his head to find out he was a psychiatrist at one of our better prisons, Wormwood Scrubs. At last, we started to

talk and I desperately tried to dredge up what I knew about criminals, which wasn't much. I had just read a paper, however, which claimed that sixty percent of murderers in North Carolina had been on amphetamine. It was obviously amphetamine psychosis they were dealing with. They had become schizophrenic on amphetamines and I had never even heard of this until I started reading the whole thing up. One thing led to another and Field and I decided to collaborate. We set up a group of aggressive psychopaths and another group of men imprisoned for white collar crimes, fraud, cooking the books, tax evasion-normal controls, you know.

DH: The things we all do, right?

MS: We compared these two groups and, surprise, surprise the aggressive psychopaths excreted significantly more phenethylamine metabolites than controls. The national press made quite a splash of the story at the time. We thought we ought to repeat the experiment and went back to Wormwood Scrubs and asked if we could have a couple of dozen more of each just so we could clinch the whole thing? But the prison gates were closed! They got scared stiff!

DH: Too much of a splash.

MS: Yes. The prison authorities were always sensitive to too much publicity. Well, I thought we'd finished with that one, really. And, then, I was at someone's dinner party. There was a young man sitting across from me and we started talking about what we did. I got on my frustrated scientist hobby horse and complained how difficult it was doing research on prisoners. This smooth young man was the British Minister of Transport. His name was...

DH: Norman Fowler!

MS: Norman Fowler, yes. He said the Home Secretary is my chum; send me the papers on the case and I'll have a word. Nothing happened for about six weeks. And then, I got a call, "the prison gates are open." It is nice to have influence. So, we confirmed our earlier data and did parallel experiments in animals, comparing dominant and non-dominant monkeys, which took us out to St. Kitts where they have monkey colonies; the dominant alpha monkeys lead the pack and are the ones that carry their tails in the air. We collected blood samples and the alpha males had higher circulating concentrations of phenylethylamine metabolites.

DH: I can see that you pick your research with care, that carries you to the Caribbean.

MS: Absolutely!

DH: You used to come to the Caribbean, as well, courtesy of Nate Kline. Tell me about that?

MS: Very true. Nate Kline, we all remember fondly. Nate Kline was a wheeler dealer. He was a New York psychiatrist of flare, talent and panache. He was a fascinating character and even quite a good psychiatrist. One of his patients, a Mrs. Denghausen, was an upstate New York millionairess, with depressive illness. Nate would give her oral tryptophan and she would cycle back to normal. And when she was relatively normal, she said “Doctor, what can I do for medical science?” So he said, “Doctors have to travel a lot and are always worried about their wives”. He persuaded her to fund a small scientific meeting on a Caribbean island every March, “and bring your wives” along.

We used to line up on the beach at 8:30 in the morning in our swimming trunks under the palm trees, with just a blackboard and somebody would get up and hold forth; he would be torn to pieces by the hand-picked group of a dozen neuroscientists Nate Kline had assembled. It was hard work and wildly stimulating. Lots of contacts were made and experiments were spawned by this gathering a .really fascinating group. Unfortunately, Mrs. Denghausen died, her husband died and Nate Kline died so that the whole thing wound up. But, it was great while it lasted.

DH: Before we come back to the Caribbean and the ACNP meetings, can we hop to the first CINP meeting, because you were there, weren't you?

MS: I was, by pure chance.

DH: Tell me about that first meeting in Rome and the impact it made?

MS: That was the first foreign scientific meeting I'd ever been to.

DH: I don't know the date, so you better put it on record.

MS: It was 1958, because Mike Pare had been involved in some sort of drug trial for Hoffmann-LaRoche and they very kindly funded our trip. At that time, I had never heard of the CINP; nobody had, it was the first meeting. We were delighted to get to Rome. We'd done some very intriguing work I think should be disinterred and looked at again. We found a deficit of 5-HT in the platelets of phenylketonurics. Even more interesting was our control group, so-called “cerebral palsy” patients from the same children's hospital. I don't know what they were really suffering from; they may have been autistic, but the fact is they had wildly differing levels of 5-HT in their platelets, some astonishingly high. Others later confirmed that certain autistic kids have raised levels of 5-HT in their platelets and this finding has never been satisfactorily explained. There may be some mechanism that normally stops it building up and it's being sucked up like a sponge in children with abnormally high values. What has happened to the uptake mechanism in these subjects? I don't know, but somebody should look into it. Anyway, that was the paper Mike Pare and I presented to something like nine or ten people!

We were perfectly happy in Rome and we banqueted at the Villa of Mussolini's mistress. This was the good life. The faint whiff of corruption was in the air and it was a delight!

DH: You liked it?

MS: I loved it, yes! It was marvelous! It was nice while it lasted, David.

DH: After that you began to come to the ACNP meetings, which we are having here at the Caribbean?

MS: I came first in the mid-1970s and very soon after I was elected a foreign corresponding member of the ACNP. It was around the swimming pool at an ACNP meeting that David Wheatley, Alec Coppen and I, hatched the British Association of Psychopharmacology. Perhaps I am wrong, as there are other interpretations and other stories that compete.

DH: Was this the model you wanted to reproduce?

MS: Yes, this ACNP meeting has always been the leader of the field. There is no question in my mind it represents the front line of Psychopharmacology. I top up my psychopharmacological tanks when I come to these meetings. They are marvelous! The program committee has the right formula and they are good.

DH: So, you save your air miles each year to come here?

MS: That sort of thing.

DH: There is one more angle we need to explore. The NIH was a major mover in all this. You had Brodie, Axelrod and people like that with whom you worked closely. But, you were related to Brodie, is that right?

MS: Distantly. He was a wild one, Brodie. I will always remember the last time I saw him. He was living in retirement in Tucson, Arizona, and had this forceful old wife who looked after and drove him. She was like one of those pioneer women who went out west on the wagons, a rather harsh lady, and she really ran his life. Brodie was always sorry for himself because he never won a Nobel Prize. When his former technician, Julie Axelrod, won the Nobel Prize, Brodie said to him sadly "You always kept your operations small, Julie." Brodie had a special room, perhaps his wife looked after it, where all his certificates and honorary degrees were pasted around the walls like a shrine, but the big one was missing! It was very sad, really. He made wonderful contributions to our knowledge, especially in toxicological methodology, working with Julie Axelrod and many other famous names. Brodie was the driving force, a very strange man and a bit of a junky. He took amphetamines during the day and barbiturates at night, uppers and downers. He had a very strange idea of time and would phone his associates at twelve o'clock at night to come into the lab to have discussions. He would never put

in an appearance there until around lunch time. Yes, there is a distant relationship but there isn't much Brodie blood in my veins!

DH: Or the other way around?

MS: Yes.

DH: Sandler blood in his veins. Brodie was actually born in Liverpool.

MS: And went out to Canada as a boy.

DH: How did you rate Julie.

MS: Ah, a lovely man. I first visited America in 1963, and Julie very kindly organized a party in my honor that night. Well, the plane was diverted to New York. It was a mess! So, I missed Julie's party, with great regret. I had met him at that first CINP meeting. We sat next to each other on a conference bus, by chance. I thought to myself I'd never met a man less likely to succeed and I never thought this little guy would make it. He was overdressed in the bright sunshine in a dirty old rain coat! I have a dirty old rain coat myself but his was dirtier and older. He was obviously very hot. The whole conference, around three hundred people in those days, was bussed out to Castelgandolfo to see the Pope. The Pope made a speech and none of us could understand him, in Latin perhaps? But, in fact, it was broken English. Then he died twelve days later. It didn't seem strange to me at that time.

DH: OK. But, there's another issue here. You have described elsewhere the powerful role that displaced Jewish physicians and scientists, forced to leave central and eastern Europe before World War II, played in the UK, but they also played a huge role here in the US.

MS: Oh, a huge role! During my seminal 1963 visit, when I first visited the NIH, Seymour Kety was in his prime as chief of the Laboratory of Clinical Science; he is a chap who should have won a Nobel Prize, if there had been any justice in the world. Anyway, he assembled a random group of his colleagues to go out to lunch. There were a dozen of us sitting around the table and by pure chance, all were Jewish! People like Sol Snyder, Irv Kopin, Joe Fisher and Dick Wurtman all were there. Of course, I don't know, but I suspect that Jews manifest survival genes. They have survived, despite the odds. The individuals, who survived, evolved tricks and mechanisms which, somehow, provide the ability to see through to the heart of a problem, and not to accept revealed truth. I believe that this is the key to scientific ability. Well, it's just as good a hypothesis as anybody else's. Anyway, there are a lot of Jewish scientists in the United States and an awful lot in our own field of psychiatry and psychopharmacology.

DH: When the field coalesced, it was very much driven by clinical observation and people who were working in the basic sciences had to come

in and try to explain what was going on. At the meetings now there is an awful lot of basic science and you're not sure of what, if any, are the clinical implications. Do you think we have moved too far down the neuroscience route?

MS: No I do not. I think it has become clear this is the only way to make progress; and now we have the human genome mapped. So, it's a new ball game completely, isn't it? We don't have all the pieces in the jigsaw yet, but we can be much more confident in our predictions than before. These ACNP meetings are an eye opener now, where basic science rules. Ok!

DH: Good. Do you have any other thoughts on things we need to cover?

MS: I don't think so. I think you have done a jolly good job, David, if I may say so. I am happy and thank you very much for doing the job so well and courteously.

SOLOMON H. SNYDER

**Interviewed by Floyd E Bloom
Waikoloa, Hawaii, December 11, 1996**

FB: We are in San Juan, Puerto Rico at the annual meeting of the ACNP. It is December 1996. I am Floyd Bloom. I have the pleasure this morning of talking to my good friend for many, many years, Dr. Solomon Snyder,* who is the Director of the Department of Neurosciences at Johns Hopkins University. We were just together in the plenary session where we heard about the generation of neurons that go to make up our cortex, and, the purpose of our conversation is to talk to the future generations of scientists who will come through the College. So, let me ask you to think back about your earliest reminiscences of coming to ACNP in Puerto Rico and how you got involved.

SS: After medical school and internship I was a Research Associate at the NIH with Julie Axelrod, and then I came to Johns Hopkins as a psychiatry resident. I could see a connection between being a psychiatrist and doing basic research on how drugs act in the brain, and decided that was what I would be interested to do. I was very fortunate in that the Chairman of Psychiatry, Joel Elkes, and the Chairman of Pharmacology, Paul Talalay, created a hybrid residency, in which I could be a faculty member in pharmacology in the second and third years of residency. It also enabled me to get some research going. I've never left Johns Hopkins. Joel Elkes, of course, was one of the founders of the ACNP and very enthusiastic about it. Early on, perhaps in the third year of my psychiatry residency, or just when I finished, he said to me, "Solly," and Joel was the only person besides my grandfather I allowed to call me Solly, "you must attend the ACNP". So I attended as a guest of Joel Elkes. I don't remember if I gave a talk at the first meeting, but I've talked at many ACNP meetings after that.

FB: How did you get into pharmacology? How did you come to work with Julie Axelrod?

SS: I went to college in order to be a psychiatrist but I had no interest in science. I thought it was boring. Memorizing textbooks was not much fun. In high school, I liked reading about philosophy; but I knew that's not a fit job for a nice Jewish boy. I didn't know what to do. In the 1950's, everybody was going into engineering. Those were the Eisenhower years, the build-up in the Defense Department, and I couldn't stand that sort of thing. But, some friends were going to be in pre-med in college so I thought maybe I'll be a psychiatrist. I liked thinking about how the

* Solomon H. Snyder was born in Washington, Disrrict of Columbia in 1938.

brain works and I care about people's feelings. I figured all I'd have to do would be go to medical school and somehow survive the biological sciences. In the summer, before I started medical school, I worked at the NIH. I was going to Georgetown Medical School and, before that, I went to Georgetown College. I worked my way through college giving classical guitar lessons, because that was the thing I did best of all, playing the guitar. One of my students was Donald Brown, who was in the first research associate class at the NIH. In that program, you would spend two years doing your military service and getting research training. Don needed somebody to work in the lab with him and that somebody became me. I soon discovered that lab research was very different from science in textbooks and college courses. It was creative, very artistic and a lot of fun. I spent all of my elective periods in medical school, and all of my summers, at the NIH.

Working at the NIH in summers and elective periods during medical school taught me that laboratory research was fun and inculcated fascination with the power of biochemical tools to address all sorts of questions. While in medical school I also made use of the NIMH schizophrenia research to administer tests of Gestalt-like perceptual functioning. I found diminished "perceptual closure" in chronic schizophrenics and enhanced closure in more acute paranoid schizophrenics compared to normal controls. In contrast to the greater variability that schizophrenics normally display in tests, I found decreased variability in these measures. This work, done under the supervision of the great psychologist David Rosenthal, cemented my nascent desire to become a psychiatrist someday. It also gave me a feel for the exhilaration of carrying through a research project from initiation to publication. I wrote several papers on my own during medical school with publications in the *Archives of General Psychiatry*, the *Journal of Abnormal Psychology* and the *Journal of Biological Chemistry*.

These experiences were only part time avocations, respites from the more boring aspects of medical school. Toward the end of medical school, like every other male medical student, I became concerned about how to cope with the "doctors draft" that faced all of us. My hope was to do two years of psychiatry residency and return to the NIH for "military service," carrying out some clinical research and completing the residency. However, Elaine, who was to become my wife, needed to be in the Washington DC area to finish her college requirements. Hence I roamed the halls of the NIH seeking a position, even though the "match" had been completed. Julie Axelrod's lab was across the hall from the one in which I had worked during medical school, so that I

knew him reasonably well. My mentor Donald Brown had collaborated with Julie in identifying the histamine methylating enzyme, an area of my own interest, as I worked with Don Brown on histidine metabolism in normals and schizophrenics. I remember well my interview with Julie. He noted, "Sol, most of the applicants for Research Associate positions are valedictorians from Harvard or Yale and you only went to Georgetown Medical School so normally I wouldn't have a job for you. However, the fellow who was matched with you has just cancelled and I have no way of replacing him. I like what you were doing in medical school so I suppose it's okay for you to work with me."

I didn't mind the lukewarm welcome. I just needed the job. Of course, my two years with Julie were the most important in my professional life. He was a mentor par excellence and a remarkable inspiration to myself and all the others who worked with him.

FB: Say something about how you and he decided what experimental areas to probe.

SS: Let me first comment about the atmosphere of Julie's lab. He was so productive that most people thought he had 50 postdoctoral fellows. In fact, there were never more than 5 people in the lab. During my tenure, the other key individuals were Jacques Glowinski, Leslie Iversen and Dick Wurtman. Julie was remarkably open to new ideas. Anything we wanted to do was fine with him though usually the most creative ideas were Julie's. Here's an example of his strategy. Julie loved to discover new enzymes, especially methylating ones. He had already experienced great success with catechol-O-methyl transferase as well as the enzyme that methylates N-acetylserotonin to form melatonin and the histamine methylating enzyme. To seek new methylating enzymes he would incubate "out of the ordinary" tissues with radioactive S-adenosyl-L-methionine without adding any substrate. He would determine whether anything became methylated and then would try to identify the methylated product. While I was in the lab he conducted such an experiment with the pituitary gland. He extracted the methylated product into an organic solvent, evaporated it to dryness and then did paper chromatography. Whenever he evaporated the material, the radioactivity vanished indicating that the product was volatile. He enlisted the assistance of the talented organic chemist John Daly who stabilized the product and showed that a novel enzyme in the pituitary gland was methylating water to form methanol. The enzyme was enriched in various glands though it was present in all tissues. There followed a paper in *Science* "*Pituitary gland: enzymatic formation of methanol from S-adenosylmethionine*". A few years later other

investigators figured out what was going on. Julie had discovered an important enzyme, protein carboxymethyltransferase. The carboxymethyl group exchanges with water and so the enzyme appeared to be methylating water. In another instance, Julie incubated frog brain with S-adenosyl-L-methionine and found vast amounts of radiolabeled methylated product which turned out to be methylhistamine. Instead of being disheartened that he hadn't found anything new, Julie suggested to me, "The brain has so much histamine endogenously, that one gets a robust signal in the methylating experiment. There isn't any efficient, sensitive means of measuring histamine. Perhaps you could use the methylating enzyme as an assay for histamine." Based on this fleeting suggestion, in the next couple of weeks I developed a novel enzymatic-isotopic assay for histamine which became standard in the field.

Julie always said that the most important element in scientific discovery is a simple, sensitive, specific method to measure substances. Science is all about measuring things. If you can measure something readily that no one could previously, discoveries will abound.

FB: You took that message very much to heart with your methods for characterizing ligands that bind to receptors and drugs that interact with them. Can you describe how all of this came about?

SS: I worked with Julie from 1963 to 1965 at which time I came to Johns Hopkins for Psychiatry residency. During residency I was on the faculty with a research lab part time. In 1968, when I finished residency, I launched a full-fledged laboratory effort focusing primarily on neurotransmitter uptake.

In 1970 Pedro Cuatrecasas joined our faculty with his laboratory down the hall from mine. At the NIH, Pedro had identified insulin receptors and developed efficient techniques for monitoring insulin binding to receptors that enabled them to address many questions about insulin function. Since proteins or drugs can bind non-specifically to many tissue elements, it was necessary to distinguish the signal of physiologic receptor interactions from the noise of non-specific binding. Pedro did this with a vacuum manifold that could process 50 samples at a time and permitted vigorous but very rapid washing to remove non-specifically bound ligand while preserving receptor interactions.

About this time I read a paper in *Science* reporting the sequencing of nerve growth factor and noting a similarity to insulin. I suggested to Pedro that my new postdoctoral fellow Shailesh Banerjee might wish to seek a receptor for nerve growth factor utilizing Pedro's insulin binding technology. Our collaborative work led to the identification and characterization of nerve growth factor receptors.

About the same time, President Nixon declared war on drug abuse and appointed Jerry Jaffe as his drug czar. Arnie Mandell and I importuned Jerry to allocate some funds for drug abuse research centers. Biff Bunney, who headed the drug abuse division of NIMH, later to split off as NIDA, instituted an application procedure and Hopkins received one of the centers. In my application, I describe two projects, one relating to our ongoing amphetamine-dopamine research and the other a proposal to seek opiate receptors. The review committee applauded our amphetamine research, as we had already published several papers in the area, but dismissed the opiate receptor concept as fantasy, since we hadn't already published in the field. Fortunately we received the grant and could do whatever we wanted. Within a few months opiate receptor binding had been identified.

FB: Could you describe the discovery process and what happened thereafter?

SS: The most critical element of identifying a receptor by ligand binding is selecting the appropriate ligand to be radiolabeled. It must possess high affinity for the receptor, preferably about 1–10 nanomolar. Equally important, the ligand should be fully water soluble, as lipophilic agents often display massive non-specific binding. For the opiate receptor, we selected naloxone which fulfilled all of these criteria. The opiate receptor success implied that proper ligand selection might enable us to find other neurotransmitter receptors.

The muscarinic cholinergic receptor was an early success. It stemmed from a visit to Yale with my friend George Aghajanian. He had done his military service at Edgewood Arsenal outside Baltimore where the military had developed mind altering agents as potential weapons. One remarkable substance, quinuclidinyl benzilate (QNB) was a muscarinic antagonist of such great potency that it elicited an atropine-like psychosis lasting three days. George wasn't sure whether this substance was still classified but suggested that, if I could find some, it might be worth radiolabeling. By coincidence, I was anticipating a new postdoctoral fellow joining me in a few months from Edgewood Arsenal, Hank Yamamura. I phoned Hank, who was at first nervous about my knowledge of QNB. When he arrived at our lab a few months later, he brought a small vial of the substance with him and within a year had completed the identification of the muscarinic receptor. Tritiated QNB to this day remains the most widely employed neurotransmitter receptor ligand.

The properties of the opiate receptor so much resembled a neurotransmitter receptor that most people assumed there must exist an endogenous opioid-like substance that was a neurotransmitter.

In Aberdeen, Scotland, Hans Kosterlitz and John Hughes sought such a substance by showing that brain extracts could mimic the effects of morphine in inhibiting electrically induced contraction of the mouse vas deferens with the effects blocked by naloxone, ensuring specificity. In our own laboratory, my MD/PhD student, Gavril Pasternak, showed that brain extracts could compete for ligand binding to opiate receptors with the relative amount of such substances in different brain areas paralleling the relative densities of opiate receptors. A postdoctoral fellow, Rabi Simantov, purified the substance to homogeneity revealing a five amino acid peptide. Just about then, in early December 1975, Hans Kosterlitz mailed me the galley proof of his paper in *Nature* reporting the structure of the enkephalins, peptides whose amino acid composition was the same as what we had identified. About six weeks later we completed the sequencing of the enkephalins and came up with the same findings as Hughes and Kosterlitz.

FB: You've trained some splendid students and have already mentioned Hank Yamamura and Gavril Pasternak. Mike Kuhar has done distinguished work and Joe Coyle is Chairman of Psychiatry at Harvard. What is it that you conveyed to your students that enhanced their success? What do you recall inheriting from Julie that you try to pass on to your own young people?

SS: Julie was such a wonderful mentor that I've based my interactions with students on Julie's interactions with me. Being a mentor to students is similar to being a parent to your children. It's also somewhat akin to certain forms of psychotherapy, such as the "unconditional positive regard" that Carl Rogers emphasized. I try to encourage people by positive reinforcement. If something goes bad, never say "You stupid idiot", just say nothing. When things go well, provide unstinting praise. Constantly ask students for what he/she thinks should be done and always encourage his/her ideas. Of course, what we work on in the lab is typically the best idea which may come from me or from the student.

In beginning with a student in the lab, since he or she often has little background experience, the first project is most likely something I suggest. Just as Julie always did, the first project is well structured with a high probability of success, a strategy that builds self confidence. Gradually the student weans away from dependence on the mentor. This process varies greatly with different students. The goal, which I hope to attain after a year or so of time in the lab, is for the student to come up with 90% of the ideas. In terms of managing research in the lab, I believe in "management by walking around." I simply hang around the labs and brainstorm with the students.

FB: Young scientists are very tense these days with worries about grant funding. What are your thoughts? Are we training too many scientists or not enough good ones?

SS: There are many sides to this question. Though the NIH budget greatly exceeds the spending by other countries on medical research, I think we could still do better. Our brightest young people go to Wall Street, not just for the money but because the opportunities of accomplishing something important are great. Few people get rich doing biomedical research, but if resources are available to do something important, we will bring back the talented folk to the laboratory.

Doubling the NIH budget still hasn't addressed the need for new insights. You could argue that our problem isn't lack of money but its inefficient use. More than most countries, the American biomedical enterprise is spread out among a large number of universities of varying excellence. Perhaps research funding should be concentrated in a few truly outstanding institutions. Julie Axelrod always said that 99% of the discoveries are made by 1% of the scientists. If one looks carefully, his dictum is almost literally accurate. On the other hand, it wouldn't be the American way to restrict NIH funding to Harvard and Hopkins. Moreover, the big discoveries often come from out-of-place institutions.

FB: You had the chance to make many interesting discoveries. What's the most surprising thing you ever discovered? What was the thing that you couldn't believe was true and you kept going back and trying to kick yourself in the head, how could this be?

SS: One remarkable project involves the immunophilins. These are the receptors for immunosuppressant drugs such as cyclosporin and FK506. Joe Steiner and Ted Dawson, while postdoctoral fellows in our lab, discovered that they stimulate neurite outgrowth and are neuroprotective in very low doses. If one lesions nerves, these drugs stimulate their regrowth. In models of Parkinson's Disease in numerous species including monkeys, immunophilin-related drugs which are not immunosuppressants prevent the loss of dopamine neurons and have had promising effects in Parkinsonian patients.

FB: You have been involved as a consultant to the pharmaceutical industry. Could you project what areas of new drugs may emerge in the future?

SS: In the area of neuropharmacology we will certainly see more drugs interacting with receptor subtypes. For instance, there are more than a dozen serotonin receptors most of which are likely to have important behavioral roles. Sculpting drugs for one or another of these may provide great benefit with fewer side effects.

More interesting would be speculations that drugs might emerge that impact genetic mechanisms directly. My pet idea would be to develop drugs that bind to promotor elements of genes rather than to proteins. We know that transcription factors bind to promotor elements, why not drugs? Of course, drugs do bind to transcription factors themselves. For instance, steroid receptor proteins are transcription factors which interact with the steroids, themselves important pharmaceutical agents. Already the drug industry is developing antisense nucleotide agents which are efficient drugs. However, they are difficult to stabilize and have poor bioavailability. Why not screen conventional drug structures to find ones that bind to specific recognition elements in genes? Chemists worry too much about carefully designing agents that “fit” specific targets, in this case nucleotide sequences. I’d prefer a broad screen of hundreds of thousands of drug-like molecules seeking anything with micromolar affinity. Respectable “hits” could be further transformed into agents with nanomolar affinity after which the conventional drug development process would ensue.

FB: Thanks very much Sol.

SYDNEY SPECTOR

**Interviewed by Fridolin Sulser
Nashville, Tennessee, March 3, 1998**

FS: It's Tuesday, March 3, 1998, and we are sitting here in the conference room of the American College of Neuropsychopharmacology. The College has instituted a History Task Force with the purpose to interview scientists and clinicians, who have shaped the field or have helped to shape the field of Neuropsychopharmacology. My name is Fridolin Sulser and I have the great pleasure and privilege to interview Dr. Sydney Spector,* who is a colleague of mine here at Vanderbilt University and who has made many significant and seminal contributions over four decades to our field, neuropsychopharmacology. Welcome Sydney.

SS: Thank you.

FS: Now, before we start discussing some of your scientific achievements, I wonder, if you could tell us why you have chosen pharmacology as your field of scientific endeavor and what has motivated you to enter Neuropsychopharmacology.

SS: As to the reason I got into pharmacology I'm trying to think what prompted me. I was in the field of physiology, initially. I had a professor, who was interested in pharmacology, and suggested that, perhaps, I start looking into that aspect of science. I applied for a fellowship with Ollie Lowry at Washington U in St. Louis in the Department of Pharmacology. It was there that I met an exciting man named Ed Hunter. In that department, there were a number of pharmacologists who were doing some very exciting work. One was Bob Furchgott, who later went on to be awarded the Nobel Prize and Morrie Friedkin was also there, another very exciting guy to be around. Then, there were a number of post-docs in the department. One of them was Eli Robbins who later became Chairman of Psychiatry at Washington U. It was an environment that was very stimulating and pharmacology became an exciting area for me to get into. So, I pursued it. At the time, Betty, my wife and I were developing a family. So, I went to a pharmaceutical company, Wyeth, and spent a number of years there. From Wyeth I went to Jefferson Medical School and in 1957 received my PhD in Pharmacology with Kwang Soo Lee. He was an MD/Ph.D. While I was working for my PhD, Dr. Lee, who already had his MD, was working for his PhD at Johns Hopkins. He, now, is in South Korea.

* Sidney Spector was born in New York, New York in 1923.

- FS: At that time, there was very little research in Neuropsychopharmacology. I think Neuropsychopharmacology really started around the time you entered the NIH in Bethesda, Maryland.
- SS: When I graduated I had a really marvelous opportunity; I was offered the chance of going to Bernard Brodie's lab in the National Heart Institute. At the time, everyone called him Steve. He took on the name because Steve Brodie was a character who jumped off the Brooklyn Bridge and survived. And B.B. Brodie liked to be called Steve, because he, too, was making big jumps. But, in any event, when I got to Brodie's lab, he had just introduced a new method for measuring norepinephrine (NE) and serotonin (5HT), and the field started to open up. There was a tremendous amount of excitement in the area of catecholamines, because methodology, in many respects, drives science. Since we now had a method to measure NE, we could ask questions regarding catechols, and get some answers with regard to the concentrations of that amine in various brain regions as well as its turnover.
- FS: You know, Sydney, I came into Brodie's lab a little later than you as a young postdoctoral fellow from Willbrand's lab in Switzerland. You were already there, and I remember when you were talking about the ergotropic and trophotropic system, I had never left Zurich, because these were concepts W.R. Hess had developed. The first lecture I heard that you and Brodie gave, and I think Park Shore was also involved, was on the ergotropic/trophotropic systems and the role of NE in the ergotropic system. I wonder if you could talk a little bit about that period.
- SS: One needs to understand that Brodie was a chemist, but when he learned of W.R. Hess's work he jumped on that concept. It was Don Bogdanski, a member of the lab, who introduced Brodie to Hess' work on the ergotropic and trophotropic systems in the hypothalamus. He felt the brain only needed two systems, one that excited and another that inhibited brain activity. He kept talking about these systems that were in opposition to one another. He extrapolated the existence for these two systems from the existence of the sympathetic and a parasympathetic nervous system in the periphery. An important thing that occurred at that time was that Sid Udenfriend had just developed a method for detecting and measuring 5HT in the CNS. Brodie grabbed onto that and said, "now we have the two substances that I'm looking for, one of these two substances, NE is the excitatory substance and 5HT is the inhibitory substance." He also said, "that's where we go." So he started to push the ergotropic and the trophotropic systems. When I arrived he wanted me to work on monoamine oxidase (MAO), because the monoamine oxidase inhibitors (MAOI) cause excitation. He also said, that Albert Zeller and

his group at Northwestern University in Chicago had just reported that iproniazid was an inhibitory agent of MAO. Since NE and 5HT are substrates of MAO he wanted to see whether we could differentiate the role of NE and 5HT by inhibiting the MAO. So, I was assigned the problem. Before long a number of other companies developed other MAOI's. One was John Beal's company, called Lakeside, and John Beal had a number of compounds, called JB compounds, which were effective MAOI's.

FS: It should be mentioned that MAOI's were the first group of antidepressants that had been shown to be clinically effective.

SS: We found that when we administered an MAOI, both 5HT and NE levels increased but initially only 5HT levels increased. The turnover of 5HT in CNS is much faster than that of NE. So the 5HT levels rose rapidly without any indication for excitation in the animal. If we continued to administer the MAOI, the NE levels rose and the increase was accompanied by excitation. Brodie concluded that's because NE is the excitatory neurotransmitter.

FS: It was known that MAOI's are not stimulatory in their own right.

SS: That's right. They're not amphetamine like in nature.

FS: They are a neat tool for doing neuropsychopharmacological research.

SS: Since both the NE and 5HT content increased following an MAOI, we discontinued the administration of the MAOI. The animal reverted back to normal behavior and the NE content was back to basal level while 5HT brain levels remained elevated. We concluded that NE was responsible for the antidepressant activity of the MAOI, and that MAO was the important enzyme in catecholamine metabolism. That provoked quite a bit of discussion, because at the very same time, Julie Axelrod was beginning to say that catechol-O-methyl transferase was the important enzyme in the degradation of the catechols. Brodie then said, "No, it's MAO that's critical," and he used the experiment we did when we discontinued the MAOI to illustrate that it was MAO that was critical in the CNS effects and it wasn't catechol-O-methyl transferase. This argument persisted for a number of years between Axelrod and Brodie.

FS: Those studies you did with the MAOI's and, the studies your group and others in the laboratory did with reserpine on biogenic amines in the brain, were the research that provided the scientific basis for the heuristic catecholamine hypothesis of affective disorders developed by Schildkraut, Kety, Davis and Bunney.

SS: It's interesting. Brodie never talked of neuroscience, but Brodie was doing neuroscience. Today, neuroscience is the catchword, but we were doing neuroscience at the time.

- FS: Well, Sydney, I wanted to ask you, how did you jump from MAO inhibition to exploring the biosynthesis of NE and coming up with inhibitors of the synthesis of NE, compounds that became such marvelous tools in neuropsychopharmacological research?
- SS: I was with Brodie from 1956 to 1961. In 1961, I moved over to Al Sjoerdsma's group, also in the National Heart Institute and began to interact not only with Sjoerdsma, but also with Sid Udenfriend. We began to interest ourselves in the question of the biosynthetic pathway of NE. We knew all about catechols. We knew the structure of catechol, and we were just beginning to get some idea of what its synthetic pathway was. One of the ways that we attacked the issue of catechol biosynthesis was the perfusion of an isolated heart preparation with various monoamine precursors. We then did kinetic studies, and, the kinetic studies indicated that the rate limiting step in the biosynthetic pathway was tyrosine hydroxylation.
- FS: I think this was a crucial finding that advanced research on the mode of action of psychotropic drugs.
- SS: There were two experiments we did in this area that subsequently were quoted extensively. Current Contents has a citation listing of the thousand most quoted papers and the two papers we published in the course of our studies were on that list. The first one was on the *Elucidation of the Tyrosine Hydroxylase as the Rate Limiting Step*. The other one was on *α -Methyltyrosine, an Inhibitor of Tyrosine Hydroxylase*. We showed that by administering α -methyltyrosine to animals one could deplete the levels of NE. That caused quite a bit of excitement. Those two papers, from the years 1965 to 1975, were among the thousand most frequently quoted papers that Current Contents had.
- FS: Sydney, this is very interesting, because α -methyltyrosine became such an important tool in the elucidation of the mechanism of action of drugs. I remember when Marcel Bickel and I, in Brodie's lab, started to elucidate the mechanism of action of desipramine, the secondary amine of the tricyclic imipramine, we used α -methyltyrosine to prove our point. We used the reserpine-like syndrome as a "model depression" and what we found was that pretreatment with desipramine antagonized the action of reserpine. We looked at MAO first and found that it was not inhibited. Then, you gave us α -methyltyrosine, which Marcel Bickel and I used to deplete catecholamines in the brain of rats. In those animals desipramine failed to "reverse" the reserpine like syndrome. So we could prove that the tricyclic antidepressant needed catecholamines to work. You not only elucidated the synthesis of catecholamines but you also provided psychopharmacology with a marvelous research tool.

- SS: Yes, that was an excellent tool. It had that specificity one wants.
- FS: That's right.
- SS: It affected tyrosine hydroxylase selectively and if you depleted the catecholamines you were able to study many questions.
- FS: Before we go any further, I wonder if you could say a few words about the Brodie Laboratory. We have written a paper on this and referred to the Brodie Laboratory as the Mecca of Neuropsychopharmacology. I think, it would be helpful to those who will read or watch this interview if you could describe the atmosphere in that laboratory. What kind of man was Brodie?
- SS: If I were to describe that laboratory, the operational word I would use would be excitement. Brodie was an interesting man. You could go to Brodie with some little bit of data and he had the faculty for taking those data and developing stories. He would weave fanciful tales. It was exciting to be in his presence because of that. I commented earlier that he was an organic chemist and not a physiologist. Despite that, he would read, extensively, in the field of physiology and before long he became an expert. What he would do was extrapolate your data into a global picture. And he would weave patterns for you that were incredible. Granted that many times those patterns had pores and big holes in them, I think he did this purposefully to challenge you. He would challenge us by asking "Is that true or is it false?" By doing that he developed a working hypothesis to attack or to confirm, and, at times, I think he did it purposefully, because when we left his office we would say, damn it, I don't know if that's true. I'm going to do an experiment to either refute or confirm it. And, that was his strength.
- FS: I agree with you. It proves the heuristic value of a hypothesis, regardless whether correct or not, it moves the field and that's what he did.
- SS: He certainly did. The other thing about his laboratory that was exciting was that he was able to attract people from all over the world, very bright, stimulating people, and that environment was so conducive you went to work, because your colleagues were so stimulating. There was Arvid Carlsson and there was Alfred Pletscher. I was there about the time that Julie was leaving.
- FS: Julie Axelrod?
- SS: Julie Axelrod. Sid Hess, Steve Mayer and Jim Gillette were there, and he had a number of other people who were very, very stimulating. We had seminars, and when you went to present in that group, it was as though you were preparing your thesis defense. It was a very exciting period.

FS: This was the first phase of your career with Brodie. The second phase started after you moved to Sjoerdsma's laboratory. It was still in the area of catecholamines. I wonder how the transfer from a basic laboratory to a more clinically oriented laboratory changed your research- outlook?

SS: Al Sjoerdsma was also a very interesting guy. Although he was a clinician, he fostered basic research. He wanted to understand the basic mechanisms of the drugs he was giving to patients. For example, when we worked with α -methyldopa, Al Sjoerdsma was interested in knowing the mechanism of action of the substance. So we studied that and published several papers on our findings. Sjoerdsma was also able to attract some very interesting young physicians. It was a time when the Vietnam War was on. One could meet military obligations at that time by going into Public Health Service and, a number of physicians, who wanted to avoid going over to Vietnam, were recruited. Consequently, there was a group of clinical pharmacologists in Al Sjoerdsma's lab who became leaders in their field, for example, John Oates, Ken Melmon, Leon Goldberg and Carl Engleman. Al Sjoerdsma was the guy that fostered their careers.

FS: There were these two laboratories, the Brodie Laboratory and the Sjoerdsma Laboratory that produced the people who became leaders in the field. The Brodie Laboratory produced basic scientists and the Sjoerdsma Laboratory clinical pharmacologists.

SS: The NIH was also a center that attracted people, so you had in addition to the Laboratories of Brodie and Sjoerdsma, also those of Udenfriend and Axelrod. These groups all spawned bright young people, who went on and made marvelous careers for themselves.

FS: I always felt that the operation of these laboratories was driven entirely by scientific interest and not by money, because the pay in these labs was very little.

SS: Yes, indeed.

FS: People went there because they wanted to pursue scientific truth; they were truth finders. They didn't go for the green, for money.

SS: I recall the amount of money I was paid was a pittance.

FS: When you were in the clinical pharmacology laboratory, the therapeutic branch, you continued your work on the basic enzymology of tyrosine hydroxylase. For instance, there's a paper of yours in *Molecular Pharmacology* from 1967, in which you discussed tyrosine hydroxylase activity as a possible mechanism for the regulation of NE synthesis. I wonder if you could elaborate on this, because I think it would be important this is understood.

- SS: This was a paper that Al Sjoerdsma, Sid Udenfriend and I were all part of, in which we asked the question as to whether there was regulation of this biosynthetic pathway and what the regulation might be. We found when we did in vitro studies, that various catechols are capable of inhibiting tyrosine hydroxylase by binding up the cofactor, pyridoxal phosphate. We did this also in vivo and, sure enough, we could demonstrate the same phenomenon. So, as I said before, although Al Sjoerdsma's group was a clinically oriented group, he fostered basic research, and, for that, I'm very thankful. He was a good guy to be around.
- FS: Is there anything else you would like to mention about your activities in these two laboratories? I think your contributions while working there have had a far reaching impact on our field. Then, you made the decision, in 1968, to move to Hoffmann-LaRoche that was in the process of establishing a basic research institute in molecular biology.
- SS: The history of the Roche Institute is an interesting one. John Burns was vice president of research at the time. Now, John Burns had also been associated with Brodie. And the story of the Institute began at a cocktail party, which shows what can occur at cocktail parties.
- FS: Diplomats know that.
- SS: John Burns had just moved to Hoffmann-LaRoche to become vice president of research, and Hoffmann-LaRoche had, at that time, two compounds that were making more money for them than they could count. They had Librium (chlordiazepoxide) and Valium (diazepam.). So at one of those cocktail parties Sid Udenfriend said to John Burns "You know, the pharmaceutical industry doesn't have a counterpart to what Bell Labs has, where basic work is done that impinges on the communication system, and is then translated into use." So he asked John, "Why can't the pharmaceutical industry foster such an institute?" John Burns picked up on that suggestion and went to the president of Roche, Barney Mattia, and posed the question to him. Mattia grabbed onto it like a bulldog and said, that's a great idea, and said to John, "Why don't you organize it?" John went back to Sid Udenfriend and said, "It's acceptable to the administration of Hoffmann-LaRoche and they would like you to be the first director." Sid Udenfriend said he would consider it only if he were able to bring with him a cadre of people. So he approached about a half dozen of us at the NIH and said that here was an opportunity of organizing a new institute that would have as its format very much what we already had at the NIH but we needn't go out for funds because Roche would support us. We could do what we want as long as we did good work. He also told us we would have a program

of post-docs. Some of us had some reservations, initially. We couldn't understand why a pharmaceutical company was willing to do this for us so we went to talk to Mattia. Mattia was a very convincing guy. He said don't worry, if I say it's going to be, that will be sufficient.

FS: Was the Institute in Nutley founded at the same time the other Roche Institutes, the Institute of Immunology in Basel, and the Institute of Marine Biology in Australia were founded?

SS: The first one was the Roche Institute in Nutley, founded in 1968. Then, three years later, the Roche Institute of Immunology was founded in Basel, and a few years after that the Marine Biology Institute in Australia.

FS: You moved in 1968 from NIH to the Roche Institute in Nutley.

SS: Yes.

FS: And you also moved into a new area of research, immunopharmacology. This is another area in which you made significant contributions. You provided clinicians and basic researchers with tools to measure drug levels in a quantitative way.

SS: When I made this move from NIH to the Institute, there was a period of about a year while the Institute was being organized. We were housed in temporary quarters and didn't have our labs as yet. I said to Udenfriend I'd like to go on a sabbatical. He said, that's a great idea and asked where I wanted to go. So, I said, "I'm not sure where but what I'd like to do is pick up immunology. I think that immunopharmacology would be a tremendous area to get into." It was an area that had not been developed at that time. He said, "Why don't you go to Washington U in St. Louis, Herman Eisen is there." Now, Herman Eisen was a world famous immunologist and so I approached him. He was glad to accept me and I spent a year learning immunology. When I returned to Nutley, I said to Udenfriend, "Although catecholamines have been a productive field for me and very profitable, I've found a new area I'd like to get into." He replied, "Go ahead, that's what this Institute is all about; you can do what you want." So I started to develop antibodies to various drugs to follow their kinetics. Then, I asked a series of questions about the antibodies. They have characteristics that are very much like receptors; they have specificity and sensitivity that is like affinity. So, I decided to go on a fishing expedition and asked whether one could use antibodies as surrogate receptors, something like a fishing hook?

FS: What kind of antibodies did you produce relevant to neuro-psychopharmacology?

SS: For some time they used to call the antibodies I produced, the Spector Monoclonal Antibodies. Initially there were antibodies to barbiturates, morphine, reserpine, imipramine, desmethylinipramine,

chlorpromazine, and haloperidol. and also to neurotransmitters. I had antibodies to serotonin and acetylcholine. I made the antibodies to acetylcholine in collaboration with a young man from Japan, who was a post-doc, and when he left, he took them home where he continued research on that line of work and that has been very profitable for him.

FS: What do you consider the advantages of using radioimmunoassays over any other assay?

SS: One of the things that you have is specificity. As a matter of fact the antibody has a greater degree of specificity than the receptor, because the receptor will see both, the antagonist as well as the agonist, whereas the antibody will see only the agonist, if it's directed against the agonist or the antagonist if it's directed against the antagonist. So, it has that tremendous degree of specificity. With sensitivity, you can go down to nanomoles. It's incredibly sensitive. The other advantage is that you can assay a much greater number of specimens with radioimmunoassays than with other methods

FS: These assays you have developed have been used to analyze psychotropic drugs in the serum, plasma, blood and cerebrospinal fluid, right?

SS: Oh yes.

FS: Wonderful. Then comes the next big step in your life and this is a story we have to spend a little time on. How did you get to that endogenous morphine? That's one of the major research areas you developed at the Roche Institute. How did this come about?

SS: Around 1975 there was great excitement about opiate receptors, about Hughes and Kosterlitz finding enkephalins. Then C. H. Lee reported on the endorphins, and people started to develop profiles as to what was binding to what. It was apparent that the μ receptor had a greater specificity for morphine than any other endogenous peptide. I thought, let me use the antibodies as a surrogate receptor, and so I made an extract from brain. I had developed a simple method for doing the research. Sid Udenfriend once told me, "If you're going to look for something make sure that the method is a simple one. You don't want an elaborate method." And, we had a simple method. It was a radioimmunoassay; we took antibody, put labeled morphine in, and, asked whether there is anything in an extract from the brain capable of competing with that labeled morphine for the available receptor sites on the antibody. When we did that, we came up with a substance capable of bonding with the receptor on the antibody but we had no idea what the substance was. The only thing we did know was that it was not a peptide, because when we tested the brain extract after it was subjected to proteolytic enzymes, the substance was still capable of competing with the labeled

morphine. The only way we could disrupt this competition was if we oxidized it with iodine. And that's the same thing that occurs with morphine. If you oxidize morphine it disrupts the molecule. So, it looked like it was morphine. But at that point we hadn't proved it as yet. We had to go through a series of purifications with columns, HPLC, and mass spec, and sure enough, it came out as morphine.

FS: I think this was the most exciting time in your career. I would imagine it was more exciting than the work at the NIH, wasn't it?

SS: For us, it was.

FS: The fact that the brain makes morphine is exciting.

SS: The next question we had to answer was whether the substance we identified was endogenous or exogenous. When we submitted our paper for publication, the first question that was asked of us was how do you know it's endogenous and not exogenous? Initially, we put animals on a synthetic diet, and, sure enough, the substance was still there. We then decided we'd have to use precursors and show the substance that our antibody recognized could be formed from a precursor our antibody couldn't recognize. The question was which precursor should we use? Since we didn't know how morphine was synthesized in mammalian tissue, we went to the poppy plant and asked how did it make morphine? There have been a number of studies which demonstrated the synthetic pathway in the poppy plant, and we took some of those precursors and administered them to the rat. Sure enough, the rat administered the precursor was converting it into morphine. So it was an exciting time for us!

FS: Could you talk about how the endogenous levels of morphine are regulated? In other words, are your findings of physiological or pharmacological significance?

SS: That's the question we're now asking. If one thinks of morphine, one usually thinks of it in regard to its pharmacology and therefore, one thinks of analgesia. So, the first thing we did was to test whether pain would modify it.

FS: Before you proceed with this, do you know where the morphine is located in brain? Is it in neurons? Is it in glial cells?

SS: It's in neurons. It has also been shown that it's released by depolarization and there seems to be an uptake process for it.

FS: Of course there is a receptor for it that I think is the opiate receptor.

SS: Yes, but the issue is more complex. We're measuring morphine with our method. Our antibody sees morphine. It doesn't see conjugated morphine, it doesn't recognize it. So we got rid of the conjugated forms by hydrolysis and measured the free morphine. The question we tried to

answer was whether it exists in tissue as free morphine? If one subjects tissue to glucuronidase or sulfatase, the sulfatase increases the levels of morphine. Thus, we found that it exists in tissue as a conjugate of sulfate. Now, sulfated phenol sulfate transferase is present throughout the body and also in the brain. As a matter of fact, catechols form sulfated forms as well. Recently a novel new opiate receptor was shown and this receptor is for conjugated morphine. They looked at morphine-6-glucuronide and found that 6-glucuronides have a higher affinity for this novel μ -opiate receptor than morphine.

FS: Are these μ -opiate receptors G-protein linked receptors?

SS: They are G-protein linked receptors and they seem to be spliced from the μ receptor by that gene.

FS: For awhile you kicked around the idea that the endogenous morphine might actually be more than a ligand for receptors and that it could act as a second messenger, and the reason you were thinking along those lines was you had data that implicated the immune system.

SS: It was because we found that if we administered an immunostimulant drug like levamisole, or muramyl dipeptide, this stimulated morphine synthesis. We find that morphine has an effect on some intracellular nuclear sites and we're now beginning to think about that site, as well.

FS: In other words you imply a dual role for the endogenous morphine?

SS: That's correct. We found it has an effect also on some messages. That's preliminary at this point, but it's influencing a message for one of the cytokines.

FS: I can't help it, Syd, but I'm thinking this is the most exciting phase of your career, to study of the action of endogenous morphine.

SS: It is an exciting period!

FS: It's absolutely exciting. If you can forget your modesty what would you think is your greatest contribution to the field of neuropsychopharmacology? I had forgotten to mention that endogenous morphine has also a role in issues relevant to psychiatry because antidepressants, such as the tricyclics, can effect its level.

SS: Yes, the potential of the opiate system is great, because if you ask what does morphine do, you are suddenly hit with a multitude of effects. It has an effect on the CNS, there's no question about that. It stimulates certain endocrines, like prolactin, growth hormone, LH secretion. But then it inhibits respiration. It has an effect on the heart and on the gut, certainly. It has an effect on every organ you can think of.

FS: If I understand you correctly, you feel endogenous morphine is a ligand, that's like a transmitter when it's released, and it's also a second messenger, like cyclic AMP.

SS: We're thinking along those lines; whether that's the case remains to be seen. But what we think might be the role endogenous morphine plays is when we are sick, the physician in the body calls on these drugs, the pharmacist in the body prescribes these drugs and the physician in the body gives the right dose of these drugs. And that happens all within the body. The good Lord has provided us with all these key components. We think the opiate system is playing a role in all of them. For example, if you give high doses of morphine, you get convulsions. But given in low doses it's an anticonvulsant. So, we're looking at relatively low doses of morphine in the body, endogenously. If we cause convulsions in an animal, the levels of morphine go up like a shot but they only go up in the brain, not the peripheral system. We hypothesize the body doesn't like to go into convulsions. It has this endogenous anticonvulsant agent present and has prescribed we now give some morphine to counteract the convulsion. The question is, do some anticonvulsants act through this system? We've looked at carbamazepine. We've looked at metrazol and, sure enough, they, too, affect the system. If we look at the immune system, the same phenomena are going on. We think endogenous morphine is playing a number of roles as an endocoid.

FS: We have focused on some highlights in your long scientific career that goes back to the 1950's. As you look back, who were the individuals who influenced you most in terms of your development as a scientist? Who would you single out?

SS: I don't think I would single out one individual. There are three who played a role in my development. The first was Steve Brodie. Brodie gave me an approach to science that I now appreciate, this global approach that's important to generate working hypotheses. The other two have been, Al Sjoerdsma and Sid Udenfriend, but Sid Udenfriend is the one I would focus on. Sid is a scientist par excellence. He helped me to develop discipline and a way of generating or developing studies so that all the variables are controlled and all the factors are understood. For that, I really appreciate his role in my development.

FS: Like any great scientist, there is not just the science, but there are the practitioners of science and I wonder if you could say a few words about the people you produced. Looking at your CV, you had many post doctoral fellows who are all over the world, occupying leadership positions in government, universities and industry.

SS: I've been fortunate in that regard. I've been able to interact with some very bright young people, to whom I hope I've imparted something about the excitement of science and an approach to science. If I think about training students and what one has contributed to that I'm reminded of

a Chinese maxim to the effect that if you plan a year, you plant rice; if you plan for a decade, you plant trees, but if you plan for a millennium, you teach. I hope that, in teaching, some of this excitement, this feeling I have for science, has rubbed off on my students and they will impart that to their students in turn.

FS: Do you have anything you would like to say to young people; what advice would you give them?

SS: I would tell a neophyte in the field they should work with someone who is established, to pick up the techniques and approaches. That's important. Then I recommend they not be dissuaded by logic from pursuing creative ideas. There's a saying I'm reminded of to the effect that many creative ideas are slain by the arrows of logic. If you have creative ideas, pursue them. Don't let people dissuade you.

FS: It is evident you have made many seminal contributions to the field of neuropsychopharmacology and the College has been greatly enriched by what you have done, both in terms of research and the training of people. We thank you very, very much.

SS: Thank you. I must say that the College has also been a great source of inspiration for me.

FRIDOLIN SULSER

Interviewed by Leo E. Hollister
Nashville, Tennessee, May 9, 1997

- LH: It's Friday, May 9, 1997. I'm Leo Hollister. We're doing a series of interviews under the auspices of the American College of Neuropsychopharmacology with people who are instrumental in the field, have seen its development and contributed to it. Today, we're in Nashville and we'll be interviewing Fridolin Sulser,* who probably spent more of his life in Nashville than any other single place, so it's fitting to interview him here. Welcome aboard.
- FS: Thank you, Leo.
- LH: It's always interesting to find out, first of all, how people made their career choice, because I think all bright people have a lot of different choices to make. How did you decide to go into medicine?
- FS: I think this had something to do with my wife's uncle, who was a physician in a little town close to Maienfeld in the state of Graubunden, Switzerland. He was a general practitioner and I thought it would be a wonderful thing to be a physician. I thought this to be a profession beyond any other.
- LH: Were you having visions of yourself as a general practitioner taking care of people?
- FS: Yes, that's what I wanted to do but it turned out a little different in the long run. I went to medical school at the University of Zurich and Basel after I finished the gymnasium, and got my MD degree in 1955. During my medical studies in Basel I met the most remarkable man, and this was Karl Jaspers, the philosopher. He was a physician and professor of philosophy at the university. He was one of the best known existential philosophers in the German speaking world. Jaspers came from Germany because he had problems in his homeland. His wife was Jewish and, at that time, as you know, the Germans did not like Germans to marry Jews. He left Germany in 1948 and came to Switzerland. It happened at that time that the professor of philosophy retired from the university, and Karl Jaspers got his Chair. As a medical student, I attended his lectures that triggered my life long fascination with existential philosophy. This was a man with a vision, a perspective and a sense of history. And, he was also a trained psychiatrist before he jumped into existential philosophy. He was enormously critical of psychoanalysis but he liked Freud. And, when I graduated, I came away with the feeling that psychoanalysis, which was predominant at that time, was not

* Fridolin Sulser was born in Grabs, Switzerland in 1926.

what I wanted to do. So, I went to see professor Bleuler in Zurich and solicited his advice about my future education.

LH: Was this Manfred?

FS: Yes. After I worked at his hospital for about three weeks, he called me into his office. We had a serious talk behind closed doors, and he said, "Look, Dr. Sulser, I think this is not for you. I would not recommend you go for a residency in psychiatry." I asked him why, and he said, "Well, number one, you don't listen." Listening is apparently important in psychiatry. And, the second thing Bleuler mentioned was that I was too experimentally minded. Interesting. That's a good clinician, a good assessment I thought. So I took his advice and recommendation that I do something else than psychiatry and work in an experimental area more to my liking. So, I went to see people in pharmacology in Basel and got a job there.

LH: In pharmacology?

FS: In pharmacology. It was with Franz Gross, who worked on hypertension at Ciba and with Rolf Meyer at the University of Basel. After two years or so, I became an Assistant Professor at the University of Bern and started to work on cardiac function and the effect of digitalis on ion transport.

LH: What you did was quite removed from Karl Jaspers.

FS: Yes. Then I read, in the *Journal Science*, the article by Pletscher, Shore and Brodie, on the *Effect of Reserpine on the Endogenous Levels of Serotonin in Brain*. I knew from my hypertension research that a certain percentage of patients treated with reserpine developed depressive symptoms. So, I said, ah ha, there's a connection! I wrote a letter to Bernard B. Brodie at the NIH indicating I would like to come for a year or so to the United States to work in his laboratory.

LH: Did you know Pletscher before?

FS: I knew Pletscher from studies we did at CIBA. And while in medical school we had him and other people from the pharmaceutical industry visiting with us. We also went to visit Hoffmann-LaRoche where Alfred Pletscher was Director of Research.

LH: When you were still a student?

FS: When I was still a postdoctoral student. I went to see Pletscher and told him about my interest in his paper. He had just returned from Brodie's lab, and said, "Why don't you go to Brodie, it's a great place to be". He told me that there were other brilliant people there like Sidney Udenfriend, Park Shore and Julie Axelrod. And he said, "You should apply for a Fellowship to go there." So, I applied for a Fellowship to the Swiss Academy of Medical Sciences and I got \$3,000.00. I thought

- this was a lot of money and told my wife we were going to the United States, presumably for one year.
- LH: But, didn't you write to Brodie first?
- FS: Before applying for a Fellowship I wrote to Brodie who wrote back that he would take me if I brought my own money!
- LH: So, you went to the Swiss Academy after Brodie accepted you?.
- FS: That's correct. I went to the United States with only a suitcase. My wife was to join me later. It was in October 1958 I showed up at NIH and walked into Building 10. There was a Symposium in progress on catecholamines. Arvid Carlsson talked about dopamine. He had developed a method to distinguish dopamine from noradrenaline.
- LH: That was just discovered.
- FS: He reported he found very high concentrations of dopamine but not norepinephrine in the striatum and concluded dopamine is not just a precursor of noradrenaline but is a transmitter in its' own right. So my career began.
- LH: You were there when Carlsson was there.
- FS: No, Carlsson was already gone. He was there for the Catecholamine Symposium and after its conclusion he went back to Sweden.
- LH: So you started your work with Brodie. I'm always interested to find out from people who knew him what kind of person he was. Was he difficult?
- FS: I wouldn't have known whether he was or wasn't difficult in the beginning, because I didn't understand English sufficiently well. I had real difficulties and first of all I had to learn three things. First, I had to learn English. And Brodie had very slurred speech that was difficult for me to understand. Second, I had to learn new spectrofluorometric methods. And third, I had to become familiar with new concepts in biochemical neuropharmacology. I can say Brodie was very, very nice to my wife and me. He helped us to find a place to live. Mrs. Brodie was driving my wife around Washington before she learned how to drive. So I have only good things to say.
- LH: Did he allow you to pursue your own ideas?
- FS: He was very egocentric and wanted people to work on problems he had an interest in. I remember once I ran into a little problem with him. I wanted to study something I was interested in and was working on it in the late afternoon. As always, he came to the lab in the late afternoon and when he saw what I was doing he asked, "Why are you doing this?" And I said, "Because it's interesting, Dr. Brodie." Then, he said, "Well, if you want to do this, why did you come to work with me?" So, I switched to work on a problem he had an interest in. The problem

he was interested in related to imipramine. When he saw I was working on what he was interested in, he became very cordial and said, "Well, imipramine is an interesting drug. People say it works, but I don't believe it." So, I asked him, "Why don't you believe that it works?" He said, "It doesn't block monoamine oxidase." He also told me that psychiatrists can't quantitate things, and if one gives them orange juice they will find it works. So I felt I had to work with imipramine but didn't know what to do in the beginning, because imipramine did not block monoamine oxidase and behaved in many pharmacological tests like a weak phenothiazine-like compound. Then, Brodie said, "Well, maybe, we should have a model for depression." We were sitting together and I said, "Why don't we set up reserpine as a model of depression". Mimo Costa and Silvio Garattini had previously shown that imipramine antagonized some of the symptoms elicited by reserpine. So, we reserpinized rats and studied the action of imipramine. Sure enough, when we pretreated reserpinized animals with imipramine, the trophotropic syndrome became ergotropic. Instead of closed eyes, the animals had wide-open eyes, instead of miosis, they had mydriasis, instead of being motionless, they showed increased motor activity.

LH: I don't know if people who will look at this tape will know what the ergotropic and trophotropic syndromes are. Didn't this terminology come from W.R. Hess?

FS: Yes, it was W.R. Hess who coined this terminology.

LH: That's another Swiss.

FS: Yes, that's another Swiss. To put it in a nutshell, the trophotropic syndrome is a syndrome characterized by increased parasympathetic activity and decreased sympathetic activity. And this was what reserpine was doing. It induced a trophotropic syndrome.

LH: Does the name trophotropic come from tropho, to repair.

FS: Yes. Imipramine worked like a monoamine oxidase inhibitor when injected prior to reserpine. Instead of miosis, there was mydriasis, instead of ptosis, exophthalmus, instead of decreased locomotor activity, increased locomotor activity, instead of hypotension, hypertension, and instead of decreased body temperature, increased body temperature. Then, we asked how was the drug doing this? We knew it didn't block monoamine oxidase, but we had not the slightest idea how the drug, without inhibiting monoamine oxidase, "reversed" reserpine's effects. Later on we found imipramine also "reversed" the effects of tetrabenazine which is a benzoquinolizine compound with a similar action to reserpine but which works a little faster. Then, Brodie said, gee, this is interesting, maybe the drug works on brain serotonin, because he had the idea,

based on findings by Pletscher and Shore, that reserpine's behavioral effects result from depletion of serotonin. Marcel Bickel, another Swiss who was there, and I treated animals with alpha-methyltyrosine which blocks tyrosine hydroxylation, the rate limiting step in the biosynthesis of catecholamines. It depleted norepinephrine and dopamine in the brains of the animals while it left serotonin untouched. This was the first depletion experiment done long before the Yale group started doing depletion experiments in human. We found that after norepinephrine was depleted, imipramine failed to antagonize the effects of reserpine. So, we learned the availability of norepinephrine was crucial for the action of imipramine. It did not take very long however to find out why norepinephrine was needed for imipramine's action. George Hertting, who was a post-doc with Julie Axelrod, came to our lab and said "We can explain your data. Tricyclic antidepressants block the uptake of norepinephrine." So, everything became clear. Monoaminooxidase inhibitors and the tricyclic antidepressants increased the availability of norepinephrine but by different mechanisms, one by blocking the metabolism of norepinephrine, and the other by blocking its reuptake. The rest is history and people started screening for drugs which block the uptake of norepinephrine.

LH: Did Brodie's laboratory identify desipramine?

FS: Yes but what happened is another story. Brodie had the idea that the reason for giving imipramine chronically before it "reverses" the effects of reserpine was that the drug accumulated in the brain. James Gillette had developed a method that could detect imipramine by fluorimetric means in the brain. Gillette had a graduate student, Jim Dingell, so Jim and I got together and decided to see what actually happens. We treated animals chronically with imipramine and planned to measure the accumulation of imipramine in brain. But we couldn't. Instead, we found a compound in the buffer phase with fluorescence similar to imipramine that turned out to be desipramine (DMI).

LH: It had a different peak from imipramine?

FS: It had a different peak and it was extracted into the buffer phase whereas imipramine remained in the heptane phase. Using paper and gas chromatography, we were able to identify the substance in the buffer phase as DMI. This was the discovery of the first selective norepinephrine reuptake inhibitor. After that we used DMI as a tool in our research.

LH: Wasn't Brodie the first guy to put out the idea there were prodrugs and sometimes they were the metabolites that acted?

FS: He was thinking that way, even about imipramine. He thought imipramine was a prodrug, and the active compound was the demethylated

metabolite. This is true with regards to norepinephrine function, because DMI is much more potent on the noradrenergic system than imipramine which is more potent on the serotonergic system. So, in many ways, imipramine was a pro-drug in making a noradrenergic drug from a serotonergic drug. The important discovery in Brodie's laboratory was the demonstration that DMI-like antidepressants need norepinephrine to work. The importance of the availability of norepinephrine in the action of DMI-like antidepressants became evident at Vanderbilt in our research on the down regulation of the beta adrenoceptor mediated cyclic AMP second messenger cascade.

LH: I think most people have the idea that Brodie had invested heavily on serotonin, but from what you told me, you and the rest of people, had a pretty good idea that norepinephrine was very important. How did Brodie, Pletscher and Shore measure serotonin?

FS: They measured serotonin using spectrofluorimetric methodology that had just been developed by Bowman and Udenfriend.

LH: The introduction of the spectrofluorimetric method was a tremendous improvement.

FS: The person who put lots of work into developing a methodology for measuring monoamines was Sidney Udenfriend, who was at NIH before he went to the Roche Institute. It was an enormous advance that one could measure quantitatively small amounts of monoamines in different areas of the brain. In our experiments, after extraction into heptane, imipramine stayed in the heptane phase, and DMI was returned to an aqueous phase. The compounds were then measured fluorimetrically. Jim Dingell, who was instrumental in identifying desipramine, made his doctoral dissertation in this area. Jim and I learned from each other. He was teaching me methodologies in drug metabolism and I tried to teach him pharmacology. You know Jim Dingell; you interviewed him.

LH: Yes, I know Jim. He is a very modest man.

FS: He came to Vanderbilt where we continued to collaborate. You asked me before to say something about Brodie. One thing of interest is that he used to tell his postdoctoral fellows there are three things necessary to become a successful scientist. First you have to have an idea, second you have to be able to develop methods to test the idea, and third, you have to be lucky. And, I think he has been right.

LH: Methodology is tremendously important. I was thinking the other day that a sizable number of Nobel Prizes have been given to people for developing methods.

- FS: Brodie's philosophy was that if you want to find new things, you have to be able to develop new methods. With new methods, you will be able to open up new fields.
- LH: When he was at Ward's Island in New York trying to develop antimalarial agents, he had to develop new methods. He was very much into colorimetric methods in those years.
- FS: That's correct. He also told people in his laboratory how important it is to measure something quantitatively. If you just have qualitative measurements, he used to say, "Forget it, you have to be able to quantitate." This is what he and everybody in his lab had done. They used quantitative methodology and this is why the Brodie School opened up so many new fields.
- LH: Well, he opened up the whole field of pharmacokinetics.
- FS: It was opened up entirely by Brodie.
- LH: And, of course, he was into drug metabolism.
- FS: Brodie's fantasy was sometimes ahead of the data and there were a lot of people who faulted him for that. But it was his demonstration that psychoactive drugs can change the levels of monoamines in the brain, and the development of histofluorescence techniques that helped to catalyze the birth of biochemical neuropsychopharmacology and biological psychiatry.
- LH: This was than done by Fuxe. Didn't he develop the histochemical method?
- FS: Fuxe and Hillarp.
- LH: And, Annica....
- FS: Annica Dahlström. They were the ones who developed histofluorescence microscopy. And, they mapped, using these techniques, the distribution of noreadrenergic neurons, their terminals and their cell bodies, the serotonergic terminals in the raphe nuclei, and the dopaminergic terminals and so on. The origin of the idea of working on systems, like the noradrenergic, serotonergic or other systems was deeply rooted in the teachings of W.R.Hess who emphasized that one has to work on functional systems because, if a finding cannot be related to function, it has no relevance to the central nervous system. This functional orientation is something that is lost. I remember Hess, when we were looking at a slide of tissue culture under the microscope, asking "What do you think you will learn from such studies about why you fall in love with a girl?". And Brodie looked at things in the same way. It was absolutely amazing what happened in his laboratory. Of course many people went to work with him, his laboratory was a Mecca of psychopharmacology in the 1960s. There was Brodie himself, and there was Axelrod, Udenfriend,

Shore, Bogdanski, Pletscher and Carlsson. There were the Germans, Norbert Matussek, Eric Westermann, Hans Dengler and Karl Netter. There were the Italians, Mimo Costa and Luigi Gessa. Marcel Bickel from Switzerland, who later on became Chairman of Pharmacology in Bern, was there. It was a wonderful stimulating environment.

LH: How long were you there?

FS: I was there from 1958 to 1962. Four years.

LH: So, that was the high point of your life?

FS: If I could have been employed by the NIH, I would have stayed, but I couldn't.

LH: Because you were not a citizen?

FS: I wasn't a citizen and I was on a student exchange visa. I was supposed to go back to Switzerland for two years and then apply for a permanent visa. But, then, the politicians helped me to fix the problem. Jim Dingell's brother was in Congress, and his mother was Swiss. So, Congress passed a private bill to change my exchange visa and get me a green card.

LH: I gather you were at the International Congress in Moscow where Marshall Nirenberg presented his findings on the genetic code.

FS: No, I was not there but I was at NIH when Matthaei and Nirenberg discovered the genetic code. That was in 1961 or 1962. They were just around the corner from me. After I became an immigrant I went to work for two and a half years at Burroughs Wellcome in Tuckahoe, New York, as head of their pharmacology department. But, as you can imagine, working in industry was not for me. It's not my life style. So when Dan Efron told me Allan Bass at Vanderbilt was entertaining the development of a Psychopharmacology Research Center I thought that's a good opportunity for me to go back to academia, and get closer to psychiatry. This was in 1965.

LH: Sometimes we underestimate the influence administrators have, because Dan was nothing but a scientific administrator. Yet he was the one who encouraged Allan to start the Tennessee Neuropsychiatric Institute (TNI) and recruit you.

FS: Administrators, if they're smart, can do a lot by channeling things in the right direction. I think that top administrators, who are also scientists, should have membership in the ACNP as real members, and not just as administrative members. Some of them have made tremendous contributions to the field.

LH: For a very long period of time, in this country, nobody employed by industry could ever hope to be President of the Pharmacology Society. John Burns was one of the very first people from industry to be asked.

- FS: In 1958, when I came to this country, you could not even become a member of the Pharmacology Society if you were working in industry.
- LH: That's never been a bias in the ACNP. Len Cook and Larry Stein were both connected with industry while they were President, and one of the guys running for president this year is also connected with industry. I don't think we've had any biases in that respect.
- FS: I don't think so, either.
- LH: So, after you left Burroughs Wellcome, you went to Tennessee?
- FS: Yes, I went to Tennessee.
- LH: That was what year?
- FS: 1965. Then I could develop my own research, in industry, I could not. And at NIH I worked with Brodie. So, this was a tremendous opportunity.
- LH: You had to come down here, take a vacant space, and turn it into a laboratory?
- FS: Space at the State Hospital had to be turned into labs at the beginning. We got a center grant from NIMH with the enthusiastic support of Dan Efron. And the State of Tennessee gave us money to renovate the place. We had good space and we got good people to come to work in the Institute; post doc's like Elaine Sanders-Bush, Susan Robinson, Dorothy Gallagher and Phil Mobley. All these people went through TNI. Then Jerzy Vetulani came from Poland, and Janowsky.
- LH: Dave Janowsky from San Diego?
- FS: No, Aaron Janowsky from Oregon. We developed a very effective basic research group.
- LH: Didn't Jerzy Vetulani go back to Poland?
- FS: Yes, he went back.
- LH: Is he a Chair somewhere?
- FS: He is the Scientific Director of the Polish Academy of Sciences in Krakow.
- LH: What did you start doing when you came here?
- FS: The first thing we did was ask the question why antidepressant drugs take so long to work. I was convinced that norepinephrine uptake inhibition per se had probably nothing to do with the therapeutic activity of these drugs, because uptake inhibition and the reversal of the reserpine syndrome take place rapidly. I had one of my graduate students during my first-year at Vanderbilt look at how fast uptake inhibition in vivo occurs. We gave imipramine and a few minutes later the uptake of norepinephrine was blocked. So, I concluded this could not be directly responsible for the therapeutic activity.
- LH: Also, uptake into the nerves is especially fast.

FS: Yes. We looked for other mechanisms that take longer to produce an effect. This is when Earl Sutherland, another one of my heroes, with his cyclic AMP second messenger concept, came into the picture.

LH: He did most of his work on cyclic AMP at Case Reserve in Cleveland, didn't he?

FS: That's correct. He was a man with a vision. It was Earl who first talked to me about cascades in the CNS in which the interaction of a transmitter with receptors is only the first step, the step that activates these cascades. And this was before G proteins; we didn't know about them at the time. And while Earl was here at Vanderbilt he put the receptor for norepinephrine on the enzyme adenylate cyclase.

LH: So, nobody knew about G proteins then?

FS: No, the pivotal role of G proteins in signal transduction was discovered later by Rodbell and Gilman. Then, in a conversation one evening over Jack Daniels, with a fire burning in the hearth, Earl said, "If I were you, I'd look beyond the synapse at these cascades and the role they play in the action of antidepressants." Obviously his favorite one, was the cyclic AMP cascade.

LH: At that time cyclic AMP was the only second messenger, wasn't it?

FS: It was the only one and it was difficult to measure the activity of the second messenger system. We didn't have a radioimmunoassay, so we had to use enzymatic reactions to measure cyclic AMP. It was very, very complicated and time consuming. Alan Robinson was involved in that. Then we discovered that if we gave antidepressants chronically on a clinically relevant time basis there was an adaptation going on at the level of the β -adrenoceptor-coupled adenylate cyclase systems. This was in 1975, 25 years ago. It was a tremendously interesting discovery. The sensitivity of a receptor to an agonist was measured by the activation of adenylate cyclase. We found the number of receptors in the membrane was changed after chronic administration of antidepressants. Prior to this Lefkowitz and others discovered that receptor sensitivity was regulated by phosphorylation.

LH: So you had shown that the number of receptors decreased.

FS: Yes.

LH: But the decreased number of receptors was not the consequence of the decreased sensitivity.

FS: Rather the decreased sensitivity of the adenylate cyclase system was the consequence of the decreased number of receptors. So the first thing we found at Vanderbilt was that the number of receptors decreased. This led to the receptor regulation hypothesis and all kinds of other research. Importantly, we discovered that antidepressant treatments,

tricyclics, MAO inhibitors and ECT, given on a clinically relevant time basis, reduced the responsiveness of the beta adrenoceptor-coupled adenylate cyclase system to norepinephrine in limbic and cortical structures of the rat brain and that chronic, but not acute treatment with noradrenergic antidepressants, down-regulated the biologically active form of the transcription factor, CREB-P, in the frontal cortex of the rat, indicating a net deamplification of the beta adrenoceptor – cyclic AMP cascade. Conceptually, these studies switched the emphasis on the mode of action of antidepressants and on the pathophysiology of affective disorders from acute presynaptic to delayed postsynaptic second messenger mediated cascades and opened up the gateway for subsequent studies of events beyond the receptors including changes in gene expression. A little later, when Phil Mobley joined our lab, we realized we had to incorporate the glucocorticoids in our work, because, stressful life events can precipitate depressive reactions. So we started to look at glucocorticoids and found that changes in glucocorticoids were changing the sensitivity of the receptor system to catecholamines. That led to the norepinephrine-glucocorticoid link hypothesis of affective disorders. The role of serotonin we did not understand for a long time. That changed when Berridge demonstrated that serotonin, through serotonin receptors we now know are $5HT_{2A}$ and $5HT_{2C}$, activates phospholipase C, generating 2 second messengers, inositol-triphosphate (IP3) that mobilizes calcium and diacylglycerol, which activates protein kinase C.

LH: That was in the late 1960's?

FS: Yes. Then, Elaine Sanders-Bush, who worked with me, started looking at serotonin and serotonin receptors. I took care of the catecholamines and she took care of the indols. We found that the two systems, the noradrenergic and serotonergic systems converged after the receptors. And that was absolutely fascinating. Norepinephrine through the adenylate cyclase system activated protein kinase A, that initially phosphorylates the receptor in the membrane, and causes desensitization of the system. Serotonin, through phospholipase C activation, made IP3 and diacylglycerol, which activates protein kinase C, and, we found that protein kinase C and protein kinase A have a cross talk with each other. Moreover, we found in human fibroblasts, using the transcription factor CREB as a target, that both the activation of the cyclic AMP- protein kinase A pathway by the beta agonist isoproterenol and the activation of the protein kinase C pathway by the phorbol ester PMA caused phosphorylation of nuclear CREB, and that this phosphorylation is additive in nature.

LH: So you linked the activity of the serotonin system with the norepinephrine system?

FS: Yes. We're trying, now, to see what all this means. Paul Greengard at Rockefeller, who was previously at Yale, has shown that the final common pathway of signal transduction is the phosphorylation process, so the question now is, what is phosphorylated and what is less phosphorylated after desensitization, and what are the consequences of all this in the next compartment of the cell, in the nucleus. Presently, we're looking into this. Paul Rossby and I developed the hypothesis that behavior is put together by programs of gene expression. It's a large program, it's like a huge orchestra in which there are twenty thousand players (genes) and there are first violins, first cellos, the horns and so on. This is well coordinated in "normal" people like you and me. Now, if the horn comes on at the wrong time, you have dissonance. We feel in depressed people, because of stress or whatever, the plasticity of the system is lost in response to increased input; what the drugs do is help to adapt by restoring the plasticity at the level of gene expression. At the present time, we are trying to develop methods to identify the first violins and the cellos. In other words, developing methodology to measure programs of gene expression that are activated by transcription factors, phosphorylated by the kinases. Hopefully, one of these days, we will understand what's going on. The work with transcription factors is new and people don't talk about it yet, because it is very complicated. There are about two thousand eukaryotic transcription factors. Once translocated to the nucleus, they will affect only genes that have responsive elements in the promoter area (nuclear receptors).

LH: Are c-fos, c-jun genes further down the line?

FS: Yes. A transcription factor, like CREB, turns genes with CRE elements in their promoter region on via the beta adrenoceptor-cyclic AMP cascade. One will always turn on groups of genes, in other words, the first violins, the second violins etc. The question is, what are these genes and, importantly, what are their products doing. That's not easy to find out. We need new methodology; but this is where the field is going. Finally, you can envision the development of drugs that affect or restore faulty programs of gene expression.

LH: So we got away from the synapses.

FS: Yes, all the way to the nucleus. There's already fascinating work in this area from Michael Greenberg's lab at Harvard. Michael has shown that fos-b, which is a transcription factor like fos-c and jun-c, is very important for the complex behavior of nurturing in animals. Normal animals, and this was done in mice, after they give birth, collect their off-spring,

put them in the nest, put their body over them to keep them warm and nurture them. If you knock out just one transcription factor, fos-b, they don't do those things any more because nurturing behavior is interrupted. This is absolutely fascinating. By knocking out one transcription factor, the olfactory stimulus of smelling the pups doesn't work any longer.

LH: This knock out gene technique is fantastic. Who is the Japanese fellow who is using the knock out gene technique in studying behavior? The one who won the Nobel Prize.

FS: I don't remember his name either. The task in the future is to apply these sophisticated techniques in an intelligent way to behavioral problems.

LH: His name was Tonegawa.

FS: Yes, Tonegawa. So, this is where the field is moving; from presynaptic events in the 1960's, to membrane receptors in the 1970's, to second messenger mediated activation of protein kinases in the 1980's, and, now, we are moving to the last compartment, the nucleus. That's where the action is now.

LH: That's an enormous amount of progress and you've been part of all of it.

FS: It is enormous progress if you think about it. At the time I entered the field there was nothing known about cascades. When I was at the NIH in the late 1950s we were still grinding up whole brains of rats, just to measure serotonin or norepinephrine. There was nothing known about presynaptic events such as uptake, receptors, receptor subtypes. There was little or nothing known about protein kinases, G proteins, transcription factors, not to speak about the organization of the genes and how they're turned on and off.

LH: And, we still don't know anything about the gene products.

FS: That research will not be easy to do because those products are proteins, and the functions of proteins are difficult to study.

LH: You're still at the Tennessee Neuropsychiatric Institute?

FS: No, I'm in the Department of Psychiatry at Vanderbilt University. I have my laboratories there and my grant was renewed this fall for another five years.

LH: It should be easy for you to get grant support.

FS: I think so but I had to go away for a year, because I realized that the "old pharmacology" is not helping me any longer. It boxed me in with old techniques. So, I spent a year on sabbatical at the Roche Institute of Molecular Biology.

LH: So, that's how you became interested in molecular biology?

FS: Yes. When I came back and had to renew my grant, I thought this time I will have problems, because members of the study section will say, why the hell, at age 60, does that fellow want to move into a new area of research. Well, I sent the grant in and guess what happened? They liked it, so much, that instead of five years, they approved it for ten.

LH: Wonderful!

FS: I've been very lucky. The number three ingredient for successful research is luck, as Brodie said.

LH: It's a great joy to be lucky and able to do the things we like, that give us pleasure, and may even help patients.

FS: Well, that is one thing I sometimes miss, the patients. You remember I wanted to go into medicine because of the patients. The problem, if you get involved in basic research, is that you have to work with new methods, and you simply have no time for patients. The development of new methods is so demanding you cannot see patients.

LH: When you get to be my age you can go back to that Swiss town and do general practice. One of the regrets I have, and I'm sure you must too, is that we don't have enough lives to do all the creative things. I would have preferred to do more basic research but I also feel I have not spent as much time with patients as I would have liked.

FS: The last patient I saw was in the Swiss Army, before I left Switzerland. Did you know, I was in the Swiss Army?

LH: You had to do your military service?

FS: After I finished medical school, I was in the Medical Corps and that was the only place I saw patients. And after that I saw only rats and tissue cultures.

LH: We have to settle for the blessings of the day.

FS: I sometimes think that I made it up. That I helped develop two classes of drugs for affective disorders. I contributed to psychiatry with my work on the development of the secondary amine tricyclic antidepressant DMI. And, I helped develop bupropion while I was at Burroughs Wellcome.

LH: Bupropion is a very valuable antidepressant.

FS: It's a noradrenergic antidepressant like DMI.

LH: Doesn't it have dopaminergic activity?

FS: Yes, in the rat. But in man, bupropion is metabolized to hydroxybupropion which is a norepinephrine reuptake inhibitor.

LH: I must say, Fridolin, I've always considered you to be one of the most creative people in the field, as well as one of the nicest.

FS: I don't know. I think the most important discoveries are yet to be made when we get to know these subsets of instruments, the first violins, the

second cellos, the horns and so on. We're working on this now, trying to develop methods to identify specific differentially expressed genes. I am very fortunate being able to interact with Peng Liang who, while a postdoctoral fellow with Arthur Pardee at Harvard, invented the technology for cloning differentially expressed genes. This makes it possible to display about 96 % of all the genes expressed in a particular cell type and subsequently to be recovered from polyacrylamide gels. I am looking forward to the discovery of novel genes involved in providing a predisposition to psychiatric illnesses. My dream would be to develop drugs that would selectively turn on or off sets of genes that are important for certain behaviors. I consider these transcription factors, activated by second messenger mediated cascades, important as light switches. If you can't turn them on because the light switch is broken, it doesn't matter how much electricity goes in, it remains dark.

LH: It's only as strong as its weakest link.

FS: That's correct.

LH: Thank you, Fridolin.

RICHARD J. WURTMAN

**Interviewed by Thomas A. Ban
Acapulco, Mexico, December 12, 1998**

TB: We are at the 45th Annual Meeting of the American College of Neuropsychopharmacology at the Acapulco Princess Hotel in Acapulco, Mexico. It is December 12, 1998, and I am going to interview Richard Wurtman* for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Let's start from the very beginning. If you could tell us where you are from, where were you brought up, something about your education, and how you got involved in psychopharmacology?

RW: I was born in Philadelphia and went to an excellent public school, Central High School. After which I went to college at the University of Pennsylvania. At that time, I thought of myself as a pre-law student. My father was a lawyer, I was a debater. Some people say I am still a debater. I wanted to do law, I thought I liked it. And, I was a philosophy student in college. I got a Master's degree in Philosophy of History and this did have an impact on what I've done since. But, in my last year of college, I decided I wasn't sure I wanted to be a lawyer. I met a student at Harvard Medical School who convinced me if I went to medical school I could do two things; I could be a medical scientist and discover things, or I could make sick people feel better. For one reason or another, I decided at the end of summer that I wanted to be a doctor instead of a lawyer. This caused a small amount of chagrin in my family. My poor brother had to become a lawyer instead. I spent my last year in college taking a course or two in chemistry and zoology. You could do that and still get into medical school in those days. Then, I applied to a couple of medical schools and got into Harvard. I left Philadelphia, went to Boston, and haven't left since except for four years at the NIH. I told myself I wanted to work on the mind/body problem. Coming from philosophy I wanted to understand how the brain generated the mind. My son is a doctor and when I told him that he said, "gee dad, what went wrong." But one still tries and I'm delighted how recent advances in clinical psychopharmacology bring us closer to understanding mind-brain relationships. With this commitment to the mind/body problem, I wanted to initiate research as soon as I started in medical school. I was lucky; Harvard had just started a program which would encourage medical students to do laboratory research, and so by the end of my first year I had started a research project. While I was

* Richard Wurtman was born in Philadelphia, Pennsylvania in 1936.

in medical school, I spent almost as much time on research projects as on becoming a doctor. The first research project was related to what followed. It was with a professor of cardiology, Mark Altschule, who believed that schizophrenia was a disease of the pineal gland.

TB: What was his argument for that?

RW: It's the only unpaired midline structure in the brain, so it must do something fundamental. Around this time, a blood test for schizophrenia had been published in the journal *Science*. It was the Akerfeldt test. Altschule thought he could cure schizophrenia by giving patients extracts of cow pineals, so he hired me and one of my classmates to do the Akerfeldt test on people before and after they received pineal extracts. His idea was he should be able to show that not only did the extracts cure schizophrenia behaviorally, but also biochemically.

TB: Was this in the late 1950s?

RW: This was about 1957 or 1958. The one good thing that came out of that summer was that I became interested in the pineal and a few years later, while I was still in medical school, started doing research on what happened to rats if you took out the pineal or administered pineal extracts. So by the time I graduated from medical school a corpus of publications had appeared, describing effects of pinealectomy or the extracts. Just around this time Aaron Lerner at Yale University discovered melatonin in similar pineal extracts. So, one of the first things I did when I got to the NIH two years later was discuss this with my very good friend, and kind of uncle, Julius Axelrod. Together we showed that the active pineal principle which affected rats was melatonin. Our findings that it promotes sleep, and that its deficiency can lead to insomnia in the aged were not made until many years later. This led to our discovery that melatonin is actually a hormone in mammals. Melatonin had been discovered based on its action to lighten the color of tadpoles' skin; its function in mammals was not known. So, something good came out of that first summer in medical school. I enjoyed being in medical school but I also I enjoyed the role of researcher, creating much confusion concerning my career goals. A nagging question was, "Do I want to be a doctor or do I want to be a scientist?" At Harvard, at that time, there was this marvelous myth that the ideal thing for all graduates would be one-third research, one-third teaching, and one-third seeing patients. I looked around for a role model, somebody who was successful in doing all three.

TB: Did you find one?

RW: There were many people trying to do all three, but I could find no one who came across as successful. So, I decided I wouldn't try. But what

then should I choose? I didn't know. So, I went to the Massachusetts General Hospital as an intern and a resident for a few years. I really liked taking care of sick people, but, then, I went to the NIH and spent two years as a fellow with Julie Axelrod. And I didn't just like that, I loved it! It was an incredible eye opener. Partly, of course, it was Julie's extraordinary gift, his personality and his excitement about science and capacity to translate a complex question into simple experiments. At the end of my two years at the NIH, Seymour Kety, who was running the laboratory, and Julie invited me to stay permanently. But there was no room at that time, so they said the NIH would send me away for a year to any place I'd like to go. I still thought perhaps I could integrate basic science and clinical medicine. In fact, that's what I was going to do later on, but didn't know then. So I went back to the Massachusetts General Hospital (MGH) for a year in 1964-65, as a clinical Fellow in Endocrinology and Neurology. It was a good year; the experience convinced me I wanted to be a scientist. At the end of that year, in 1965, I moved back to Bethesda, planning to spend the rest of my life at the NIH. But, I spent only two years before going to MIT. And I've stayed at MIT since. My year at the MGH in 1964-1965 was good for me because I happened to make a clinical observation that paid off. There was a woman seen by the Endocrinology Group who had a pituitary infarction during the process of having a baby. It happens in some people. So, her pituitary gland didn't function. Her major symptom was that sometimes two, three or four hours after eating she had seizures that were associated with hypoglycemia. Nobody understood why pituitary insufficiency might lead to hypoglycemia after eating. People thought it might be via deficiencies in ACTH or gluconeogenesis, but that process takes too long to become manifest so soon after eating. I got the idea that since the fast process of raising blood sugar after insulin release involved adrenaline, perhaps the pituitary might have something to do with the control of adrenaline production. When I went back to the NIH my associates and I took out the pituitary from rats and dogs and showed that doing so profoundly impaired the capacity of the adrenal gland to make adrenaline and release it into the blood stream. So, I was lucky. By that time, I had been at the NIH for two 2-year periods. In the first two years with Julie I'd shown that melatonin was a hormone and that the synthesis of melatonin was controlled by light and darkness, as well as by the sympathetic nerves. And that the production of melatonin exhibited a daily rhythm. We wrote a lot about the daily rhythms and helped to popularize that field. And in the second two-year period I asked myself the question why God put the adrenal medulla inside the adrenal

cortex. and answered it by showing that the pituitary stimulates the cortex to make cortisone which is selectively delivered to the medulla and controls its production of adrenaline. So by 1967 I was known for having discovered two sets of things. I was becoming a 'hot commodity' among academic recruiters.

TB: Why did you pick MIT?

RW: One reason I picked MIT was that a Washington-area colleague, who was probably the world's greatest neuroanatomist, Walle Nauta, had moved to MIT a year earlier to join its neuroscientists. Also, I had a good offer from MIT and liked living in Boston. By 1967, my formal education was over; it included components of clinical medicine, but larger components of basic science. I went to MIT to establish and direct my own laboratory. MIT is a great place. It operates as a large number of independent systems. We have departments that give degrees, but for the most part, individual professors are nearly completely independent. I have now been at MIT for more than twenty-five years. Hundreds of students and fellows have gone through my laboratory. I've had a number of opportunities to leave MIT but never wanted to. I plan to be there until I'm a hundred if they'll have me.

TB: What have you been doing at MIT?

RW: Basically I do two things. I try to discover new facts about how the body works normally, and when it doesn't work, using molecular and neurobiologic techniques, I apply what I find in basic research to humans. I try to determine whether or not things we observe in the laboratory occur in people. We have a clinical research center at MIT, one of the seventy clinical research centers in the country funded by the NIH, the other sixty-nine being, for the most part, in university hospitals. It was established at MIT before I arrived, to facilitate translational research. A large part of my time is spent doing that sort of research. For example: we discover in rats that giving melatonin has an effect, so then we look in people to see whether it does the same. Then we look for a use for its effects, like treating insomnia. The other thing I do is teach. I do a lot of classroom teaching, which I enjoy. I also do a lot of apprenticeship teaching. Our major output is publications and talk about publications. The other output is "translation", converting laboratory discoveries into something clinically useful. I do this with companies, regulated by the government. In the course of implementing this interest I've had to learn disciplines and approaches I wouldn't have thought necessary, for example patenting. If the inventor doesn't patent a discovery no one else can, and it probably will never be developed. I discovered this in a very unfortunate way.

TB: How?

RW: One of my students, John Fernstrom, and I discovered in the early 1970's, that the amino acid tryptophan, given in very low doses, could increase brain serotonin. We speculated and then showed that this relationship could be used for influencing a variety of behaviors that depend on serotonin, like treating insomnia. We wrote a series of three articles in *Science*, and two in the *Scientific American*, and papered the walls with our discovery. I assumed this would naturally lead to tryptophan being a good and useful product. Five or six years later, I realized that this had not happened; no major company had developed tryptophan as a drug in the United States. But since tryptophan worked, and everybody knew it worked, companies were selling it as a dietary supplement without FDA approval. Even though we all love to hate the FDA, there are some situations where the FDA is quite essential. Since there was no regulation for marketing tryptophan as a dietary supplement, there was also no regulation of its purity. So, in the 1980's, a batch of impure tryptophan was introduced into America from a Japanese company. They developed a new microorganism capable of making it from aniline, and the process was very efficient. So, they lowered the price and took over the entire market for tryptophan in the United States. The trouble was the drug produced eosinophilia in some patients. Had tryptophan been under FDA regulation, the company would have had to do phase one studies on the newly synthesized tryptophan, and some of the subjects would have developed eosinophilia. This would have been evidence of an allergic type reaction, which would have caused the product to be withdrawn. Since there were no such studies, large numbers of Americans took the impure tryptophan without knowing about its toxicity, and forty-five died as a consequence of a new syndrome, the eosinophilia myalgia syndrome. And I felt a little bit responsible; if I'd done what I should have done, if my university had patented tryptophan for insomnia and controlled its use by companies that licensed the patent, this wouldn't have happened. Anyhow, I'd discovered the need to patent discoveries by the mid 1970's. I still don't patent anything but MIT almost always patents discoveries that might lead to products. For example, something my wife and I discovered; my wife is my close collaborator in a lot of ways. She's a cell biologist, whose fundamental work is in nutrition and obesity. She has a PhD, not an MD, but she listens to her patients and discovered the phenomenon of carbohydrate craving. There are very many patients, who get obese, not because of what they eat at mealtime, but because they overeat large quantities of carbohydrate-rich snacks. These snacks tend to be fat-rich, providing

about 1500 calories a day, and even more if the person suffers from seasonal depression. And they get fat. In 1970, with John Fernstrom, I found carbohydrates increased brain serotonin levels. So we made the hypothesis that these people were overeating carbohydrates to increase their brain serotonin because that made them feel better. And that is what patients said. If that's the case, the way to ameliorate their obesity is either to give them carbohydrates via foods that lack fats, and this works for some, or find drugs that do the same thing to brain serotonin that carbohydrates do. That was the origin of the concept that serotonin, and not dopamine or amphetamine in the brain, is the right target for antiobesity drugs. To make a very long story short, we discovered that dexfenfluramine, a serotonin agonist, could be highly effective in treating obesity, particularly obesity associated with carbohydrate craving.

TB: Can you identify the obesities which are associated with carbohydrate craving?

RW: One example is seasonal depression. There are people with seasonal depression who put on 15 pounds every winter and take off 10 every summer. There are women overeating with the pre-menstrual syndrome or when trying to stop smoking. There are also people who have stress-induced overeating. We worked with a French company, Servier, to develop dexfenfluramine as a treatment for this kind of obesity and the substance was ultimately marketed under the name of Redux. It was sold in the United States for about a year but was withdrawn about two years ago, because it became confused with Fen-Phen. Fen Phen actually consists of three chemicals; dexfenfluramine, L-fenfluramine, and phentermine, an antidote to the side effects of L-fenfluramine, a dopamine receptor antagonist. Phentermine turns out to be a potent MAO inhibitor and you're not supposed to give an MAO inhibitor with a serotonin-uptake blocker like dexfenfluramine, Prozac (fluoxetine), Zoloft (sertraline) or Paxil (paroxetine.). The trouble was that phentermine was not labeled as an MAO inhibitor. A bunch of us are trying to persuade the FDA it should require that phentermine be labeled as an MAO inhibitor. So, Fen-Phen, in a certain number of people, by blocking both the serotonin uptake into platelets and the enzyme MAO, allowed plasma serotonin levels, to rise transiently to very high levels, which produced vascular lesions in some people. Dexfenfluramine doesn't do that by itself, nor does Prozac, Zoloft, Paxil, and other serotonin reuptake inhibitors. They do it only when they are taken with an MAO inhibitor like phentermine.

TB: Do you think dexphenfluramine might be revived?

RW: I don't think dexphenfluramine will come back, but there will be other similar drugs that either release serotonin or that act on the right receptor in the brain to suppress eating. Anyhow, dexfenfluramine, Redux, was for a while a great success story. Here was a university discovery and a university patent that was marketed and used in the treatment of a large number of people. There are very many who need treatment with a serotonergic drug. One example might be a 50-year-old man, who weighs 270 pounds, has hypertension and diabetes, and can't stop eating. He will die if he's not treated. So I hope we get other drugs like dexphenfluramine. We've had a few other successes that relate to the use of drugs were discovered in our laboratory and patented by my university. Universities, in general, cannot come up with new compounds; we're not drug companies and don't have the medicinal chemists to generate the new compounds. But what the universities are good at doing is discovering additional, off-label uses for old compounds and then trying to get the drugs developed for those uses. We had a sort of triumph about three or four weeks ago. My wife had the idea that women with pre-menstrual syndrome gained weight because they developed carbohydrate craving.

TB: Why do women with pre-menstrual syndrome develop carbohydrate craving?

RW: They develop carbohydrate craving because they feel lousy. They're angry; they're depressed; they're miserable and they've learned that by consuming carbohydrates they can transiently ameliorate these feelings because the carbohydrates increase brain serotonin. There are a couple of ways to treat this. She invented a carbohydrate based food packet, called PMS Escape, which is still being sold, that helps a lot of women. It's giving the carbohydrates without fat, so the women get increased brain serotonin but don't get the increased waistline. Together we showed that a variety of serotonin drugs could also be used, specifically, to treat the pre-menstrual syndrome. So MIT went ahead and patented the use of these drugs for treating PMS. One of them was Prozac. Lilly licensed that patent and did large-scale clinical trials. On the basis of their findings, a few weeks ago, an FDA Advisory Board unanimously approved our invention, the use of Prozac (now "Sarafem") for treating pre-menstrual syndrome. It's safe to anticipate that early next year Lilly will be marketing Prozac, under its new name, for this MIT discovery. And maybe there will be other drugs in the patent, too. Another compound we don't know the outcome on yet is for the treatment of stroke.

TB: What kind of compound is that?

RW: It's a compound that acts directly on the brain, as opposed to the clot busters like TPA. When you get a thrombotic stroke what happens in the next three or four days causes a 75 or 100 percent increase in the size of the affected area. The dying necrotic tissue releases unsaturated fatty acids, like arachidonic acid, which become autooxidized or diverted to form thromboxanes and prostaglandins which diffuse around the dead tissue, and extend the affected area. So one theoretical goal of stroke therapy is to invent a drug that either blocks the release of these compounds or blocks their conversion to toxic metabolites. We showed in the laboratory our compound could do that. There are three doctoral theses written by our graduate students showing that if you present the brain with increased amounts of phosphatide precursors, such as choline and cytidine, cytidine becomes CTP, which is needed to make phosphatides, and choline becomes phosphocholine, enhancing the formation of phosphatidylcholine and other phosphatides.

TB: Why is it good to enhance the formation of phosphatides?

RW: Making more phosphatides is good for two reasons. Firstly, the last step in making phosphatides involves adding diacylglycerol, much of which contains arachidonic acid. You can show in experimental preparations that giving a source of choline and cytidine decreases the level of free arachidonic acid, and, thereby, the size of the stroke. The second thing is that a stroke kills a bunch of cells, damages a much larger number so the brain needs to regenerate those axons. There's much more optimism now about neuronal regeneration in the brain than before. Since phosphatides are by far the major component of membranes, enhancing phosphatide synthesis should enhance membrane formation and accelerate recovery from stroke. The way we picked to provide choline and cytidine was to use an old, controversial compound, citicoline. Citicoline has undergone patient Phase Three clinical trials and awaits complete analysis. Another thing we invented is the use of melatonin to promote sleep. It's another MIT patent, based on studies done in our clinical research center, which followed decades of studies done on rats, showing nocturnal release of melatonin. It's had a checkered course, because melatonin unfortunately is regulated as a dietary supplement.

TB: Why is melatonin qualified as a dietary supplement?

RW: Congress passed the Dietary Supplement Act in 1994 which labeled certain categories of compounds as dietary supplements. So, vitamins, minerals, herbs, amino acids, anything that is present in food, was declared a dietary supplement regardless of safety. There is a tiny amount of melatonin in food; thirty bowls of rice or 120 bananas give

you one dose of melatonin. No food has ever been shown to elevate plasma melatonin levels. But on that basis, melatonin is called a dietary supplement. Since it is called a dietary supplement any company can sell it in health food stores in any dose they want with no evidence of purity or efficacy. And, that's happened. The MIT patent is on the use of melatonin doses up to a pharmacologically appropriate level, usually 0.3 mg, and it's not a good idea to sell higher doses. People get nightmares then. They get receptor desensitization; receptors stop working. So, what I've learned is that if you want to take things out of the laboratory, it's not enough simply to have something that works. That's the starting point. You also have to work through, with your university, the patent situation, and then you have to find a licensee that will do the large-scale clinical trials and invest in the toxicity studies. Then, will the FDA approve this sort of thing. Finally, as we learned from Redux, one has to hope the compound doesn't have some unanticipated side effect when combined with another drug. But, it's well worth doing this sort of work. And I'm glad to see that numerous other investigators in universities are trying to convert basic science findings to clinically useful products.

TB: In so far as your own work is concerned how would you describe your activities?

RW: I do three things. I run a basic science laboratory and I direct the clinical research center where we do studies trying to see whether our findings in the lab also work in people. And I'm interested in translation, in taking the discovery out of the laboratory by developing products that might be useful for people. Is that the longest answer to a simple question that you've ever had?

TB: It certainly answers the question. Am I correct that the starting point of your research at MIT was your interest in tryptophan?

RW: That's right. Do you want to know the history to that?

TB: Yes.

RW: It's a wonderful story. When I was at the NIH, in my second period there working with Julie Axelrod, we got interested in circadian rhythms. Why? Because, the pineal released melatonin at nighttime and we thought we'd like to have something we could measure in rats to indicate whether or not melatonin has an effect on the circadian rhythms. We knew that adrenal cortisone manifested a circadian rhythm and so I decided to try to set up an assay for corticosterone in the rat, define that rhythm, and see whether melatonin affected it. At that time, the only assay that could be done in a regular laboratory for corticosterone was a fluorescence assay that was very difficult to do. So Julie

and I decided that instead of looking at corticosterone, we should look at something controlled by corticosterone that might be measurable. There is an enzyme in the liver, called tyrosine transaminase that can be induced by corticosterone. So I thought, let's see if there is a rhythm in tyrosine transaminase and if so whether it parallels the corticosterone rhythm. We took rats and measured their tyrosine transaminase activity at different times during the day and night, and discovered there is a rhythm. Assuming the rhythm was due to corticosterone, we thought if we removed the adrenals that would block it. It didn't. By this time, I'd moved to MIT and got interested in what was causing the rhythm. I was very fortunate. Down the hall from me was an extraordinary scientist, Hamish Munro, who was an enormously well regarded student of nutrition. Through Hamish, I learned nutrition could be relevant to generating rhythms. For instance, the amount of tryptophan and other amino acids delivered to the liver controls whether it's making protein or not. We discovered the rhythm in tyrosine transaminase depended on what the rat ate. If the rat consumed food that contained protein, then amino acids got to its liver and turned on protein synthesis. So, we learned that eating controls the rhythm in tyrosine transaminase synthesis. Since tyrosine transaminase transmits the amino acid tyrosine, we hypothesized there might also be an inverse rhythm in the amount of tyrosine. After all, if you have more of an enzyme you ought to have less of its substrate. So, we started doing studies on rats to see whether there is a daily rhythm in tyrosine synthesis. Yes, there was. Since tyrosine is a substrate for tyrosine transaminase, but tryptophan isn't, there should not be a rhythm in tryptophan levels. We took people at our clinical center and collected their blood around the clock and found there were rhythms in the levels of almost all of the amino acids. Here again, we did the experiment to test an erroneous hypothesis, and in the process, found something perhaps more interesting. We discovered all amino acids undergo daily rhythms, including tryptophan. I had previously done some work on serotonin, and knew the enzyme that converts tryptophan to serotonin exhibited low affinity for this substrate. At normal tryptophan concentrations this enzyme was not doing very much, because only a little bit of it was saturated. It seemed to me that if there were daily rhythms in blood and in brain tryptophan there might also be changes in the production of serotonin. After I moved from NIH to MIT I had an excellent graduate student, John Fernstrom, who worked with me on it. We found that very small changes in brain tryptophan levels, produced by giving tryptophan, could cause major changes in serotonin synthesis. So why not give a high protein meal, since protein contains

tryptophan. We also thought if we lowered blood tryptophan levels by giving insulin this should interfere with brain serotonin synthesis. So, we gave animals insulin injections, lowered blood tryptophan, but, lo and behold, brain tryptophan levels and serotonin synthesis increased. This seemed very strange, so we decided instead of giving insulin we should give the animal carbohydrate to make it secrete its own insulin. Rats eating a carbohydrate meal showed the same response as those given insulin; it raised brain tryptophan and serotonin synthesis. What this suggested was that the amount of tryptophan that gets into the brain doesn't just depend on blood tryptophan, but also on other amino acids that compete with tryptophan for entry to the brain. What actually happens is that insulin pushes other amino acids, such as leucine, isoleucine, and valine into muscle, where they're metabolized. The effect of carbohydrate is to cause blood tryptophan levels to decline a little, but levels of its competitors to decline a lot, so even though there's no tryptophan in dietary carbohydrates, there's a tremendous increase in the amount of tryptophan getting into the brain, and a corresponding increase in serotonin synthesis. Conversely, if the animal had a protein meal, blood tryptophan does rise a little bit, but levels of the competitors rise much more.

TB: Why?

RW: Because only one percent of most protein is tryptophan whereas 25 percent is tryptophan's competitors. So, there was this beautiful paradox: eating a meal that contained no tryptophan, a carbohydrate meal, raised brain tryptophan and enhanced serotonin synthesis, whereas eating a meal that contained tryptophan, because it contained protein, had the opposite effect. After struggling with this for a couple of years we realized our findings indicated that serotonin neurons have a special capability. They can, on-line, monitor changes in plasma composition generated by eating and report to the brain what you're digesting, whether those foods are principally carbohydrate or principally protein. And, the brain uses this information. People from all cultures, unless they're limited by poverty, have about 13 percent of their calories as protein and eat about 4 or 5 times as much carbohydrate as protein, however, they aren't aware they're doing so. People think they're picking food, but they're also picking nutrients.

TB: How does the brain know what we are eating?

RW: The brain knows by monitoring plasma amino acids, levels of which are changed selectively by the composition of the food. Later on, my wife Dr. Judith Wurtman, discovered the phenomenon of carbohydrate craving. People who overeat carbohydrate-rich, protein-poor foods or snacks

do so because it makes them feel better, less depressed. By the way, serotonin is involved in depression, besides control of what's chosen to be eaten.

TB: Your studies with tryptophan started your research at MIT but the whole story really began with your interest in the pineal gland and melatonin. Your findings seem to suggest that the organism regulates its nutrient intake.

RW: In most cultures, even cultures of poverty where people eat combinations of beans and rice, they consume enough protein and carbohydrate. What people of poverty tend to have least is fat. Fat is very expensive. You may have to go kill an animal to get it. There seems to be no brain neurochemical system that monitors body fat composition and no central regulation of fat intake. People like fat, it has a good taste. So the desire for fat is based on taste and not any central neurochemical effect. During our evolutionary history fat was not something people could count on having. People could always have their beans, rice and vegetables to provide carbohydrate and protein,. But not so readily fats.

TB: Would your findings regarding the net effect of eating carbohydrates or protein on brain tryptophan and serotonin synthesis imply that if tryptophan is used for insomnia, it must be given in a small dose to be effective?

RW: That's right.

TB: Are we talking about 500 milligrams or so?

RW: In fact, 250 would have been adequate. In terms of utility, what we found with tryptophan, we are finding also with melatonin. We've just finished a study with melatonin which relates to this. We took a large number of older people with or without insomnia and measured their plasma melatonin levels during the night and during the day. Our findings confirmed what we and others had shown, namely that as you age, nocturnal plasma melatonin levels decrease from 100 to 150 picograms per ml in 20 year olds to perhaps 30 to 50 in people over the age of 50; melatonin levels decrease regardless of whether or not the person had insomnia. Some exhibit insomnia whereas others do not. The nature of the insomnia in aging is not trouble falling asleep; they tend to fall asleep early, because they're exhausted from not having slept well the night before. The problem is staying asleep or awakening too many times. We gave these people three different doses of melatonin, 0.1 mg, 0.3 mg, or 3.0 mg, and found all of the doses improved sleep, but the most effective dose, which brought them up to normal sleep, was the dose that raised nighttime plasma levels to what they are in young

people, 0.3 mg. given orally at nighttime. Giving 0.3 mg to older people with insomnia brings sleep efficiency back to normal, but has no effect on people who already sleep normally. Nothing is broke in them, so there is nothing there to fix.

TB: Are you suggesting melatonin in the dose of 0.3 mg at bedtime for the treatment of insomnia in the elderly?

RW: Yes, and not in the 10 to 20 times higher doses commonly sold in health food stores.

TB: Are you suggesting for insomnia, tryptophan in a dose of 250 mg for the young, but melatonin, in a dose of 0.3 mg for the old?

RW: That would be perfectly rational.

TB: Am I correct that the development of dexfenfluramine was based on the notion that obesity is the result of a kind of depression in which people, without being aware of it, try to increase their brain serotonin by consuming excessive amounts of carbohydrates?

RW: Yes. Obesity is a heterogeneous disease, but one large subset includes such people. When dexfenfluramine was available it worked in 79 percent of obese people and this included many who did not have that kind of depression; so it's apparent that serotonin also has an additional role in eating. It's a major satiety factor. But we were able to compare the responses to dexfenfluramine of obese people, with or without carbohydrate craving, in a large study in the Netherlands and found that carbohydrate cravers invariably had an even better response to the drug than the non-carbohydrate cravers. So, you're right.

TB: Was dexfenfluramine tested in the treatment of depression?

RW: It was tested in seasonal depression. The reason it was not tested for depression in general is that the companies that marketed it wanted to get one indication clearly established before looking at another. That was unfortunate because it could have been tested in a variety of other circumstances. For example, when women stop smoking, what's the main reason they start again? They get fat. Why do they get fat? One thing nicotine does is to act on raphé neurons to release serotonin. So, when they withdraw from nicotine they release less serotonin and the person selectively overeats carbohydrates, becoming a "carbohydrate craver." It makes very good sense to treat these people with an agent that releases serotonin.

TB: Are you suggesting 5-HT_{2c} agonists should be tested in the treatment of nicotine withdrawal?

RW: That's right.

TB: You have a clinical unit; why are you not doing it?

RW: There aren't any 5-HT_{2C} agonists available to my knowledge. A number of companies are working on such agents and finding they're safe enough, so they could be tested. I'd love to test these drugs. When Redux was available, my wife and I used it as a probe to find out whether brain serotonin is involved in a variety of conditions. For example, PMS and smoking withdrawal; there might well be additional clinical situations that could benefit from a 5-HT_{2C} agonist. Parenthetically, one of the great things about psychopharmacology, more than any other field of medicine, is how people have taken advantage of the existence of drugs developed for one purpose, to find entirely new uses, extending our knowledge of the chemistry of the brain. There are many examples. I wish other aspects of medicine were as successful as psychiatry and psychopharmacology have been.

TB: After discovering the therapeutic potential of tryptophan and melatonin in insomnia, and dexphenfluramine in obesity, you also discovered the therapeutic potential of citicoline in stroke. I think citicoline is sold in Italy and possibly in some other countries.

RW: Yes, citicoline is sold in some countries. Once we found out serotonin synthesis is controlled by the amount of tryptophan consumed, because the key enzyme, tryptophan hydroxylase, is a low affinity enzyme, I started wondering whether there might be other neurotransmitters or brain chemicals, whose synthesis is also are controlled by the availability of precursors. The obvious other neurotransmitter to consider was acetylcholine.

TB: Why?

RW: Choline acetyltransferase, CAT, is also a very low affinity enzyme and it was known for years, based on in vitro studies, that the amount of acetylcholine one makes could be controlled by the amount of available choline. So a graduate student and I did some studies to see whether the availability of choline within its normal range affects brain acetylcholine synthesis; we found that it did. Our findings were quickly confirmed by many other people. So, this got me thinking about choline. I realized that just as most of the tryptophan in the body doesn't go to make serotonin, it goes to make protein, similarly, most of the choline in the body doesn't go to make acetylcholine. Most of it goes into making membranes. At that point one of my graduate students became interested in the relationship between choline availability and membrane biosynthesis and showed that production of phosphorylcholine, the first step in acetylcholine synthesis, goes up or down depending on the availability of choline. I was deeply interested in Alzheimer's disease about twenty years ago with a colleague and friend, John Growdon, who

was head of the Alzheimer Unit at the Massachusetts General Hospital. We both became interested because, just around that time, two English groups had discovered there was a selective reduction in acetylcholine levels in the brains of people with Alzheimer's disease. We wondered perhaps just as giving L-DOPA can replace deficient dopamine in Parkinson's, maybe giving choline would replace deficient acetylcholine in Alzheimer's. It didn't work, but it did get us into Alzheimer's disease research.

TB: But citicoline, as you mentioned it before, seems to be working in stroke, right?

RW: It does seem to be working because there's a clearly defined chemical mechanism involved. In stroke one wants to remove the free arachidonic acid liberated from the infarcted tissue, and citicoline does that. It pushes it back into membrane by incorporating it in phosphatides. The same thing may be true with brain injury of any type, with motorcycle accidents, for example.

TB: How did you get from the treatment of stroke to the treatment of Alzheimer's disease?

RW: We began organizing a series of meetings every two years, the so-called Zurich meetings on Alzheimer's disease so we could learn more; the next meeting will take place in February. They involve about one hundred participants, and a lot of information is transferred. At one of our meetings I was visited by somebody from a Spanish company that sells citicoline, and he told me he was aware of the work we had done on choline, acetylcholine and phosphatide synthesis and wondered whether I might be interested in finding out if citicoline also affects acetylcholine or phosphatides. He also told me his company was selling this compound in Spain and elsewhere but people laughed at it and called it an expensive placebo. I couldn't dismiss the possibility there might be something to citicoline, so we started doing research. The first thing we discovered was the substance breaks down immediately and totally in the body. People had been speculating that if one eats it, it goes right into the brain. This does not happen, it's totally metabolized. But what it does do is raise blood levels of choline and cytidine, at least in animals. In people this is different; it raises blood levels of choline and uridine. The uridine then gets into the brain and is converted into UTP and to CTP. After we found citicoline is broken down completely, we did studies on cultured cells, then on brain slices, and finally, on whole rats which showed if one increased choline and cytidine levels, one actively promoted membrane biosynthesis. We took rats or mice and fed them for six weeks on a diet enriched with citicoline. Then, we

removed their brains; measured the amount of phosphatidylcholine per cell, and found it went up about 15 percent. So, the joke is, if you want a fat brain, all you have to do is eat citicoline for six weeks in a very large dose. Just as giving tryptophan increases serotonin synthesis so also choline affects acetylcholine synthesis. This algorithm also applies to tyrosine. Tyrosine can affect catecholamine synthesis. This is another story. Are you interested?

TB: Of course. Please elaborate.

RW: Tyrosine hydroxylase, the rate-limiting enzyme in catecholamine formation, is more complicated than tryptophan hydroxylase and choline acetyltransferase, in that if a catecholamine releasing neuron fires, tyrosine hydroxylase becomes phosphorylated and its kinetic properties shift. When it's not phosphorylated, the rate limiting factor in hydroxylating tyrosine is the level of a cofactor, tetrahydrobiopterin, but when the neuron fires and the enzyme becomes phosphorylated its affinity for the cofactor goes up two hundred fold, and now the activity of the enzyme is limited by the availability of tyrosine. One can demonstrate this by doing something that makes a certain set of catecholamine neurons fire more rapidly. For instance, after destroying 80 percent of the nigrostriatal neurons, the surviving 20 percent will fire more rapidly, becoming critically dependent on tyrosine levels. One can destroy 80 percent of the neurons on one side of the brain and not destroy any on the other side before giving the animal tyrosine, which is distributed everywhere in the brain. On the side where neurons have been destroyed giving tyrosine doubles dopamine release, whereas on the other side, where the neurons are intact, it has no effect on dopamine release. We've not tried to apply these findings. We've not done enough work to try to apply these findings in humans, because the treatment of Parkinson's disease has moved ahead of us. We did some small studies in Parkinsonian patients and saw effects, but they weren't as good as L-DOPA's. Somewhere down the line, there may be a circumstance in which we can take advantage of tyrosine in treatment, too.

TB: Am I correct that you have been instrumental in the discovery of a therapeutic indication for at least four substances?

RW: Actually, there's a few more. There's tryptophan, which has not become a drug because MIT didn't patent it, unfortunately. Then, there is dexfenfluramine, which did become a drug but is no longer. There's one substance that my wife did, based on our work. It's called PMS Escape, a mixture of carbohydrates that increases brain serotonin. It's currently been marketed. There's the recent FDA approval of fluoxetine for treating PMS, called "Sarafem". And there's melatonin for the treatment of

insomnia. As long as, in America, melatonin remains a dietary supplement I'm not sure what to do with it. It's very difficult to get a company to invest and develop it in the United States, so I've turned my attention to Europe, where it's still a drug. I'm hoping a company can be found in Europe that will make a drug out of it.

TB: And, what else?

RW: Some years ago, we took blood from people running in the Boston Marathon, before and after, and measured choline in it. Then, we did the same on people swimming long distances and basketball players, and found all of the endurance exercises deplete plasma choline. It goes down 40 to 50 percent, thus suppressing acetylcholine release at the neuromuscular junction. I suspect this may be why runners talk about hitting the wall after 20 miles. There are a number of sports drinks like Gatorade that include supplemental choline, based on this finding. I've never done enough endurance work, myself, to tell whether or not it works.

TB: Was it tested?

RW: It was tested and it does work in the lab. You have to convince the Federal Trade Commission that your claims are substantiated and this requires publications in peer reviewed journals.

TB: During the years you have collaborated with many people. You talked about your work with Julie Axelrod, your wife, and your graduate student, John Fernstrom. You have also mentioned the name of John Growden.

RW: John is professor of neurology at Harvard and directs the Alzheimer's Center. He's been my very close friend and collaborator for decades now and we have done research together on blocking the synthesis of APP, the source of amyloid, which might be therapeutic in Alzheimer's disease. We've discovered that the synthesis and metabolism of APP are both controlled by neurotransmitters. We also found that any neurotransmitter that increases the formation of diacylglycerol (DAG), a second messenger, will enhance the formation of soluble APP and block the formation of β -amyloid. That also may be useful in Alzheimer's disease. Then, with Robert Lee in my laboratory, we found that the synthesis of APP is controlled by cyclic AMP, and anything that increases cAMP, like noradrenergic β -receptor activation, will enhance the production of APP, while anything that suppresses the formation of cAMP will have the opposite effect.

TB: So, anti-inflammatory drugs might be useful in the treatment of Alzheimer's disease, and possibly also in the treatment of Down syndrome.

RW: When this was first suggested by Pat and Edith McGeer, some people laughed. I didn't, I thought it made good sense. The suggestion was based on findings that women with rheumatoid arthritis, who had been taking large doses of aspirin for a long time, or people with leprosy taking dapsone, tended to have less Alzheimer's. But, you're quite right that anti-inflammatory drugs might be useful in the treatment of Alzheimer's. The origin of the idea was in epidemiologic studies, as is the origin of so much medical knowledge.

TB: During the years you have been at MIT you trained many people. You already mentioned a couple. Would you like to mention a few more?

RW: It's hard to do this, because those who don't get mentioned may be unhappy, and I love them all!

TB: You have had many publications. How many approximately?

RW: About a thousand publications.

TB: A thousand?

RW: Yes, but I've always had a big laboratory.

TB: How many people are in your laboratory?

RW: Now, the number is down. If you include the clinical people it's down to about 18 or 20 people. But most of the time it's been more like 30 people.

TB: So, it's a large laboratory.

RW: Yes, it's been a large laboratory.

TB: You have also written several books. Could you say something about them?

RW: My first book was on melatonin. It was done with Julie and with an anatomist, Doug Kelly. Another early book I wrote was on catecholamines. Then, I compiled a series of books with my wife on nutrition and the brain. These may have contributed to getting that field started. I have also published a series of books emanating from the Zurich Alzheimer's meetings. What I'm working on right now is not a book but a summary article which goes back to my origins in philosophy of history. I got interested a few years ago in the question, why is it that when I was a child, in the 40's, 50's and early 60's, every year some terrible disease that had been untreatable became treatable for the first time. The list of the medications that first appeared during the 40's, 50's, and 60's is extraordinary. And, then, starting around the mid 1960's, even though there was four times as much money available, and, a vast increase in basic knowledge, this process apparently came to an end. If one makes a list of things that killed people in 1965 and you looked at it again in 1995, it contains more or less the same diseases in the same proportions; the major cancers, congestive heart failure,

Alzheimer's disease or lupus, drug addiction, alcoholism. There has been a slowing of progress. What is responsible for this paradoxical relationship between treatment discovery and basic knowledge? I've interviewed many scientists and clinicians, and am trying to identify the factors that seem to be most important in enabling the discovery of effective treatments for diseases. And, by the way, effective treatments don't necessarily mean new drugs. We've also seen over and over again that off label discoveries, for instance, the discovery that spironolactone, which was used 30 or 40 years ago for treating hyperadrenocorticism, markedly reduces death from heart failure. The same applies to the ACE inhibitors, developed for treating hypertension, which are now shown to reduce death from heart failure. So, I've been interested generically, in what factors determine whether a society is or is not successful in discovering effective new treatments. One major set of factors is resource allocation. One conclusion, which is hardly radical, is that we haven't spent enough on clinical physiology. For decades we've endured starvation of funds for training and supporting the research of clinical investigators. I hasten to add, I'm not talking about myself; I'm fortunate to be well supported. Another factor is the failure sometimes to include the other key disciplines involved in treatment discovery, such as medicinal chemistry, epidemiology, pharmacology. And, then, a year or two after starting this project, I realized that at least one horrible disease had become treatable, perhaps an exception to the rule.

TB: What is that horrible disease?

RW: It's HIV/AIDS. The natural history of AIDS is so transformed from the way it was five years ago, that it's almost unbelievable. Here was a disease that was almost universally fatal and now, my friends who are AIDS doctors, tell me, people who come in with a brand new diagnosis of HIV and can afford treatment are probably not going to die of AIDS. So, I tried to analyze, wherein was that disease different? Why did AIDS become treatable when other diseases didn't? It turned out the limiting factor was not science. The key scientific publication that led to the treatment of AIDS came from a Japanese pharmaceutical company six months after the virus was discovered. So, if fundamental research on HIV had stopped in 1986, it would have made no difference. The key fact was the discovery that the particular protease which the HIV makes is an aspartyl protease. Since human renin is an aspartyl protease, for a long time drug companies were trying to make aspartyl protease inhibitors for treating hypertension. Eventually, they found that ACE inhibitors were better, so they had large numbers of aspartyl protease inhibitors on their shelves. They knew how to make them. The discovery you

have to combine several drugs to treat AIDS wasn't really a discovery. Any doctor who had treated tuberculosis or childhood leukemia, knew that when you're dealing with a rapidly mutating organism, you've got to combine several drugs. What was needed were the drugs. In the latter part of the 1980's, enough political pressure was brought on the FDA to change the way it regulated AIDS drugs. Instead of taking four or five or six years to go through the regulatory process, it now takes four or five or six months, or even less. So the pharmaceutical companies decided now there was the chance of making some money out of AIDS and society would pay for the drugs. So, bang, bang, bang, within a very short period of time there were ten approved aspartyl protease inhibitors. The point is that a lot of different factors can influence our success in inventing treatments. They can be basic scientific. They can be epidemiologic. They can be clinical. They can be regulatory. They can be political. They can be all kinds of things.

TB: I understood you have a clinical center and patients available for research. How much are you involved in the clinical center and in evaluating patients?

RW: The patients, who come into the CRC are not there for primary diagnosis or treatment. They're people that satisfy certain inclusion criteria for admission to a study. So, I'm the principal investigator of three programs at the CRC, but a very strong co-investigator runs each of the studies. My wife runs the studies related to carbohydrates, serotonin, eating, etc., and she has her own staff and her own independence. Another person runs the melatonin studies.

TB: Do you see any of the patients associated with the three programs of which you are the principal investigator?

RW: Now and then, but I don't see them very much. I see and sign all the records. Basically my role is hypothesis and protocol generation, overseeing the protocols are followed, and trying to make some sense of the findings when the studies are completed. But, having this clinical research center is marvelous, because, without it, there's no way I could afford to have nurses dieticians and the other people we need in our studies.

TB: Now, one of your major interests is related to eating.

RW: This happens to be the interest of my wife. I married somebody who wanted to make a career out of studying rats.

TB: Rats?

RW: When we were married 40 years ago my wife wanted to be a teacher; she thought she'd get a Master's in teaching and, then, retire to the suburbs. That lasted about six weeks. Then she went back to school

and took a PhD at George Washington University, while I was at the NIH, and finished her thesis at MIT in the biology department. After she finished her PhD, with two young children and a very demanding husband, she couldn't embark on a full time career, so she taught at a local college and made exhibits for the Boston Science Museum. Then, around the mid 1970's I had found that foods affect the brain and decided I needed somebody with knowledge of nutrition to help me develop this field. While she had been teaching biochemistry at a local girls' Catholic college, she was asked, "to teach nutrition." And she said, "I don't know any nutrition and to teach it I'll need to learn some." So, she took a two year post-doc in nutrition during which she became interested in the area and particularly, in obesity. So, when I discovered I needed a collaborator, I invited her to become that person. She agreed to do so. After we'd been married 15 years, we started to collaborate in the lab. The purpose of our collaboration, initially, was to see whether this ability of serotonin neurons to monitor eating is involved in nutrient selection. We found that it was in rats. We published papers on it, and then, she got interested, and started working for free, in an obesity clinic. It was especially important: she listened to her patients and asked what they were eating. The patients described to her what they ate at mealtime. She also asked them what did you eat between meals, how many potato chips, and how many cookies. So she came up with this concept of carbohydrate craving. Then we started to work on obesity, because that was where her interest was and there was something to do.

TB: What about your interest in nutrition?

RW: I entered basic research in nutrition through an MIT colleague, Hamish Munro, as I mentioned

TB: Is there anything else you would like to add?

RW: I can't imagine.

TB: On this note we should conclude this interview with Dr. Richard Wurtman. Thank you very much Dick for sharing this information.

RW: Well, it's been great pleasure.

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The American College of Neuropsychopharmacology (ACNP), founded in 1961, is a professional organization of leading scientists. The core purpose of the College is to contribute to alleviating human suffering by advancing the dissemination of knowledge related to the biology of the brain as well as the biology, prevention, and treatment of brain disorders; by promoting emergence of pioneering young scientists as leaders within our College and within their fields of science; and by facilitating the collaboration among relevant organizations and agencies.

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