



An Oral History Of Neuropsychopharmacology

The First Fifty Years
Peer Interviews

SERIES EDITED BY: Thomas A. Ban



Volume Five:
NEUROPSYCHOPHARMACOLOGY

EDITED BY: Samuel Gershon

American College of Neuropsychopharmacology

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

Peer Interviews

Volume Five: Neuropsychopharmacology

Copyright © 2011 ACNP

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

Samuel Gershon (volume editor)
VOLUME 5: NEUROPSYCHOPHARMACOLOGY

All rights reserved. No part of this book may be used or reproduced in any manner without written permission from the American College of Neuropsychopharmacology (ACNP).

Library of Congress Cataloging-in-Publication Data
Thomas A. Ban, Samuel Gershon (eds):
An Oral History of Neuropsychopharmacology: The First Fifty Years, Peer Interviews
Includes bibliographical references and index
ISBN: 1461161711
ISBN-13: 9781461161714

1. Neuropsychopharmacology
2. Biochemical hypotheses
3. Psychotropic drugs
4. Schizophrenia
5. Depression
6. Pharmacotherapy of psychiatric disorders

Publisher: ACNP
ACNP Executive Office
5034A Thoroughbred Lane
Brentwood, Tennessee 37027
U.S.A.
Email: acnp@acnp.org
Website: www.acnp.org

Cover design by Jessie Blackwell; JBlackwell Design www.jblackwelldesign.com

AMERICAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY
THE FIRST FIFTY YEARS
Peer Interviews

Edited by
Thomas A. Ban

Co-editors

- Volume 1: Starting Up - Edward Shorter
- Volume 2: Neurophysiology - Max Fink
- Volume 3: Neuropharmacology - Fridolin Sulser
- Volume 4: Psychopharmacology - Jerome Levine
- Volume 5: Neuropsychopharmacology - Samuel Gershon
- Volume 6: Addiction - Herbert D. Kleber
- Volume 7: Special Areas - Barry Blackwell
- Volume 8: Diverse Topics - Carl Salzman
- Volume 9: Update - Barry Blackwell
- Volume 10: History of the ACNP - Martin M. Katz

VOLUME 5

NEUROPSYCHOPHARMACOLOGY

ACNP
2011

VOLUME 5

Samuel Gershon

NEUROPSYCHOPHARMACOLOGY

Preface
Thomas A. Ban

Dedicated to the Memory of Leo E. Hollister, President ACNP, 1974

PREFACE

Thomas A. Ban

Neuropsychopharmacology studies the relationship between neuronal and mental events with the use of psychotropic drugs.¹

Instrumental to the development of Neuropsychopharmacology was the introduction of effective pharmacological treatments for mental illness, the demonstration of monoamine neurotransmitters in the brain, the recognition of chemical mediation at the site of the synapse, and the construction of the spectrophotofluorimeter.² With the employment of the new instrument in the mid-1950s Alfred Pletscher (see Pletscher Volume 3), in collaboration with Parkhurst Shore and Brodie found a decrease in serotonin (5HT) levels after the administration of reserpine,^{3,4} a substance that was seen to induce depression in some hypertensive patients,⁵ and an increase in brain 5HT levels after the administration of iproniazid, a monoamine oxidase inhibitor (MAOI)⁶ that was seen to induce euphoria in some tubercular patients.⁷

Neuropsychopharmacology is based on the assumption that one might “deduce the biochemical and physiological basis of the disorders treated” from the mode of action of drugs with “known therapeutic effects.” The idea was that the information on the biology of disease would guide the development of rational pharmacological treatments.^{8,9}

During the past fifty years Neuropsychopharmacology was driven by advances in the methodology for tracking the action of psychotropic drugs in the brain. The rate limiting step has been difficulty in identifying homogeneous clinical populations whose responsiveness to psychotropic drugs would have predictive validity.

In the first four volumes in this series interviewees reflected on their contributions to studying drug induced changes on behavioural measures and conditioned reflex parameters (Volume One: Starting Up), on electrical activity of the brain and cerebral metabolism (Volume Two: Neurophysiology), on molecular and sub-molecular brain structures (Volume Three: Neuropharmacology), and on mental faculties and psychopathology (Volume Four: Psychopharmacology). In this volume (Volume Five: Neuropsychopharmacology) interviewees reflect on their contributions towards understanding the pathophysiology of mental disorders and development of rational pharmacological treatments.

Model Psychosis

The roots of Neuropsychopharmacology are in the discovery of Joseph Moreau de Tours that the effect of dawamseck, an electuary of hashish, is different in depressed (melancholic) and in regressed (“aliéné stupide”) patients,¹⁰ and in the recognition by Claude Bernard that drugs provide a means for the study of brain physiology.¹¹ By exploring the effect of dawamsec on himself in escalating and diminishing doses, and on his students and his patients with different diagnoses¹² in the mid-19th century, Moreau de Tours was first to use what was to be referred to as “model psychosis” in the study of mental disorders.

Research with “model psychosis” took wing in the mid-1890s with the isolation of mescaline from peyote,¹³ a cactus used for centuries in religious ceremonies by American Indians to induce ecstatic and hallucinatory experiences.^{14,15} In the early years of the 20th century mescaline, was studied by many, including Alwyn Knauer, a disciple of Kraepelin, who administered it to himself and to some of his colleagues.¹⁶ In the mid-1920s the phenomenology of mescaline-induced psychosis was elaborated by Kurt Beringer¹⁷ and Heinrich Klüver,¹⁸ and in the early 1930s, Quastel and Wheatley showed that the substance inhibited *in vitro* oxidation in the brain.¹⁹

Another major impetus for research with “model psychosis” was the synthesis of lysergic acid diethylamide (LSD-25), isolated from ergot in the mid-1930s by Jacobs and and Craig,²⁰ and the discovery of its psychomimetic effects by Albert Hofmann in 1943.²¹ Albert Stoll’s report in 1947 on the mental pathology induced by LSD-25²² was followed by a series of publications on the behavioural and mental effects of the substance.^{23, 24, 25} In the mid-1950s John Gaddum and independently Wooley and Shaw proposed that the pharmacological antagonism between LSD-25 and 5HT,^{26, 27, 28, 29, 30, 31} caused the psychosis induced by the drug. It proved not to be the case; in 1965 Cerletti and Rothlin showed that 2-bromo-LSD (BOL), a substance which has no effect on mental faculties, is just as potent an inhibitor of 5HT’s action as LSD-25.^{32, 33}

While mescaline and LSD-25 remained for years in the center of human research interest,^{34,35,36} in the mid-1950s, the hallucinogenic effect of N,N-dimethyltryptamine (DMT), one of the ingredients of the South American snuff “cohoba,” entered the scene. The substance was extracted along with bufotenin (dimethyl-N-oxide, 5-hydroxydimethyltryptamine) from the seeds of *Piptadenia peregrina* and *macrocarpa* by Fish, Johnson and Horning,³⁷ and in 1956 Stephen Szara (see Szara Volume 1), demonstrated its psychomimetic properties.³⁸ His initial findings were further substantiated in the late 1950s by several investigators,^{39, 40, 41} including Turner and Merlis⁴² (see Turner Volume 1). Szara also compared, in self-experiments, the psychopathology induced by DMT, mescaline and LSD-25.⁴³

In 1959 the armamentarium of psychomimetic drugs was further extended with the inclusion of phencyclidine (Sernyl), a fast-acting anaesthetic^{44, 45} that was found to induce “symptoms of sensory isolation” by Meyer and his associates,⁴⁶ and was characterized as a “schizophrenomimetic” by Luby and his associates.^{47,48} The psychopathology induced by Sernyl was further refined by Ban, Lohrenz and Lehmann⁴⁹ (see Lehmann Volume 1 and Ban Volumes 4 & 9) who found that in low doses Sernyl had a disinhibiting effect that gave way in increasing doses to a feeling of weightlessness and body image disturbances, and then, in psychiatric patients accentuated pre-existing features of psychopathology.⁵⁰

By the end of the 1950s there were numerous psychomimetic indoles, phenylethylamines and piperidines available for inducing “model psychosis,” including psilocybin,^{51, 52} reserpine,^{53, 54} yohimbine,⁵⁵ amphetamine,⁵⁶ atropine,⁵⁷ Ditrán (1-ethyl-3-piperidyl-cyclopentylglycolate)⁵⁸ and many others. The “psychosis” induced by atropine, a substance isolated in the early 19th century from the Belladonna plant,⁵⁹ was in the center of a debate concerning “association” or “dissociation“, between electroencephalographic changes and behaviour. (See Fink and Bradley Volume 2).

In the 1950s atropine was used, in the “pharmacotoxic therapy” of schizophrenia^{60, 61} and in studying the neurophysiology of hallucinations.⁶² The psychopathology it induced was an “acute organic syndrome,” Bonhoeffer’s exogenous reaction type,⁶³ dominated by delirium, whereas the psychopathology seen with reserpine was dominated by depression, with iproniazid by euphoria, with yohimbine by anxiety and with amphetamine by delusions, a clinical picture resembling some forms of schizophrenia.^{64, 65.}

Psychotoxic Metabolites.

In the 1950s psychoanalysis dominated psychiatric teaching in North America⁶⁶ and psychomimetics were used mainly as adjuvants to various forms of psychotherapy.^{67, 68, 69} Yet it was in the mid-1950s that the shift in the site of psychiatric practice from psychiatric hospitals to the community began with the introduction of effective psychotropic drugs.⁷⁰ It followed the transformation of the diagnostic distribution of hospitalized psychiatric patients, resulting from the introduction of causal treatments in the 1940s⁷¹ such as nicotinic acid for pellagra,^{72, 73} and penicillin for cerebral syphilis,^{74,75} as well as the introduction of diphenylhydantoin for controlling epilepsy,⁷⁶ and thiamine for treating the amnestic syndrome.^{77, 78} Priorities for psychiatric research turned from the so-called “organic” to the “functional” psychoses.

The idea that some “functional psychoses” are metabolic in origin was first entertained in the mid-19th century after the introduction of lithium in the

treatment of gout by Alfred Baring Garrod in London.^{79,80} Given that acute symptoms of gout develop suddenly and persist if untreated, in the early 1870s William Hammond in New York assumed that mood disorders might be a form of cerebral gout and introduced lithium in their treatment.⁸¹ In the mid-1880s Carl and Fritz Lange⁸² in Copenhagen also started to use lithium salts in the treatment of periodic mood disorders.^{83, 84}

Rolv Gjessing was first, in the mid-1930s,⁸⁵ to identify an “endogenous psychosis”⁸⁶ assumed to be the result of faulty metabolism induced “auto-intoxication”.⁸⁷ By recording biochemical measures in a group of patients characterized by recurrent catatonic (psychotic) manifestations with “more or less lucid” intervals in between,⁸⁸ Gjessing found a periodic change in nitrogen balance passing from a peak of retention to a trough of loss, with the nitrogen cycles having the same duration as the mental cycles, even if the phases did not always coincide.⁸⁹ He attributed the psychotoxicity to urea,⁹⁰ a substance that in the late 1940s was identified by John Cade as the likely culprit for the enhanced toxicity of urine from manic depressed patients in guinea pigs, leading to the re-discovery of the effectiveness of lithium in the treatments of manic-depressive disease.^{91, 92} Gjessing also detected changes in biological measures; temperature, pulse rate, basal metabolic rate, 17-corticosteroids and glucocorticoid excretion, and oxygen saturation of capillary blood⁹³ that corresponded with the different phases of nitrogen metabolism and mental state during the “attacks”. Furthermore, in spite of the fact that patients were euthyroid, Gjessing found that retention of nitrogen and the occurrence of psychotic episodes could be prevented by the administration of thyroxine.⁹⁴ (See Winokur, Volume 4). Rolv Gjessing’s findings were complemented by Leiv Gjessing in the 1960s. He demonstrated an increased excretion of vanilylmandelic acid, metanephrine and normetanephrine during the catatonic phase of the disease⁹⁵ and had also shown that depletion of catecholamines by reserpine could abort the catatonic phase⁹⁶ whereas the administration of α -methyldopa could only mitigate it.⁹⁷ He also showed that “periodic catatonia” was distinct from manic-depressive disease in lithium responsiveness.^{98, 99, 100}

Harley-Mason was first, in 1952, to entertain the possibility that the cause of schizophrenia was autointoxication with a mescaline like substance,¹⁰¹ such as 3, 4-dimethoxyphenylalanine (DMPEA), a transmethylation product of catecholamine metabolism,¹⁰² produced in the body. At the time the only finding indicating that DMPEA might have mental effects was Noteboom’s demonstration in the early 1930s that it induced experimental catatonia.¹⁰³ For about ten years, Harley-Mason’s proposition was dormant, but in the 1960s, after the reported presence of a “pink spot”, identified as DMPEA in acute schizophrenia but not in chronic schizophrenia,¹⁰⁴ a controversy arose. It was argued that DMPEA was not specific for schizophrenia, was present at a low level in all

urines, was not present in either schizophrenic or normal urine, was not an endogenous substance but a dietary artefact, and finally, that the “pink spot” was not DMPEA.^{105, 106} In the midst of this controversy Fujimori and Halpern found that in subjects pre-treated with MAOIs, DMPEA had psychomimetic effects,¹⁰⁷ and Bourdillon and his associates demonstrated that by dividing patients on the basis of their psychopathology the “pink spot” was present in more than 4 of 5 patients in the non-paranoid group of patients diagnosed as schizophrenia on the basis of Schneider’s¹⁰⁸ first rank symptoms but in less than 1 of 5 patients in the paranoid group.^{109, 110}

As an alternative to DMPEA in 1954 Hoffer, Osmond and Smythies suggested that adrenochrome, an oxidation product of epinephrine, might be the culprit in schizophrenia.¹¹¹ At the time the only support for this was Green and Richter’s finding, in the mid-1930s, that adrenochrome was formed *in vitro* by treating epinephrine with various oxidants.¹¹² It was only in the mid-1960s that adrenochrome’s psychomimetic effect was first demonstrated.¹¹³ It was about the same time that the enzyme that could catalyze adrenochrome formation from epinephrine was identified by Julius Axelrod in the cytoplasmic fraction of the salivary gland.¹¹⁴ (See Axelrod Volume 3). Nevertheless, in 1970 Altschule and Yanak reported that the activity of Axelrod’s enzyme was below the normal range in schizophrenia.¹¹⁵ The presence of adrenochrome *in vivo* could not be detected with the employment of even highly sensitive radioactive tracer techniques.¹¹⁶

The first data based “psychotoxic” hypothesis of schizophrenia was presented by Brune and Himwich who found in the early 1960s a decrease in N-methyl-nicotinamide excretion together with an increase in tryptamine, 3-indoleacetic acid and 5-hydroxyindoleacetic acid excretion in patients with acute or exacerbated schizophrenia.^{117, 118} They hypothesized in schizophrenia that a blockage of the kynurenine pathway of tryptophan metabolism reduced the biological formation of nicotinic acid and increased tryptophan metabolism along its serotonin and tryptamine pathways, leading to the formation of psychotoxic dimethylated metabolites,¹¹⁹ N,N dimethyl serotonin (bufotenin)¹²⁰, and DMT.¹²¹ The psychotomimetic effect of bufotenin was uncertain¹²² but the psychotomimetic effect of DMT was unequivocally confirmed.¹²³ Supportive of the hypothesis was the demonstration that urinary excretion of DMT was increased during aggravation of schizophrenic psychopathology.¹²⁴ Nevertheless, in 1971, Faurbey and Pind found that both DMT and bufotenin were present in normal urine.¹²⁵

Seymour Kety in the mid-1960 reformulated Harley-Mason’s transmethylation hypothesis of schizophrenia. He shifted emphasis from a psychotoxic substance to the biochemical process of methylation, aggravated by the formation of abnormally methylated psychotoxic compounds.¹²⁶ (See Kety

Volume 2). In keeping with the hypothesis were findings that incubating deproteinized blood with betain or methionine as a methyl donor and nicotinamide as a methyl acceptor yielded a much greater increase in N-methylnicotinamide formation in schizophrenic than in normal blood.¹²⁷ Also in keeping were findings that parenteral administration of catechol-O-methyl transferase,¹²⁸ as well as combined administration of methionine and an MAOI, exacerbated the clinical symptoms of schizophrenia.^{129, 130}

The first report on the therapeutic effect of nicotinic acid in schizophrenia was published by Hoffer and his associates in 1957.¹³¹ They hypothesized that in stressful conditions administration of nicotinic acid (NA), a substance that converts into nicotinamide, a methyl acceptor, would prevent excessive epinephrine production and thereby restrict the supply of α reporting on the favourable effects of nicotinic acid in the treatment of schizophrenia.^{132, 133, 134} Findings in these studies could not be replicated in the Canadian Mental Health Association Collaborative Studies, a series of clinical trials in which NA was given alone and in combinations with neuroleptics and other vitamins, pyridoxine, ascorbic acid, to acute and chronic schizophrenic patients.^{135, 136, 137}

During the 1950s and 1960s several other toxic “factors” were isolated from plasma or serum of patients with schizophrenia.¹³⁸ One of these “factors,” taraxein, a protein, was shown to produce dramatic effects in monkeys and normal subjects with spiking and slow wave activity in the septal and hippocampal areas^{139, 140} resembling the spontaneous electrical activity reported from those areas in schizophrenic patients by Heath and Leach.¹⁴¹ Another factor usually referred to as “plasma protein factor” or “Frohman factor,” an, α_2 globulin, was found to increase the lactate/pyruvate (L/P) ratio by allegedly changing membrane permeability in schizophrenia. The purified “plasma protein factor” produced striking behaviour changes in female spire monkeys; within forty-five minutes after injection the animals became quiet, motionless and unresponsive to handling.^{142, 143} A third “factor,” a prealbumin, isolated by Walaas and his associates, was found to inhibit the incorporation of glucose into glycogen, and phenylalanine into protein, in the isolated rat diaphragm.¹⁴⁴ Ultimately, none of these “factors” proved to be specific for schizophrenia.

Neuropsychopharmacology of Schizophrenia

Based on findings which indicated that nicotinic acid, the precursor of nicotinamide adenine dinucleotide (NAD), was effective in the treatment of schizophrenia (see above) it was hypothesized that schizophrenia is a NAD deficiency disease, a form of “cerebral pellagra”.¹⁴⁵ Nevertheless, Hoffer and Osmond’s dramatic results with NAD treatment¹⁴⁶ could not be replicated; there was no NAD deficiency in schizophrenic blood.^{147, 148, 149}

Based on pharmacological findings in the mid-1950s which indicated a linear relationship between the sedative and anti-5HT effect of chlorpromazine and its congeners¹⁵⁰ and the demonstrated psychotomimetic effect of DMT, it was hypothesized that 5HT might be involved in the pathophysiology of schizophrenia. Yet, Bertlet and his associates found that a diet in which tryptophan, the precursor of 5HT, and methionine was reduced, had no effect on schizophrenia.¹⁵¹

Based on the findings of Carlsson in 1963 (see Carlsson Volume 3) that chlorpromazine and haloperidol increased 3-methoxytyramine and normetanephrine levels in the mouse brain, assumed to be a result of catecholamine receptor blockade,¹⁵² it was hypothesized that catecholamines are involved in the pathophysiology of schizophrenia. Gershon and his associates' findings that α -methyl-para-tyrosine (AMT), a substance that blocks the formation of NE, had no effect on schizophrenia¹⁵³ (see Gershon Volume 1), coupled with Heath and his associates findings that disulfiram, a dopamine- β -hydroxylase inhibitor, which decreases the breakdown of dopamine (DA), aggravated schizophrenia,¹⁵⁴ opened the path for the development of a dopamine hypothesis of schizophrenia.^{155, 156}

There was an inverse relationship between the potency of neuroleptics to produce extapyramidal signs (EPS), an indicator of dopamine antagonism, and neuroleptic dose requirements. The difference was restricted to dose; there was no difference in therapeutic efficacy between drugs like thioproperazine,¹⁵⁷ a potent dopamine antagonists which produced marked EPS and drugs like methotrimeprazine¹⁵⁸ that produced only mild EPS.^{159, 160, 161} In the mid-1950s Hans Joachim Haase suggested that there is a neuroleptic threshold dose, at which the drug becomes effective without further increases in effectiveness at higher dosages. He also developed a test for the detection of this dose from the changes in the size of letters in hand-writing.^{162, 163}

Neuropsychopharmacology of Depression

Developments in the neuropsychopharmacology of depression began with the assumption of a relationship between MAO inhibition and iproniazid's antidepressant effect. It was a tenuous relationship¹⁶⁴ because isoniazid¹⁶⁵, the parent of iproniazid, a substance with virtually no MAO inhibiting property, was also reported to have antidepressant effects.^{166, 167, 168, 169} The problem was further confounded by findings which indicated that iproniazid was¹⁷⁰ more of a "psychic energizer" than an antidepressant.^{171, 172} It was effective in a form of depression that became referred to as "atypical" (see Quitkin Volume 4), and its effectiveness was not restricted to depression but also included anxiety states.

173, 174, 175, 176

Imipramine^{177,178} was one of 42 substances selected in the mid-1950s from the chemical library of Geigy in the search for a promethazine-like antihistaminic or chlorpromazine-like tranquilizing drug.¹⁷⁹ It took about eight years from the time it was discovered¹⁸⁰ for Klerman and Cole (see Cole Volumes 4, 9 & 10) to demonstrate its statistically significant superiority (65% improvement) to an inactive placebo (31% improvement).¹⁸¹

Pharmacological studies in the late 1950s indicated that imipramine has antihistaminic, anticholinergic, noradrenergic and serotonergic properties¹⁸² without offering any clues which of these actions might be related to its antidepressant effect. The finding that imipramine antagonized and reversed reserpine - induced sedation, hypothermia, ptosis and diarrhoea¹⁸³ did not advance this issue, because reserpine, in addition to depleting NE and 5HT from brain storage sites, also has cholinomimetic effects. Far from being clearly a mood depressant,¹⁸⁴ reserpine was classified by the World Health Organization as a neuroleptic¹⁸⁵ and was reported to be effective in the treatment of anxious and depressed patients.¹⁸⁶

Imipramine blocks muscarinic acetylcholine receptors and has central and peripheral anticholinergic effects.¹⁸⁷ In 1961 Helmut Selbach attributed the antidepressant effect of imipramine to its action on autonomic regulation, producing an imbalance in which the parasympathetic-trophotropic, acetylcholine system is more strongly inhibited than the sympathetic-ergotropic, adrenaline-epinephrine system.¹⁸⁸ He also described three successive stages in the course of treatment, the first characterized by “trophotropic actions”, such as feelings of tiredness and decrease of blood pressure, the second by “lability,” manifest in tremor and fluctuation of blood pressure, and the third by “ergotropic actions” displayed in elation and increased interest.¹⁸⁹

The noradrenergic properties of imipramine were further elaborated in the late 1950s by Ernest Sigg, who demonstrated that imipramine enhanced and prolonged physiological responses to exogenous NE and to endogenous NE released by pre- or postganglionic sympathetic nerve stimulation.¹⁹⁰ The only findings which indicated this might translate into an effect on behaviour and psychopathology was Elmadjian and associates' report of a correlation between urinary excretion of NE and aggression¹⁹¹, and Ström-Olsen and Weil-Malherbe' report of higher urinary excretion of epinephrine and NE in the manic compared to the depressive phase of manic-depressive psychosis¹⁹² Then, in 1961, Axelrod (see Axelrod Volume 3) and his associates discovered¹⁹³ that imipramine and amitriptyline blocked neuronal reuptake of NE, and in 1964 Sulser (see Sulser Volume 3) and his associates demonstrated that imipramine's reserpine reversal was blocked after depletion of NE in the brain. These preclinical findings were instrumental in the formulation of a catecholamine hypothesis of depression. Clinical findings with desipramine, the demethylated

metabolite of imipramine, and a selective NE reuptake inhibitor¹⁹⁴ had shown that it was not more effective in the treatment of depression than its parent substance.^{195, 196, 197, 198, 199}

The serotonergic properties of imipramine were further elaborated in 1960 by Gyermek and Possemanto who demonstrated that the pharmacological effects of 5HT were enhanced by administration of the drug.²⁰⁰ There were some indications that imipramine's serotonergic action was related to its antidepressant effect. In 1959 Pare and Sandler reported decreased urinary excretion of 5-hydroxyindoleacetic acid (5HIAA) in depressed patients²⁰¹ and in 1960 Aschcroft and Sharma found lower concentrations of 5-hydroxyindoles in the cerebrospinal fluid of depressed patients than in normal controls.²⁰² Furthermore, in 1963, Coppen, Shaw and Farrell had shown that the antidepressant effect of MAOIs was potentiated by tryptophan²⁰³. Their findings were further substantiated by Pare in the same year²⁰⁴. Yet, the first selective serotonin re-uptake inhibitor, zimelidine, was only introduced almost 20 years later, in the early 1980s.²⁰⁵

Trimipramine, a structurally similar substance to imipramine which neither blocks NE reuptake nor potentiates the pharmacological effects of tryptophan, was introduced in the treatment of depression in the early 1960s.^{206, 207} Trimipramine is a dopamine-D₂ and serotonin-5HT₂ antagonist.²⁰⁸

Endocrine Measures

After some isolated reports in the 1940s,²⁰⁹ developments in endocrine psychiatry began in 1951 with a Ciba-Foundation Symposium on The Influence of Steroid Hormones on Behavioural and Psychological Reactions²¹⁰ that was followed in 1954 by the controversial publication of Manfred Bleuler's *Endokrino-logische Psychiatrie (Endocrine Psychiatry)*²¹¹ and Max Reiss' *Psychoendocrinology* in 1958.²¹² By the end of the 1950s it was shown that increased adrenocortical activity was not restricted to depression²¹³ but was present in anxiety states, schizophrenia²¹⁴, and in both the manic and depressive phases of manic-depressive illness.^{215, 216} Another early finding was that increased adrenocortical activity correlates with emotional turmoil and stress and not with type or severity of depressive illness.^{217, 218, 219}

An elevation of plasma cortisol level in depressive illness was first reported by Gibbons and McHugh in 1962.²²⁰ They also showed that in depression cortisol's diurnal rhythm was abolished. In the mid-1960s it was first demonstrated that morning cortisol levels in depressed patients are significantly higher than in normal subjects.^{221, 222} It was also in the mid-1960s that Krieger and Krieger discovered that the circadian rise of 17-hydroxycorticosteroids was blocked in a dose dependent manner by atropine and other anticholinergic drugs.²²³

Introduction of neuroendocrine tests in neuropsychopharmacologic research began in the late 1960s²²⁴ with the first reports indicating that in severely depressed patients, dexamethasone might not suppress their morning rise of cortisol, and that the resistance to dexamethasone correlated with the severity of depression.²²⁵ In the 1970s research interest in endocrine psychiatry was extended to growth hormone (GH) and thyroid stimulating hormone (TSH) with reports of a blunted GH response in endogenous depression to insulin in 1971,²²⁶ to L-5-hydroxytryptophan in 1973,²²⁷ to the thyrotropin releasing hormone (TRH) in 1975,²²⁸ to amphetamine in 1976,²²⁹ and to clonidine in 1978.²³⁰ The first report on a decreased thyroid stimulating hormone (TSH) response to TRH was published in the late 1970s.²³¹

Interviewees and Interviewers

The preceding information provides orientation points in the development of neuropsychopharmacology, placing in perspective historical contributions of the interviewees.

All thirty interviewees of Volume Five are psychiatrists and ACNP members. One of the interviewees, Arnold Friedhoff, is founder and past president, and four, William Bunney, William Carpenter, Herbert Meltzer and Arthur Prange, are past presidents.

All interviews were done in a period from 1995 to 2007, and with the exception of one, at annual meetings. Claude de Mintigny was interviewed in Paris, France, between meetings.

The thirty interviews were done by fifteen interviewers with one interviewee (Carroll) interviewed by two interviewers (Hollister and Ban). Ten interviewers (Belmaker, Braslow, Bromley, Bunney, Calabrese, Davis, Detre, Goodwin, Greden, and Koslow) conducted one interview; one interviewer (Hollister) three; two interviewers (Healy and Tone) four; and one (Ban) nine.

By the time the editing of Volume Five was completed, two of the interviewees (Friedhoff and Schildkraut) and two of the interviewers (Detre and Hollister) had passed away.

Contributions of Interviewees

The thirty interviewees were involved in six broadly defined areas of research in neuropsychopharmacology; most of the interviewees were involved in more than one area. Eight interviewees (Angrist, Baldessarini, Carpenter, Chouinard, Friedhoff, Kapur, Meltzer, and van Kammen) were engaged in research related to the **neuropsychopharmacology of schizophrenia**. *William T. Carpenter* divided schizophrenia into “deficit schizophrenia” and “non-deficit schizophrenia”²³²,

²³³ and demonstrated that “deficit schizophrenia” responds differently to neuroleptics than “non-deficit schizophrenia”.²³⁴

In 1962 *Arnold J. Friedhoff* detected a “pink spot” in the urine of schizophrenic patients and identified it as DMPEA, the endogenous psychotoxic mescaline-like substance that *Harley-Mason* suggested as the cause of schizophrenia.^{235, 236} Ten years later, in 1972, in collaboration with *Schweitzer* and *Miller*, he demonstrated the biosynthesis of mescaline and N-acetylmescaline by mammalian liver.²³⁷

In the late 1970s *Ross J. Baldessarini* had shown that administration of SAME, a methyl donor did not result in an increase in the formation of psychotoxic DMT.²³⁸ In collaboration with *Giorgio Stramentolini*, *Baldessarini* demonstrated that N-methyltransferase, the enzyme involved in the formation of DMT is saturated under normal conditions.²³⁹ *Baldessarini* also contributed to the determination of the maintenance dose of neuroleptics in the treatment of schizophrenia.²⁴⁰

In the 1970s *Burt Angrist*, a disciple of *Samuel Gershon* (see *Gershon* Volume 1) reported that not only amphetamine but also other dopamine agonists could induce psychosis in normal subjects and exacerbate symptoms of schizophrenia. He also found a positive correlation between the intensity of psychotic symptoms and homovanillic acid (HVA) levels in the cerebrospinal fluid (CSF) of schizophrenic patients.²⁴¹ *Angrist* demonstrated that both positive and negative symptoms can be induced by amphetamine²⁴² and that neuroleptics have a differential effect on the positive and negative symptoms of schizophrenia.²⁴³

In the early 1980s *Daniel Van Kammen* reported on low CSF γ -amino butyric acid (GABA) levels in recently ill schizophrenic patients.²⁴⁴ He also found an inverse relationship between CSF dopamine beta-hydroxylase (DBH) levels and treatment response to neuroleptics.²⁴⁵ *Van Kammen* demonstrated that elevated CSF-NE levels are predictive of relapse after withdrawal of haloperidol²⁴⁶ and provided further substantiation for the pharmacological heterogeneity of schizophrenia to a d-amphetamine challenge.²⁴⁷ *Van Kammen* contributed to the clinical development of clonidine²⁴⁸ and several atypical neuroleptic drugs, including quetiapine, risperidone, sertindol and ziprasidone.^{249, 250}

Guy Chouinard was first, in the late 1970s, to describe the clinical and pharmacologic characteristics of a supersensitivity psychosis to neuroleptics.^{251, 252} He was also among the first to propose that schizophrenia is a dopamine deficiency disease.^{253, 254} (See *Lecrubier* Volume 4). *Chouinard* contributed to the clinical development of numerous psychotropic drugs, including alprazolam,²⁵⁵ bupropion,²⁵⁶ clonazepam,²⁵⁷ clozapine,²⁵⁸ fluoxetine,²⁵⁹ fluspirilene,²⁶⁰ gabapentine,²⁶¹ nitrazepam,²⁶² pimozone,²⁶³ risperidone,²⁶⁴ sertraline,²⁶⁵ tomoxetine,²⁶⁶ tryptophan,²⁶⁷ and zimelidine.²⁶⁸

Shitij Kapur studied the relationship between dopamine-D₂ receptor occupancy, clinical response and side effects of neuroleptics with the employment of positron emission tomography (PET).²⁶⁹ He found high levels of dopamine-D₂ receptor occupancy with relatively low doses of haloperidol.²⁷⁰ Together with Philip Seeman, Kapur demonstrated that atypical neuroleptics dissociate more rapidly from the dopamine-D₂ receptor than typical neuroleptics.^{271, 272}

Herbert H. Meltzer was among the first to demonstrate that atypical neuroleptics have a reversed affinity to dopamine-D₂ and serotonin-5HT₂ receptors²⁷³ compared to typical neuroleptics. He was a member of the team that demonstrated the efficacy of clozapine in treatment refractory schizophrenia²⁷⁴ and also the team which showed its favourable effect on “cognitive function” in schizophrenia.²⁷⁵ Meltzer contributed to the clinical development of several “atypical neuroleptics,” including olanzepine, risperidone²⁷⁶, melperone²⁷⁷ and others.²⁷⁸

The research of one interviewee, *Donald Robinson*, was focused on the relationship between **MAO inhibition and therapeutic effects**. With the employment of a modification of the assay developed by Wurtman and Axelrod²⁷⁹ (see Wurtman Volume 3), Robinson revealed an association between the dose of phenelzine, platelet MAO inhibition and urinary tryptamine excretion.²⁸⁰ In the early 1970s, he reported on the therapeutic effects of phenelzine in depression and anxiety states,²⁸¹ established that 80% or higher inhibition of monoamine oxidase (MAO) was a prerequisite for effective treatment with MAOIs,²⁸² and demonstrated the therapeutic efficacy of phenelzine in the continuation and maintenance therapy of major depression.²⁸³

Twelve interviewees (Bunney, Davis, Fawcett, de Montigny, Halaris, Janowsky, Oxenkrug, Potter, Ritchelton, Schildkraut, Shopsin and Van Praag) were engaged in research related to the **neuropsychopharmacology of depression**. In 1964 *Joseph J. Schildkraut* reported that urinary output of vanilylmandelic acid (VMA) was decreased²⁸⁴ and normetanephrine increased in imipramine treated patients.²⁸⁵ He also demonstrated that the increase of normetanephrine in the urine was temporarily related to the clinical effects of antidepressants. In 1965, Schildkraut put forward the “catecholamine hypothesis of affective disorders”.²⁸⁶ Schildkraut was a member of Irwin Kopin’s team (see Kopin Volume 2) which identified MHPG in urine and showed that it was the major metabolite of normetanephrine.²⁸⁷ He also demonstrated that urinary MHPG levels are significantly lower in bipolar than unipolar depression.²⁸⁸

William E. Bunney’s review with John Davis on “*Norepinephrine in Depressive Reactions*”²⁸⁹ was in print within a month after Schildkraut published his “catecholamine hypothesis of affective disorder.” In the late 1960s Bunney led the team which found high 17-hydroxycorticosteroid levels in suicidal patients.²⁹⁰ He was also the leader of the team in the early 1970s that documented the

relationship between sequential behavioural changes,²⁹¹ catecholamine metabolism and rapid eye movement (REM) sleep in manic depressive patients.²⁹² Bunney and his team in the late 1970s corroborated the effectiveness of lithium in both unipolar and bipolar depression.²⁹³ In the mid-1990s, Bunney with his associates found that gene expression for glutamic acid decarboxylase was reduced in schizophrenic brains without loss of neurons in the prefrontal cortex²⁹⁴ and reported on molecular “clock genes” in man and lower animals.²⁹⁵

John M Davis co-authored the review with Bunney which implicated NE in the etiology of depression. He was also a member of Bunney’s team that showed high 17-hydroxycorticosteroid levels in suicidal patients. Davis collaborated with Stephen Curry in studying the relationship between chlorpromazine plasma levels and therapeutic response in schizophrenia²⁹⁶ and with David Janowsky in studies which led to a cholinergic-adrenergic hypothesis of mania and depression, the use of methylphenidate as a challenge test in schizophrenia and the recognition that chlorpromazine blocks guanethidine’s antihypertensive effects. In the early 1970s Davis introduced meta-analysis in psychopharmacology and reported the first meta-analyses on the effectiveness of maintenance treatment with neuroleptics in schizophrenia^{297, 298} and with antidepressants in depression.^{299,300}

Jan A. Fawcett was also a member of Bunney’s team which showed adrenal hyperactivity, as measured by increased urinary 17-hydroxycorticosteroid levels, preceding suicide. He introduced the amphetamine load test in predicting response to antidepressants and found that “feeling better” after an “amphetamine challenge”³⁰¹ as well as low urinary MHPG levels³⁰² were predictors of a favourable response to desipramine. Fawcett was among the first in the USA to show that amphetamines and MAOIs could potentiate the therapeutic effect of tricyclic antidepressants.³⁰³

In the early 1970s *David S. Janowsky* reviewed findings which indicated that the ovarian hormones, estrogen and progesterone, have an effect on sexual and emotional behaviour by altering monoamine release and uptake.³⁰⁴ He demonstrated a correlation between mood, weight and electrolytes during the menstrual cycle and put forward a renin-angiotensin-aldosterone hypothesis of premenstrual tension.³⁰⁵ Based on his findings that physostigmine, a cholinesterase inhibitor, could control mania and aggravate depression, he also put forward a “cholinergic-adrenergic” hypothesis of affective disorders.³⁰⁶ During the 1970s Janowsky had shown that methylphenidate, a dopamine agonist, could activate pre-existing psychotic symptoms in some schizophrenic patients,³⁰⁷ and that the antihypertensive effect of guanethidine was antagonized by chlorpromazine.³⁰⁸

In the late 1960s *Gregory F. Oxenkrug* and *Iziaslav Lapin* found that antidepressants intensified central serotonergic processes in the frog and suggested

that the cause of the antidepressant effect of imipramine-type drugs was their serotonergic property.³⁰⁹ In the mid 1980s Oxenkrug demonstrated that selective inhibition of MAO-A activity increased melatonin synthesis in the pineal gland of rats.³¹⁰ (See Wurtman Volume 3).

In the late 1970s *Claude de Montigny* in collaboration with George Aghajanian reported that long-term treatment with tricyclic antidepressants increased the responsiveness of rat forebrain neurons to serotonin.³¹¹ (See Aghajanian Volume 2). In the 1980s with Pierre Blier, he tracked the electrophysiological change affected by antidepressants on serotonin mediated neurotransmission^{312, 313} and found that it was potentiated by lithium.^{314, 315} In 1994, de Montigny demonstrated that in treatment resistant depression lithium potentiated the effect of antidepressants.³¹⁶

Herman M. Van Praag was among the first to use the probenecid technique for measuring monoamine metabolites in the CSF.^{317, 318} In the early 1970s he divided endogenous depression into two groups, one with and one without a disturbance of serotonin metabolism.^{319, 320} In 1980, Van Praag postulated that central serotonin deficiency increases vulnerability for depression.³²¹ He had also shown changes in dopamine metabolism in retarded depression.³²²

Baron Shopsin was first to show, in the mid-1970s, that blocking the synthesis of serotonin by para-chlorophenylalanine reversed the therapeutic effect of imipramine³²³ and tranylcypromine³²⁴ whereas blocking the synthesis of NE by α -methylparatyrosine did not. He was also among the first to show the therapeutic effect of dopamine receptor stimulation by piribedil in depression.³²⁵ Shopsin contributed to the clinical development of lithium,^{326, 327, 328, 329} bupropion,³³⁰ clozapine,³³¹ and several other drugs.

In the mid-1980s *William Z. Potter* demonstrated that both the selective NE inhibitor desipramine and the selective serotonin reuptake inhibitor zimelidine decreased both the serotonin metabolite 5-hydroxyindole acetic acid (5HIAA) and the norepinephrine metabolite MHPG in the CSF.^{332, 333, 334} He also contributed to the clinical development of clorgyline.³³⁵

Elliott Richelson demonstrated in the late 1970s that tricyclic antidepressants (TCAs) block muscarinic acetylcholine^{336, 337} and histamine receptors.³³⁸ He had also shown that the histamine receptor blocking potency of TCAs is greater than their muscarinic acetylcholine receptor blocking potency and that the histamine receptor blocking potency of tertiary amine TCAs is greater than of secondary amine TCAs.³³⁹ In the 1980s Richelson spearheaded research in studying receptor affinities in normal human brain³⁴⁰ and reported on the receptor binding profiles of clinically used antidepressants^{341, 342} and antipsychotics.^{343, 344} Richelson also contributed to the development of neurotensin peptide analogs.³⁴⁵

In the mid-1990s *Angelos E. Halaris* and associates found that platelet 1-imidazoline receptor binding sites are elevated only in depressive and not in anxiety states and that the elevated 1-imidazoline binding sites are down-regulated by treatment with antidepressants.^{346, 347, 348} Halaris also contributed to the clinical development of bupropion³⁴⁹; he demonstrated that elevated 1-imidazoline receptor binding sites are down-regulated after bupropion treatment.^{350, 351}

Three interviewees (Carroll, Graden and Brown) were engaged in research centered on the **dexamethasone suppression test**. *Bernard Carroll* was first in 1968 to use the DST for complementing clinical information on depressive illness.³⁵² In 1970 he found, in collaboration with William McLeod and Brian Davies, that suppression of the morning rise of cortisol by dexamethasone was predictive of a favourable response to treatment with antidepressants.³⁵³ During the 1970s Carroll developed the DST for the “neuroendocrine identification” of depressed patients³⁵⁴ and for the study of the “neuroendocrine regulation” of depressive illness.^{355, 356} In the 1980s he developed a self-rating instrument, The Carroll Rating Scale for Depression, for measuring the severity of depression.^{357, 358}

In the early 1980s *John F. Greden*, a disciple of Carroll, demonstrated that normalization of DST was a laboratory indicator of improvement in depression.^{359, 360} Greden introduced “speech-pause time” as a marker of psychomotor retardation to complement the characterization of patients with endogenous depression.³⁶¹

Walter A. Brown was first to report that some depressed patients with increased pituitary adrenocortical activity are intolerant to several of the selective serotonin re-uptake inhibitors.³⁶² He also corroborated findings that patients with increased pituitary adrenocortical activity did poorly on placebo.³⁶³

Two of the interviewees (Prange and Whybrow) were focused in their research on **thyroid hormones**. (See Winokur Volume 4). In the early 1960s *Arthur J Prange* noted that “imipramine mortality” in mice was dependent on the thyroid status of the animals^{364, 365} and with the employment of desipramine, he linked the increase in toxicity to NE.^{366, 367} In the late 1960s Prange demonstrated that the antidepressant effect of imipramine was enhanced by the addition of thyroid hormone,³⁶⁸ and in the early 1970s he had shown that the thyrotropin releasing hormone (TRH) has antidepressant effects when given alone.³⁶⁹ During the 1980s and 1990s Prange contributed to characterizing the behavioural effects of several neuropeptides, including neurotensin,^{370, 371} and oxytocin.^{372, 373}

Peter C. Whybrow contributed to the body of information on mental changes in thyroid gland dysfunction³⁷⁴ and on the relationship between thyroid function and the response to l-iodothyronine in depression.³⁷⁵ In the 1990s,

in collaboration with Michael Bauer, Whybrow found a relationship between Grade I hypothyroidism and rapid cycling^{376, 377} and demonstrated the effectiveness of adjuvant thyroxine in treatment refractory rapid cycling patients.³⁷⁸

The remaining four interviewees (Belmaker, Goodwin, Lowy, and Post) were engaged in research related to the **neuropsychopharmacology of bipolar disorders**. *Frederick K. Goodwin* was among the first in the United States to demonstrate the therapeutic effect of lithium in mania³⁷⁹ and in depression.³⁸⁰ He was also among the first in the United States to study central dopamine function in affective disorders. In collaboration with Sack, Goodwin had shown that dopamine is the culprit of psychotic symptoms in mania.³⁸¹

In the late 1970s *Alfred J. Lewy* developed an assay for the detection of melatonin in the human plasma³⁸² and demonstrated in humans that light suppresses melatonin secretion from the pineal gland.^{383, 384} (See Wurtman Volume 3). In the 1980s Lewy developed bright light treatment for manic-depressive disease with a seasonal mood cycle³⁸⁵ and for phase typed chronobiologic sleep and mood disorders.³⁸⁶ He was a member of the team which described Seasonal Affective Disorder and its treatment with “light therapy”.³⁸⁷ In the 1990s Lewy had shown that melatonin shifts human circadian rhythm according to a phase-response curve³⁸⁸ and introduced melatonin treatment for winter depression³⁸⁹ as well as for some other conditions.

In the mid-1970s *Robert Haim Belmaker* found that lithium blocked the rise of cyclic adenosine monophosphate (cAMP) to epinephrine in humans.³⁹⁰ He had also shown that lithium inhibits adrenergic and cholinergic increases in guanosine triphosphate (GTP) binding in rat cortex.³⁹¹ In the early 1980s Belmaker was first to demonstrate that treatment of depression with salbutamol, an adrenergic agonist, produced sub-sensitivity of the β -adrenergic adenylate cyclase in humans.³⁹² (See Sulser and Frazer Volume 3). Based on his findings in a series of “add on” studies, Belmaker reported that the effectiveness of a combination of lithium carbonate and haloperidol in schizoaffective disorder was unrelated whether the illness was dominated by affective or schizophrenic symptoms³⁹³ and the effectiveness of a combination of carbamazepine and haloperidol in excited psychoses was unrelated to diagnosis.³⁹⁴

In the mid-1970s *Robert M Post* noted that repeated administration of cocaine produced sensitization and a kindling like phenomenon³⁹⁵, described by Goddard in the 1960s.³⁹⁶ In the late 1970s, in collaboration with James Ballanger, he replicated Okuma’s findings³⁹⁷ about the effectiveness of carbamazepine in manic-depressive illness.^{398, 399} In the mid-1980s Post reported on sensitization and kindling like phenomena in bipolar disorder.^{400, 401} Post contributed to the clinical development of nimodipine,⁴⁰² gabapentine and lamotrigine⁴⁰³ for the treatment of bipolar disease.⁴⁰⁴

Interviewees included in Volume 4 entered the field at different stages in the development of neuropsychopharmacology. Hence the transcripts cover fifty years of history including the generation of hypotheses about the pathophysiology of depression, the mode of action of tricyclic antidepressants, the generation of hypotheses about the pathophysiology of bipolar disorder and the mode of action of anticonvulsants.

Samuel Gershon, the editor of this volume, is one of the pioneers of neuropsychopharmacology. (See Gershon Volume 1). His Introduction and Dramatis Personae that complement the volume is a personal note on the interviewees.

REFERENCES

- 1 Ban TA, Ucha Udabe R. The neurotransmitter Era in Neuropsychopharmacology. In: Ban TA, Ucha Udabe R, editors. *The Neurotransmitter Era in neuropsychopharmacology*. Buenos Aires: Editorial Polemos; 2006. p. 265-74.
- 2 Ban TA. Pharmacotherapy of mental illness. A historical analysis. *Prog Neuropsychopharmacol & Biol Psychiatry* 2001; 25: 709-27.
- 3 Pletscher A, Shore PA, Brodie BB. Serotonin release as a possible mechanism of reserpine psychosis. *Science* 1955; 122: 574-5.
- 4 Pletscher A, Shore PA, Brodie BB. Serotonin as a modulator of reserpine action in brain. *J Pharmacol Exper Ther* 1956; 116: 84-9.
- 5 Freis ED. Mental depression in hypertensive patients treated for long-periods with large doses of reserpine. *New Engl J Med* 1954; 251: 1006-8.
- 6 Pletscher A. Beeinflussung des 5-hydroxytryptamine-stoffwechsels in Gehirn durch Isonicotinsäurehydrazide. *Experientia* 1956; 1956; 12: 479- 80.
- 7 Selikoff IJ, Robitzek EH, Orenstein GG. Treatment of pulmonary tuberculosis with hydrazine derivatives of isonicotinic acid. *JAMA* 1952; 150: 973-87.
- 8 Wikler A. *The Relation of Psychiatry to Pharmacology*. Baltimore; American Society for Pharmacology and Experimental Therapeutics and the Williams & Wilkins Company; 1957.
- 9 Hollister LE. Review of Wikler's *The Relation of Psychiatry to Pharmacology*. In: Ban TA, Ray OS, editors. *A History of the CINP*. Brentwood; JM Productions; 1996. p. 339-43.
- 10 Moreau de Tours J. *Du Hachisch et de l'Alienation Mentale*. *Etudes Psychologiques*. Paris: Fortin & Masson; 1845. p. 432-2
- 11 Bernard C. *Introduction a l'étude de la médecine expérimentale*. Paris: Baillière; 1865.
- 12 Caldwell AE. *Origins of Psychopharmacology. From CPZ' to LSD*. Springfield: Charles C. Thomas; 1970. p. 185-187.
- 13 Lewin L. *Phantastica, Narcotic and Stimulating Drugs: Their Use and Abuse*. New York:Dutton; 1964.
- 14 Shonle R. Peyote, the giver of visions. *American Anthropologist* 1925; 27: 53-75.
- 15 Heffter A.Über Cactenalkaloide. *Berl Deutsch Chem Ges* 1986; 29: 216-27.de
- 16 Knauer A, Maloney WJ. A preliminary note on the psychic action of mescaline. *J Nerv Ment Dis* 1913; 40: 397-398.
- 17 Beringer G. *Mescalindrausch*. Berlin: Julius Springer; 1927.
- 18 Klüver H. *Mescal: The Divine Plant*. London: Kegan; 1928.
- 19 Quastel JH, Wheatley AHM. The effect of amines on oxidation of the brain. *Biochem J* 1933; 27: 1609-10.
- 20 Jacobs WA, Craig IC. The ergot alkaloids III. On lysergic acid. *J Biol Chem* 1934; 106: 93-6.
- 21 Hofmann A. The discovery of LSD and subsequent investigations on naturally occurring hallucinogens. In: Ayd FJ, Blackwell B, editors. *Discoveries in Biological Psychiatry*. Philadelphia: JB Lippincott; 1970. p. 91-106.
- 22 Stoll WA. Lysergic acid diethylamide, a "phantasticum" derived from the ergot group of drugs. *Schweiz Arch Neurol Psychiat* 1947; 60:279-80.
- 23 Elkes J, Elkes C, Bradley PB. The effects of some drugs on the electrical activity of the brain and behavior. *J Ment Sci*. 1954; 100: 125-8.

- 24 Arnold OH, Hofmann G. Untersuchungen über Bernsteinsäureeffekte bei LSD-25-Vergiftungen und Schizophrenia. *Wien Z Nervenheilk* 1955; 11: 92-3.
- 25 Abramson AJ, Jarvik ME, Kaufman MR, Kornetsky C, Levine A, Wagner M. Lysergic acid diethylamide (LSD-25) : Physiological and perceptual responses. *J Psychol* 1955; 39: 3-6.
- 26 Gaddum JH. Antagonism between lysergic acid diethylamide and 5-hydroxytryptophan. *J Physiol (London)* 1953; 121: 15-8.
- 27 Gaddum JH, Hamead KA. Drugs which antagonize 5-hydroxytryptamine . *Br J Pharmacol* 1954; 9: 240-8.
- 28 Amin AH, Crawford TBB, Gaddum JH. The distribution of Substance P and 5-hydroxytryptamine in the central nervous system of the dog. *J Physiol* 1954; 125: 596-618.
- 29 Gaddum JH. Serotonin-LSD interaction. *Annals of the New York Academy of Sciences* 1957; 66: 643-8.
- 30 Woolley DW, Shaw E. A biochemical and pharmacological suggestion about certain mental disorders. *Proc Natl Acad Sci* 1954; 40: 23841.
- 31 Graham-Smith DG. Serotonin and the neurotransmitter era in Neuropsychopharmacology. In: Ban TA, Ucha Udabe R, editors. *The Neurotransmitter Era in Neuropsychopharmacology*. Buenos-Aires: Editorial Polemos; 2006. p. 65-77.
- 32 Cerletti A, Rothlin E. Role of 5-hydroxytryptamine in mental diseases and its antagonism to lysergic acid derivatives. *Nature* 1955; 176: 785-6
- 33 Rothlin E. Lysergic acid diethylamide and related substances. *Annals of the New York Academy of Sciences* 1957; 66: 668-76.
- 34 Mayer-Gross W. Experimental psychosis and other mental abnormalities produced by drugs. *Brit Med J* 1951; 57: 317-21.
- 35 Hoch PH. Experimentally produced psychoses. *Amer J Psychiat* 1951; 107: 607-11.
- 36 Hollister LE, Hartman AM. Mescaline, lysergic acid diethylamide and psilocybin: comparison of clinical syndromes , effects on color perception and biochemical measures. *Comp Psychiat* 1962; 3: 235-41.
- 37 Fish MS, Horning JR. Studies of hallucinogenic snuffs. *J Nerv Ment Dis* 1956; 124-37.
- 38 Szara S. Dimethyltryptamine: its metabolism in man; the relation of its psychotoxic effect to serotonin metabolism. *Experientia* 1956; 12: 441-2.
- 39 Arnold OH, Hofmann G. Zur Psychopathologie des Dimethyltryptamin. *Wien Z Nervenheilk* 1957; 13: 438-45.
- 40 Sai-Halasz A, Brunecker` G, Szara SI. Dimethyltryptamine ein neues Psychoticum. *Psychiat Neurol* 1958: 285-301.
- 41 Böszörményi Z, Déri P, Nagy T. Observations on the psychotogenic effect of N,N-dimethyltryptamine, a new tryptamine derivative. *J Ment Sci* 1959; 105: 171-81.
- 42 Turner WJ, Merlis S. Effect of some indole alkylamines on man. *Arch Neurol Psychiat* 1959; 81: 121-9.
- 43 Szara S. Comparison of the psychotic effect of tryptamine derivatives with the effects of mescaline and LSD-25 in self-experiments. In: Garattini S, Ghetti V, editors. *Psychotropic Drugs*. Amstradam: Elsevier; 1957. p. 460-7.
- 44 Catenacci AJ. Evaluation of 1-(1-phenylcyclohexyl)-piperidine (Sernyl) as an anesthetic and pre-anesthetic . *Fed Proc* 1958; 17: 357-8.
- 45 Chen G. Pharmacology of 1-(1-phenylcyclohexyl)-piperidine HCl. *Fed Proc* 1968; 17: 358-9.
- 46 Meyers JS, Griefenstein F, Devault M. A new drug causing symptoms of sensory deprivation. *J Nerv Ment Dis* 1959; 54: 54-61.
- 47 Luby ED, Cohen BD, Rosenbaum G, et al. Study of a new schziophrenomimetic drug – Sernyl. *AMA Arch Neurol Psychiat* 1959; 81: 363-9.
- 48 Brown FC. *Hallucinogenic Drugs*. Springfield: Charles C. Thomas; 1972. p. 131-4.
- 49 Ban TA, Lohrenz J, Lehmann HE. Observations on the action of Sernyl, a new psychotropic drug. *Can Psychiat Assoc J* 1961; 6: 10-7.
- 50 Ban TA. Action of psychotogenic drugs in animal and man. Discussion. In: Bente D, Bradley PB, editors. *Neuropsychopharmacology*. Amsterdam: Elsevier; 1965. p. 127-8.
- 51 Hofmann A, Heim R, Brack A, Kobel H. Psilocybin, ein psychotroper Wirkstoff aus dem mexikanischen Rauchpilz Psilocybe Mexicana Heim. *Experientia* 1958; 14: 107-9.
- 52 Hofmann A, Troxler F. Identifizierung von psilocin. *Experientia* 1959; 15: 101-2.
- 53 Krogsgaard AR. Side-effects of reserpine in the treatment of arterial hypertension. *Journal of Internal Medicine* 1958; 162: 465-74.

-
- 54 Jensen K. Depression in patients treated with reserpine for arterial hypertension. *Acta Psychiatrica Scandinavica* 1959; 34: 195-204.
- 55 Holmberg G, Gershon S. Autonomic and psychic effects of yohimbine hydrochloride 1961; 2: 93-106.
- 56 Connell PH. Amphetamine Psychoses. London: Chapman and Hall; 1958.
- 57 Forrer GR. Atropine toxicity in the treatment of mental disease. *Am J Psychiatry* 1951; 108: 107-12.
- 58 Meduna LJ, Abood LG. Studies of a new drug (Ditran) in depressive states. *J Neuropsychiat* 1959; 1: 20-22,
- 59 Innes IR, Nickerson M. Drugs inhibiting the action of acetylcholine structures innervated by postganglionic parasympathetic nerves. In: Goodman C, Gilman A, editors. *The Pharmacological Basis of Therapeutics*. New York: Macmillan; 1965.
- 60 Alexander L. *Treatment of Mental Disorders*. Philadelphia: Saunders; 1953.
- 61 Gaszner P. Az atropine-coma terápia methodikájáról, különös tekintettel az atropine-érzékenység változására. *Ideggyógyászati Szemle*. 1974; 27: 172-7.
- 62 Giljarovskij AW. *Pszihiatrija*. Moscow: Medgiz; 1954.
- 63 Bonhoeffer K. Zur Frage der exogenen Psychosen. *Neur Zlb* 1909; 32: 499-505.
- 64 Mayer-Gross W, Slater E, Roth M. *Clinical Psychiatry*. Second edition. Melbourne: Cassell; 1960. p. 336-87.
- 65 Brown FC. *Hallucinogenic Drugs*. Springfield: Charles C Thomas; 1972.
- 66 Shorter E. *A History of Psychiatry*. New York: John Wiley & Sons; 1997. p.145-189.
- 67 Leuner H. *Die Experimentelle Psychose, Ihre Pharmakologie, Phänomenologie und Dynamik in Beziehung zur Person*. Berlin: Springer; 1962.
- 68 Kalinowsky LB, Hoch PH. *Somatic Treatments in Psychiatry*. New York; Grune & Stratton : 1961.
- 69 Ban TA. *Psychopharmacology*. Baltimore: Williams & Wilkins; 1969. p. 373-390.
- 70 Brill H, Patton RE. Analysis of 1955-56 population fall in New York State Mental Hospitals in the first year of large-scale use of tranquilizing drugs. *Am J Psychiatry* 1957; 114: 509-17.
- 71 Ban TA. Academic psychiatry and the pharmaceutical industry. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2006; 30: 420-41.
- 72 Elvehjem CA, Madden RJ, Strong FM, Wooley DW. The isolation and the identification of the anti-blacktongue factor. *J Biol Chem* 1937; 123: 137-49.
- 73 Fouts PJ, Helmer OM, Lepkowsy YS, Jukes TH. Treatment of human pellagra with nicotinic acid. *Proc Soc Exp Biol Med* 1937; 37: 405-7.
- 74 Fleming A. On the antibacterial action of cultures of penicillium with special reference to their use in the isolation of B influenzae. *Br J Exp Pathol* 1929; 1: 226-36.
- 75 Stokes JH, Seinberg TH, Schwartz W, Mahoney JF, Moore JE, Wood WB. The action of penicillin in late syphilis including neurosyphilis. *JAMA* 1944; 126: 73-9.
- 76 Putnam TJ. The demonstration of the specific anticonvulsant action of diphenylhydantoin and related compounds. In: Ayd FJ, Blackwell B, editors. *Discoveries in Biological Psychiatry*. Philadelphia: J.B.Lippincott; 1970. p. 85-90.
- 77 Wernicke C. Die acute hemorrhagische Polienccephalitis superior. In: Wernicke C. *Lehrbuch der Gehirnkrankheiten für Ärzte und Studierende*. Bd II. Kassel: Fischer; 1881. p. 1176-8.
- 78 De Werdener HE, Lennox B. Cerebral beri-beri (Wernicke encephalopathy) : Review of 52 cases in a Singapore prisoner-of-war hospital. *Lancet* 1947; 1: 11-7.
- 79 Garrod AB. *Gout and Rheumatic Gout*. London: Walton and Moberly; 1858.
- 80 Johnson FN. *The History of Lithium*. Basingstoke (UK): Macmillan; 1984.
- 81 Hammond WA. *A Treatise of Diseases of the Nervous System*. New York: Appleton; 1871.
- 82 Rybakowsky J. *The Faces of Manic – Depressive Illness*. Poznan (Poland): Termedia Wydawnictwa Meyczne; 2009. p. 107-18.
- 83 Lange C. On periodiske Depressionstilstande og deres Patogenese. 1886: Copenhagen; 1886.
- 84 Yeragani VK, Gershon S. Lithium: a historical update. *Biol Psychiatry* 1986; 21: 1101-2.
- 85 Gjessing R. Beiträge zur Kenntnis der Pathophysiologie des katonen Stupor. I. Mitteilung *Arch Psychiatr* 1932; 96: 319-473.
- 86 Moebius JP. *Abriss der Lehre im den Nervenkrankheiten*. Leipzig: Barth; 1893.
- 87 Thudichum JW. *A Treatise on the Chemical Constitution of the Brain*. London: Balliere, Tindall and Cox; 1864.
- 88 Ungvari GS. *Catatonia. An Anthology of Classical Contributions*. Hong Kong: Scientific Communications International Ltd; 2006.
- 89 Weil-Malherbe, Szara S. *The Biochemistry of Functional and Experimental Psychoses. The Biochemistry of Periodic Catatonia*. Springfield: Charles C Thomas; 1971. p. 189 – 203.

- 90 Gjessing R. Beiträge zur Somatologie der periodischen Katatonie. X. Mitteilung. Pathogenetische Erwägungen. Arch Psychiatr 200; 366-89.
- 91 Cade JF. Lithium salts in the treatment of psychotic excitement. Med J Aust 1949; 2: 349-52.
- 92 Cade JF. The story of lithium. In: Ayd FJ, Blackwell B, editors. Discoveries in Biological Psychiatry. Philadelphia: J Lippincott; 1970. p. 218-29.
- 93 Gjessing R. Beiträge zur Somatologie der periodischen Katatonie. IX. Mitteilung. Die periodische Katatonie in der Literture. Arch Psychiatr 1960; 200: 350-65.
- 94 Gjessing R. Disturbances of somatic function in catatonia with periodic course and their compensation. J Ment Sci 1938; 8: 608-21.
- 95 Gjessing L. Studies of periodic catatonia. 1. Blood levels of protein-bound iodine and urinary excretion of vanilic-mandelic acid in relation to clinical course. J Psychiat Res 1964; 2: 123-9.
- 96 Gjessing L. Effects of thyroxine, pyridoxine, ephedrine HCl, reserpine and disulfiram in periodic catatonia. Acta Psychiatr Scand 1967; 43: 376-41.
- 97 Gjessing L. Studies of urinary phenolic compounds in man. II. Phenolic acids and amines during a load of α -methyl-dopa and disulfiram in periodic catatonia. Scand J Clin Lab Invest 1965; 17: 549-65.
- 98 Gjessing L. Lithium citrate loading of a patient. Report of a case. Acta Psychiatr Scand 1967; 43: 372-5.
- 99 Gjessing L. A review of periodic catatonia. Biol Psychiatry 1974; 1974; 8: 23-45.
- 100 Gjessing L. The switch process in periodic catatonia and manic-depressive disorder. Chronologia 1975; 1975; 2: 306-16.
- 101 Harley-Mason J, Laird A, Smythies JR. The metabolism of mescaline in human. Confin Neurol. 1958; 18: 152-5.
- 102 Osmond H, Smythies J. Schizophrenia: A new approach. J Ment Sci 1952; 98: 309-15.
- 103 Noteboom L. Experimental catatonia by a derivative of mescaline and adrenaline. Proc Acad Sci USA 1934; 37: 562-74.
- 104 Faurbye A, Pind K. Investigation on the occurrence of the dopamine metabolite 3,4-dimethoxyphenylethyl amine in the urine of schizophrenia. Acta Psychiatr Scand 1964; 40: 240-3.
- 105 Feldstein A. Biochemical aspects of schizophrenia and antipsychotic drugs. In: DiMascio A, Shader RI, editors. Clinical Handbook of Psychopharmacology. New York: Science House; 1970.
- 106 Siegel M, Tefft H. The "Pink spot" and its components in normal and schizophrenic urine. J Nerv Ment Dis 1971; 152: 412-26.
- 107 Fujimori M, Alpers HS. Psychomimetic compounds in man and animals. In: Himwich HK, editors. Biochemistry, Schizophrenia and Affective Illness. Baltimore: Williams & Wilkins; 1971.
- 108 Schneider K. Die Schichtung des emotionalen Lebens und der Aufbau der Depressions zustände. Z Ges Neurol Psychiatr 1929; 59: 281-5.
- 109 Bourdillon RE, Clarke CE, Ridges AP, Sheppard PM, Harper P, Leslie AS. "Pink spot" in the urine of schizophrenics. Nature (London) 1965; 208: 453-5
- 110 Ridges AP, Bourdillon RE. The Pink spot. Proc R Soc Med 1967; 60: 555-7.
- 111 Hoffer A, Osmond H, Smythies J. Schizophrenia: A new approach. J Ment Sci 1954; 100: 29-54.
- 112 Green DE, Richter D. Adrenalin and adrenochrome. Biochemical J 1937; 31: 596-616.
- 113 Grof S, Vojtechovsky M, Vitek M, Prankova S. Clinical and experimental study of the central effects of adrenochrome. J Neuropsychiatry 1963; 5: 35-50.
- 114 Axelrod J. Enzymic oxidation of epinephrine to adrenochrome by the salivary gland. Biochim Biophys Acta 1964; 85: 247-54.
- 115 Altschule MD, Nayak U. Epinephrine-cyclizing enzyme in schizophrenic serum. Dis Nerv Syst 1970; 32: 51-2
- 116 Weil-Malherbe H, Szara SI. The Biochemistry of Functional and Experimental Psychoses. Schizophrenia and Neurotransmitters. Springfield; Charles C Thomas; 1971. p. 148-62.
- 117 Ban TA. Recent Advances in the Biology of Schizophrenia. Springfield ; 1973. p. 33-4.
- 118 Brune GG, Himwich HE. Biogenic amines and behavior in schizophrenic patients. In: Wortis J, editor. Recent Advances in Biological Psychiatry. Volume 5. New York: Plenum Press; 1963.
- 119 Brune GG. Tryptophan metabolism in psychoses. In: Himwich HE, Kety SS, Smythies JR, editors. Amines and Schizophrenia. Oxford: Pergamon Press; 1967. p. 87-96.
- 120 Fabing HD, Hawkins JR. Intravenous injection of bufotenin in man. Science 1956; 123: 886-7.
- 121 Brune GG. Tryptophan metabolism in psychoses. In: Himwich HE, Kety S, Smythies JR, editors. Amines and Schizophrenia. Oxford: Pergamon Press; 1967. p. 87-96.

-
- 122 Weil-Malherbe H, Szara SI. The Biochemistry of Functional and Experimental Psychoses. The Experimental Model of Psychoses. Springfield: Charles C. Thoms; 1971. p. 257-68.
- 123 Szara S, Aitkens A. Persistent behavioral effects of the hallucinogen: N, N-diethyltryptamine. *Fed Proc* 1970; 28: 618-20.
- 124 Heller B, Narasimhachari N, Spaide J, Heskovec L, Himwich HE. N-dimethylated indoleamines in blood of acute schizophrenics. *Experientia* 1970; 26: 503-4.
- 125 Faurbye A, Pind K. The presence of N-methylated and N-acetylated indole amines in the urine from patients with schizophrenia and from normal individuals. *Ugeskr Laeg* 1971; 133: 1356-8.
- 126 Kety SS. Current biochemical approaches to schizophrenia. *N Eng J Med* 1967; 276: 325-31.
- 127 Buscaino GA, Spadetta A, Carella A. In vitro methylation of nicotinamide: a biochemical test for schizophrenia. In: Lopez Ibor JJ, editor. *Proceedings of the IVth World Congress of Psychiatry*. Amsterdam: Excerpta Medica Foundation; 1966.
- 128 Hall P, Hartridge G, Van Leeuwen GH. Effect of catechol-O methyltransferase in schizophrenia. *Arch Gen Psychiatry* 1969; 20: 573-5.
- 129 Pollin W, Cardon PV, Kety S. Effect of amino acid feedings in schizophrenic patients treated with iproniazid. *Science* 1961; 133: 104-5.
- 130 Spaide J, Nevel L, Tolentino J, Himwich HE. Methionine and tryptophan loading in schizophrenic patients receiving a MAO inhibitor: correlation of behavioral and biochemical changes. *Biol Psychiatry* 1969; 1: 227-35.
- 131 Hoffer A, Osmond H, Callbeck MJ, Kahan L. Treatment of schizophrenia with nicotinic acid and nicotinamide. *J Clin Exp Psychopath* 1957; 18: 131-58.
- 132 Hoffer A. Nicotinic acid – an adjunct in the treatment of schizophrenia. *Am J Psychiatry* 1963; 120: 171-3.
- 133 Hoffer A. *Niacin Therapy in Psychiatry*. Springfield: Charles C. Thomas; 1962.
- 134 Hoffer A, Osmond H. Treatment of schizophrenia with nicotinic acid - a ten year follow-up study. *Acta Psychiatrica Scandinavica* 1964; 40: 171-89.
- 135 Ban TA. *Nicotinic Acid in the Treatment of Schizophrenias*. Toronto: Canadian Mental Health Association; 1971
- 136 Ban TA, Lehmann HE. *Nicotinic Acid in the Treatment of Schizophrenia*. Progress Report I. Toronto: Canadian Mental Health Association; 1970.
- 137 Ban TA. *Nicotinic Acid in the Treatment of Schizophrenia*. Complementary Report. Toronto: Canadian Mental Health Association; 1971.
- 138 Weil-Malherbe S, Szara SI. The Biochemistry of Functional and Experimental Psychoses. Toxic Factors in Plasma and Serum of Schizophrenics. Springfield: Charles C. Thomas; 1971. p. 132-45.
- 139 Heath RG, Martens S, Leach BE, Cohen M, Angel C. Effects on behavior in humans with the administration of taraxein. *Am J Psychiatr* 1957; 114: 14-24.
- 140 Heath RG, Martens S, Leach BE, Cohen M, Fengley CA. Behavioral changes in non-psychotic volunteers following the administration of taraxein a substance obtained from serum of schizophrenic patients. *Am J Psychiat* 1958; 114: 017-20.
- 141 Heath G, Leach BE. Brain recording with schizophrenic behavior: some metabolic factors responsible for physiological alterations. *Ann NY Acad Sci* 1962; 96: 425-35.
- 142 Frohman CE, Goodman M, Beckett PGS, Latham LK, Senf R, Gottlieb JS. The isolation of an active factor from serum of schizophrenic patients. *Ann NY Acad Sci* 1962; 96: 438-46.
- 143 Frohman CE, Latham LK, Beckett PGS, Gottlieb JS. Biochemical studies of a serum factor in schizophrenia. In: Walaas O, editor. *Molecular Basis of Some Aspects of Mental Activity*. Volume 2. New York: Academia; 1967. p. 241-51.
- 144 Walaas E, Lingjaerde O, Sovik O, et al. Abnormal effects of a prealbumin from sera of psychotic patients on metabolism of rat diaphragm. *Acta Psychiatrica Scandinavica* 1865; 40 (supplement) : 423-33.:
- 145 Pauling L. Orthomolecular psychiatry. *Science* 1968; 160: 265-71.
- 146 Hoffer A, Osmond H. Nicotinamide adenine dinucleotide as treatment for schizophrenia. *J Psychopharmacology* 1966; 1: 79 - 96.
- 147 Gallant DM, Bishop MP, Steele CA. DPN NAD-oxidized form: a preliminary evaluation in chronic schizophrenic patients. *Current Therapeutic Resurch* 1966; 8: 542-8.
- 148 Kline NS, Barclay GL, Cole JO, Esser AH, Lehmann HE, Wittenborn R. Controlled evaluation of nicotinamide adenine nucleotide in the treatment of chronic schizophrenic patients. *Br J Psychiat* 1967; 113: 375-81.

- 149 Meltzer H, Shader R, Greenspoon L. The behavioral effects of nicotinamide adenine nucleotide in chronic schizophrenia. *Psychopharmacologia* 1969; 15: 144-52.
- 150 Gyermek L, Lázár GT, Csák Zs. The antiserotonin action of chlorpromazine and some other phenothiazine derivatives. *Arch Int Pharmacodyn* 1957; 107, 62-74.
- 151 Bertlet HH, Bull C, Himwich H, Kuhl H, Matsumoto K, Pscheidt GR, Spaide J, Tourlentes TT, Valverde JM. Effect of diet on schizophrenic behavior. Proceedings of . Annual Meeting. American Psychopathological Akksociation 1966; 54: 42-52.
- 152 Carlsson A, Lindqvist M, Effectof chlorpromazine and haloperidol on formation of 4-methoxytyramine and normetanephrine in mouse brain. *Acta Phramcol Toxicol* 1963; 20: 140-4.
- 153 Gershon S, Hekimian LJ, Floyd A Jr, Hollister LE. α -Methyl-paratyrosine (AMP) in schizophrenia. *Psychopharmacology* 1967; 11: 189-94.
- 154 Heath RG, Nesselhof W, Bishop MP, Byers LW. Behavioral and metabolic changes associated with administration of tetraethyl-thiuram disulfide. *Dis Nerv Syst* 1965; 29: 99-105.
- 155 Van Rossum JM. The significance of dopamine receptor blockade for the action of neuroleptic drugs. In: Brill H, Cole JO, Deniker P, Hippius H, Bradely PB, editors. *Neuropsychopharmacology. The Proceedings of the Fifth International Congress of the Collegium Internationale Neuro-Psychopharmacologicum*. Amsterdam: Excerpta Medica Foudation; 1966. p. 321-9.
- 156 Seeman P. Dopamine and dopamine receptors. In: Ban TA, Ucha Udabe R, editors. *The Neurotransmitter Era in Neuropsychopharmacolgy*. Buenos Aires: Polemos; 2006. p. 79-94.
- 157 Ban TA, Papat homopoulos E, Schwarz L. Clinical studies with thioproperazine (Majepetil). *Comprehensive Psychiatry* 1962; 3: 284-91.
- 158 Ban TA, Schwarz L. Systematic studies with levomepromazine. *Journal of Neuropsychiatry* 1963; 5: 112-7.
- 159 Fügel F. Clinical observations on the effects of the phenothiazine derivative Megaphen on psychic disorders in children. *J Med Klinik* 1953; 48; 1027-9.
- 160 Brook GW. Experience with the use of chlorpromazine and reserpine in psychiatry with special reference to the management of extrapyramidal dysfunction. *New England Journa of Medicine* 1956; 254: 119-26.
- 161 Ayd FJ. Neuroleptics and extrapyramidal reactions.in psychiatric patents. *Rev Canad Biol* 1961; 20:42-49.
- 162 Haase H-J. The presentation and meaning of the psychomotor Parkinson syndrome during long-term treatment. In: Haase H-J, Janssen PAJ. *The Action of Neuroleptic Drugs*. Chicago: Medical Year Book; 1965
- 163 Haase H-J, Janssen PAJ. *The Action of Neuroleptic Drugs*. Chicago: Medical Year Book; 1965.
- 164 Burger A. History. In: Usdin E, Forrest IS, editors. *Psychotropic Drugs. Part I*. New York: Marcel Dekker; 1977. p. 11-57.
- 165 Fox HH, Gibbas JT. Synthetic tuberculostats. VII. Monoalkyl derivatives of isonicotinyldrazine . *J Org Chem* 1953; 18: 992-1002.
- 166 Zeller EA, Barsky JR, Fouts W, Kirchheimer WF, Van Orden LS. Influence of isonicotonic acid hydrazide (INH) and 1-isonicotinyl-2-isopropyl hydrazide (IH) on bacterial and mammalian enzymes . *Experientia* 1952; 8: 349-50.
- 167 Delay J, Laine R, Buisson JF. Note concenant l'action de 1-isonicotinylhydrazide dans le traitements des etats dépressifs. *Ann Medico-Psychol* 1952; 110: 689-92.
- 168 Delay J, Laine R, Buisson JF. Anxiety and depressive states treated with 1-isonicotinylhydrazide (isoniazid). *Arch Neurol Psychiat* 1953; 70: 317-24.
- 169 Salzer HM, Lurie ML. Anxiety and depressive states treated with isonicotinyl hydrazine (Isoniazid). *Arch Neurol Psychiatry* 1953; 70: 317-24.
- 170 Salter HM, Lurie ML. Depressive states treated with isonicotinyl-hydarazide (Isoniazid): A follow-up study. *Ohio State Medical Journal* 1955; 51: 437-41.
- 171 Crane GE. Isoniazid (Marsilid) phosphate: a therapeutic agent for mental disorders. *Psychiatr Res Reports* 1957; 8: 142-54.
- 172 Loomers HP, Saunders JC, Kline NS. A clinical and phramacodynamic evaluation of iproniazid as a psychic energizer. *Psychiatr Res Reports* 1957; 8: 129-41.
- 173 Rees WL. Treatment of depression by drugs and other means. *Nature* 1960; 186: 114-20.
- 174 Sargant W. Drugs in the treatment of depression. *BMJ* 1961; 1: 225-7.
- 175 West ED, Dally PJ. Effects of iproniazid in depressive syndromes. *BMJ* 1959; 1: 1491-9.
- 176 Sargant W, Dally PJ. Treatment of anxiety states by antidepressant drugs. *BMJ* 1962; 1: 6-9.

-
- 177 Ban TA. Depression and the Tricyclic Antidepressants. Montreal: Ronalds Federated; 1974. p.7-8.
- 178 Ban TA. Psychopharmacology of Depression. New York: Karger. p. 3-37.
- 179 Ban TA. Pharmacotherapy of Depression: A historical analysis. *J Neurol Transm* 2001; 108: 207-11.
- 180 Kuhn R. Über die Behandlung depressives Zustände mit einem iminodibenzylderivat (G22 355). *Schweiz med Wchschr* 1957; 87: 1135-40.
- 181 Klerman GL, Cole JO. Clinical pharmacology of imipramine and related antidepressant compounds. *Pharmacol Review* 1965; 17: 101-41.
- 182 Domenjoz R, Theobald W. Zur Pharmacologie des Tofranil. *Arch Int Pharmacodyn* 1959; 120: 450-89.
- 183 Costa E, Garattin S, Valzelli L. Interaction between reserpine, chlorpromazine and imipramine. *Experientia* 1960; 15: 461-3.
- 184 Mueller JC, Pryor WW, Gibbons JE, Orgain ES. Depression and anxiety occurring during reserpine therapy. *JAMA* 1955; 159: 836-9.
- 185 World Health Organization. Research in Psychopharmacology. Technical Report Series No.371. Geneva: WHO; 1967.
- 186 Davies DI, Shepherd M. Reserpine in the treatment of anxious and depressed patients. *Lancet* 1955; 2: 117-21.
- 187 Sulser F, Watts F. On the antireserpine action of imipramine (Tofranil). In: Tonini G, editor. *Techniques for the Study of Psychotropic Drugs*. Modena: Societa Tipographica Modenese; 1960.
- 188 Selbach H. Über die vegetative Dynamik in der psychiatrischen Pharmakotherapie. *Dtsch med J* 1961; 12: 511-7.
- 189 Selbach H. Über die vegetative Dynamik in der psychiatrischen Pharmakotherapie. *Med exp* 1962; 7 (supplement): 133-65.
- 190 Sigg EG. Pharmacological studies with Tofranil. *Canad Psychiat Assoc J* 1959; 4: 75-83.
- 191 Elmadjian F, Hope JM, Lawson ET. Excretion of epinephrine and norepinephrine in various emotional states. *J Clin Endocr* 1957 17: 608-20.
- 192 Ström-Olsen R, Weil-Malherbe H. Humoral changes in manic-depressive psychosis with particular reference to excretion of catecholamines in urine. *J Ment Sci* 1958; 101: 696-706.
- 193 Hertting G, Axelrod J, Whitby LC. Effect of drugs on the uptake and metabolism of 3H-norepinephrine. *J Pharmacol Exp Ther* 1961; 134: 146-53.
- 194 Sulser F, Bickel MH, Brodie BB. The action of desmethylimipramine in counteracting sedation and cholinergic effects of reserpine-like drugs. *J Pharmacol Exp Ther* 1964; 144: 321-30
- 195 Kline NS, Simpson G, Brodie BB. The clinical application of desmethylimipramine. A new type of antidepressant. *International Journal of Neuropsychopharmacology* 1962; 1: 55-60.
- 196 Brodie BB, Dick P, Kielholz P, Pöldinger W, Theobald W. Preliminary pharmacological and clinical results with desmethylimipramine (DMI) G 35020, a metabolite of Tofranil. *Psychopharmacologia* 1961; 19: 46-74.
- 197 Ban TA, Lehmann HE. Clinical trial with desmethylimipramine (G-35020) a new antidepressant. *Can Med Assoc J* 1962; 86: 1030-1
- 198 Oltman JE, Freedman S. Preliminary investigation of desmethylimipramine (G 35020). *Am J Psychiatry* 1962; 119: 370-1.
- 199 Mann AM. Clinical trial with desmethylimipramine (G35020), a new antidepressive compound. *Can Med Assoc J* 1962; 86: 1830-1.
- 200 Gyermek L, Posemanto C. Potentiation of 5-hydroxytryptamine by imipramine. *Medicina Exper* 1960; 3: 225-9.
- 201 Pare CMB, Sandler M. A clinical and biochemical study of a trial of iproniazid in the treatment of depression. *J Neurol Neurosurg Psychiat* 1959; 22: 247-51.
- 202 Aschcroft GW, Sharman DF. 5-Hydroxyindoles in human cerebrospinal fluid. *Nature* 1960; 186: 1050-1.
- 203 Coppen A, Shaw DM, Farrell JP. Potentiation of the antidepressant effect of a monoamine oxidase inhibitor by tryptophan. *Lancet* 1963; 1: 79-81.
- 204 Pare CMB. Potentiation of monoamine oxidase inhibitors by tryptophan. *Lancet* 1963; 2: 527-8.
- 205 Hope K, Attley J, editors. Zimelidine (Zelmid). The First Antidepressant to Specifically Block 5HT re-uptake. *British Journal Clinical Practice*. 1982; 19 (supplement): 1-125.
- 206 Lambert PA, Guyotat J. Un nouvel antidépresseur sédatif dérivé de l'iminodibenzille, le 7162 RP. *Essais thérapeutiques*. Presse méd 1961; 69: 1425-8.
- 207 Ban TA. Trimipramine in psychiatry. In Lehmann HE, Berthiaume M, Ban TA, editors. *Trimipramine A New Antidepressant*. Montreal; Quebec Psychopharmacological Research Association; 1964. p. 95-98.

- 208 Baghai TC, Gruze H, Sartorius N, editors. Antidepressant medications and other treatments of depressive Disorders: A CINP Task Force report based on a review of evidence. *The International Journal of Neuropsychopharmacology* 2007; 10 (supplement); S1-S207.
- 209 Hemphill R. Endocrinology in clinical psychiatry. *Journal of Mental Science* 1940; 80: 410-34.
- 210 Reiss M. Die Entwicklung der Psycho-Endokrinologie. *Berliner Gesundheitsblatt* 1955; 20: 517-22.
- 211 Bleuler M. *Endocrinologische Psychiatrie*. Stuttgart: Georg Thieme; 1954.
- 212 Reiss M. *Psychoendocrinology*. New York: Grune & Stratton; 1958.
- 213 Bryson RW, Martin DF. 17-Ketosteroid excretion in a case of manic-depressive psychosis. *Lancet* 1954; 2: 365-6.
- 214 Lingjaerde O. Plasma hydrocortisone in mental disease. *Brit J Psychiat* 1964; 110: 423-6.
- 215 Schwartz M, Mandell AJ, Green R, Ferman R. Mood, motility and 17-hydroxycorticoid excretion: a case study. *Brit J Psychiat* 1966; 112: 149-53.
- 216 Weil-Malherbe H, Szara SI. *The Biochemistry of Functional and Experimental Psychoses. Pituitary Adrenocortical Function in Affective Disorders*. Springfield: Charles C Thomas; 1971. p.87-9
- 217 Persky H. Adrenal cortical function in anxious human subjects. *Arch Neurol Psychiat* 1957; 78: 95-6.
- 218 Bliss EL, Migren CJ, Branch CH, Samuels LT. Reaction of the adrenal cortex to emotional stress. *Psychosom Med* 1956; 18: 56-76.
- 219 Price DB, Thaler M, Mason JW. Preoperative emotional states and adrenal cortical activity. *Arch Neurol Psychiat* 1957; 77: 623-34.
- 220 Gibbons JL, McHugh PR. Plasma cortisol in depressive illness. *J Psychiatr Res* 1962; 1: 162-71.
- 221 Doig RJ, Mummery RV, Wills MR, Elkes A. Plasma cortisol levels in depression. *Brit J Psychiatry* 1966; 112: 1263-7.
- 222 Bridges PK, Jones MT. The diurnal rhythm of plasma cortisol concentration in depression. *Brit J Psychiat* 1966; 112: 1257-61.
- 223 Krieger DT, Krieger HP. Circadian pattern of plasma 17-hydroxycorticosteroids: Alteration by anticholinergic drugs. *Science* 1967; 155: 1421-2.
- 224 Matussek N. The neurotransmitter era. Reflections of a neuropsychopharmacologist. In: Ban TA, Ucha Udabe R, editors. *The Neurotransmitter Era in Neuropsychopharmacology*. Buenos Aires: Polemos; 2006. p. 195-200.
- 225 Butler PWP, Besser GM. Pituitary-adrenal function in severe depressive illness. *Lancet* 1968; 1: 1234 – 6
- 226 Sachar EJ, Finkelstein J, Hellman L. Growth hormone responses in depressive illness. I. Response to insulin tolerance test. *Arch Gen Psychiatry* 1971; 25: 263-9.
- 227 Takahashi R, Kondo H, Yoshimura et al. Growth hormone response to administration of L-5-hydroxytryptophan (L-5-HTP) in manic-depressive psychosis. *Folia Psychiatr Neurol Jap* 173; 27: 198-205.
- 228 Maeda K, Kato K, Ohgo S, et al. Growth hormone and prolactin release after injection of TRH in patients with depression. *J Clin Endocr Metab* 1975; 40: 501-5.
- 229 Langer D, Heinze G, Reim B, Matussek N. Reduced growth hormone response to amphetamine in endogenous depressive patients. *Arch Gen Psychiatry* 1976; 33: 1471-5.
- 230 Matussek N, Ackenheil M, Hippus H, et al. Effect of clonidine on growth hormone release in psychiatric patients and controls. *Psychiatry Res* 1980; 2: 25-36.
- 231 Kirkegaard C, Bjorum N, Cohn D, Lauridson UB. Thyrotropin-releasing hormone (TRH) stimulation test in manic depressive illness. *Arch Gen Psychiatry* 1978; 35: 1017-21.
- 232 Carpenter WT, Heinrichs DW, Wagman AMI. Deficit and non-deficit forms of schizophrenia: The concept. *Am J Psychiatry*. 1988; 145: 578-83.
- 233 Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT. A separate disease within the syndrome of schizophrenia. *Arch Gen Psychiatry* 2001; 58: 165-71.
- 234 Carpenter WT, Hanlon TE, Heinrichs DW, Summerfelt A, Kirkpatrick B, Levine J, Buchanan RW. Continuous vs. targeted medication in schizophrenic outpatients: Outcome results. *Am J Psychiatry* 1990; 147: 1138-48.
- 235 Friedhoff AJ, Van Winkle E. Isolation and characterization of a compound from the urine of the schizophrenic. *Nature*. 1962; 194: 897-898.
- 236 Friedhoff AJ. Biosynthesis of endogenous hallucinogens: In Usdin E, Hamburg DA, Barchas JD, editors. *Neuro-Regulators and Psychiatric Disorders*. New York: Oxford University Press; 1977. p. 557-64.
- 237 Friedhoff AJ, Schweitzer JW, Miller JC. Biosynthesis of mescaline and N-acetylmescaline by mammalian liver. *Nature*. 1972; 237: 454-55.

-
- 238 Stramentolini G, Baldessarini RJ. Lack of enhancement of dimethyltryptamine formation in rat brain and rabbit lung in vivo by methionine and S-adenosylmethionine. *Journal of Neurochemistry* 1978; 31: 1015-20.
- 239 Baldessarini RJ, Stramentolini G, Lipinski JF. Methionine hypothesis. *Arch Gen Psychiatry* 1979; 36: 303-7.
- 240 Baldessarini RJ, Davis JM. What is the best maintenance dose of neuroleptics. *Psychiatry Research* 1980; 3: 115-22.
- 241 Angrist B, Sathananthan G, Wilk S, Gershon S. Amphetamine psychosis: Behavioral and biochemical aspects. *J Psychiatr Res* 1974; 11: 13-23.
- 242 Angrist B, Gershon S. The phenomenology of experimentally induced amphetamine psychosis: preliminary observations. *Biol Psychiatry* 1970; 2: 95-107.
- 243 Angrist B, Rotrosen J, Gershon S. Differential effects of amphetamine and neuroleptics on negative vs. positive symptoms in schizophrenia. *Psychopharmacology*. 1980; 72: 17-9.
- 244 Van Kammen DP, Steinberg WA, Hare TA, Waters RN, Bunney WE. CSF levels of γ -aminobutyric acid in schizophrenia. Low values in recently ill patients. *Arh Gen Psychiatry* 1982; 39: 91-7.
- 245 Sternberg DE, van Kammen DP, Lerner P, Bunney WE Jr. Schizophrenia: Dopamine- β -hydroxylase activity and treatment response. *Science*. 1982; 216: 1423-5.
- 246 Van Kammen DP, Peters JC, Van Kammen WB, Nugent A, Goetz KL, Yao J, Linnoila M. CSF norepinephrine in schizophrenia is elevated prior to relapse after haloperidol withdrawal. *Biological Psychiatry* 1989; 2: 175-88.
- 247 Van Kammen, DP, Bunney WE, Docherty JP, Marder S, Ebert MH, Goodwin FK, Rosenblatt JE, Rayner JN. D-amphetamine induced heterogeneous changes in psychotic behaviour in schizophrenia. *Am J Psychiatry* 1982; 139: 991-7.
- 248 Van Kammen DP, Peters JL, Van Kammen WB, Rosen J, Yao JK, McAdam D, Linnoila M. Clonidine treatment of schizophrenia: can we predict treatment response? *Psychiatry Research* 1989; 27: 297- 11.
- 249 Van Kammen DP, McEvoy JP, Targum SD, Kardayzke T. A randomized, controlled dose ranging trial of sertindole in patients with schizophrenia. *Psychopharmacology* 1996; 124: 168-75.
- 250 Van Kammen D. Pursuing the demons of schizophrenia. In: Ban TA, Healy D, Shorter E, editors. *From Psychopharmacology to Neuropsychopharmacology and The Story of CINP*. Budapest: Animula; 2002/. p. 252-9.
- 251 Chouinard G, Jones BD, Annable L. Neuroleptic-induced supersensitivity psychosis. *Am J Psychiatry* 1978; 135: 1409-10.
- 252 Chouinard G, Jones BD. Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. *Am J Psychiatry* 1980;137: 16-21
- 253 Chouinard G, Jones BD. Evidence of brain dopamine deficiency in schizophrenia. *Can J Psychiatry* 1979; 24: 661-7.
- 254 Chouinard G, Jones BD. Schizophrenia; a dopamine deficiency disease. *Lancet* 1980; 2: 99-100
- 255 Chouinard G, Annable L, Fontaine R, et al. Alprazolam in the treatment of generalized anxiety and panic disorders: a double-blind placebo-controlled study. *Psychopharmacology (Berl)* 1982; 77: 229-33.
- 256 Chouinard G. Bupropion and amitriptyline in the treatment of depressed patients. *J Clin Psychiatry* 1983; 44: 121-9.
- 257 Chouinard G, Young SN, Annable L. Antimanic effect of clonazepam. *Biol Psychiatry* 1983; 18: 451-66.
- 258 Chouinard G, Annable L. Clozapine in the treatment of newly admitted schizophrenic patients. A pilot study. *J Clin Pharmacol* 1976; 16: 289-97.
- 259 Chouinard G. A double-blind controlled trial of fluoxetine and amitriptyline in the treatment of outpatients with major depressive disorder. *J Clin Psychiatry*. 1985; 47: 32-7.
- 260 Chouinard G, Lehmann HE, Ban TA, Ananth JV. Fluspiriline in the treatment of chronic schizophrenic patients. *Current Therapeutic Research* 1970; 12: 604-8.
- 261 Chouinard G, Beauclair L, Belanger MC. Gabapentin: long-term antianxiety and hypnotic effects in psychiatric patients with comorbid anxiety-related disorders. *Can J Psychiatry* 1998; 43: 305-9.
- 262 Bordoleauu JM, Chouinard G, Tetreault L. Study of the hypnotic properties of a new benzodiazepine preparation (Mogedon.). *Comparative evaluation*. *Union Med* 1966; 95: 50-3.
- 263 Chouinard G, Lehmann HE, Ban TA. Pimozide in the treatment of chronic schizophrenic patients. *Current Therapeutic Research* 1970; 12: 598-603.

- 264 Chouinard G, Jones BD, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 1993; 13: 25-40.
- 265 Chouinard G, Goodman W, Greist J, Jenike M, Rasmussen S, White K, Hackett E, Gaffney M, Bick PA. Results of a double-blind placebo-controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive disorder. *Psychopharmacol Bull.* 1990; 26: 279-84.
- 266 Chouinard G, Annable L, Bradwejn J. An early phase II clinical trial of tomoxetine (LY139603) in the treatment of newly admitted depressed patients. *Psychopharmacology (Berl)* 1984; 83: 126-8.
- 267 Chouinard G, Young SN, Bradwejn J, et al. Tryptophan in the treatment of depression and mania. In: van Praag HM, Mendlewicz J, editors. *Advances in Biological Psychiatry*. Volume. 10. Basel: Karger; 1983. p. 47-66.
- 268 Fontaine R, Chouinard G, Ivy L. An open clinical trial of zimelidine in the treatment of obsessive compulsive disorder. *Curr Ther Res* 1985; 37: 326-32.
- 269 Kapur SJ, Zipursky R, Jones C, Remington G, Houle S: Relationship between dopamine-D₂ occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry* 2000; 157: 514-52
- 270 Kapur S, Remington G, Jones C, Wilson A, DaSilva J, Houle S, Zipursky R. High level of dopamine-D₂ occupancy with low doses of haloperidol a PET study. *Am J Psychiatry* 1996; 153: 942-50
- 271 Kapur S, Remington G: Dopamine-D₂ receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol Psychiatry* 2001; 50: 873-83
- 272 Kapur S, Seeman P: Does fast dissociation from the dopamine-D₂ receptor explain the action of atypical antipsychotics?: A new hypothesis. *Am J Psychiatry* 2001; 158:360-9
- 273 Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D₁, D₂ and serotonin₂ pk1 values. *J Exp Ther* 1989; 251: 238-48.
- 274 Kane J, Honigfeld G, Singer J, Meltzer HY, The Clozaril Collaborative Study Group. Clozapine for treatment resistant schizophrenia: A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; 45: 789-98.
- 275 Hagger C, Buckley P, Kenny JT, Friedman L, Ubogy D, Meltzer HY. Improvement in cognitive functions and psychiatric symptoms in treatment refractory schizophrenic patients receiving clozapine. *Biol Psychiatry* 1993; 34: 702-12.
- 276 Meltzer HY, McGurk SR. The effect of clozapine, risperidone, and olanzepine on cognitive functions in schizophrenia. *Schizophrenia Bulletin* 1999; 25: 233-5.
- 277 Meltzer HY, Sumiyoshi T, Yavathilake K. Melperone in the treatment of neuroleptic-resistant schizophrenia. *Psychiatr Res* 2001; 96: 201-9.
- 278 Meltzer HY, Park S, Kessler R. Cognition, schizophrenia and atypical antipsychotic drugs. *Proc Natl Acad Sci USA* 1999; 96: 13591-3.
- 279 Wurtman RJ, Axelrod J. A sensitive and specific assay for the estimation of monoamine oxidase. *Biochem Pharmacol* 1963; 12: 1439-41.
- 280 Robinson DS, Lovenberg W, Keiser H, Sjoersma A. Effects of drugs on human blood platelet and plasma amine oxidase activity in vitro and in vivo. *Biochem Pharmacol.* 1969; 17: 109-119.
- 281 Robinson DS, Nies A, Ravaris CL, Lamborn KR. The monoamine oxidase inhibitor, phenelzine, in the treatment of depressive-anxiety states; a controlled clinical trial. *Arch Gen Psychiatry.* 1973; 29: 407-413.
- 282 Ravaris CL, Nies A, Robinson DS, Ives JO, Lamborn KR, Korson L. A multiple-dose controlled study of phenelzine in depression and anxiety states. *Arch Gen Psychiatry* 1976; 33: 347-50.
- 283 Robinson DS, Lerfold SC, Bennett B, Laux D, Devereaux E, Kayser A, Corcella J, Albright D. Continuation and maintenance treatment of major depression with the monoamine oxidase inhibitor phenelzine: A double-blind placebo-controlled discontinuation study. *Psychopharm Bull.* 1991; 27: 31-39.
- 284 Schildkraut JJ, Klerman GL, Hammond R, Friend DG. Excretion of 3-methoxy-4-hydroxymandelic acid (VMA) in depressed patients treated with antidepressant drugs. *Br J Psychiatr Res.* 1964; 2: 251-66.
- 285 Schildkraut JJ, Gordon EK, Durell J. Catecholamine metabolites in affective disorders: I. Normetanephrine and VMA excretion in depressed patients treated with imipramine. *J Psychiatr Res* 1965; 3: 213-28
- 286 Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry.* 1965; 122: 509-22.

-
- 287 Schanberg SM, Schildkraut JJ, Breese DR, Kopin IJ. Metabolism of noremetanephrine (3H) in rat brain: identification of conjugated 3-methoxy-4-hydroxy-phenyl glycol as the major metabolite. *Biochem Pharmacol* 1968; 17: 247-54.
- 288 Schildkraut JJ, Orsulak PJ, Schatzberg AF, Gudeman JE, Cole JO, Rohde WA, Larie RA. Toward a biochemical classification of depressive disorders I: Differences in urinary MHPG and other catecholamine metabolites in clinically defined subtypes of depressions. *Arch Gen Psychiatry* 1978; 35: 1427-33.
- 289 Bunney WE Jr, Davis JM. Norepinephrine in depressive reactions. *Arch Gen Psychiatry*. 1965; 3: 483-494.
- 290 Bunney WE, Fawcett JA, Davis JM, Gifford S. Further analysis of urinary 17-hydroxycorticosteroids in suicidal patients. *Arch Gen Psychiatry* 1968; 2: 138-50
- 291 Bunney WE, Murphy DL, Goodwin DK, Borge GF. The "switch process" in manic-depressive illness. I. A systematic study of sequential behavioral changes. *Arch Gen Psychiatry* 1972; ; 27: 304-9.
- 292 Bunney WE, Goodwin FK, Murphy DL, House KM, Gordon EK. The "switch process" in manic-depressive illness. II. Relationship to catecholamines, REM sleep and drugs. *Arch Gen Psychiatry* 1972; 27: 304-9.
- 293 Goodwin FK, Murphy DL, Dunner DL, Bunney WE. Lithium response in unipolar versus bipolar depression. *Am J Psychiatry* 1972; 129: 44-7.
- 294 Akbarim S, Kim JJ, Potkin SG, Hagman JO, Taffazzoli A, Bunney WE, Jones EG. Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in the prefrontal cortex in schizophrenia. *Arch Gen Psychiatry* 1995; 52: 258-66.
- 295 Bunney WE, Bunney BG. Molecular clock genes in man and lower animals: Possible implications for circadian abnormalities in depression. *Neuropsychopharmacology* 2000; 22: 335-45.
- 296 Curry SH, Marshall JH, Davis JM, Janowsky DS. Chlorpromazine plasma levels and effects. *Arch Gen Psychiatry*. 1970; 22: 289-96.
- 297 Davis JM. Overview: Maintenance therapy in psychiatry. I Schizophrenia. *Am J Psychiatry* 1975; 132: 1237-45
- 298 Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second generation of antipsychotics. *Archives of General Psychiatry* 2003; 60: 553-64.
- 299 Davis JM. Overview: Maintenance therapy in psychiatry. II. Affective disorders. *Am J Psychiat* 1976; 133: 1-13.
- 300 Davis JM, Wang Z, Janicak PG. A Quantitative analysis of clinical drug trials for the treatment of affective disorders. *Psychopharmacol Bull* 1993; 175-81.
- 301 Fawcett JA, Simopoulos V. Dextroamphetamine. Response as possible predictor of improvement with tricyclic antidepressants in depression. *Arch Gen Psychiatry* 1971; 25: 247-55.
- 302 Fawcett JA, Maas JW, Dekermenjian H. Depression and MHPG excretion. *Arch Gen Psychiatry* 1972; 25: 247-55.
- 303 Fawcett JA, Kravits HM, Zajecka JM, Schaff MR. CNS stimulant potentiation of monoamine oxidase inhibitors in treatment refractory depression. *J Clin Psychopharmacol* 1991; 11: 127-32.
- 304 Janowsky DS, Fann WE, Davis JM. Monoamines and ovarian hormone-linked sexual and emotional changes: A review. *Arch Sex Behav*. 1971; 1: 205-18.
- 305 Janowsky DS, Berens SC, Davis JM. Correlations between mood, weight, and electrolytes during the menstrual cycle: A renin-angiotensin-aldosterone hypothesis of premenstrual tension. *Psychosom Med*. 1973; 35: 143-54.
- 306 Janowsky DS, El-Yousef MK, Davis JM, Sekerke HJ. A cholinergic-adrenergic hypothesis of mania and depression. *Lancet*. 1972; 2: 632-635.
- 307 Janowsky DS, El-Yousef MK, Davis JM, Sekerke HJ. Provocation of schizophrenic symptoms by intravenous administration of methylphenidate. *Arch Gen Psychiatry* 1972; 28: 185-191
- 308 Janowsky DS, El-Yousef MK, Fann EW. Antagonism of guanethidine by chlorpromazine. *Am J Psychiatry* 1973; 103: 808-12.
- 309 Lapin JP, Oxenkrug GF. Intensification of the central serotonergic processes as a possible determinant of the thymoleptic effect. *Lancet*. 1969; 1: 32-9.
- 310 Oxenkrug GF, McCauley RB, McIntyre IM, Filipowicz C. Selective inhibition of MAO-A but not MAO-B activity increases rat pineal melatonin. *J Neural Transm*. 1985; 61: 265-70.
- 311 De Montigny C, Aghajanian GK. Tricyclic antidepressants: long-term treatment increases responsivity of rat forebrain neurons to serotonin. *Science* 1978; 20: 1302-6.

- 312 Blier P, de Montigny C. Electrophysiological assessment of the effects of antidepressant treatment on the efficacy of 5HT neurotransmission. *Clinical Neuropharmacology* 1988; 11 (supplement): 51-60.
- 313 De Montigny C, Blier C. The role of the serotonin system in the mechanism of antidepressant action of antidepressant treatment: preclinical evidence. *The Journal of Clinical Psychiatry* 1990; 51 (supplement): 14-20.
- 314 Blier P, de Montigny C. Short term lithium administration enhances serotonergic neurotransmission: electrophysiological evidence. *European Journal of Pharmacology* 1985; 113: 69-77.
- 315 De Montigny C, Blier P. Potentiation of 5-HT neurotransmission by short-term lithium: in vivo electrophysiological studies. *Clinical Neuropharmacology* 1992; 15 (supplement): 610-11.
- 316 De Montigny C. Lithium addition in treatment resistant depression. *International Clinical Psychopharmacology* 1994; 9 (supplement): 31-5.
- 317 Van Praag HM, Korf J, Puite J. 5-Hydroxyindoleacetic acid levels in the cerebrospinal fluid of depressive patients treated with probenecid. *Nature*. 1970; 225: 1259-1260.
- 318 Van Praag HM, Korf J, Schut T. Cerebral monoamines and depression. An investigation with the probenecid technique *Arch Gen Psychiatry* 1973; 28:827-31.
- 319 Van Praag HM, Korf J. Endogenous depression with and without disturbances of 5-hydroxytryptamine metabolism.: A biochemical classification? *Psychopharmacol* 1971; 19: 148-52.
- 320 Van Praag. Towards a biochemical typology of depression. *Pharmacopsychiat* 1974; 7: 281-92.
- 321 Van Praag, HM, De Haan S. Central serotonin deficiency. A factor which increases depression vulnerability. *Acta Psychiatr Scandinavica* 1980; 61: 89-95.
- 322 Van Praag HM, Korf J. Retarded depression and dopamine metabolism. *Psychopharmacol* 1971; 19: 199-203.
- 323 Shopsin B, Gershon S, Goldstein M, et al. Use of synthesis inhibitors in defining a role for biogenic amines during imipramine treatment in depressed patients. *Psychopharmacology Communications* 1975; 1: 238-49.
- 324 Shopsin B, Friedman E, Gershon S. Parachlorophenylalanine reversal of tranylcypromine effects in depressed patients. *Arch Gen Psychiatry* 1976; 33: 811-9.
- 325 Shopsin B, Gershon S. Dopamine receptor stimulation in the treatment of depression : Piribedil (ET-495.) *Neuropsychobiology* 1978; 4: 1-14.
- 326 Gershon S, Shopsin B, editors. *Lithium: Its Role in Psychiatric Research and Treatment*. New York: Plenum Press; 1973.
- 327 Shopsin B, Kim SS, Gershon S. A controlled study of lithium vs chlorpromazine in acute schizophrenia. *The British Journal of Psychiatry* 1971; 119: 435-40.
- 328 Shopsin B, Gershon S, Thompson S, Collins P. Psychoactive drugs in mania. A controlled comparison of lithium carbonate, chlorpromazine and haloperidol. *Archives of General Psychiatry* 1975; 32: 34-42.
- 329 Shopsin B, Gershon S. Cogwheel rigidity related to lithium maintenance *Am J Psychiatr* 1975; 132: 526-8.
- 330 Shopsin B. Bupropion's prophylactic effect in bipolar affective illness. *J Clin Psychiatry* 1983; 44: 163-9.
- 331 Shopsin B, Klein H, Aronson M, et al. Clozapine, chlorpromazine and placebo in newly hospitalized acutely ill schizophrenic patients: a controlled, double-blind, placebo comparison. *Arch Gen Psychiatry* 1979; 36: 657-74.
- 332 Linnoila M, Karoum F, Calil HM, Kopin IJ, Potter WZ. Alteration of norepinephrine metabolites with desipramine and zimelidine in depressed patients. *Archives of General Psychiatr* 1982; 39: 1025-8.
- 333 Calil M, Lesier P, Gold PW, Brown GM, Zavadil AP, Potter WZ. Humoral responses to zimelidine and desipramine in depressed patients. *Psychiatric Research* 1984; 13: 231-42.
- 334 Potter WZ, Scheinin M, Goden RN, Rudorfer MV, Cowdry RW, Calil HM, Ross RJ, Linnoila M. Selective antidepressants and cerebrospinal fluid: Lack of specificity on norepinephrine and serotonin metabolites. *Arch Gen Psychiatry* 1985; 47: 1171-77.
- 335 Potter WZ, Murphy DL, Wehr TA, Linnoila M, Goodwin FK. Clorgyline: a new treatment of refractory rapid cycling disorder. *Arch Gen Psychiatry* 1982; 39: 505-10.
- 336 Richelson E, Divinetz-Romero S. Blockade by psychotropic drugs of the muscarinic acetylcholine receptor in cultured nerve cells. *Biol Psychiatry* 1977; 12:771-85.
- 337 Petersen RC, Richelson E. Anticholinergic activity of imipramine and some analogs at muscarinic receptors of cultured mouse neuroblastoma cells. *Psychopharmacology (Berl)* 1982; 76: 26-8.
- 338 Richelson E. Tricyclic antidepressants block histamine H₁ receptors of mouse neuroblastoma cells. *Nature* 1978; 274:176-7.

-
- 339 Figge J, Leonard P, Richelson E. Tricyclic antidepressants: potent blockade of histamine-H1 receptors of guinea pig ileum. *Eur J Pharmacol.* 1979; 58: 479-83
- 340 Richelson E, Nelson A. Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. *J Pharmacol Exp Ther.* 1984; 230: 94-102.
- 341 Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain receptors. Focus on newer generation compounds. *Psychopharmacol* 1994; 114: 559-65.
- 342 Tutsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol* 1997; 340: 248-58.
- 343 Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors: focus on new generation compounds. *Life Sci* 2000; 68: 29-39.
- 344 Tutsumi M, Jansen K, Blakely RD, Richelson E. Pharmacological profile of neuroleptics at human monoamine transporters. *Eur J Pharmacol* 1999; 368: 277-83.
- 345 Cusack B, Boules M, Tyler BQ, Fauq A, McCormick DJ, Richelson E. Effects of novel neurotensin peptide analog given extracranially on CNS behaviors mediated by apomorphine and haloperidol. *Brain Res* 2000; 856: 48-54.
- 346 Piletz JE, Halaris A, Nelson J, Qu Y, Bari M. Platelet 1-imidazoline binding sites are elevated in depression but not generalized anxiety disorder. *J Psychiatr Res* 1996; 30: 147-68.
- 347 Piletz JE, Halaris AE, Chikkala D, Qu Y. Platelet 1-imidazoline binding sites are decreased by two dissimilar antidepressant agents in depressed patients. *J Psychiatr Res* 1996; 30: 169-80.
- 348 Halaris A, Piletz JE. Imidazoline receptors: possible involvement in the pathophysiology and treatment of depression. *Human Psychopharmacol* 2001; 16: 65-9.
- 349 Halaris AE, Stern W, Van Wyck Fleet J, Reno RM. Evaluation of the safety and efficacy of bupropion in depression. *J Clin Psychiatry* 1983; 44: 101-3
- 350 Zhu H, Halaris A, Madakasira S, Pazzaglia P, Goldman N, De Vane CL, et al. Effect of bupropion on immunodensity of putative imidazoline receptors on platelets of depressed patients. *J Psychiatry Res* 1999;33:323-33.
- 351 Halaris A, Zhu H, Ali J, Nasrallah A, De Vane CL, Piletz JE. Down-regulation of platelet imidazoline-1-binding sites after bupropion treatment. *Int J Neuropsychopharmacol* 2002;5(1):37-46.
- 352 Carroll BJ, Martin FI, Davies B. Resistance to suppression by dexamethasone of plasma 11-OHCS levels in severe depressive illness. *Brit Med J* 1958; 3: 285-7.
- 353 McLeod WR, Carroll BJ, Davies B. Hypothalamic dysfunction and antidepressant drugs. *Brit Med J* 1970; 2: 480-2
- 354 Carroll BJ, Curtis GC. Neuroendocrine identification of depressed patients. *Aust NZJ Psychiat* 1976; 10: 13-20.
- 355 Carroll BJ, Curtis GC, Mendels J. Neuroendocrine regulation in depression. I. Limbic system-adrenocortical dysfunction. *Arch Gen Psychiatry* 1976; 33: 1039-33.
- 356 Carroll BJ, Curtis GC, Mendels J. Neuroendocrine regulation of depression. II. Discrimination of depressed and non-depressed patients. *Arch Gen Psychiatry* 1976; 33: 1051-8
- 357 Carroll BJ, Feinberg M, Souse PE, Rawson SG, Greden JF. The Carroll Rating Scale for Depression. I. Development, reliability and validation. *Brit J Psychiatry* 1981; 138: 194-200.
- 358 Feinberg M, Carroll BJ. The Carroll Rating Scale for Depression. In: Sartorius N, Ban TA, editors. *Assessment of Depression*. Berlin: Springer-Verlag; 1986. p. 188-200
- 359 Greden JF, De Vigne JP, Albala AA, Tarika J, Buttenheim M, Eiser A, Carroll BJ. Serial dexamethasone suppression tests among rapidly cycling bipolar patients. *Biol Psychiatry* 1982; 17: 455-62.
- 360 Grunhaus L, Tiongco D, Roehrich A, Eiser A, Feinberg M, Greden JF. Serial monitoring of antidepressant response to electroconvulsive therapy with sleep EEG recordings and dexamethasone suppression tests. *Biol Psychiatry* 1985; 20: 805-8
- 361 Greden JF, Albala AA, Smokler IA, Gardner R, Carroll BJ. Speech-pause time: A marker of psychomotor retardation among endogenous depressives. *Biol Psychiatry* 1981; 16: 851-9.
- 362 Brown WA, Arato M, Shrivastava R. Pituitary-adrenocortical hyperfunction and intolerance to fluvoxamine, a selective serotonin uptake inhibitor. *Am J Psychiatry* 1986; 143: 88-90.
- 363 Brown WA. Treatment response in melancholia. *Acta Psychiatrica Scandinavica* 2007; 115: 125-9.
- 364 Prange AJ Jr, Lipton MA. Enhancement of imipramine mortality in hyperthyroid mice. *Nature.* 1962; 196: 588-9.
- 365 Prange AJ Jr, Lipton MA, Love GN. Diminution of imipramine mortality in hypothyroid mice. *Nature.* 1963;197: 1212-3.

- 366 Pange AJ Jr, Lipton MA, Love GN. Effect of altered thyroid status on desmethylimipramine mortality in mice *Nature*. 1964; 204: 1204-5.
- 367 Prange AJ Jr. The pharmacology and biochemistry of depression. *Dis Nerv Syst* 1964; 25: 217-21.
- 368 Prange AJ Jr, Wilson IC, Rabon AM, Lipton MA. Enhancement of imipramine antidepressant activity by thyroid hormone. *Am J Psychiatry*. 1969; 126: 457-69.
- 369 Prange AJ Jr, Wilson IC, Lara PP, Alltop LB, Breese GR. Effects of thyrotropin releasing hormone in depression. *Lancet*. 1972; 2: 999-1002.
- 370 Prange AJ Jr. The manifold actions of neurotensin: A first synthesis. *Ann NY Acad Sci* 1982; 400: 368-76.
- 371 Prange AJ Jr. The manifold actions of neurotensin, a trophotropic agent. In: Nemeroff C., editor. *Neurobiology of Neurotensin*. Ann N Y Acad Sci. 1992; 668: 298-336.
- 372 Pedersen CA, Prange A Jr. Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin. *Proc Natl Acad Sci USA* 1979; 76: 666 -75.
- 373 Caldwell JD, Prange AJ Jr, Pedersen CA. Oxytocin facilitates the sexual receptivity of estrogen-treated female rats. *Neuropeptides* 1986; 7: 175-89
- 374 Whybrow PC, Prange AJ, Treadway CW. Mental changes accompanying thyroid gland dysfunction. *Arch Gen Psychiatry*. 1969; 20: 48-53.
- 375 Whybrow PC, Coppen A, Prange AJ, Noguera R, Bailey JE. Thyroid function and the response to diiodothyronine in depression. *Arch Gen Psychiatry*. 1972; 26: 242-5.
- 376 Bauer MS, Whybrow PC, Winokur A. Rapid cycling bipolar affective disorder, I. Association with Grade I hypothyroidism: *Arch Gen Psychiatry*. 1990; 47: 427-32
- 377 Gyulai L, Bauer M, Bauer MS, Garcia-Espana F, Cnaan A, Whybrow PC. Thyroid hypofunction in patients with rapid cycling bipolar disorder and lithium challenge. *Biol Psychiatry* 2003; 53: 899-905.
- 378 Bauer MS, Whybrow PC. Rapid cycling bipolar affective disorder II: Adjuvant treatment of refractory rapid cycling with high dose thyroxine. *Arch Gen Psychiatry*. 1990; 47: 435-40.
- 379 Goodwin FK, Ebert M. Lithium in mania: Clinical trials and controlled studies. In: Gershon S, Shopsin B, editors. *Lithium: Its Role in Psychiatric Research and Treatment*. New York: Plenum Press; 1973. p. 237-52. Goodwin FK, Sack RL. Central dopamine function in affective illness. Evidence from precursors, enzyme inhibitors, and studies of central dopamine turnover. In Usdin E, editor. *The Neuropsychopharmacology of Monoamines and Their Regulatory Enzymes*. New York: Raven Press; 1974. p. 261-79.
- 380 Goodwin FK, Murphy DL, Bunney WE. Lithium carbonate treatment in depression and mania: a longitudinal double-blind study. *Arch Gen Psychiatry* 1969; 21: 486-96.
- 381 Goodwin FK, Sack RL. Central dopamine function in affective illness. Evidence from precursors, enzyme inhibitors, and studies of central dopamine turnover. In Usdin E, editor. *The Neuropsychopharmacology of Monoamines and Their Regulatory Enzymes*. New York: Raven Press; 1974. p. 261-79.
- 382 Lewy AJ, Markey SP. Analysis of melatonin in human plasma by gas chromatography. *Science* 1978; 201: 741-3.
- 383 Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in human. *Science* 1980; 210: 1257-9.
- 384 Lewy AJ, Emens J, Jackman A, Yuhas K. Circadian uses of melatonin in human. *Chronobiology International* 2006; 23: 403-12.
- 385 Lewy AJ, Kern HA, Rosenthal NE, Wehr TA. Bright artificial light treatment of a manic-depressive patient with a seasonal mood cycle. *Am J Psychiatry* 1982; 139: 1496-8.
- 386 Lewy AJ, Sack RL, Singer CM. Treating phase typed chronobiologic sleep and mood disorders using appropriately timed artificial bright light *Psychopharmacology Bulletin* 1985; 21: 368-72.
- 387 Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y, Mueller PS, Newsome DA, Wehr TA. Seasonal Affective Disorder: A description of the syndrome and preliminary findings with Light Therapy. *Archives of General Psychiatry* 1984; 41: 72-80
- 388 Lewy AJ, Ahmad S, Jackson JML, Sack RL. Melatonin shifts circadian rhythm according to a phase response curve. *Chronobiol* 1992; 9: 390-92.
- 389 Lewy AJ, Bauer V K., Cutler N, Sack RL. Melatonin treatment of winter depression: A pilot study. *Psychiatry Res*. 1998; 77, 57-61
- 390 Ebstein RP, Belmaker RH, Grunhaus L, Rimon R. Lithium inhibition of adrenaline sensitive adenylate cyclase in human. *Nature* 1976; 259: 41-3.
- 391 Avissar S, Schreiber G, Danon A, Belmaker RH. Lithium inhibits adrenergic and cholinergic increases in GTP binding in rat cortex. *Nature*. 1988; 331: 440-2.

-
- 392 Lerer B, Ebstein RP, Belmaker RH. Subsensitivity of human β -adrenergic adenylate cyclase after salbutamol treatment of depression. *Psychopharmacology* 1981; 75: 169-72.
- 393 Biederman J, Lerer Y, Belmaker RH. Combination of Lithium carbonate and haloperidol in schizoaffective disorder *Archives of General Psychiatry* 1979; 7: 327-33.
- 394 Klein E, Bental E, Lerer B, Belmaker RH. Carbamazepine and haloperidol versus placebo and haloperidol in excited psychoses: A controlled study. *Arch Gen Psychiatry*. 1984; 41: 165-170.
- 395 Post RM. Cocaine psychoses: a continuum model. *Am J Psychiatry*. 1975; 32: 225-31.
- 396 Goddard GV. Development of epileptic seizures through brain stimulation at low intensity. *Nature* 1967; 214: 1020-1.
- 397 Okuma T, Kishimoto A, Inoue K, Matsumoto T, Nakao T, Ogura C, Antimanic and prophylactic effects of carbamazepine (Tegretol) in manic depressive psychosis. A preliminary report. *Folia Psychiatr Neurol Jpn* 1973; 27: 283-97.
- 398 Ballanger JC, Post RM. Therapeutic effect of carbamazepine in affective illness. A preliminary report. *Commun Psychopharmacol* 1978; 2: 159-75.
- 399 Ballanger JC, Post RM. Carbamazepine in manic-depressive illness. A new treatment . *Am J Psychiatry* 1980; 137: 782-90.
- 400 Post RM, Rubinow DR, Ballanger JC. Conditioning and sensitization in the longitudinal course of affective illness. *Br J Psychiatry* 1986; 149: 191-201.
- 401 Post RM, Weiss SRB, Leverich GS, Smith M, Li-Xin Z. Sensitization and kindling-like phenomena in bipolar disorder: implications for psychopharmacology. *Clinical Neuroscience* 2001; 1: 69-78.
- 402 Pazzaglia P, Post RM, Ketter TA, et al. Preliminary controlled trial of nimodipine in ultra-rapid cycling affective dysregulation. *Psychiatr Research* 1993; 49: 257-72.
- 403 Frye MA, Ketter TA, Kimrell TA, Dunn RT, Speer AM, Osuch EA, Luckenbaugh DA, Cora-Locatelli G, Leverich GS, Post RM. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *Journal of Clinical Psychopharmacology* 2000; 20: 607-14.
- 404 .Post RM, Speer AM, Obrocea G, Leverich GS. Acute and prophylactic effects of anticonvulsants in bipolar depression. *Clin Neurosci Res*. 2002; 2: 228-51.

CONTENTS

<i>Preface, Thomas A. Ban</i>	ix
Abbreviations	xliii
Introduction & Dramatis Personae, Samuel Gershon	li

Interviewees and Interviewers

Burton Angrist	3
interviewed by David S. Janowsky	
Ross J. Baldessarini	13
interviewed by David Healy	
Robert H. Belmaker	37
interviewed by Joseph R. Calabrese	
Walter A. Brown	47
interviewed by John F. Greden	
William E. Bunney, Jr.	57
interviewed by Thomas A. Ban	
William T. Carpenter Jr.	71
interviewed by Thomas A. Ban	
Bernard J. Carroll	85
interviewed by Leo E. Hollister & Thomas A. Ban	
Guy Chouinard	103
interviewed by Andrea Tone	
John M. Davis	113
interviewed by David Healy	
Claude de Montigny	127
interviewed by Andrea Tone	
Jan A. Fawcett	131
interviewed by Frederick K. Goodwin	
Arnold J. Friedhoff	147
interviewed by Benjamin S. Bunney	
Frederick K. Goodwin	155
interviewed by Thomas Detre	
John F. Greden	165
interviewed by Thomas A. Ban	
Angelos E. Halaris	177
interviewed by Leo E. Hollister	

David S. Janowsky	187
interviewed by Leo E. Hollister	
Shitij Kapur	201
interviewed by Elizabeth Bromley	
Alfred J. Lewy	211
interviewed by John M. Davis	
Herbert Y. Meltzer	221
interviewed by Stephen H. Koslow	
Gregory F. Oxenkrug	229
interviewed by Thomas A. Ban	
Robert M. Post	241
interviewed by Thomas A. Ban	
William Z. Potter	261
interviewed by Thomas A. Ban	
Arthur J. Prange	273
interviewed by Robert H. Belmaker	
Elliott Richelson	281
interviewed by Thomas A. Ban	
Donald S. Robinson	295
interviewed by Joel Braslow	
Joseph J. Schildkraut	317
interviewed by David Healy	
Baron Shopsin	333
interviewed by Andrea Tone	
Daniel P. van Kammen	341
interviewed by Thomas A. Ban	
Herman M. van Praag	355
interviewed by David Healy	
Peter Whybrow	365
interviewed by Andrea Tone	
Index	383

ABBREVIATIONS

AA	Alcoholic Anonymous
ACNP	American College of Neurosychopharmacology
ACTH	adrenocorticotropic hormone
ADAMHA	Alcohol, Drug Abuse and Mental Health Administration
ADHD	attention deficit hyperactivity disorder
AIDS	acquired immune deficiency syndrome
ALS	amyotrophic lateral sclerosis
AMI	Allan Memorial Institute
AMP	adenosine monophosphate
AMPT	alphamethylparatyrosine
APA	American Psychiatric Association
Ativan	lorazepam
BASF	Badische Anilin and Soda Factory
BD	bipolar disorder
BuSpar	bupirone
AUB	American University of Beirut
cAMP	cyclic adenosine monophosphate
CATIE	clinical antipsychotic trial for intervention effectiveness
cGMP	cyclic guanosine monophosphate
CHDI	Clinton Hunter Development Initiative
CIA	Central Intelligence Agency
CIDCAD	Clinical Inventory for the Diagnosis and Classification of Affective Disorders
CINP	Collegium Internationale Neuro-Psychopharmacologicum
Clozaril	clozapine
CMAJ	Canadian Medical Association Journal
CME	continuing medical education
CNS	central nervous system
Cogentin	benztropine mesylate
CNS	central nervous system
COMT	catechol-O-methyl transferase
Co-PI	co-principle investigator
CPK	creatinine phosphokinase
CPZ	chlorpromazine
CRC	Clinical Research Center
CRF	corticotrophin releasing factor
CRH	corticotrophin releasing hormone
CRO	clinical research organization

CSF	cerebrospinal fluid
CSU	clinical studies unit
CV	curriculum vita
D	dopamine receptor
DA	dopamine
DARP 32	dopamine and cAMP regulated phosphoprotein 32K
DC	District of Colombia
DET	diethyltryptamine
Desyrel	trazodone
detox	detoxification
DIMD	drug-induced movement disorders
DLMO	dim light melatonin onset
DMDA	Depressive Manic Depressive Association
DMT	dimethyltryptamine
DNA	deoxyribonucleic acid
DOPA	dihydroxyphenylalanine
DSM	Diagnostic and Statistical Manual
DSM-II	Diagnostic and Statistical Manual – Second Edition
DSM-III	Diagnostic and Statistical Manual-Third Edition
DSM-IV	Diagnostic and Statistical Manual-Fourth Edition
DST	dexamethasone suppression test
DTO	deodorized tincture of opium
ECNP	European College of Neuropsychopharmacology
EEG	electroencephalography
ECDEU	Early Clinical Drug Evaluation Unit
ECT	electroconvulsive treatment
ECFMG	Educational Commission for Foreign Medical Graduates
ED50	Effective dose 50%
Effexor	venlafaxine
EMG	electromyography
ENT	ear nose and throat
EPS	extrapyramidal symptoms
ESAS	extrapyramidal symptom rating scale
Exam	examination
FDA	Food and Drug Administration
FFA	free fatty acid
FLEX	Foreign Graduates Licensing Examination
fMRI	functional magnetic resonance imaging
FRS	first rank symptoms
FSC	Flexible System Criteria
FTEs	full time equivalents

GABA	gamma-amino-butyrlic acid
GAD	glutamic acid decarboxylase
GC	gas chromatography
GCRC	General Clinical Research Center
GE	General Electric
GH	growth hormone
GI	gastrointestinal
GMP	guanosine monophosphate
GP	general practitioner
GPI	general paralysis of the insane
H ₁	Histamine ₁ receptor H ₁
Haldol	haloperidol
5-HIAA	5-hydroxyindoleacetic acid
HPA	hypothalamic pituitary axis
HPLC	high pressure liquid chromatography
5-HT	(5HT) 5-hydroxytryptamine; serotonin
HVA	homovanillic acid
Hz	Herz
ICD	International Classification of Disease
ICD-10	International Classification of Diseases-10th edition
IBM	International Business Machine Corporation
IND	Investigational New Drug
IOM	Institute of Medicine
IOM/NAS	Institute of Medicine/National Academy of Sciences
IPSS	International Pilot Study for Schizophrenia
IRB	Institutional Review Board
IRP	intramural research program
ISP	Illinois State Psychiatric Hospital
ISPI	International Society for Performance Improvement Illinois State Psychiatric Institute
IU	Indiana University
IV	intravenous
JAMA	Journal of the American Medical Association
JB	John Biel
JB 529	Ditran
JHH	Johns Hopkins Hospital
JPET	Journal of Positron Emission Tomography
KGB	Committee for State Security (translated into English)
Klonopin	clonazepam
Lab	laboratory
L-DOPA	levo-dihydroxyphenylalanine

MAO	monoamine oxidase
Marplan	isocarboxazide
Mass	Massachusetts
MATRICES	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MD	medical doctor
MGH	Massachusetts General Hospital
MHPG	3-methoxy-4-hydroxy phenylglycol
MHRI	Mental Health Research Institute
Mogedon	nitrazepam
MRA	mating-type-regulated-auxotrophy
MRC	Medical Research Council
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NARSAD	National Association for Research in Schizophrenia and Affective Disorder
Nardil	phenelzine
NAS	National Academy of Sciences
NaSS	noradrenergic and selective serotonergic antidepressants
NE	norepinephrine
NEO-PIN	Neuroticism-Extroversion-Openness Personality Inventory
NIDA	National Institute for Drug Abuse
NIH	National Institute of Health
NIMH	National Institute of Mental Health
NIMH MATRICS	National Institutes of Mental Health - Measurement & Treatment Research to Improve Cognition in Schizophrenia
NIMH TURNS	National Institutes of Mental Health - Treatment Units for Research on Neurocognition & Schizophrenia
NMDA	N-methyl-D-aspartic acid
NMR	nuclear magnetic resonance
NMSP	N-methylpiperone
NOS	not otherwise specified
NYU	New York University
PANSS	positive and negative syndrome scale
Parnate	tranylcypromine
Paxil	paroxetine
PCP	phencyclidine
PCPA	parachlorophenylalanine
PD	pure data, pharmacodynamics
PET	positron emission tomography
PhD	doctor of philosophy

PI	Principal Investigator
PMDD	premenopausal dysphoric disease
PMI	Patient Matched Instrumentation
PNA	peptide nucleic acid
PNAS	Proceedings of the National Academy of Sciences
PNA	particular nucleic acid
Post-doc	post doctoral
PPI	Protein Pump Inhibition
PRAT	Pharmacology Research Associate Program
Prolixin	fluphenazine
Prozac	fluoxetine
PSE	Present State Examination
PSH	phase shift hypothesis
Psychopharm	psychopharmacology
PTSD	post traumatic stress disorder
R & D	research and development
RDC	Research Diagnostic Criteria
REM	rapid eye movement
R&D	Research and Development
Ritalin	methylphenidate
RO-1	Research Project - First Year (Research Grant)
RSPS	Rating Scale for Psychotic Symptoms
rTMS	repeated transcranial magnetic stimulation
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RWJ	Robert Wood Johnson
SAD	seasonal affective disorder
SADS	Seasonal Affective Disorder Society
SAMe	S-adenosylmethionine
SCID	Structured Clinical Interview for DSM-IV
SFU	Special Follow-Up Clinic
SHR	spontaneous hypertensive rats
SKF	Smith, Kline & French
SNP	single nucleotide polymorphism
SNRI	serotonin-norepinephrine uptake inhibitor
SNUB	super neurotransmitter blocker
SPECT	single photon electron emission tomography
SSRI	selective serotonin reuptake inhibitor
Star D	Sequenced Treatment Alternatives to Relieve Depression
SV40	simian virus 40
TCA	tricyclic antidepressant
TD	tardive dyskinesia

Tegretol	carbamazepine
Thorazine	chlorpromazine
t.i.d.	three times a day
TMS	transmagnetic stimulation
TPQ	Three Dimensional Personality Questionnaire
TRH	thyrotropin releasing hormone
Trilafon	perphenazine
TSH	thyroid stimulating hormone
UCI	University of California Irvine
UCLA	University of California Los Angeles
UCSF	University of California San Francisco
UNC	University of North Carolina
UK	United Kingdom
US	United States
VA	Veterans Administration Hospital
VIP	very important person
VMA	vanilmandelic acid
VNS	vagus nerve stimulation
Warfarin	dicoumarin
Washington U	Washington University
WHO	World Health Organization
WKY	Wystar Kyoto Rats
Xanax	alprazolam
Zoloft	sertraline

INTRODUCTION & DRAMATIS PERSONAE

Samuel Gershon

I am pleased to be given this opportunity of talking about these 30 scientists who contributed to the body of knowledge in neuropsychopharmacology. As most of them are well known to me and many are friends, I can hopefully acquaint the reader with them from my personal point of view.

This 50 year period was a major turning point for the discipline of psychiatry. The change was dramatic in perspective, if not fully in fact. It shifted from a general view of therapeutic nihilism to a belief, held by some, that everything would be accessible to therapeutic pharmacological intervention. It would appear from the lay media, including television, that a little bit of “this” or a little bit of “that” will help you. So much so that psychopharmacological over medication and inappropriate usage have become topics for comedians.

Dramatis Personae

Now we will look at scientists who developed some of the major advances in Neuropsychopharmacology, contributed to new therapies and to understanding the underlying diseases. Approaching the pioneers alphabetically I start with Dr. Burt Angrist.

Burton Angrist, MD. Burt graduated MD from Albert Einstein College of Medicine in 1962 and completed his psychiatric residency at Hillside Hospital in New York in 1966. He then came to New York University School of Medicine (NYU) in 1966 as a research fellow in the Psychopharmacology Research Unit. Burt became a full professor at NYU in 1980.

Burt’s research work was extensive in scope but his main interests were studies in schizophrenia and the role of dopamine in its pathogenesis. He pioneered a series of studies with amphetamines and related substances and demonstrated that amphetamine could induce a model psychosis of schizophrenia. The clinical condition induced was not just an overactive state but showed the negative syndrome of schizophrenia as well. This chemically induced model could be terminated with any of the dopamine blocker antipsychotics. Dr. Angrist’s findings were groundbreaking and remain a major building block for the field.

Burt was a dedicated teacher. He also demonstrated remarkable clinical skills.

Dr. Angrist is now retired but participates in scientific meetings. He is a Life Fellow of ACNP and a Fellow of CINP.

Ross J. Baldessarini, MD, DSc. Ross obtained his MD from Johns Hopkins University in 1963 and completed his psychiatric residency there in 1969. He became Professor of Psychiatry at Harvard Medical School in 1978. Dr. Baldessarini has contributed to psychopharmacology greatly through his many publications, lectures and mentoring of investigators in the US and from around the world. He is an Emeritus Fellow of ACNP.

Robert Henry (Haim) Belmaker, MD. Bob graduated from Harvard College in 1967, received his MD from Duke University Medical School in 1971 and did his psychiatric residency there. From Duke he became a Clinical Associate to NIMH.

Bob immigrated to Israel and was Research Director of the Jerusalem Mental Health Center from 1974 to 1985. In 1986, he became Professor of Psychiatry at Ben-Gurion University in Beer Sheva. In both positions in Israel he contributed greatly to the development of biological psychiatry. He is a dedicated teacher and mentor to many young investigators who have attained independent scientific stature.

Dr. Belmaker's publications and scientific work cover a broad spectrum including clinical and basic neuroscience research. He was President of CINP from 2008 to 2010 and is a Foreign Corresponding Fellow of ACNP.

Walter A. Brown, MD. Walter Brown graduated from Duke University with an MD in 1967 and completed his psychiatric residency at Yale in 1972. He became Clinical Professor of Psychiatry in 1994 and retains that position.

Dr. Brown set up a group to conduct clinical trials which developed into Clinical Research Centers International. The organization was formally established in 2000 with Dr. Brown as its president.

Dr. Brown has published extensively on findings in clinical trials with a variety of psychotropic agents and is a Member of ACNP

William E. Bunney Jr., MD. Dr. Bunney has had a celebrated career as a scientist and administrator. He obtained his MD in 1956 from the University of Pennsylvania Medical School and completed his residency in psychiatry at Yale in 1960.

From 1960 to 1982 Dr. Bunney played a major role in a number of research programs at NIMH in both senior administrative and research positions, involving affective disorders and many new research areas. He accepted the position of Chairman of Psychiatry at the University of California at Irvine in 1982. He has remained active in research and is currently Co-Chairman of the Department.

Dr. Bunney was President of ACNP in 1983 and of CINP from 1986 to 1988.

William T Carpenter Jr., MD. Dr. Carpenter has been a major figure in Schizophrenia research for most of his career.

He was a research psychiatrist at NIMH from 1966 to 1975. In 1977 he became Director of the Maryland Psychiatric Research Center and Professor of Psychiatry at the University of Maryland. He continues in these positions and is still actively engaged as a productive scientist and administrator.

Dr. Carpenter was President of ACNP in 2007.

Bernard J. Carroll, MD, PhD. Dr. Carroll went to medical school in Melbourne, Australia. He graduated with a BSc degree in pharmacology 1961 and received his MD in 1964. He also completed his psychiatric training in Melbourne in 1969 with a DPM (Diploma in Psychological Medicine) and a PhD in Psychobiology in 1971. During his training he acquired a solid background in the basic neurosciences.

In 1971 Dr. Carroll joined the Department of Psychiatry, University of Pennsylvania, as a research fellow and stayed in the department for another year as Assistant Professor. He moved to the Department of Psychiatry, University of Michigan, in 1973 as an Associate Professor and became full Professor in 1976. In 1983 he was appointed Chairman of the Department of Psychiatry at Duke University in Durham, North Carolina.

Dr. Carroll has been active in research, primarily in affective disorders. He used psychoendocrinology to identify different types of depression, research that produced a major impact on understanding the nosology and etiology of these disorders.

Dr. Carroll is an Emeritus Fellow of ACNP.

Guy Chouinard, MD. Dr. Chouinard received his MD from the University of Montreal in 1968. He had intensive training in psychiatry and pharmacology. He was appointed Professor of Psychiatry at the University of Montreal in 1987 and McGill University in 1990.

Dr. Chouinard has been a prolific research investigator in neuropsychopharmacology. In schizophrenia he contributed to the understanding of its pathophysiology. He studied the mode of action and side effects of neuroleptic drugs. Chouinard's contributions have been diverse and extensive. His work has had a major impact on treatment practices.

Dr. Chouinard is a Member of ACNP and a Fellow of CINP.

John M. Davis, M.D. John was born in Kansas City, Missouri in 1933 and did his undergraduate work at Princeton in creative writing. He went to medical school at Yale, graduating in 1960 and completed psychiatric residency at the Massachusetts General Hospital in 1964 when the dominant theoretical structure for psychiatric training was psychoanalytic. From there he went to NIMH to work with William Bunney on the biochemistry of depression.

John Davis and Joseph Schildkraut (see, Schildkraut in this Volume,) published the key papers on the role of biogenic amines in depression separately

and independently, but at about the same time. John began treating the first patients with lithium after a lecture at NIMH by Sam Gershon.

In 1969 Davis and Don Klein (see, D. Klein, Volumes 3 and 9,) published a comprehensive textbook on psychopharmacology which became a standard reference at the time.

After he left NIMH John went to work at Vanderbilt and together with David Janowsky (see, Janowsky, in this Volume,) published interesting clinical experiments using physostigmine to study the role of acetylcholine in depression.

From Vanderbilt John Davis went to the Illinois State Psychiatric Institute as the Director of Research.

Dr. Davis has been very active and productive scientifically and has published numerous scientific papers and books.

He is a Fellow of ACNP and CINP.

Claude de Montigny, MD, PhD. Dr. de Montigny received his MD in 1968 from the University of Montreal and his PhD in 1974. From 1976 to 1977 he spent a fellowship with Dr. Aghajanian at Yale (see, Aghajanian, Volume 2) and started some of his most important neurophysiologic studies.

De Montigny became Professor of Psychiatry in 1985 at the University of Montreal and in 1987 at McGill. His scientific work continued in many areas of neurophysiology and he contributed immensely to understanding of the role of serotonin in the action of antidepressants.

Dr. de Montigny is Emeritus Member of ACNP and President of CINP from 1996 to 1998.

Jan A. Fawcett, MD. Dr. Fawcett graduated from Yale in 1960 as an MD. He had his psychiatric residency training at Langlely Porter Institute at the University of San Francisco and then at the University of Rochester. In 1964 and 1965 he was a Clinical Associate at NIMH and went on to the Illinois State Psychiatric Institute (ISPI) to work with James Maas.

At ISPI he established a major research program on depression and the role of catecholamines. He has been especially interested in suicide and suicidality in various disorders.

In 1972 Fawcett became Professor and Chairman of Psychiatry at Rush Medical College where he continued his research and has become a strong advocate of education and research in depression,

Dr. Fawcett is a Fellow of ACNP.

Arnold J. Friedhoff, MD. Arnold was a close and dear friend of mine. I joined him at the NYU and we spent 17 years together in the Department of Psychiatry.

He graduated MD from the University of Pennsylvania in 1947 and became Professor of Psychiatry and Director of the Millhauser Laboratories at NYU in 1969.

From my personal experience he combined a clear, committed and close interest in clinical research together with studies in basic neuroscience. This permitted him to ask and answer highly clinically relevant questions.

Dr. Friedhoff was one of the first people to propose and use L-DOPA as a treatment for Parkinsonism although the dose he used was too small to show a consistent therapeutic effect. Others continued and demonstrated a clear effect at a higher dosage. He was also involved in research with the “pink spot,” he identified in the urine of schizophrenics, assumed to be caused by a toxic substance, but which turned out to be an artefact.

Arnold died in 2001 and the field of psychopharmacology lost not only an important pioneer, but a major colleague, friend and mentor.

Frederick K Goodwin, MD. Fred, a laboratory and clinical researcher, is a truly central figure in psychiatry and psychopharmacology. He joined the NIMH in 1965 and has become an internationally recognized authority on the research and treatment of major depression and manic depressive illness. He and Kay Jamison authored the classic textbook on *Manic Depressive Disorder* in 1990.

He made substantial contributions as a senior administrator from 1981 to 1988 as Scientific Director and Chief of the Intramural Research Program of NIMH and as Director of ADAMHA from 1988 to 1994.

Dr. Goodwin is a recipient of several major research awards including the Hofheimer Prize from APA and the Anna Monika Prize for research in depression. He has authored over 400 publications.

He is currently Professor of Psychiatry and Director of the Center on Neuroscience, Behaviour and Society at the George Washington University Medical Center in Washington, DC.

Dr. Goodwin is a Fellow of ACNP and CINP

John F. Greden, MD. Dr Greden received his medical degree from the University of Minnesota Medical School, completed an internship at UCLA Harbor General Hospital in Los Angeles, and was a resident in psychiatry at the University of Minnesota hospitals and Walter Reed Army medical Center. Prior to joining the Michigan faculty he served as Director of Psychiatry Research at Walter Reed. He joined the faculty of the medical school of the University of Michigan in 1974 and served as Chair of the Department of Psychiatry from 1985 to 2007.

Dr. Greden’s clinical and research activities have emphasised the study of the longitudinal course of depression, linkages between stress hormones and depressive recurrences, and clinical strategies for preventing such recurrences. He was the senior editor of scientific publications for the American College of Neuropsychopharmacology (ACNP) from 1998 to 2001.

Angelos E. Halaris, MD, PhD. Dr. Halaris had his early education in Athens, Greece and then went to medical school at the University of Munich and graduated MD, PhD. in 1967. He did his residency in psychiatry at the University of Chicago from 1974 to 1977.

In 1984 Halaris became Professor of Psychiatry and Pharmacology and Vice Chairman at Case Western Reserve University. He devoted a major part of his work to studies in depression and bipolar disorders. His work was truly translational in scope.

Dr. Halaris is a Fellow of ACNP and CINP.

David S. Janowsky, MD. Dr. Janowsky obtained his MD from the University of California at San Francisco in 1964 and did his psychiatric residency at University of California at Los Angeles from 1956 to 1966. Subsequently he was clinical associate at NIMH, worked with John Davis in the Clinical Division of the Tennessee Neuropsychiatric Institute, and in the Department of Psychiatry of the University of California in San Diego. Dr. Janowsky became Chairman and Professor of Psychiatry at the University of North Carolina at Chapel Hill in 1986. He stepped down from the chair in 1994 but stayed at Chapel Hill to conduct research in the Alcoholism Center.

Janowsky published extensively in psychopharmacology including some extremely interesting studies exploring the role of cholinergic systems in bipolar disorder (BD) and the effect of drugs on that system.

Shitij Kapur, MD, PhD. Dr. Kapur obtained his medical degree from the All India Institute of Medical Sciences in New Delhi and then came to Pittsburgh (USA) and Toronto (Canada) to complete his psychiatric residency. He obtained his PhD. at the University of Toronto in 1996.

Dr. Kapur carried out research on receptor function employing many different techniques including PET in schizophrenia and Alzheimer's' Disease. He also studied the mode of action of antipsychotic agents for many years and has made immense contributions in many areas of neuropsychopharmacology

Kapur is a member of ACNP and a Fellow of CINP.

Alfred J. Lewy, MD, PhD. Dr. Lewy obtained his MD, PhD from the University of Chicago in 1973 and was at NIMH from 1975 to 1981. He then went to work at the University of Oregon in Portland in Pharmacology and Ophthalmology.

Dr. Lewy's research over many years involved control systems in circadian cycles and especially the role of melatonin and the connections between circadian rhythms, mental illness and sleep disorders.

Lewy is a Fellow of ACNP.

Herbert Y. Meltzer, M.D. Herb Meltzer has been an outstanding figure in psychopharmacology and an established scientist in the field. He obtained his MD at Yale in 1963 and was Professor of Psychiatry at the University of Chicago from 1974 to 1985. In 1985 he moved to Case Western Reserve,

Medical School in Psychiatry and Pharmacology. In 1996, he moved on to Vanderbilt University as Professor of Psychiatry.

Dr. Meltzer's research into all aspects of schizophrenia and the mode of action of antipsychotics has established him as a major contributor in his field of expertise.

Meltzer was President of ACNP in 1985 and of CINP from 2002 to 2004.

Gregory F. Oxenkrug, M.D., Ph.D. Dr. Oxenkrug obtained his early training in Russia and I had the opportunity to visit him in his laboratory in Leningrad before his arrival in the US. His co-worker at the Bekhterev Institute in Leningrad was Dr. Lapin. Their work in Leningrad was an early forerunner in proposing the major role of serotonin in the action of antidepressant drugs.

In 1980 Oxenkrug came to the US. as an Associate Professor of Psychiatry at Boston University. In 1982 he joined me as an Associate Professor of Psychiatry at Wayne State University and worked at the Lafayette Research Clinic in Detroit.

Dr. Oxenkrug's scientific work has included studies on the psychopharmacology of the pineal gland. He studied the role of its hormone, melatonin, in psychiatric conditions.

He is now a Professor of Psychiatry at Tufts University and very active in his scientific pursuits.

Dr. Oxenkrug is an Emeritus fellow of ACNP.

Robert M. Post, MD. Dr. Post is an internationally recognized expert on bipolar disorder and has published and lectured extensively on related topics around the world.

Bob Post obtained his MD in 1968 from the University of Pennsylvania and completed his psychiatric residency at Massachusetts General Hospital in Boston in 1970. He then went to NIMH and in 1981 was appointed Chief, Biological Research Branch; he has recently retired from that position but continues to write and lecture widely and is contributing to discussions on bipolar disorder in DSM-V.

Post is a Fellow of ACNP and CINP.

William Z. Potter, MD, PhD. Dr. Potter received his MD in 1970 and PhD in 1972, both from Indiana University. He is trained in both psychiatry and pharmacology.

From 1971 to 1974 he was a Research Associate in Pharmacology and Toxicology at NIH. After completing residency training in psychiatry in 1976 at NIMH, he continued on the staff of the Intramural Program till 1988.

Potter's initial work at NIH was in drug metabolism in the course of which he became keenly interested in psychiatric drugs. Together with Dr. Goodwin, he carried out a number of projects on the biology of affective illness.

Dr. Potter has published approximately 300 scientific papers. After leaving NIMH he joined industry and worked first at Eli Lilly and currently at Merck.

Potter is Fellow of ACNP and CINP.

Arthur J. Prange Jr, MD. Dr. Prange stood out among his colleagues for a number of reasons. First, he was taller than most and had a distinctly loud and rumbling voice. More importantly he used this voice to bring focus and reason into discussions sometimes overloaded with more heat than focus.

Prange obtained his MD from the University of Michigan in 1950 and completed his psychiatric residency in 1957 at the University of North Carolina at Chapel Hill. He became the Boshamer Professor of Psychiatry at Chapel Hill in 1983.

Dr. Prange's area of research interest was Psychoendocrinology. He was especially interested in the role of the thyroid in affective disorders. His contributions to this theme have influenced current interest in using thyroid preparations to augment treatment effects in depression.

Prange is a Fellow of ACNP and was President in 1987.

Elliot Richelson, MD. Dr. Richelson received his MD from the Johns Hopkins University School of Medicine in 1969 and continued with his residency and research training there till 1975.

In 1975 Richelson joined the Mayo Clinic as an assistant professor; he became Director for Research at the Mayo Clinic in Jacksonville, Florida. He has been involved in basic and clinical research in psychopharmacology.

In 1977 Dr. Richelson received the A.E. Bennett Basic Science Research Award of the Society of Biological Psychiatry and in 1985 the Daniel Efron Award of the ACNP.

Richelson is Fellow of ACNP and CINP.

Donald S. Robinson, MD. Don Robinson graduated MD from the University of Pennsylvania in 1959 and obtained an MS in Pharmacology from the University of Vermont in 1966. He trained in Internal Medicine in Burlington, Vermont from 1960 to 1965.

Dr. Robinson became Professor and Chairman, Departments of Pharmacology and Professor of Psychiatry and Medicine in 1977 at the University of Vermont. His primary area of research interest was in the relationship between MAO inhibition and antidepressant effects. In 1984 Robinson left academic psychiatry and joined Bristol-Myers Squibb in Connecticut as Vice-President for Clinical Research where he was involved in a number of drug studies with agents such as a gepirone, buspirone and trazodone.

Robinson is Emeritus Fellow of ACNP.

Joseph J. Schildkraut, MD. Joe had a special reputation in psychopharmacology. He was a protagonist and crusader for the role of catecholamines in the pathogenesis of depression. Dr. Schildkraut obtained his MD from Harvard

Medical School in 1959 and completed his residency in Psychiatry at the Massachusetts Mental Health Center. After residency he spent five years, from 1963 to 1968' at NIMH. From NIMH, he returned to Harvard Medical School in Boston and became a full Professor in 1974.

Dr. Schildkraut was a co-awardee of the Anna Monika Foundation Prize in 1967 for his work on norepinephrine metabolism in depression.

Joe retired from Harvard due to ill health, developed a major interest in paintings and became an art expert. He died in 2006.

He was Fellow of ACNP and CINP.

Baron Shopsin, MD. Dr. Shopsin was born in New York and had his early education there, graduating as a Far Eastern history major from Brooklyn College. He went to medical school in Belgium and after returning to the United States did a residency in psychiatry at Cornell and New York University School of Medicine.

Shopsin was involved in early research with lithium in the United States. His studies with monoamine oxidase inhibitors contributed to the identification of the possible cause of antidepressant action. After his stint in research Dr. Shopsin served as consultant to the pharmaceutical industry and was involved in developing psychotropic drugs.

Daniel P. van Kammen, M., PhD. Dr. van Kammen was born in the Netherlands and had his early education there. He obtained his MD and PhD in Pharmacology at the University of Utrecht.

He came to the US. and did his psychiatric residency at Johns Hopkins Hospital in Baltimore from 1970 to 1973 and then worked at NIMH for five years. In 1982 he moved to the VA Hospital, affiliated with the University of Pittsburgh.

Dr. van Kammen left Pittsburgh in 1998 to join RWJ Pharmaceutical Research Institute in New Jersey. Currently he is Chief Medical Officer of CHDI Foundation, Inc, a private non profit organization working on Huntington's disease.

During his professional career Dr. van Kammen was involved in research on schizophrenia, bipolar disorder and post-traumatic stress disorder.

He published extensively and was a widely sought after lecturer.

Van Kammen is a Fellow of ACNP and CINP.

Herman M. van Praag, M., PhD. Dr. Van Praag obtained his MD in 1956 from the State University, Leiden, the Netherlands and his PhD. degree in Neurobiology from the University of Utrecht.

He became Professor of Psychiatry at the University of Groningen in 1970 and Professor and Chairman, Department of Psychiatry at Albert Einstein College of Medicine in New York in 1982. In 1992 he returned to Maastricht

University in The Netherlands as Professor and Chairman of the Department of Psychiatry. He retired from that position in 1997.

Dr. Van Praag published extensively on the biological aspects of schizophrenia and affective disorder, as well as the mode of action of psychiatric drugs. He is the recipient of many honorific awards, including the CINP Pioneer Award.

Van Praag is Emeritus Fellow of ACNP.

Peter Charles Whybrow, MD. Dr. Whybrow had his original education in England and received his MD in London from the University College Hospital Medical School in 1962.

He came to the US. in 1965 as a Resident in Psychiatry at the University of North Carolina. In 1969 he took the position of Assistant Professor of Psychiatry at the Dartmouth Medical School in New Hampshire and in 1971 became Professor and Chairman there. In 1984 he was appointed Chairman of the Department of Psychiatry at the University of Pennsylvania School of Medicine in Philadelphia. He is currently the Chair of Psychiatry at University of California at Los Angeles School of Medicine.

Dr. Whybrow has been active in teaching and research where he has been a leading figure in exploring the role of thyroid function in depression and its treatment.

Whybrow is Member of ACNP and a Fellow of CINP.

INTERVIEWEES & INTERVIEWERS

BURTON ANGRIST

Interviewed by David S. Janowsky
Waikoloa Village, Hawaii, December 9, 1997

DJ: I am David Janowsky, Professor of Psychiatry at the University of North Carolina in Chapel Hill for the ACNP History Task Force. I'm going to be interviewing Dr. Burton Angrist,* who is Professor of Psychiatry at NYU (New York University) and, also, a researcher at the Manhattan VA (Veterans Administration Hospital).

BA: Thank you.

DJ: So, here we are. Does this officially make us antiques?

BA: Does it make us antiques is a major question to be asked. I think so.

DJ: Why don't you let me know about the kind of training that you've had over the years?

BA: When I was doing psychiatric residency I hadn't the foggiest notion of going into research. I thought I was going to be a clinician. You've got to remember, in those days, psychoanalysis was very influential.

DJ: When was that?

BA: About 1963 to 1966.

BA: I was what Don Klein would call a deep thinker. I was a gung ho, psycho-dynamic fellow and I did all sorts of enthusiastic psychotherapy but my patients didn't get better. They were headed for the state hospital. Don Klein was at Hillside where I was a resident; he was the psychopharmacology expert so I asked him, "Please review my caseload. I'm stuck". I was using drugs but not with any sophistication. As he went over my caseload we spoke about each patient and he'd say, "Change the drug on this guy and change the dose on that guy and give ECT to that one." I did as he said, and they all got better and I realized I'd better learn more about this stuff. So I did a postdoctoral fellowship with Sam Gershon at Bellevue.

DJ: Where did you do medical school, at Einstein?

BA: Yes.

DJ: And, where did you go to college?

BA: Colby, up in Maine.

DJ: Did you always know you were going to be a psychiatrist?

BA: When I was eighteen, I thought I might be, and, on the basis of that, my Pop got me a job as a nurse's aid in the State hospital and I did that for a couple of summers; so I had been heading in that direction for quite awhile. In college, I got enamoured with English literature and my Pop

* Burton Angrist was born in New York City, New York in 1936.

gave me advice that, rebellious as I was, I couldn't argue with, because it made so much sense. He said, "Take all the literature courses you want. Just don't shut any doors and take a pre-med course, once a year". And, I did that.

DJ: So, you were in your residency when you got this bug about psychopharmacology?

BA: Yes, but it still it wasn't research. I thought it was just a powerful clinical tool.

DJ: Was that a time when most of your teachers and fellow residents wouldn't give drugs or gave them under the table?

BA: They gave them, but not with sophistication and expertise. I didn't know what akathisia was until the middle of my second year of residency, I was really quite naive.

DJ: When you joined Sam Gershon, what kind of Fellowship was that?

BA: It was an NIMH (National Institute of Mental Health) post-doctoral position NYU had. We had to do a couple of group classes, but I wish it had been more structured, because a lot of basic research stuff, like statistics, I've learned by the seat of my pants and it shows. I'm not so good at it. I would have liked a bit more background, but with Sam it was learning by doing.

DJ: Was there a group of you in this Fellowship or were you the only one?

BA: There were two or three of us.

DJ: What was your project?

BA: Sam sat me down and said, "You need something that will turn you on, so what would you like to do"? I wasn't sure but I said, "I'm interested in phenomenology. We call someone who is hyper-aroused, referential and fearful, "paranoid", yet we use the same word to describe a person who is completely delusional but indifferent and says, "The Mafia has been after me for fifteen years". They must be different. Sam replied, "That's very commendable. Why don't you start looking at similarities and differences between amphetamine psychosis and schizophrenia"? I was interested in thought disorder and phenomenology in general, so I did not start doing that project from an impartial scientist's viewpoint. I thought no drug-induced psychosis could mimic the richness of schizophrenia. But, over time, the data convinced me otherwise.

DJ: What was involved with this project?

BA: The first step was to collect cases of amphetamine psychosis and evaluate them. People came to Bellevue crazy after taking amphetamine, and it became apparent that schizophrenics take amphetamine too. So how would one know what was the symptomatology of a pure amphetamine psychosis if the patient also looks like a residual schizophrenic? After he

gets better, how much was drug and how much was vulnerability? I still feel that to learn what a pure drug psychosis is you have to find a person without co-morbid psychiatric disorder. Today, we understand that. Clinically, you've seen a huge range of cocaine-induced symptomatology, and yet, if you speak to the patients on a detox ward for uncomplicated substance abuse, the psychoses they describe are very different. So, that was one issue. We'd document all the symptoms and we'd have other psychiatrists look at them when they were back to baseline and make an independent diagnosis; is this schizophrenia or not?

DJ: So it was a phenomenologic study?

BA: Yes. But then the pharmacology came in. John Griffith did the first prospective studies on amphetamine psychosis. He took speed-freaks and he kept them in the hospital until they got to their base line. Then, he gave them amphetamine until they became psychotic. At a meeting he reported findings different from those we saw in patients at Bellevue. He said it was paranoid psychosis, with no thought disorder or hallucinations. We had certainly seen both, so I argued at the meeting, and said, "John, we've seen they do have those symptoms at Bellevue". He argued back, "How do you know what other drugs they took and how do you know their baseline psychiatric state". So I asked, "Sam, can we do what Griffith's done? He's worked out safety methods, taking the blood pressure, pulse and temperature every hour and things like that? Sam said, "I think we can". So, we wrote a protocol and got permission.

DJ: You were still a Fellow at that time?

BA: It was supposed to be two years, but Sam suggested I cut it short because I could get a better salary by joining the Neuropsychopharmacology Center, so I did.

DJ: In terms of Sam, how do you see his role in your development?

BA: He's enormously influential. I was not the most mature fellow in those days. I'd get upset, why did the bureaucrats make me want to jump through this and that hoop, so he would settle me down and put up with my youthful impetuosity. He was enormously helpful and a wonderful influence on me.

DJ: Was he an idea man?

BA: Yes.

DJ: Did you feel that?

BA: Yes, he was bold and had clarity of thought. Once I was obsessing about the issue, if a person takes a drug and remains crazy, is that the drug or the person? When I said, "Sam, I'm going around and around with this", he replied, "Of course, you are, Doctor; you're trying to decide between

the chicken and the egg”. So, he had a remarkable lucidity of thought that was very helpful.

DJ: What year was it you became a faculty member?

BA: Probably around 1967 or 1968.

DJ: Didn't you stay at Bellevue?

BA: I stayed at Bellevue and kept doing the same work until we got permission to do the kind of study John Griffith reported. By then, I knew a large number of the speedfreaks in New York from their Bellevue hospitalizations and since we had good relationships they were more than willing to volunteer for the studies. We did them and we documented hallucinations and thought disorders. So the responses to amphetamine were pretty damn schizophreniform and that impressed me.

DJ: That was in the 1960's. Did you write it up or present it in places?

BA: Sam suggested I present it at the annual meeting of the Society of Biological Psychiatry. I think it was in 1969 in Miami. It was my first meeting, and my first presentation. Subsequently I went to other meetings and at some I presented papers. I thought the senior people in the field would be wise old men who would say, who's this kid, but they were enormously supportive, positive and enthusiastic, commenting, "You're doing nice work, kid. Keep it up". That gave me such a boost, it made an enormous impact and a big difference to me. The ACNP has done the same thing; it charges your batteries every year.

DJ: Did you get any heat from anybody about giving amphetamine to amphetamine addicts?

BA: No. At that point, there was still some argument about addiction to stimulants. It was prior to the cocaine epidemic which showed that clearly. Since amphetamine did not produce a physiological withdrawal syndrome, people thought it could not be addictive. It was not the kind of thing the IRB (Institutional Review Board) was concerned about. As far as the psychosis induced by the drug was concerned, the addicts in our trial had done it to themselves, dozens of times.

DJ: After you established you could induce psychosis in amphetamine addicts and characterized it, what did you do next?

BA: The next question was how did amphetamine induce the psychosis? By then, Randrup in Denmark had done elegant pre-clinical studies, in which he showed you could mimic all the behavioural effects of amphetamine, with micro-injections of dopamine into the basal ganglia, and the effects of both amphetamine and dopamine could be completely blocked by classical neuroleptics. He had already constructed a very clear story of amphetamine action that keyed us into the possible role of dopamine, so we did studies to test this. We did one study where we gave amphetamine

and did spinal taps in an addict willing to have one before and another after high dose amphetamine where we showed that HVA (homovanillic acid) went up. We did another study in which we induced psychosis and found that a single injection of Haldol (haloperidol) wiped it out, so one couldn't tell the person had a drug-induced psychosis. It was almost eerie. That was very impressive proof of the role of dopamine in amphetamine-induced psychosis. Then, we did other studies to see if this was the case with other dopamine agonists and not just amphetamine. We got a chance to look at Parkinsonian patients who were given dopamine agonists. Bromocriptine was just released for clinical use, so we studied that, and also DOPA in schizophrenic and in non-schizophrenic patients. We also looked at peribedil and other dopamine agonists as well.

DJ: What happened?

BA: In some cases, we saw psychoses that looked like amphetamine psychosis.

DJ: Were you giving massive or normal clinical doses?

BA: You see, with bromocriptine and peribedil, the neurologists were giving those to treatment refractory Parkinsonian patients, and were using relatively big doses. For our purpose of documenting psychosis that was great.

DJ: At what point in time was that?

BA: From mid 1970's to late 1970's, I guess. The other thing that we did, because Janowsky had given methylphenidate to schizophrenic patients and was publishing very striking responses, we also looked at it. Methylphenidate did the same as the amphetamines. But, when Crow proposed, in the 1980s, the Type 1 and Type 2 distinction in schizophrenia, we looked at the effects of neuroleptics on positive and negative symptoms in amphetamine-induced psychosis. Dopaminergic psychosis is predominantly a florid positive symptom psychosis, and what we found was that the positive symptoms increased massively with amphetamine and improved with neuroleptics but the negative symptoms did not increase.

DJ: Not even if they had symptoms like anergia, lack of talking and that sort of thing?

BA: If there was any change it was slightly in the direction of improvement.

DJ: But, not much?

BA: It was not significant. We did see significant improvement in negative symptoms induced by amphetamine in non-psychotic outpatients. In the absence of psychosis negative symptoms improved when patients were given amphetamine. In that situation, we saw some benefit, particularly in affect. If you ask, "what's your contribution?" I'd say I extended Griffith's

work on amphetamine psychosis by showing that other dopamine agonists also induce psychosis and exacerbate positive symptoms of schizophrenia as well; that in dopamine induced psychosis there is an increase of HVA in the CSF (cerebrospinal fluid) and positive symptoms dominate the clinical picture while the psychosis induced by dopamine agonists is promptly blocked by dopamine antagonists like Haldol. I think there is substantial evidence supportive of the role of dopamine in producing positive symptoms.

DJ: These are very important findings. That brings us up to the mid 1970's, maybe early 1980's. How has your career gone from that point on?

BA: We followed up on your observation that some schizophrenics did not relapse when they were given methylphenidate.

DJ: What other things have been interesting to you?

BA: I've never truly decided whether I'm interested in CNS stimulants or schizophrenia. I've bounced back and forth between them and became interested in stimulants, maybe because there's so much cocaine use. Back in the 1970s we never saw clinically meaningful sensitization with cocaine. Now, we see it very often and clearly. I did a study on cocaine sensitization, a follow up to the reports of Sally Satel and Linda Brady from your part of the world. Anyway, they both reported that some cocaine patients would say things like, "I used to have a wonderful time smoking fifty dollars worth but now, if I take one puff, I have to hide in the closet." So, they go crazy at much lower doses. When we replicated their study we got more or less the same results. We also found that psychosis related symptoms were the ones sensitized. Then, Terry Robinson proposed that addiction might be sensitization of mesolimbic neurons because addiction had something to do with appetitive behaviour. So we thought mesolimbic sensitization to psychosis could be a marker for separating those who would relapse. We tested it in a study but the results were not convincing.

DJ: You've done some imaging work, as well, haven't you?

BA: Yes, with Adam Wolkin. We looked at schizophrenics with PET (positron emission tomography) at baseline state, hyperdopaminergic state induced by amphetamine, and neuroleptic treated state.

DJ: What did PET show?

BA: There was not a great deal of difference. Stimulants, like Edythe London had shown with cocaine, decreased glucose metabolism. There was not much correlation between changes in metabolism and symptoms.

DJ: Where do you see the place of imaging in the study of schizophrenia?

BA: There is a wonderful imaging study done by Steve Dewey with radioactive labelled neuroleptics. He found less binding in the basal ganglia after treatment with Cogentin (benztropine mesylate).

- DJ: With Cogentin?
- BA: Cogentin. Then, he thought amphetamine might do the same and gave amphetamine to baboons and he found that amphetamine treated animals also had lower binding of labelled NMSP (N-Methylspiperone).
- DJ: That brings us up to now.
- BA: Yes. The cocaine sensitization paper is pretty much the last thing I've done.
- DJ: Looking at your career it seems you were using amphetamine as a tool to understand schizophrenia.
- BA: Yes, I would say that. The high tech stuff is built on a foundation of the fundamentals of pharmacology done twenty or thirty years ago.
- DJ: You played a major part in establishing that foundation. There was parallel animal pharmacology going on.
- BA: Probably the animal pharmacology is the most basic and might have advanced the field without clinical contributions. But there's something about seeing clinical effects that convinces people the work in animals must be important.
- DJ: I want to shift gears to more of a global issue. How has your career been? What do you think about having been an academic in one city all of your life? I'm just curious philosophically, was it fun, worth it, a good deal?
- BA: It was fun; it was great and continues to be. It's been a big satisfaction in my life. If I was told, Angrist, you have a rapidly progressive fatal disease, I wouldn't be happy, but I could say, goddamn it, at least I made some contribution, and not everybody has that. It gives you a nice feeling.
- DJ: How did your work interact with your personal life?
- BA: The amount of work has kept me from having some fun. I've had to skip a lot of outdoor trips with my friends.
- DJ: But, you get to see a lot of nice places like Hawaii, where we are now.
- BA: I've made sure to balance things out. On the one hand, it's nice to feel you've accomplished something. I've not sacrificed everything else so I've had fun along the way. It's tremendous to meet your fellow researchers, too. I really enjoy it.
- DJ: I frequently hear from younger people these days that it feels a grind, like survival of the fittest. So I'm curious how you see your career in that way. Has it been easy or have you felt you've had to struggle to get where you're going?
- BA: There are several things. Both of us have been lucky to have been in medicine at a time when efficiency wasn't the be all and end all, when every moment in the hospital wasn't watched by a bureaucrat with a stop watch. I'm grateful for that; it made it a lot easier to do the work. I've had it better than the kids do today, no doubt about that. Another issue is

the struggle for grants. I've always had a philosophy that did not make me popular with chairmen of departments; I would rather spend my time doing a project by the sweat of my brow, keeping my own records rather than writing a grant. Most of my work has not been high tech. When you use PET scans, you need a grant, but if you are just giving a drug to document the clinical effect, you can do that yourself. So the kind of research I did kept me out of some of the competition for funding.

DJ: Are you a clinician?

BA: Yes.

DJ: What do you do, clinically?

BA: I work full time on inpatient wards. Currently, I'm working two-thirds of the time on resident training. I love teaching residents. That's fun.

DJ: What do you think is going to happen in the next two decades?

BA: After plenary sessions where they show gene therapy re-growing coronary arteries and things like that, I have to say there'll be changes I can't begin to imagine. That's the safest thing to say. What is as powerful as molecular biology? Gee, I don't know where it'll go. In psychiatry and psychopharmacology there certainly are places we need to make progress. The response has been one of tremendous enthusiasm. We've made some non-responders better and that is a tremendous accomplishment, but we can't forget that only one-third of those non-responders improved. If you're a non-responder with schizophrenia on classical neuroleptics, the odds are still sixty-five percent you will not respond to anything. So, there's plenty of room for more effective therapy for these poor guys.

DJ: What would have happened if clozapine had been invented before Haldol and Prolixin (fluphenazine) and had been the drug that was always given when somebody invented Haldol? You might see the miracle drug, Haldol, with a thirty percent response rate in people who didn't get better on Clozaril (clozapine.) Who's to know?

BA: We have to focus on refractory patients, that's for sure. There are many conditions we don't have a treatment for. We don't have any medicine we can give to cocaine addicts. I work in a VA hospital, and I see a lot of patients with PTSD (post traumatic stress disorder.) We don't have any incisive treatment for that; we treat it symptomatically. If they're crazy, we give them antipsychotics and if they're depressed we give them antidepressants, but we don't have anything that's really impacting that disorder. There are plenty of conditions where there is need to develop a treatment and with enough smart people working on these problems, things will get better.

DJ: I'm glad you mentioned cocaine addiction. There is no biologic treatment for cocaine addiction; there's this theory about dopamine, the work you did, and all these antagonists and agonists. What do you think?

BA: Nothing has been demonstrated effective so far.

DJ: It was great to interview you. I really enjoyed it.

BA: Thank you.

ROSS J. BALDESSARINI

Interviewed by David Healy
Las Croabas, Puerto Rico, December 15, 1998

DH: This is the 15th of December 1998. We're in Puerto Rico at the ACNP meeting and I'm going to interview Ross Baldessarini.* I'm David Healy. Ross, to begin, where and when were you born?

RB: I was born in 1937 in North Adams, a small town in western Massachusetts.

DH: During school, did you have any hunch that you'd ultimately go into medicine and onto psychiatry?

RB: By the time I was in high school, I wanted to do something scientific, but exactly what, was not clear. I was more interested in chemistry in those days and that interest intensified in college, where I majored in organic chemistry.

DH: How did you get from organic chemistry to medicine?

RB: In high school, I had a series of summer jobs in industrial laboratories. For example, one of these jobs was in developing tiny ferromagnetic doughnuts or toroids wired into matrices for use as electronic memory components for, of all things, jukeboxes. The same technology used in early computers in the early 1950s. Next, I began working in industrial chemistry labs at the end of high school and while I attended Williams College. For a while I hoped to become an industrial organic chemist. However, in one summer, memorably, I experienced an industrial merger and saw half of the scientists I worked with put out on the street without any warning. That experience left an indelible mark, and led me to think there must be a more secure way to make a living. Academic medicine has been anything but secure, but that was my thinking at the time.

DH: At that time, academic medicine was more secure, though, things have changed recently.

RB: Certainly, through the 1960s and early 1970s, the grant system was somewhat more predictable than recently. Then, if you worked hard and got into a decent department, you could usually keep working and building a career. Now, it's not so sure.

DH: After you went into medicine, why did you move toward psychiatry?

RB: I started at Johns Hopkins, not really knowing what medical school is all about. I had very little family experience with graduate school, so medical school was a surprise; I thought it was going to be an extension of senior year of college, which was mostly about having tea in professors' homes and thinking great thoughts. However, I found out that medical

* Ross J. Baldessarini was born in North Adams, Massachusetts in 1937

school was a lot more like trade school. You are expected to learn a lot of facts and not ask too many questions, and certainly never to challenge a professor. That was difficult and not a mould I easily fit into. The thing that probably turned me away from dropping out and heading toward a PhD in chemistry was an experience in a physiology course with Philip Bard and Vernon Mountcastle. They had a tradition of inviting students to do a research paper and presentation for extra credit. I remember sitting through many of these presentations and watching both professors dose off in the middle of them. I prepared one on the reticular activating system, and though I knew very little about neuroanatomy and neurophysiology at the time, I found the material very interesting and even exciting. The most remarkable thing was that Mountcastle stayed awake during my presentation and seemed interested. When the seminar was over, he said I seemed to be interested in neurophysiology and invited me to work in his laboratory. I spent a summer, plus some free periods, to total an entire academic year of work on the auditory system of the cat. The research involved single-unit recording from the eighth cranial nerve to work out frequency coding to detect and code the pitch of sounds, based on neuronal response rates. The technology was somewhat primitive by current standards, but fascinating, and I enjoyed it very much. However, in the process, I learned I was not cut out for the kind of quantitative and mathematical methods that were evolving at the time, including shifting from old fashioned, hand-counting of spike discharges recorded on film from an oscilloscope to the use of computers.

By luck, around that time, Seymour Kety came to Johns Hopkins from the NIH to take the chair in psychiatry, third in line after Adolf Meyer and John Whitehorn. I heard him lecture on his rather strange but very stimulating view of the future of psychiatry as a type of neuroscience, based increasingly on pharmacology, which sounded a lot more like chemistry than what I had been doing in electrophysiology. He encouraged me to work with him on a research project. However, after a year at Hopkins, with no clinical training in psychiatry, Kety seemed like a fish out of water and resigned to return to the NIH. Somehow, he felt obligated and asked if I would like to join him at the NIH to see what was going on in this new form of psychiatric neuroscience. I jumped at the chance, and again spent the equivalent of an academic year there. I worked in Irwin Kopin's laboratory and also had the chance to collaborate with Julius Axelrod and members of his laboratory, including Jacques Glowinski, Leslie Iversen, Gören Sedvall, Solomon Snyder, Richard Wurtman, and other postdoctoral fellows who became very well known. It was an incredible time, with many new ideas, high energy and enthusiasm; in the belief all things were

possible, even though many of the ideas were very premature and wrong-headed. Nevertheless, I was caught up in this vision of a new and comprehensive neuroscience that might relate to psychiatry and neurology.

After the year in Kopin's lab as a graduate student, I returned to Johns Hopkins to complete my clinical training and then went to Boston to pursue an internship in internal medicine at the Boston City Hospital during its centennial year of 1964. Immediately after internship, I was able to obtain a position in the same laboratory at the NIH as a member of the uniformed Public Health Service, and avoided being drafted in the Vietnam-war. I remained in a fulltime postdoctoral research fellowship in biochemical neuropsychopharmacology for two years. At that point, I began to reconsider the need for additional clinical training, but was uncertain whether to continue in internal medicine, or switch into neurology or psychiatry. I had made two grand tours of the leading departments of psychiatry in the country, and returned, very confused by the disparity between what was going on in the field and what people at the NIH were thinking about as the future.

DH: What was going on in the field?

RB: It was very old fashioned, in keeping with the traditions of the 1950s and 1960s. The clinical teaching and practice were firmly based on psychodynamic theories and practices. The new psychopharmacological treatments were just beginning to be considered, but with great reluctance and ambivalence at best, and were not used routinely until well into the 1960s. Leading academic departments were virtually uniformly led by psychoanalysts. Some of them acknowledged, grudgingly, that medications might be useful clinically if they could help people to gain better control on their thinking, emotions, and behaviour, and facilitate their progress in psychotherapy. I was highly sceptical about getting involved in this very foreign scene.

DH: I see.

RB: At that point, I had a fateful encounter. In a discussion of my impressions of American departments of psychiatry with Seymour Kety, he suggested I talk with his friend Joel Elkes, who was about to move from Saint Elizabeths' Hospital in Washington, DC, to follow Kety into the chairmanship of psychiatry at Johns Hopkins. I remember spending a very influential afternoon with him at his home outside of Washington, where he showed me his paintings, his English garden, and his vision of the future. They were all beautiful, but his vision of the future of psychiatry would later turn out to be premature. He encouraged me to visit his new department in Baltimore, and I ended up applying and being accepted as a resident.

DH: What was the clinical base for psychiatry at Hopkins?

RB: The department of psychiatry was based at the Henry Phipps Clinic, which had been founded by Adolf Meyer in 1913. The Clinic cared for a range of acute and chronic psychiatric inpatients and outpatients, and provided rich experiences in consultation psychiatry for the rest of the medical center. Phipps was one of the early experiments with the psychopathic institute model, along with the New York State Psychiatric Institute, where Meyer had worked, the Massachusetts Mental Health Center in Boston, and several other university medical centers.

DH: What about pharmacotherapy in those years?

RB: When I was there from 1966 to 1969, the neuroleptic drugs had an established and accepted place, although what they were and were not good for was somewhat misunderstood. Initially, they were considered a special kind of sedative or “tranquilizer” but by the 1960s, they were considered specific anti-schizophrenia agents. This was in an era when “schizophrenia” in this country could include any kind of psychotic illness or, in some centers, virtually any severe mental illness. The antidepressants were just beginning to be accepted, having been introduced only a few years earlier, and in the face of considerable ambivalence about whether a drug could effectively treat a condition that was “so obviously psychological,” as you have written about insightfully in your own book about the antidepressants. I remember Gerald Klerman having to struggle to gather a massive assembly of evidence in order to get American psychiatrists to take the antidepressants seriously. Also, by the mid-1960s, some American psychiatrists were beginning to accept lithium and to understand there was a bipolar manic-depressive illness, which had often been confused with schizophrenia. FDA approval of lithium was not to occur until the early 1970s. So, by the late 1960s, we were using phenothiazines, thioxanthenes, and haloperidol for psychotic disorders and mania, tricyclic and monoamine oxidase inhibitor antidepressants for depression, and a number of new sedative-anxiolytics for severe anxiety disorders. I was chatting recently with Uhli Uhlenluth about the American view that anxiety disorders were perceived as minor conditions that are not central to the field, even though that view is surely incorrect. The anxiety disorders are among the most common, often disabling, but relatively treatable disorders. Moreover, they might be among the first to yield to genetic and biologic understanding. However, in the 1960s, major mental illness and hospital-level psychopathology, including psychotic and major mood disorders, were considered the core of psychiatry, at least to colleagues in academic departments and other institutions. The very founding of the APA arose from the establishment of mental hospitals in

the 19th century, and there has always been a strong bond between institutional and academic psychiatry in the United States, with office-based psychiatry being considered somewhat peripheral.

DH: From Hopkins, where did you move next?

RB: At that point, I had a very lucky break, because Seymour Kety became restless once again, and was determined to be a professor of psychiatry in a leading department. This time, he went to the Massachusetts General Hospital (MGH) in Boston to work with the child psychiatrist Leon Eisenberg, who was another great teacher of mine at Johns Hopkins. Their plan was that Leon would deal with the clinical side of the department and Seymour would be the scientific leader. They went to Boston about a year before I moved to the MGH in 1969. We all started from scratch, designing new laboratories and inventing new methodologies. It took several years to get a research program organized and staffed.

DH: When you moved to Boston it was still very analytically-oriented with people like Elvin Semrad.

RB: Semrad was across town at Massachusetts Mental Health Center. The geography of Boston psychiatry is complicated. At the time, Mass. Mental Health Center was one of the country's leading training centers. It was very analytic, even though, as a psychopathic institute of a state mental hospital, it dealt largely with severely mentally ill and indigent patients. Semrad, in particular, was a very charismatic and gifted clinician who seemed able to get himself into the heads of severely disturbed patients and to communicate his empathic understanding both to patients and to anyone else listening, including trainees and staff members. He was a highly influential teacher and espoused a model, firmly grounded in psychodynamic theory and therapeutic practice that dominated American academic psychiatry for several decades in the mid-20th century. Indeed, Mass. Mental Health Center produced many leading academic psychiatrists who came out of that psychodynamic tradition. Mass. General Hospital had always been somewhat eccentric and different from other departments of psychiatry in Boston. From its founding in the 1930s, it included psychoanalytically oriented people mainly interested in psychosomatic medicine, trying to understand medical illnesses from a psychological and psychoanalytic perspective. There were also people like Stanley Cobb, with a neuropathological-descriptive neuropsychiatric orientation, that represented a continuation of an Anglo-German tradition in academic psychiatry which became somewhat lost in the American enthusiasm for psychoanalytic approaches from the 1930s. Cobb was the critical scientific progenitor of that department. His descriptive-neuropathological views, coupled with a strong interest in psychological aspects of general medicine in a leading

general hospital, made it entirely plausible to attract people like Eisenberg and Kety, and to seek a more biological approach to balance the psychodynamic approach that continued to be important at MGH, as in other Boston departments of psychiatry.

DH: Was there not also a man in Boston named Mandel Cohen?

RB: Yes; he is now an elderly man, who continued to remain active in the field for a very long time. I remember encountering him when I went to Mass General to grand rounds in the Ether Dome, where ether was first used for surgery, in an antique amphitheatre. An elderly man, would sit at the highest circle of the amphitheatre and, at the end of every lecture, would stand up and pontificate his point of view about what the speaker had presented. After a few grand-rounds, I learned this was Mandel Cohen. He was more a member of the departments of medicine and neurology, even though he was a traditionally trained psychiatrist. He served as an important bridge between psychiatry and general medicine, and encouraged interest in descriptive psychiatry and operational diagnostic criteria. He had an important influence on Eli Robbins, who had worked at the MGH before moving to St. Louis, and so can be considered an important source of the movement that led to the major changes in American psychiatric nosology represented in DSM-III.

DH: I understand he said that psychoanalysts were a plague of locusts that came from Europe in the 1930s and 1940s, just when the descriptive, Kraepelinian, tradition in psychiatry was starting to gain a firm influence.

RB: I once had an opportunity to discuss Boston psychiatry and the tension between descriptive and psychodynamic psychiatry with Eli Robbins on a visit to Washington University in St. Louis in the early 1970s. At the time, I only vaguely knew that his ideas and those of his department were different from most of the departments in which I had worked. I had a long lunch with him and we spent an afternoon chatting. He said he got out of Boston just in time, because his mind was about to be destroyed by the fuzzy thinking that was coming to dominate Boston psychiatry. He was ahead of his time in renewing or keeping alive an older European tradition. It was not until the 1980s that the ideas of the St. Louis department were widely accepted. In the early 1970s, when I first visited Robbins and his colleagues, they felt like an endangered species, living inside a castle behind a wall and a moat. Only slowly did their ideas come to revolutionize American psychiatric diagnostics, with DSM-III and its successors.

DH: So, you were aware and in contact of this neo-Kraepelinian group?

RJB: Yes, I viewed them initially as prophets without followers, clever and interesting people who were trying to be more clear-headed, logical and objective, but very much out of the mainstream of American psychiatry.

At the time, if I had to bet money on how it would turn out, I would have bet against them.

DH: It was an amazing development.

RB: It was indeed, and I suspect the key to emergence of the neo-Kraepelinian movement in this country was getting APA to make it officially acceptable in DSM-III.

DH: In the early 1970s in Boston, wasn't tardive dyskinesia one of the things you became involved with?

RB: That interest developed somewhat later. Initially, I pursued two lines of investigation that I had begun at the NIH as a student and postdoctoral fellow; amine methylation and the storage and release of neurotransmitters from nerve terminals, in addition to becoming interested in the effects of antipsychotic drugs on the functioning of the cerebral dopaminergic system. One line of investigation was based on the idea that methylation of monoamines might have something to do with the pathophysiology of psychotic disorders, including production of hallucinogenic methylated amines. One of my first efforts was to work out a radioenzymatic assay technique for the major methyl donor, *S*-adenosyl-*L*-methionine (SAME), and related assays to measure activities of methyltransferase enzymes, and their substrates and products, including histamine and methylhistamine, tryptamine and *N*-methyltryptamine, as well as the activity of the methionine-adenosyl transferase that produced SAME. The basic concepts involved came from Axelrod's work on the biochemistry of catechol-*O*-methyltransferase (COMT). That work was picked up again in the late 1970s, around the time I moved our research group to the then-new Maiman Research Center at McLean Hospital. At the time I had been doing some consulting work in Milan with a small, privately-owned pharmaceutical company, BioResearch, which was later bought by BASF Corporation. Their director of research was Giorgio Stramentinoli, a very talented biochemist who took a sabbatical from the company to work with me on our shared interest in methylation. His company was developing SAME as a potential substance that might improve liver functioning, in keeping with a peculiar Southern European medical tradition. When Stramentinoli came to my lab, we designed a critical experiment that seems to have destroyed the methylation hypothesis of psychotic illnesses. Based on my work showing that large doses of methionine markedly increased tissue concentrations of SAME, our hypothesis was that giving methionine to psychotic patients might increase some of their symptoms by "pushing" methylation pathways through increased tissue concentrations of the methyl donor SAME. We worked out an assay for the hallucinogenic compound *N*-methyltryptamine, and tested for its

increased production in animal tissues under normal conditions and after loading with L-methionine. Although we could increase tissue concentrations of SAME greatly, the process of *N*-methylation could not be pushed. We then figured out that *N*-methyltransferases are normally saturated with the methyl donor, and that simply increasing this cofactor has little impact on methyl-transfer processes, since the usual amounts of endogenous SAME in cells are more than enough. This finding tended to undermine the hypothesis that methionine loading might increase production of methylated aromatic amines with adverse psychotropic effects, and left the symptom-worsening clinical effects of methionine loading on psychotic patients unexplained to this day. However, by the late 1970s when we did that work, the matter already was largely moot since the field had moved on and lost interest in methylation and effects of hallucinogenic amines.

DH: That's what happens when the field moves on.

RB: Nevertheless, it was nice to have some closure on a hypothesis that had been interesting in its time. In addition, our studies at least made some contribution to better understanding the biochemistry of methylation processes.

To go back to the story of the early 1970s, I also continued another line of work that had begun during my postdoctoral years at the NIH. At the time, I was trying to develop a way of studying the release process of monoamine neurotransmitters from nerve terminals. This project involved, off and on, about two years of my fellowship time working on methods doomed to failure. They included using surgically demanding vascular perfusion of cat spinal cord segments, trying to catch monoamines released from nerve terminals by assaying them in venous effluents by laborious techniques of limited sensitivity. This approach never worked. I had been greatly helped in working on methods of perfusing cat spinal cord segments by a surgeon, Josef Fischer, who was also a postdoctoral fellow in Kopin's laboratory. We later collaborated at the MGH through the 1970s, until he moved to become chairman of surgery at the University of Cincinnati. When Fischer was a postdoctoral fellow with Irv Kopin, they worked together on what we called "false transmitters." Under some conditions, sympathetic and other norepinephrine-producing nerve terminals could be loaded up with tyramine, octopamine, or other aromatic amines that would compete with the natural endogenous transmitter for storage and release, reducing postsynaptic effects since they lacked intrinsic pharmacodynamic activity at adrenergic receptors. Fischer picked up on that theme as a possible contributor to the pathophysiology of hepatic encephalopathy. One of the marvellous things

about working on metabolic problems in hepatic encephalopathy is you can't miss, because almost everything you measure is abnormal. Our hypothesis was that aromatic monoamines produced from dietary amino acids would not be as well metabolized by a failing liver, and might tend to accumulate in monoaminergic nerve terminals, including in the brain, to interfere as false transmitters with the normal functioning of norepinephrine, dopamine, serotonin, and other endogenous neurotransmitters. Fischer worked on the clinical side of the problem and I worked at animal and in vitro modeling. I spent several years trying to work out the molecular rules of the game, what a molecule needed to look like to be taken up, stored in intraneuronal vesicles, and released on depolarization. Together, we developed a large body of evidence supporting a false transmitter theory of the pathophysiology of hepatic encephalopathy. Richard Wurtman, who was then across the Charles River at the Massachusetts Institute of Technology (MIT), found that you could change the proportion of aromatic amino acids that pass through the blood-brain diffusion barrier by altering the normal proportion of aromatic and neutral aliphatic amino acids, which compete for the same transport system to enter the brain. Wurtman and I also found that L-DOPA can compete with tyrosine for access to brain, and suggested it might be useful in hepatic encephalopathy. Fischer followed these findings by designing a therapeutic intervention with modified intravenous hyperalimentation fluids with reduced concentrations of aromatic acids and increased proportions of neutral aliphatic amino acids. This method could actually pull patients out of hepatic coma, and that finding added strong support to our false transmitter hypothesis for hepatic encephalopathy. However, the findings soon became moot when liver transplantation surgery became feasible and increasingly routine in the 1980s. As an epitaph for this work, I recently saw a review on the metabolic basis of hepatic encephalopathy, which concluded that the false transmitter hypothesis had strong support and had never been refuted. It was at this point that my interest in the actions of the antipsychotic drugs on the central dopaminergic system was emerging, including ideas about the pathophysiology of tardive dyskinesia.

DH: I've recently heard stories from Frank Ayd about when he was called, I think by Schering-Plough, producer of perphenazine, to consider a report their drug seemed to be causing abnormal movements in patients. These observations, associated with neuroleptic treatment, originated with colleagues in Europe as well as with William Winkelman in Philadelphia, one of the first American psychiatrists to report on the clinical use of chlorpromazine in the 1950s, soon after Heinz Lehmann in Montréal.

RB: That's right.

DH: William Winkelman was in court in the 1960s concerning the issue of tardive dyskinesia (TD), as we now know it. He reported having presented a woman with severe mouth movements on rounds, whom many colleagues considered had TD. They asked her to leave the room and when she returned a few minutes later, she seemed to have been cured by replacing her missing dentures. I also remember that at the 1966 CINP meeting, a European psychiatrist named R. Degkwitz tried to convince American psychiatrists that late movement disorders were a real problem associated with long-term neuroleptic treatment. It took quite a while for people to recognize the problem for what it was, and then it became a hot political item. Could you take me through the story of your work on TD?

RB: In America, TD entered the medico-legal scene and was considered a major liability issue. However, based on reading reports of several of these cases in some detail, many appeared to involve broader non-practice rather than malpractice. Typical cases involved patients in public institutions for mentally retarded people or nursing homes for elderly demented people, in whom neuroleptics were being used non-specifically as sedative-tranquilizers aimed at keeping them quiet and less agitated. These were patients who were seen only very occasionally and briefly, usually by a physician who was not an expert in psychiatry or neurology, and who did not realize what TD was. These circumstances made it quite easy for plaintiffs' attorneys to launch successful malpractice suits.

DH: When did this began to happen?

RB: By the middle to late 1970s TD had become a hot topic, at least from the potential liability perspective, which fuelled professional interest in it, leading the APA to set up their first task force on the topic.

DH: A task force that you chaired. How did you get pulled into the problem?

RB: By that time, I had done a fair amount of theoretical work related to the pathophysiology of TD and had written some clinical papers on the topic. We gradually learned to distinguish among drug-associated Parkinsonism, akathisia, acute dyskinesia, and late or tardive dyskinesia, as well as the neuroleptic malignant syndrome (NMS.). Neurologist colleagues, including David Marsden and Daniel Tarsy, helped in the 1970s to make critically important distinctions among the various types of EPS. Some of these continue to be clinical problems, even with modern antipsychotic agents. Notably, akathisia remains poorly understood, often hard to diagnose (and to spell), and frequently distressing or disabling.

DH: Could you tell us something about the research you did in this area?

RB: We used the dopamine agonist *R*-(-)-apomorphine to provoke behavioural arousal in normal rats and in those given repeated doses of various dopamine receptor blocking antipsychotic agents, reserpine to deplete

monoamine pools, or alpha-methyl-dopa to prevent synthesis of dopamine and norepinephrine. In such pre-treated rats, we saw markedly increased behavioural sensitivity to apomorphine, as shown by “leftward shifts” of dose-response curves to lower ED₅₀ values. We interpreted the lower ED₅₀ for apomorphine as a sign of dopaminergic supersensitivity. Dopaminergic supersensitivity produced by antipsychotic agents had already been anticipated by a Russian pharmacologist, Shelkunov, working with chlorpromazine and with apomorphine several years before our work, and similar studies by neurologist Harold Klawans of Chicago. Even though it may not have been an entirely original discovery, the work with Dan Tarsy helped to popularize the concept of receptor plasticity as a response to prolonged drug treatments in psychiatry. It is also important to clarify that the dopamine supersensitivity hypothesis for TD is unlikely to be a full explanation of its pathophysiology since only a minority of patients exposed to neuroleptic agents develop dyskinesias. There are several risk factors for TD, including evident but largely unknown individual “host” factors. Among risk factors, age is the most important. We provided strong evidence for the importance of age in risk for TD in a study done in collaboration with James Smith, an epidemiologist in the state hospital system in New York. The older the patient, the higher the risk for TD, and the less likely to have spontaneous remission after stopping the treatment. I was also puzzled by literature reporting that risk of TD appeared to be independent of antipsychotic drug dose. As a pharmacologist, I couldn’t accept that conclusion, since there is virtually always a dose-risk relationship if a drug is more than incidentally related to the cause of a condition. What I eventually figured out was that most reported studies of neuroleptic dose and risk of TD involved doses ranging from about 300 to perhaps 3,000 mg/day chlorpromazine-equivalent. My guess was that such doses may be near the top of a dose-risk curve. Around that time, John Kane in New York was beginning to do important, prospective dose-response studies with dilutions of depot fluphenazine decanoate, finding remarkably low clinical ED₅₀ doses. In addition, a less well known finding was a relationship between drug dose and incidence of new cases of TD, such that a ten-fold reduction of dose was associated with a two-fold lower risk, suggesting a log-dose vs. risk relationship that would make perfect sense to a toxicologist.

An additional spin-off of these interests was a critical appraisal of the matter of appropriate dosing of antipsychotic drugs. I ended up spending a lot of time combing through the literature and putting together the available data in a semi-quantitative way, as I have done a number of times since then. Our findings strongly suggested that quite moderate doses

were sufficient for most patients, particularly for long-term maintenance treatment. As it happened, this conclusion had long been accepted by many European colleagues, based on clinical experience. The findings regarding effective doses of antipsychotic drugs also served to underscore the striking tendency among American psychiatrists to use psychotropic agents unusually aggressively, then in very high total daily doses, and currently in complex combinations. These are examples of what I have termed the “allopathic compulsion.”

DH: Perhaps fortuitously, your article in the *Archives of General Psychiatry* on dose-responses of antipsychotic agents was soon followed by objective evidence based on PET scanning with radioligand binding techniques. Those studies have quantified the doses of various antipsychotics required to occupy the dopamine-D₂ receptors.

RB: Indeed, that work helped to solidify our analysis of dose-requirements based on clinical responses, and to reinforce the point that moderate doses of antipsychotics were sufficient to produce sufficient dopamine-D₂ receptor occupancy for clinical benefit, and that more was associated with increased risk of adverse neurological effects.

DH: You’re opening up a theme I’d like to discuss further. Once you introduce the idea there is an optimal dosing range and further efforts to saturate the occupancy of dopamine receptors is not likely to produce better antipsychotic effects, you are suggesting there are limits on how much we can do. This is not a message the average practicing psychiatrist wants to hear, but it is one that comes across clearly in your chapters in the Goodman and Gilman textbook of pharmacology.

RB: Let me take a step back and give you a philosophical preamble to this question about dosing and what one can achieve clinically. One of the things I’m exquisitely sensitive about, particularly in American psychiatry, as a teacher of psychiatry and trainer of young psychiatrists, is that we have long been a fad-prone group of professionals. Whatever new trendy thing comes along, we not only buy into it, but we package it, market it, push it to extremes and overdo it. I think we did it with psychoanalytic thinking. It is a very powerful way of looking at certain problems. It was not a cure-all, and didn’t answer all the questions, but we overdid it to the point that it came to dominate American academic psychiatry until some colleagues concluded that the movement had attained the point of becoming ridiculous, and in need of being largely ignored or abandoned. We also did it with community psychiatry and deinstitutionalization, which became overvalued and overdone, to the point of no longer having institutions that can care for the severely and chronically mentally ill, institutions that are now all too often being replaced by jails and prisons. We’ve also

done this in much of biological psychiatry, including grossly overvaluing our partial understanding of the pharmacodynamics of some drugs as a putative route to clarifying the pathophysiology of psychiatric illnesses. In turn, this view has encouraged massive but largely fruitless efforts to support a dopamine excess hypothesis of schizophrenia or mania, a norepinephrine or serotonin deficiency theory of major depression, a serotonin deficiency hypothesis in obsessive-compulsive disorder, and so on. This “pharmacocentric” approach in biological psychiatry has not moved the field very far forward and ironically may have limited progress on therapeutic innovation by keeping us stuck on old mechanisms and old theories. I surely do not like to see this pattern of overdoing and killing of useful, if imperfect, developments in psychiatry. In trying to explain the limitations of pharmacocentric reasoning to residents and medical students, I sometimes say that if you knew that willow bark extract helped people who had fevers and coughs, you might develop a theory based on the pharmacology of the salicylates that was highly unlikely to lead to the discovery of the pneumococcus or to antibiotics. If you knew that mercurials were good for patients who retain fluid and swell up and you studied the renal effects of mercury, you might miss the significance of congestive heart failure.

DH: If we’d had the neuroleptic drugs earlier, we could have managed GPI with them.

RB: That’s right, but it might have led to disaster if we pursued a dopamine theory of GPI rather than implicating syphilis and using penicillin. What I’m saying is that I am very uneasy about throwing babies out with bathwater in the American tendency to commercialize and overdo, oversell, push to the point of the ridiculous and then crash, and move on to the next new thing. That process seems excessively costly and inefficient. It tends toward devaluing and prematurely abandoning imperfect concepts or methods, and failing to build on past knowledge while adding new knowledge.

There are serious risks of booms and busts in psychopharmacology. One aspect of the problem that may be particularly American is the tendency to overdo a good thing. We often seem to follow the principle that if a little doesn’t do it, then give a lot. When I first started tracking down what clinicians were doing in the Boston area, I found out that the average dose of neuroleptics was getting into the thousands of mg/day chlorpromazine-equivalents because “rapid neuroleptization” and “mega dosing” were trendy, unrealistically optimistic, but wrong-headed fads. Worse yet, they sort of worked (though not necessarily better than moderate doses), and it took a while to realize that they were neither necessary nor safe.

DH: So, how did people respond to your article on neuroleptic dosing, which seemed to say they were wrong in using very high doses of neuroleptics?

RB: That article in the *Archives* came after many years of smaller articles and efforts at teaching and consultation with colleagues and trainees. It seemed such efforts eventually paid off, and that many colleagues became more inclined to seek minimum effective doses of antipsychotics, especially for long-term treatment. Clearly, this effort was aided and reinforced by liability concerns about adverse effects of aggressive dosing, including extrapyramidal effects and probably also TD, as well as deaths from asphyxiation due to acute dystonic reactions and from NMS. Many of these problems have become much less pressing with the slow acceptance of more conservative dosing with older drugs, and particularly with the advent of safer modern antipsychotics.

DH: They give much lower doses now of the old drugs.

RB: The problem of overdoing treatment has not disappeared, however. My colleague Franca Centorrino and I regularly monitor drug dosing at McLean Hospital. What we've seen is that doses of antipsychotics have come down over the past decade, and have stayed at an average of 200–300 mg/day chlorpromazine-equivalent, similar to doses that have always been typical of European practices. However, what has changed is a shift toward use of multiple drugs or “polytherapy.” This practice is a growing temptation as the number and variety of agents increase and frustrations with less-than-ideal clinical responses continue. This now-dominant trend toward polytherapy in many American centers is also leading to higher total daily doses of drugs, including antipsychotics. Moreover, non-rational cocktails involving several classes of psychotropics are also increasingly common, and in need of critical assessment of relative efficacy and safety.

DH: For a person who is persuaded that we need drugs, you've done a lot of work to encourage their more limited clinical use.

RB: This is because I value them enough to be concerned that reckless, nonspecific, and non-rational over-use with increased risks of adverse outcomes may undermine their value and acceptance in the long-run. If available psychotropic drugs are used well and safely, one can get a lot of good work done and avoid harming patients.

DH: What about the discontinuation syndrome story?

RB: That's a newer theme, and involves an intriguing mystery story. It started with a memorable case conference in the early 1990s with a young woman named Trisha Suppes, who was a senior resident at the time and a superbly trained neurophysiologist. Eventually she became a clinical investigator and directs a program on bipolar disorder in Dallas, Texas.

She presented a young man who had an acute episode of psychotic mania while he was in college. He was hospitalized, responded well to treatment, and had been maintained mainly on lithium for several years, doing quite well clinically and professionally, but increasingly bothered by side effects, including weight-gain and worsening of acne. He wanted to stop treatment and convinced his private psychiatrist to let him stop using lithium, and did so quite abruptly. He did fine for several weeks and actually felt better physically. However, he then had an acute recurrence of a very severe psychotic manic episode that was very hard to treat. Eventually, he became well enough to leave the hospital. At rounds, Dr. Suppes asked what this pattern might mean, and wondered specifically whether the case might represent more than the natural and spontaneous return of a serious recurring illness, perhaps involving an iatrogenic component related to stopping the treatment. I commented that the case brought to mind a tongue-in-cheek comment made at a meeting in Europe some years earlier by London neurologist David Marsden about the temporal pattern of relapses among schizophrenia patients who discontinued neuroleptic treatment in long-term, placebo-controlled trials. The pattern was of a sharp increase in morbidity largely limited to the several months after stopping treatment. He asked whether anyone had considered that the observed pattern might suggest an “addiction model”? At the time, those at the meeting laughed, and I took the comment as a joke. However, the Suppes’ case suggested there might be a kernel of truth in Marsden’s comment. Such responses may not be addiction, in the usual physiological sense that we conceive it with opiates, alcohol, or sedatives. Nevertheless, it seemed plausible that the nervous system would adapt to the presence of a long-standing treatment, whose removal might lead to efforts to readjust to the un-medicated state. Such neurophysiological adjustments might act as a “pharmacodynamic stressor” to create an adverse interaction with an underlying clinical vulnerability. As a physiologist, this idea seemed highly plausible to Dr. Suppes. I suggested we look further into the matter by reviewing what the published literature on effects of stopping maintenance treatment in bipolar disorder patients might reveal. After a great deal of searching, we found many relevant cases. As in the case seen on rounds, their average time to a new recurrence after stopping lithium was much shorter than would be predicted by the natural history of bipolar disorder, again suggesting that discontinuing treatment might represent a pharmacodynamic stressor. However, it seemed risky to report such findings without a comparison group. It turned out that a small number of the reported cases provided data on inter-episode intervals before treatment with lithium, in addition

to the latency to a first recurrence after stopping treatment. To make the exercise more credible, we selected the shortest interval before treatment for each patient for comparison to the latency to recurrence after stopping lithium. These latencies turned out to be about seven times shorter after stopping lithium, and this finding led us to submit the findings to the *Archives of General Psychiatry*, where they appeared in 1991.

The next step in the story involves an amusing telephone call from Alan Frazer, then at the University of Pennsylvania, who said that a friend from the University of Cagliari in Sardinia knew a psychiatric resident who wanted a laboratory research fellowship in the US. He had the chance for a peculiar fellowship that would support training only at Harvard. I agreed to accept the trainee, Gianni Faedda, who spent two years in my lab, initially doing some early pharmacological characterizations of the dopamine D₁ receptor based on the application of novel radioligands. He did well, but really wanted to be a clinical investigator. Moreover, he liked American psychiatry so much that he completed an entire second clinical training program with us. During that residency, in 1992, he came back from a visit to his family in Sardinia with a “Christmas gift.” It was a set of data from a mood disorders research clinic in Cagliari where he had trained with Leonardo Tondo, who has since then become a major collaborator. The data involved approximately 65 bipolar disorder patients who had done well on lithium maintenance treatment for several years and wanted to stop treatment. The data from the Tondo clinic were of particular interest because they included estimates of the number of days taken to discontinue lithium in each case. Faedda and Tondo suggested that we might look at the rate of discontinuation for its impact on latency to a first recurrence, hoping to see that rapid discontinuation would lead to earlier recurrence than gradual dose-tapering. If so, such evidence would provide strong support for the hypothesis that lithium discontinuation indeed represented an iatrogenic, pharmacodynamic stressor. In order to generate two groups of approximately equal size, we separated subjects by a median-split of days to discontinue lithium, and indeed found markedly dissimilar risk-by-time functions by survival analysis, such that those who discontinued abruptly or rapidly fell ill several-fold earlier than those who tapered off over at least two weeks. Tondo and Faedda had been careful to select subjects for this analysis by excluding anyone who appeared to be hypomanic or depressed at the time of stopping lithium, lest they already be in an impending new episode; perhaps with poor judgment about their continued need for treatment. As it turned out, the most common reason for stopping was, ironically, doing *well* for prolonged periods and being unwilling to continue bearing the burden of side effects.

Nevertheless, there was a striking characteristic of the data that made me very reluctant to report the findings, much to the disappointment of my collaborators.

DH: What was the problem?

RB: The problem was that the data extended to five years of follow-up after discontinuing lithium for patients who did not experience a recurrence earlier. The survival functions for rapid versus gradual discontinuation of lithium remained strongly separated across the entire range of observation periods. My concern was that no one would believe us if we reported that minor differences in tapering times at the start of the risk period would influence outcomes for the next five years. So, the data sat on the back of my desk under a brick for a very long time. Then one night, I had a dream. It was a classic psychiatric dream, including snakes, and I woke up in the middle of the night, with a genuine "Eureka!" experience, scribbled some notes, and went back to sleep. Several days later, I looked at the notes and finally figured out what I was thinking, realizing that the dream about snakes was really about the puzzling survival curves. My new-found understanding was that the risk-by-time slope or rate functions differed only within the initial several months, and thereafter remained parallel out to five years. This was doubly good news, since it supported the idea of a pharmacodynamic stressor at work for a few months after stopping treatment, and could also be interpreted as indicating a *reduction* of iatrogenic risk and not merely a delay of time to recurrence, since the survival curves remained displaced over several years. This insight allowed us to submit the paper, and it appeared in the *Archives* in 1993.

Since then, we have replicated these findings in several independent clinical samples and extended them to neuroleptic agents in schizophrenia in collaboration with Adele Viguera, again showing that abrupt or rapid discontinuation was much more dangerous than gradual tapering off medication. With Viguera and Tondo, we also found that stopping lithium abruptly in pregnancy, specifically, carried a much higher risk of early recurrences than tapering off slowly. Tondo and I also found that risk of suicidal acts was twice as great within months of stopping lithium rapidly. Our efforts with Viguera to test the discontinuation stressor concept further with antidepressants in major depression found again that recurrences arise surprisingly soon after stopping maintenance antidepressant treatment, and that risk tended, paradoxically, to rise somewhat with longer treatment, again suggesting a drug-dependence phenomenon. However, we were not able to find data arising from the same trials that involved rapid vs. gradual discontinuation. We found little difference

in average times-to-recurrence after stopping antidepressants of short duration of action versus long-acting agents, e.g., monoamine oxidase inhibitors or fluoxetine, but could not find contrasting treatment or discontinuation conditions in the same study to limit between-study variance. These circumstances made it impossible to test adequately for an effect of the rate of discontinuing antidepressants, which we consider a critical test of the concept of iatrogenic risk arising from a pharmacodynamic stressor effect.

DH: I think the good thing about all this work is that it has been done by a person who is clearly an advocate of pharmacotherapy, but it might look as if you are suggesting that treatments increase risk of later illness, or even that the pharmaceutical industry is deliberately trying to make patients dependent on their drugs.

RB: There may be tendencies to oversell psychotropic drugs, but I had not thought of our work on discontinuation-related early recurrence risks as a product of a deliberate industrial scheme, and doubt that anyone realized before our work that such effects might arise.

DH: It has been very good to get such information out, and to encourage more cautious and slow discontinuation when that is clinically possible.

RB: I'd like to believe that psychotropic drugs are promoted and used clinically in the hope that they will do some good, knowing that all drugs have adverse effects, and that these need to be identified, limited, and managed as best one can clinically. I also think that this basic principle is not inconsistent with the inevitable profit motive behind pharmaceutical marketing efforts. Moreover, identifying a previously unrecognized adverse effect of treatment and means of limiting or avoiding it is likely to be integrated into good clinical practice and is also of interest to the manufacturers to the extent that it can limit their liability risks.

DH: Sure, but there is some risk of emphasizing the negative, with TD, withdrawal syndromes, and the like, to the point of creating a clinical quagmire.

RB: There is always a need to balance potential benefits against potential risks in clinical psychopharmacology. There is also a need for differential assessment of clinical conditions that may arise during treatment. In psychiatry, this process remains largely an art form, despite having standardized diagnostic systems and rating schemes. One can see clinical conditions in more than one way, with perfectly good will and with no fraud intended. I'm reminded of another story from when I first moved to McLean Hospital. I was advising an outpatient clinic that was setting up some new drug trials. The colleague directing the program at the time had two grant proposal site visits back-to-back within a few weeks. One

project was an antidepressant study and the other was an antianxiety study. One reviewer happened to attend both visits, and did some quick calculations pertaining to patient flow through the clinic, from which study subjects would be recruited. He expressed surprise in that the numbers did not seem to add up. The clinic director blushed, and acknowledged that many patients could meet criteria for either study!

DH: But, if you were to say that to people, there would be those who would not be surprised and others who would be quite horrified, probably including neo-Kraepelinians, who seem to believe there are discrete disorders with different causes requiring different, specific treatments.

RB: Let me give you one more anecdote from an experience that brought this point about the specificity of psychiatric diagnoses home to me. In the late 1980s, there was a young investigator in our program who was studying a physiological aspect of psychotic patients and had collected about 100 patients who were tested. He needed verification of diagnoses and asked me to join a panel of three colleagues to put together a consensus diagnosis, based on our independent assessments of the available clinical data. We worked independently and as a panel, we came up with better than 95% agreement on diagnoses. There was an important trick involved; we could diagnose within the full range of DSM-III categories for psychotic disorders, including schizoaffective disorder, but we could also label cases as “diagnosis uncertain” when necessary. Allowed all of these choices, we had nearly perfect agreement, independently. Now, do you want to know what percentage of patients was neither schizoaffective nor diagnosis-not-certain?

DH: Tell me.

RB: About sixty percent!

DH: Really?

RB: If we were allowed to be honest, that’s what we came up with, and it seems to square with clinical reality.

DH: Did you publish that?

RB: No; it was too embarrassing. However, you have captured the point here, and that may suffice.

DH: A related issue is that of the specificity of classes of psychotropic agents when used for particular indications. For example, the neuroleptics are not specific anti-schizophrenia agents; they also do a lot of other clinically useful things, across a broad spectrum. We have also learned that the SSRIs are useful in various anxiety disorders as well as in major depression. There is some tension between developing new agents for specific and narrow indications, so as to gain regulatory approval versus expanding the indications for marketing purposes.

RB: I have for years encouraged people in the pharmaceutical industry to think more broadly about antipsychotic agents as being useful for far more than schizophrenia, including mania and a variety of psychotic disorders. My impression is that the majority of cases with psychotic symptoms are, in fact, not schizophrenia, but instead represent a broad range of acute and chronic primary psychotic disorders as well as organic mental disorders. Just recently, I've been working with Mauricio Tohen on a study of long term outcomes in all first-break psychotic disorder patients admitted to our hospital over several years. The great majority of these patients had major affective disorders, based on strict DSM-IV criteria with multiple SCID assessments and long-term clinical follow-up. Most were treated with antipsychotic drugs at sometime. Experiences like this suggest that antipsychotic drugs may indeed have a very broad range of clinical utility and marketing potential. However, when I have discussed this point with colleagues in the pharmaceutical industry, I have often run into certain sociological constraints and folkways that call for narrow aims in drug development for highly specific and limited indications. There seems to be a fear of muddying up drug development and marketing strategies by considering more than one indication at a time, especially during initial development aimed at rapid licensing. There is also concern about taking on financial responsibility for a broad drug development program before a new agent begins to produce an income stream based on its initially licensed indication. FDA has a culture, too, and they're used to receiving data in a certain format and with a specific target indication. I understand the nature of such conservatism, but wonder if it may limit innovation. In the recent past this stalemate has loosened somewhat, in that most companies at least try for anti-mania as well as anti-schizophrenia indications, and probably rely on approval for schizophrenia to lead to abundant, off-label empirical extensions to use in other psychotic disorders. A major remaining problem is that standards for approval of long-term indications remain remarkably divorced from clinical realities. Many agents are now approved based only on discontinuation shortly after initial recovery from an acute episode, in comparison with continuation for several months. There are at least two problems with such study designs. First, they are "enriched" to find a subpopulation of cases that respond to the sponsor's product in initial acute illness, and so may not be broadly representative. Second, the discontinuation strategy may well invoke a discontinuation stressor at a time of relatively high vulnerability, shortly following partial recovery from the acute index episode of illness, with an uncertain contribution of an iatrogenic artefact. It is unlikely that such trials provide compelling support for long-term, prophylactic protection against later

recurrences or exacerbations of illness. Such important effects might better be evaluated by taking on all-comers at any phase of illness, and comparing randomized treatments over very long follow-up for more than a year. Such trials are difficult to conduct, risk high dropout rates, and can be very expensive. It is not surprising they are not favoured by the industry, but somewhat surprising that the less convincing alternatives are accepted by regulators.

DH: In the US, anticonvulsants are being used very liberally these days, including for patients with very broadly diagnosed “bipolar” disorders, some of whom formerly may have been considered to have a personality disorder. Much of such usage lacks strong empirical scientific support and remains off-label. What do you think about this development?

RB: What you’re raising is the philosophical and practical point ACNP and other learned organizations need to consider. There is a range of off-label clinical practices in modern psychiatric therapeutics. Most are untested, and many are not likely to be tested by manufacturers. Given these circumstances, efforts to test for efficacy and safety of innovative applications of known treatments are likely to fall to individual investigators with federal or foundation support. There are many other issues under vigorous discussion these days, including the ethics of discontinuing ongoing treatments in severely ill patients for the sake of scientific study design, and about what constitutes adequate informed consent, particularly if a study is designed to add a degree of clinical risk.

We also need to figure out some more clever, scientifically acceptable, humane, and clinically appropriate ways of designing long-term trials, which are a major challenge for the field right now. It may help to design a buffer zone in which you move patient-subjects from clinical-treatment to protocol status, with a period of adjustment and tapering off ongoing treatments. Such aspects in the design of experimental treatment trials are important, not only clinically and scientifically, but also to the pharmaceutical industry and to regulatory bodies. It is getting very difficult to design even a short-term trial to provide unambiguous results. One of the challenges is that it is virtually impossible to find pharmacological virgins to study, especially in North American and Western European academic centers. Additionally, in most long-term studies, patient-subjects are discontinued from a standard treatment as part of most protocols. Such circumstances lead to artefacts associated with treatment-discontinuation stress and to carry-over effects of previous treatments, as we have already discussed. In addition, even initial improvement with study treatment may be limited, since most patients have already been more or less optimally treated with available treatments. To some extent, artefacts can

be limited by slow removal of ongoing treatments and introducing experimental treatments with an initial period of re-stabilization. Options being considered include seeking classic and untreated cases in other, less-developed countries. It may also be of interest to consider protocols that involve dose-response designs rather than discontinuation to a placebo, or use of patient-advocate data-referees, by whom a trial is terminated as soon as an end-point has been attained.

DH: From what you've said, you appear to feel that some of the newer treatments represent significant steps forward. With antipsychotic agents, for example, can the neurological safety of second-generation agents be matched by use of lower doses of older neuroleptics?

RB: That's a difficult question. Clinically, I'm sceptical there are major differences in effectiveness of new and older antipsychotics. Even EPS risks can be quite low when moderate doses of standard antipsychotics are compared to modern drugs. Such findings are not always easy to interpret since antipsychotic agents used previously are likely to yield carry-over effects, including adding artifactual risk of EPS early in trials of modern antipsychotics.

DH: But the shift to newer drugs seems to be a bandwagon we have to jump on.

RB: In this country we tend to jump to anything new, perhaps more readily than in Europe and elsewhere. This reminds me of the comment by the poet who said, "Be not the first by whom the new is tried, nor yet the last to lay the old aside."

DH: That famous quotation is by Alexander Pope.

RB: There are too many good things out there to dump them and move on. We need to remember they're still there when things aren't going well with the latest fad. For example lithium has developed a bad reputation in recent times in the US.

DH: We've talked a lot about the hazards of treatment. Yet, here at the ACNP meeting, there are reports of a lot of work on genes and about predicting who's going to have the best and safest response. Even neuroimaging techniques promise to allow us to select the right drug for a specific patient

RB: Imaging methods can guide dosage selection much more quickly and efficiently than in empirical, dose-finding trials, when a drug target-protein is known and can be labelled, as in a PET or SPECT study.

DH: How do you feel about the future?

RB: I have very mixed feelings about the future of clinically helpful biological psychiatry, and sometimes feel as if I've been waiting for Godot for several decades now. I'd go back to what I said about my visit to Joel Elkes

in his rose garden, when he laid out a vision of a new psychiatry. It was very premature then, and it continues to remain elusive.

- DH: In addition to moving away from simple blocking of particular neurotransmitter receptors, there is a growing interest in considering neural systems that do not involve traditional monoamines and amino acid transmitters to target novel treatments.
- RB: Perhaps having come into neuroscience through neurophysiology, I am left somewhat uneasy by the recent preoccupation of the field with the identification of growing numbers of novel molecules and gene products in the brain. Many are being targeted for drug development, even before we have learned how these novel molecules contribute to neuronal function, let alone to behaviour.
- DH: Do we have to go this way?
- RB: We have to go through a phase of molecular and genetic preoccupation. The technology that drives the approach is too powerful and compelling not to pursue. I just wish younger colleagues coming into the field will try to appreciate the need for a broader view. We need to place the increasing numbers of receptor subtypes, effectors, second-messengers, and other downstream molecules back into a working nervous system. We need to figure out what these new molecules are doing in animal brains and then in normal and psychiatrically ill human beings, as a basis for rational innovation in psychopharmacology. Such efforts are very challenging and require long-term physiological-pharmacological investments to address questions such as, "Where does this fit into the working brain and how does it work?"
- DH: How long will it take before the newer molecular discoveries start to pay off at the clinical level?
- RB: There is already some evidence of progress. New molecular gene products, known for only a few years, are being studied at a physiological level. Such progress may well lead to novel and clinically useful new drugs.
- DH: One of the things that I've heard from a few people here, and especially those with clinical interests, is that the ACNP has become overly interested in basic neuroscience, and much less in its clinical applications. When do you suspect we will return to clinical neuroscience?
- RB: In going through the abstracts from this year's annual meeting of the ACNP, I have been impressed with a sharp, biphasic distribution of topics being presented, ranging from the most esoteric basic molecular studies all the way to clinical drug trials. This suggests the College continues to be broad enough for all sorts of bedfellows and that's a good thing.
- DH: That's a reasonable note on which to end this interview. Thank you for your comments.

ROBERT H. BELMAKER

**Interviewed by Joseph R. Calabrese
Las Croabas, Puerto Rico, December 10, 2007**

JC: Good morning. My name is Joe Calabrese and I am a psychiatrist. We are at the 2007 Annual Meeting of the ACNP in Boca Raton. I have the pleasure of interviewing a friend, Dr. Robert Belmaker* about his history. Could you start by sharing where you are currently and what you are doing?

RB: Good morning, Joe. I am now a Professor of Psychiatry at Ben Gurion University in Beersheva, Israel. A lot of my friends know me as Bob, and also as Haim, which is my Hebrew name. I have been living in Israel since 1974 although I was born in Los Angeles, California. I am involved in teaching and in research as well as patient care. I have a bipolar affective disorders clinic every Monday and I see somewhere between 20-30 patients that day as a team with a clinical psychologist; we see the patients together. She also helps administratively with filling out of psychosocial and insurance forms. She is available to meet with the patients for psychotherapy outside the day I am there for medication follow up. I thereby treat a panel of about two hundred patients. I am also Assistant Director at Beersheva Mental Health Center, in charge of inpatient care; so when one of my patients needs to be hospitalized I can be involved. Our hospital is the only inpatient facility for the southern half of Israel, about one half a million person catchment area and every bipolar patient in that area comes through our clinical facility, so we have a representative sample. Over the years I have also been in charge of residency training and research. I have a laboratory I co-direct with Professor Galila Agam, who is a neurochemist, and we have several post docs, half a dozen doctoral students and an active neurochemistry program involved in mood stabilizers. I have always loved both research and patient care. Ever since leaving NIMH in 1974, I never wanted to keep my fingers out of the wet lab either, so I have managed to do all three things.

JC: It is quite remarkable that you still spend a full day each week seeing patients.

RB: This involves clinical care in addition to supervising clinical assessors, rating patients in studies.

JC: Maybe we could go back a few years and talk about where you were born and how you were raised?

* Robert H. Belmaker was born in Los Angeles, California in 1947

RB: I was born in Los Angeles, California in 1947, in a tent city for demobilized soldiers. My parents moved back to New York City when I was very young and I have no memory of California. I grew up in Brooklyn in the public school system. My mother was a housewife and my father was an electronics technician. Later, he began working for the United States Defense Department in electronics procurement. My father's whole family, his many brothers, sisters, nephews and nieces all died in Treblinka, so they had great hopes for me and my only sister. There was a great emphasis in the house on education. My father spoke frequently against medical experimentation; he identified that with the Nazis. To the end of his life he never understood why I was involved with medical experimentation, and he preferred not to know. My parents were simple people, interested in intellectual things. My father retired to Florida when I was entering tenth grade and I finished my high school education not far from here in North Miami High School. I was lucky enough to have two summer Fellowships in high school at the Howard Hughes Institute in immunology. I learned a lot of wet lab techniques, but it didn't grab me. I had an interest also in philosophy and knew by the end of high school that I wanted to do something in which I could combine philosophy with biology. I started Harvard College in 1963 as a philosophy major and then I heard from my friends what great economics courses I was missing. The only way I could take economics and philosophy was to become a biology major, which was basically pre-med, so you could take biology and chemistry while the rest was free. I took philosophy and economics as well some history of religion.

JC: That was a well rounded classic education.

RB: I enjoyed those four years and I've gone back to every college reunion. As soon as I retire I'd like to go back and take some more courses in philosophy.

JC: When did you finish at Harvard?

RB: With the class of 1967 and at that point I knew I wanted to be a psychiatrist. I was fascinated with the mind/body problem and I had taken some seminars to learn about psychiatry. I even had a senior seminar with John Meyer, who was the editor of the American Journal of Psychiatry. I was already engaged to my wife, who wanted to do medical school as well. We found out the Duke Medical School curriculum would give us two full years of electives so we decided to go to there together.

JC: How was it at Duke? What do you remember?

RB: We had a great time at Duke and we go back to all of those reunions, as well. The basic science courses were marvellous and we had teachers at the forefront of the field. I remember Handler, who wrote the Textbook of

Biochemistry. We became close and I loved biochemistry. By the end of the first year we had finished all of our basic sciences and in the second year we rotated through all of the major specialties, including psychiatry, each for seven weeks. The psychiatry rotation was marvellous and confirmed that I wanted to do that. The third year I did a full year elective in autonomic physiology and that was my first project in psychiatry research; it had a great influence on me. The field of autonomic physiology was influenced by the paper of Neil Miller in *Science* in the early seventies, claiming the autonomic nervous system could be operantly conditioned with reward and punishment, not only in a Pavlovian way. I spent a year trying to replicate that in a slightly different system but couldn't. I had a high impact experience by being taken to a conference by my mentor, Ben Feather, where Neil Miller publicly retracted his data, not under pressure from our group. It was amazing to see. It has influenced my whole concept of science ever since; one of our major problems in psychopharmacology is that a large percentage of what we find can't be replicated. Sometimes, even excellent work that was done with the best of intentions. I don't think we've dealt with this as a field. I would like to see a symposium at every meeting about this problem. A few years ago I proposed to organize such a symposium, but it wasn't accepted.

JC: You did your first research project while still a medical student?

RB: I was a third year medical student and we were given an elective to do research for a year.

JC: What do you think about research early on in medical school years?

RB: I have not been involved with planning curricula, so that I can't say that I have an opinion on that. In the medical school I have been involved with for the last 20 years only a very small percentage of students have any interest in research. My opinion is perhaps affected by that fact.

JC: What happened next in your career?

RB: On finishing up medical school at Duke there was a very smooth transition. We both stayed at Duke, my wife started in pediatrics and I began psychiatry. I started as a psychiatry resident and then did neurology. It was a seamless transition from medical school to residency. After a couple of years of residency I was accepted to NIMH into the clinical associate program. I was originally accepted into Bill Pollin's lab, but before I arrived he became the director of NIDA, the Drug Abuse Institute, which was established that year, in 1972. Pollin's unit on twin studies and genetics was taken over by Dick Wyatt. Wyatt already had his finding of low platelet monoamine oxidase (MAO) in schizophrenia and was eager to see if this was genetic. Bill Pollin had done a series of identical twin studies in subjects discordant for schizophrenia about ten years previously in

a large multi-disciplinary inpatient evaluation, and Dick Wyatt asked me to get those old records find those patients and take blood samples for platelet (MAO). The idea was that if in both twins MAO activity was low it was a genetic marker but if only the ill twin was low, then it was secondary to schizophrenia. They expected it would take two-years to do it because the twins were all over the United States. I got a free ticket to go on any airline I wanted. We had by then a little baby, our oldest daughter. Six months later I came back to Dick Wyatt and said, I've found all the twins and got all the blood. The paper came out in Science later that year. Of course, that is not the end of the story. I will jump ahead a couple of years and then go back. The first thing I did when I arrived in Israel and set up my own lab was to develop an assay for MAO activity in platelets. We couldn't replicate the original finding that monoamine oxidase activity is low in the platelets of schizophrenic patients. A struggle ensued, both within my-self and in correspondence with Dick Wyatt. We didn't have faxes then and we didn't have e-mails. So it was some phone conversations and a lot of letters. When and how to publish and especially the lack of replication was an informative experience for me. We eventually published it and that story is basically over now. But through the seventies and eighties there were about fifty papers on MAO in platelets of schizophrenics. Most people didn't find low MAO activity in schizophrenic patients, but a few did. It could be an artefact of antipsychotics because brain studies didn't find it. It was an experience for me; a high profile paper published in Science that ended up probably being not true. It doesn't mean that MAO isn't important in psychiatry. MAO inhibitors are important and it might be that MAO has something to do with schizophrenia, but if it is, it is not because of the findings in platelets. Even then, we couldn't say we saw it first. Our finding was an accident. That and my experience with Neil Miller affected me a lot. When I talk to young people I explain what research is for and it isn't only for the results, because often the results don't work out. You have to find other reasons why research is important, for example it helps patient care. If you do research only for getting results you are going to become depressed.

JC: That's quite a remarkable thing you just said. Maybe you could say more about that?

RB: Oakley Ray wrote a book called, *The Good Life*. Good life means, at least partly, that you don't put all your eggs in one basket. Sure, research is important, helping patients is really important, teaching students is important but having your own family life is also important. Doing some things outside of science was very important for me. I wanted very much to go

to Israel and help Israel, as this was important for my sense of achieving a worthwhile life.

JC: Very interesting. Tell us about the next phase in your scientific development.

RB: I finished that platelet MAO study in six months and was ready to do my next study. I loved NIMH; I had wonderful colleagues there. I learned a lot from Dennis Murphy about serotonin, drug metabolism and precursor strategies. I also had some time in that period to look in on Bob Post's clinical ward.

JC: We are up to what year now?

RB: I completed my clinical associate Fellowship in July 1974. In the months before my wife and I had to decide what we were going to do for the next few years I wrote to an old friend of mine, Elliott Gershon, who had been in Israel for three years, set up a small laboratory at the Jerusalem Mental Health Center, and I asked if I could join him for a year. He wrote back and stated he would be happy to have me. That year has lasted until now.

JC: That was a very long year!

RB: Right. Elliott decided to return to the States; his position opened up and was perfect for me. The Jerusalem Mental Health Center, where I was for ten years, was a hospital of about 300 beds with a catchment area of Northern Jerusalem. It was affiliated with the Hadassah Medical School, where I had an academic appointment, and where we had medical students. Elliott had hired a neurochemist and had a small neurochemistry laboratory; he had done a couple of clinical trials, especially one you have quoted in some of your reviews on lithium in depression. He had developed a tradition and I had the benefit of that when I started. I very much wanted to have the NIMH model, which didn't exist in Israel; for example, to have clinical trials on the ward, a laboratory program and cross fertilization. The first clinical trial I planned was with a young resident in psychiatry named Joseph Biederman. I gave Joe the job of seeing whether there was a cut off at a particular place along the dimension between bipolar disorder and schizoaffective disorder where lithium ceased to work. The design was to do an "add-on" of lithium or placebo to haloperidol treated, acutely psychotic patients. Some of the patients were bipolar manics; others were schizophrenic patients with "excited psychosis." All the studies I have done in Israel were "add-on" studies. The findings of that first study were published in the Archives of General Psychiatry, I think in 1979. There were about thirty-five patients included in it. We found highly significant benefits for lithium without any difference between the bipolar manics, and other patients. We were very proud of that study and have a gripe it was almost never quoted. One of the reasons why is that DSM-III was introduced and we didn't use DSM criteria.

Patients had DSM diagnoses but we didn't use that for the analysis. The other thing is that it was an "add-on" study and, at the time, "add-on" studies were unpopular and criticized. Now, we are coming back to them. That was the first of a series of "add-on" studies that followed basically the same design, Lithium added benefit whenever there was an affective component; it really didn't matter whether the patients met DSM criteria for bipolar disorder or schizoaffective disorder or schizophrenia. That conclusion might have been unpopular and hence the very few quotes of that study. Meanwhile, in the lab, we started to pursue the idea I had at NIH of trying to look at second messengers. I started to work in Jerusalem with an excellent neurochemist, Richard Ebstein and continued even after I left Jerusalem. He set up an assay for measuring cyclic AMP in human plasma, based on a paper by Sutherland, a Nobel Prize winner. That was a publication in which he describes if one gives a dose of epinephrine in an asthma attack subcutaneously and takes blood samples every ten minutes, you see a rise in cyclic AMP, exactly the same as occurs inside cells in response to stimulation of the adrenergic receptor. What we were able to show was, in patients on lithium at therapeutic dosages, the cyclic AMP response to epinephrine was completely blocked, compared to controls. We published our findings in *Nature* in 1976 and they have been replicated since then. Ours was one of the first translational research studies where a finding in basic science, namely that mood stabilizers affect second messengers was replicated in humans. Something which might have been put aside as occurring at non-therapeutic concentrations was shown to work in patients. We also did another "add-on" study in patients which was also published in the *Archives of General Psychiatry*. It was "add on" carbamazepine or placebo in haloperidol treated patients with "excited psychosis". Again, we found benefit without any relationship to diagnosis. That study was done by Ehud Klein who is now Chairman of psychiatry at the medical school in Haifa. He was a young resident of mine at the time. Joseph Zohar was also a resident and he is now a Professor of psychiatry in Tel Aviv and the President of the ECNP. We were studying second messenger measures in spinal fluid and Zohar published a series of studies showing elevations of cyclic AMP in acute psychosis. Bernard Lerer was also a resident with me then. He is now a Professor of psychiatry at Hadassah Hospital and past editor of CINP's *International Journal of Neuropsychopharmacology*. It was about that time Vetulani and Sulser published findings that turned the old catecholamine hypothesis on its head, saying antidepressants induce postsynaptic sub-sensitivity rather than an increase in synaptic monoamines. Salbutamol had just been released for clinical use in the

treatment of asthma. I thought intravenously Salbutamol should increase plasma cyclic AMP just like other adrenergic agonists and proposed that project to Bernard Lerer. He did a great job. Patients were tested at baseline for cyclic AMP level, and then treated for depression; after a short wash-out IV salbutamol was given for a month. We were able to demonstrate in vivo in humans the sub-sensitivity of the β -receptor second messenger response. For this work, along with the lithium paper in Nature, I received the AE Bennett Award of the American Society for Biological Psychiatry in 1980.

JC: You have received quite a few awards. Anything you want to say about those accomplishments?

RB: When I receive an award, it does make me think of why I am getting it. Often, by the time I get the award, the reason why either has not been replicated or shown not to be true. I have continued my research with second messengers for some time. But each time we push away the border of our ignorance we find a whole new layer. We didn't find the answers to mental illness and psychotropic drug actions with second messengers. So, we have gone on to third messengers. But we may be wrong and our problem is in the biological heterogeneity of psychiatric diagnoses.

JC: When you look back at the contributions you have made, what are the most important?

RB: I prepared a bit for this interview, but that doesn't make answering your question any easier. I remember reading a paper in about 1990 by Mark Hallett on magnetic stimulation of the brain and was amazed that one can stimulate an area of the motor cortex and move a person's finger or toe. I thought this has got to be important for psychiatry. So, I got a grant to study it. This is how I became one of the first to propose the use of transcranial magnetic stimulation (TMS) in psychiatry.

I remember reading, about the same time, Bob Cloninger's first papers on the genetics of personality, using his tri-dimensional personality scale that supposedly teased out the genetic components, and also the first papers on the dopamine- D_4 receptor, a highly polymorphic receptor in humans. I wondered might the two be brought together so we did a study with 150 normal subjects to see if they could. I realize that is a small number.

JC: Embarrassingly small!

RB: Anyway, subjects completed Cloninger's tri-dimensional personality scale and Dick Ebstein's lab genotyped them for D_4 polymorphism. There were relationships. I called one of my students who was doing a two year post doc at NIMH with Dean Hamer. His name is Jonathan Benjamin, now

Professor of psychiatry in Haifa. He had access to normal-volunteers at NIH and within two weeks replicated our findings. Our papers were published back to back in Nature. I am proud of being part of founding the field of molecular genetics for personality. The idea of looking at monoamine related polymorphisms in the context of personality, rather than psychopathology, was a contribution I was very much involved in. I edited a book with Johnny Benjamin on that. I also edited a couple of books with Mark George on TMS. We continued to do some good work in personality genetics after Johnny Benjamin came back from NIMH. But since he has moved to Haifa, we have not done much research on that. We remain very active in the second messenger field with lithium in the laboratory, especially since we have calbindin, a protein with a site that activates inositol monophosphatase. We have been screening peptides on that binding site looking for possible lithium like compounds. Some of our more exciting new work involves knockout mice. The inositol monophosphatase-1 knockout mice have pilocarpine sensitivity and behave on the Porsolt forced swimming test as if the animal is taking lithium. The inositol transporter knockout mouse has exquisite sensitivity to pilocarpine, and behaves on the Porsolt test as if the animal was taking an antidepressant. Our clinical trials program has also continued. We are currently finishing a clinical trial with valnoctamide. It is a valproate derivative that is not teratogenic. We are doing it with the “add-on” design I have been using for the last thirty years. Patients are on risperidol and valnoctamide or placebo is added. If it works valnoctamide would be an alternative to valproate for patients who desire to become pregnant.

JC: Interesting. What do you think is going to happen in the field over the next five to ten years?

RB: When I think about the future, I like to think in terms much longer than five to ten years. We have been over promising quick results and new treatments. Of course, the public is desperate for new treatments but part of medical tradition is not to make promises, even under pressure. It is unfortunate patients go to a quack who makes irresponsible promises and not to the ethical physician. I don't think we can predict medical progress at a time when you have hundreds of variables, when you have second and third messengers and so on. Statistical models can get so complicated it may or may not be possible to get a significant answer. So we need to lower our promises. I am not sure we can promise the public, anytime in the near future, genes for psychiatric disorders. I don't think it is wrong to say we all want more treatments quickly but we need to make an ethical agreement among scientists we are not going to promise what we can't deliver. And we need to quit writing papers which sound as if

we have the final answers. To have a symposium on ethics, like we do at the ACNP, is wonderful but we also need symposia on replication issues. That is what I would to see happen in the future.

JC: Thank you.

WALTER A. BROWN

**Interviewed by John F. Greden
Scottsdale Arizona, December 9, 2008**

JG: Good morning. My name is John Greden and today is December ninth, 2008, and I am here on behalf of the ACNP interviewing Walter Brown.* We are at the ACNP Annual Meeting in Scottsdale, Arizona. Walter and I have known each other for a number of decades. What I would like to is walk you through your life chronologically. Tell me first where you were born and about your background?

WB: I was born in Manhattan, New York City, and lived there until I was about seven years old. Then we moved to Westchester County, so I grew up in the suburbs of New York. I went to local public schools and did my undergraduate degree at Hamilton College in Upstate New York. Then, I went to Duke University for my MD and following that I was an intern in 1967 and 1968 at George Washington University Hospital before doing my residency in psychiatry at Yale.

JG: That was a very prominent time for Yale in psychiatry. You were there during some halcyon years.

WB: Ted Lidz had just taken over as Chair from Fritz Redlich and Mort Reiser came while I was a resident. I split up my residency with two years at NIH, for which I got one year of residency credit.

JG: You have done a number of very important things, but how did you start to get interested in neuropsychopharmacology?

WB: I was interested in how the brain works and particularly in what was going on in the brain during certain psychological states. When I first started doing research, in the last year of my residency, one of the leading approaches for getting at brain mechanisms was the so-called neuroendocrine strategy. Radioimmunoassay had just become available and you could measure blood levels of pituitary hormones. A handful of people felt that measuring things like growth hormone (GH,) prolactin, and cortisol would be a window into the brain. So, that's how I started and I did my first study in the early seventies while still a resident. Then, I continued with my research as a Fellow at Yale, looking at cortisol, GH and free fatty acids (FFA), which reflect peripheral norepinephrine (NE) activity during experimentally induced specific affective states. We used films to make people anxious, angry or sexually aroused, put catheters in their vessels, drew blood and measured all kinds of stuff.

* Walter A. Brown was born in Manhattan, New York City, New York in 1941.

JG: We're still using some of those strategies. You have also done some early work on pain. Were those linked with this exploration?

WB: Not really. I did a pain study while I was still a medical student. Now you asked the question makes me think they were linked but I didn't see that at the time.

JG: What did you do after residency?

WB: I did a Fellowship in neuroendocrinology supported by the Foundation's Fund. It was a two year Fellowship I spent doing the research I previously mentioned. It was at that time I learned how to measure FFA and so forth. I spent the second year working with Dorothy Krieger at Mount Sinai Hospital, one of the leading centers of endocrinology, commuting from New Haven down to New York everyday, which was quite a commute. I spent the whole year in her lab learning neuroendocrine techniques. She was very interested in the ACTH-cortisol relationship and I worked with her on that. Although I didn't learn all that much it did provide me with a kind of neuroendocrine credential and she was quite supportive of my later grant applications. I also visited Bob Rose who was at Walter Reed, doing work with GH.

JG: He did some research with air traffic controllers?

WB: Yes. I was also in touch with John Mason who was originally at Walter Reed and then came to the Yale department. Seymour Reichlin, who was not a psychiatrist but involved in basic neuroendocrine research, was a distant mentor. I used to talk to him about research and somehow got connected with him. He was very supportive and helpful. George Heninger at Yale was also a mentor and I came to ACNP meetings as his guest. I worked closely with him initially on my research projects.

JG: Some of your mentors at Walter Reed were there during the time I was. There were not as many people involved in neuroendocrine research in psychiatry in those early years.

WB: Right, there were very few.

JG: During your residency you won the Seymour Lustman Award didn't you? Do you remember the research you got the award for?

WB: I am not sure, but I was the first recipient of that award. I was probably the only resident doing research so I can't claim I did anything outstanding.

JG: Did you start off in the neuroendocrine arena with any hypothesis, or were you trying to learn a strategy?

WB: I was trying to learn a strategy. Our ideas about what these endocrine measures were going to tell us were extraordinarily naïve at the time. But one of the ideas I had was that we could demonstrate differences in brain activity associated with different affective states. I also wanted to learn strategy and was interested in higher brain regulatory mechanisms

for the endocrine system; that was the reason I started looking at the relationship between dopamine (DA) and GH. I also did studies on drugs with fairly specific and well defined effects on neurotransmitter systems in the endocrine system. So, I was interested in both the output as well as what might be going on in relevant brain sites that produce changes in endocrine activity.

JG: What were some of the challenge drugs you were using to understand underlying mechanisms and as a potential window into the brain?

WB: I used apomorphine, a dopamine receptor agonist, in rat and in human studies and looked at growth hormone and cortisol responses. I also used methylphenidate and amphetamine as challenges. There was a period from about 1975 to 1985 when I was looking at the effect of psychotropic drugs on the endocrine system, not as much to identify basic brain mechanisms, but to see what these drugs were doing to hormones, and if that had clinical implications.

JG: Were you working at the time with normal volunteers, patients, or both?

WB: Initially, I worked with healthy volunteers.

JG: So, you were trying to clarify some of the underlying mechanisms in the brain?

WB: Yes! In collaboration with Harbans Lal at the University of Rhode Island, we did studies in rats, looking at provocative stimuli to prolactin and growth hormone.

JG: In many ways you were doing translational research, working in animals and wondering how those results translate into patients. Did you accomplish that?

WB: I am very much drawn to the idea of trying to uncover basic mechanisms. So, the answer is probably yes. I have tried to do all of those things, working on animals, normal volunteers and patients, sometimes simultaneously but certainly not always successfully.

JG: How long did you stay active in laboratory work throughout your career?

WB: I started in about 1972, and probably continued for twenty years. That would be a fair guess.

JG: Do you remember the first time you presented a paper at a scientific meeting?

WB: I am not sure I have it quite straight but I do remember going to London to present a paper at an obstetrics and gynaecology conference.

JG: So, it was a presentation at an international meeting. What was it about?

WB: While I was working at NIH I had done studies in psychosis during pregnancy and I presented our findings.

JG: Was it a good experience?

WB: Yes, it was very exciting.

JG: Let us go back to the neuroendocrine story. At the time you started there was a lot of emphasis on possible laboratory correlates of depression. Do you want to reflect on that?

WB: When I read the work of Barney Carroll and his associates in 1976, that galvanized my interest, and the first clinical research I did was to try to replicate those findings with the dexamethasone suppression test (DST) in depression. So we were the first group to replicate Carroll et al's work.

JG: I remember it!

WB: We replicated it down to the last detail. We had about a forty percent abnormal DST response in depressed patients, and none in our non-depressed comparison group. It was the first research ever done at the VA hospital in Providence and that started me on a decade of work on the DST. I was very much taken by the idea this might be a diagnostic test for depression. But, I diverged from Carroll's group by being interested in how depressed people who were abnormal on the test differed from those who did not have an endocrine abnormality. But then the DST was thrown out with the bath water, it was abandoned much too abruptly. I still think there is probably a sub-set of depressed patients who have pituitary–adrenocortical abnormality. I believe there is some value in those measures in depressed patients, but people have gone on to other things.

JG: It is one of the better documented neurobiological parameters associated with depression but its translation into clinical practice became too much of a hurdle.

WB: Absolutely!

JG: You also had a moderately influential letter to *Lancet* where you talked about possible treatment response associated with DST abnormality?

WB: We thought people who were abnormal on the DST, might respond to a different class of antidepressants than those who were normal. The idea was that antidepressants primarily affecting NE would be effective in people who were DST non-suppressors; whereas those drugs affecting serotonin might work better in suppressors. It was based on a study with a small sample size. I don't think our findings held up, but what has held up with respect to treatment response, is the notion that people who have excessive cortisol secretion, DST non-suppressors, don't do well on placebo. That has been replicated many times.

JG: I don't know whether that led you into studying placebo mechanisms, but you have stayed in that area of research for a long time. Could you talk about that?

WB: I backed into placebo research. Mihaly Arato joined me for a short period and we were looking at treatment outcome in DST suppressors and in non-suppressors using data from clinical trials conducted by Ram

Shrivastava's in New York and Providence in patients who were randomly assigned to receive fluvoxamine or placebo. The idea was to look at whether DST non-suppressors and suppressors differed in their response to fluvoxamine. As it turned out they didn't. But they differed dramatically in their response to placebo. The suppressors had about a fifty to sixty percent placebo response rate and the non-suppressors placebo response rate was close to zero. It was Mihaly who noticed that in the data. So, that got me interested in the placebo response in relationship to pituitary-adrenocortical measures and in placebo research in general. Although, I have written a good number of papers that deal with placebo, most of my writings in this area are not based on our original research.

JG: So, it started with the research you did with Arato. Wasn't he Hungarian? Do you recall when you and I were actually in a meeting in Budapest in the 1980s?

WB: It was a meeting of the World Psychiatric Association. I remember it very fondly!

JG: Let us shift to another area of your interest, suicide.

WB: I was involved with collaborators at Brown, looking at the extent to which depressed patients with pituitary-adrenocortical hyperfunction may be at risk for suicide. We have a large psychiatric hospital in Providence called Butler Hospital that started doing DST on all their admissions. So, we had a large database to sort out whether pituitary-adrenocortical hyperactivity had any relationship to suicide risk. And we found it did, as have Coryell and others. One of the ideas about suicide that has been around for a long time is that depressed patients are at heightened risk for suicide in the early stages of recovery because of their increased energy to act on suicidal impulses. I was interested in how that idea came about and we were able to trace it back to Benjamin Rush and Kraepelin, who both had patients who committed suicide just as they looked better. That doesn't mean people are at any particular risk for suicide when they start to get better, but it means it can happen. There is no direct data tracing suicide in relation to symptoms during recovery, but looking at epidemiologic data one sees the rate of completed suicides is higher before people begin treatment. So, we wrote a paper about this and it is coming out soon. It is interesting how certain ideas get passed around and accepted as received wisdom, even though they may not be true.

JG: You also have had some interest in whether adolescents or young adults are at special risk if they are being treated. Would you like to comment on the current controversy in this area, the black box warnings about prescribing some drugs for that age group, and give some advice to the field?

WB: I would love to be on record about this! I think that the black box warning is ridiculous! It largely came out of political concerns and a desire on the part of the FDA to assuage the concerns of people who had family members who committed suicide while on antidepressants. The data do not support the notion people kill themselves because of the things antidepressants do to them. The whole idea is bogus!

JG: Thank you for sharing this with us because suicide is a risk associated with depression more than with any other diagnosis, and the worst approach to enhancing suicide risk is not treating depression.

WB: Right! There are lots of irrational things that go on and this is one.

JG: During your activities you have worked with a number of students and mentees. Would you like to comment about your experience with them?

WB: Working with students is a most gratifying experience. I have worked with a good number of medical students, residents and did research with them. I have also worked with a good number of psychology interns at Brown, who then went on to do research related to the areas that we were working on. I did studies on testosterone and behaviour and a number of our students continued that research. I have always valued collaborations, both with peers, with my own mentors and with younger faculty.

JG: It dawns on me, as we have been talking, that we still have to walk through your different appointments after your residency.

WB: After my Fellowship at Yale from 1972 to 1974, I joined the faculty at Brown Medical School and have been there ever since. I went up through the ranks, starting as an assistant professor and, then, became a full professor in due course. I was at the VA, one of the Brown affiliated hospitals, but I left the VA in 1995 and joined the part-time faculty at Brown, which I continue to be on. In 1997, Gregory Oxenkrug asked me to help teach the residents at Tufts where he had moved to from Brown and I started to do that. So, I am now teaching part-time, both at Brown and at Tufts, Saint Elizabeth Medical Center in Boston. In the middle eighties, I also started a parallel career in clinical trials.

JG: Clinical trials?

WB: It is a commercial endeavour. I started a free standing clinical trials clinic first, but then it became a multi-center organization. I never put as much time in that as into my academic work, but that certainly is a parallel career.

JG: You watched, I would guess the department of psychiatry at Brown University and specifically at Butler and the VA in Providence during the years you have been there. Do you want to reflect on that?

WB: I think of Brown as a new medical school although other people think it has been around for a long time. It really started in 1975 and I was one

of the first faculty members in the department of psychiatry. I wasn't the first, but I was in the first group of full time faculty members. That was one of the reasons I went there. I thought it would give me freedom to pursue things I might not have had in a more mature setting, like Yale. Brown changed dramatically during the years. We have now more than one hundred faculty members; at the time I started we were just a handful. In those early years I was always on search committees looking for people, because I was one of the few faculty members. There was very little research money at Brown at the time; now there is a substantial amount and the department includes several hospitals. The residency program in the early years was quite weak. In the 1980s we had so many problems recruiting residents that, at one point, I suggested we delete the residency program and focus on medical school education and other things. But then we got a new residency director and things started to turn around; now it is a fantastic program. We are getting great residents and that is probably one of the most significant changes.

JG: Let's talk about your linkages with the ACNP. When did you join?

WB: In 1983. I went to a meeting before I joined and I was on a couple of panels. I think there was one panel Barney Carroll chaired and I was invited to talk about my DST work. I also presented some of my work on hormones and affective state before I became a member. According to the records I think I have missed two meetings since. It is the meeting I most value; it's the place where I have always presented my new findings first. It has been extraordinarily valuable in having contact with colleagues, being able to hear the latest stuff, and meeting informally with people doing what I was doing. It has also been a lot of fun.

JG: The annual meetings of the college have provided the best blend of basic and clinical scientists for fertile discussions.

WB: A lot of people say, and I think it is true, that there is a little less clinical stuff now, but I think that is okay. The program committee works very hard to make sure clinical topics are included. There is very much a move towards molecular genetics but probably that is appropriate.

JG: What impact do you think the ACNP has on our field and on psychiatry and what would you predict for the future?

WB: The ACNP has provided a tremendous source of information and in that sense it nourishes the field. It will probably continue to do that. Maybe I can give you a specific example; you know, I am writing a book about the placebo effect.

JG: Yes.

WB: I am pulling together a lot of information on placebo and somebody came up to me at the poster session and asked whether I heard Ellen Frank's

talk? Apparently in a study she was doing there was a difference in placebo response between people with different intelligence.

JG: I was there.

WB: It was something I never heard before so I am going to find out what she actually discovered.

JG: They found it in a collaborative study between Italy and Pittsburgh. It is another illustration that we still don't understand the placebo response and all of its ramifications. If you were to give advice to the College about what it should do to sustain its influence over the next decade, what would it be?

WB: One complaint I have about the ACNP is how they select members. I am concerned that sometimes the process gets politicized. It would be good to make sure that people who have a primary clinical background and are doing good clinical research have as much access to membership as those working in the basic sciences. It is also important to keep the annual meetings small and allow a lot of time for discussion.

JG: I noticed that in your early years you did some work on amyotrophic lateral sclerosis (ALS). I find myself thinking we are closing a loop by having a drug, riluzole, which was explored for refractory depression but ended up as an agent that has a use in ALS.

WB: Riluzole, yes.

JG: It illustrates how little we still understand about underlying mechanisms and how we need to keep exploring new avenues.

WB: Oh, absolutely!

JG: Haven't you given some presentations on ALS recently?

WB: As a sort of third career, I started freelance writing and I wrote a paper for a magazine called Applied Neurology about ALS. I summarized what is known about its psychological features. There is a big controversy whether it's true people with ALS are unusually nice. That's at the heart of ALS psychology. There are many experienced neurologists who are absolutely convinced there is something psychologically unusual about people with ALS.

JG: Again, an illustration of how much more we need to understand. You have spent some time in Nicaragua in your early years. What was that about?

WB: I went there for two summers as a medical student, as part of a team to some remote areas to provide medical services to the population. I haven't done anything like that since, but it was a very gripping experience to be in that environment.

JG: Did it influence any of your subsequent thinking about research?

WB: I wouldn't think it influenced my research but perhaps it influenced my thinking about some broader issues.

-
- JG: Are you happy with the way your academic career turned out and the various explorations you have made?
- WB: I think so! Would I have done anything differently? Probably not. I don't think that anybody does research with a primary motive of discovering something great, helping mankind or winning the Nobel Prize. You do it because you enjoy the process.
- JG: I believing all of us are engaged in constructing a pyramid. I am not sure it ever reaches completion, but we all make little contributions to it. You have put blocks into this pyramid in a number of arenas, neuroendocrine mechanisms, challenge strategies, clinical trials, placebo response and suicide. They all are oriented toward striving for better approaches to clinical delivery. Where do you think the field is going to go, with regard to those arenas? Could you give us some predictions as we near the end of this interview?
- WB: We are going to learn more about the pathophysiology of the major psychiatric disorders like depression, schizophrenia, ADHD. We are on the path of that. With some of the brain imaging findings in depression we are moving towards uncovering its pathophysiology. And, when that happens we will have much better treatments. The treatments we now have are lousy; I don't think the antidepressants work very well. The antipsychotics work a little bit better for positive symptoms of schizophrenia than the antidepressants do for depression. We need much better and more specific targeted treatments and I think that is where the field is moving.
- JG: Would you have any advice to the next generation of investigators?
- WB: Do what they are interested in and, when they are using a technique, learn about it in depth so they understand what it measures and what its value is.
- JG: That is good advice. Are there any items that we have not talked about that you would like to put into this historical perspective?
- WB: You asked great questions which caused me to consider things I haven't thought about in a long time. We covered a lot of material!
- JG: You jokingly said you weren't sure about the historical significance of some of the things you have done. As we have made this four decade journey, does it not strike you that you have made a lot of contributions?
- WB: I think I have made some contributions, but what I most value is not necessarily the same as what the field might. And, that intrigues me! Because of this interview I went over my CV and recalled some things I have done so I believe maybe I made some small contributions to the pyramid.
- JG: And, the pyramid is better because of those contributions. Thank you on behalf of the college for participating in this historical documentation and for the contributions you have made in the past and those that are still to come.
- WB: And, I thank you.

WILLIAM E. BUNNEY, JR.

**Interviewed by Thomas A. Ban
Waikoloa Village, Hawaii, December 10, 2001**

T.B: This will be an interview with Dr. William Bunney* for ACNP's Archives of Neuropsychopharmacology. We are at the annual meeting of the College in 2001 in Hawaii. I'm Thomas Ban. Let us start from the very beginning. Tell us where and when were you born, say something about your early interests, education, professional training, and how did you become involved with neuropsychopharmacology.

W.B: I was born on June 27th, 1930, in Boston, Massachusetts. After six months, we moved to East Lansing, Michigan, and after eight years we moved to New Jersey, near Princeton. We stayed there until I went off to college in Oberlin. Then, I went to the University of Pennsylvania Medical School; took an internship at Henry Ford Hospital, and a residency in psychiatry at Yale. After Yale, I had my first job at the National Institute of Mental Health.

TB: When did you decide about medical school?

WB: Very early in high school, in my sophomore year. I had a really great biology teacher. She asked everyone in the class to do a science project. In reading through our biology book, I noticed that they did not know the digestive enzymes in the earthworm, *lumbricus terrestris*. I thought that would be an exciting topic to study so I bred earthworms, dissected three areas of their digestive system and did crude assays for three enzymes. Prior to doing this, I went to the University Library and read up and talked to a couple of experts in biology about the work I intended to do. I found that in fact no one did know what digestive enzymes there were in the *lumbricus terrestris*. So, I wrote it up and got an A+ on the project, and was hooked on science from then on.

TB: That's great!

WB: So that was the beginning of my interest in science. When I was in college I wasn't sure whether I wanted to go into psychology, psychiatry or either. I also went through periods of time when I wanted to be a minister. One summer I served as a minister for a rural community and that was fun. There were three people and four dogs in my first congregation and by the time I left two hundred more people had joined. But even though I enjoyed that, I decided very rapidly that I did not want to be a minister. Before finishing college, I was pre-med, applied to a couple of medical schools and got into Cornell University and the University of Pennsylvania.

* William E. Bunney, Jr. was born in Boston, Massachusetts in 1930.

I decided to go the University of Pennsylvania. During medical school, I did some research on the thalamus, none of which was ever published.

TB: Could you tell us something about the research you were doing?

WB: I don't remember the details but it was in anatomy, studying the thalamus in rats. After I finished medical school, I decided I wanted to go into science so I went to the National Institute of Health (NIH). My dad had previously hired Jim Shannon who was then director. He had hired him to head up research for E.R. Squibb & Son where my dad ended up being Executive Vice President. Jim Shannon headed up their Research Institute and was then recruited from that position to head up the NIH. He was probably one of the most famous scientists to hold that position. My dad got me an appointment with Shannon and I went in to see Jim. I remember it was a hot summer day, Jim was in a totally rumpled seersucker suit and said, "I think you should go back and take your internship, take a residency, and then come back to see me." So I got an internship at Henry Ford Hospital and, about half way through, I began interviewing because I was still interested in psychiatry. I liked it in medical school and in my rotating internship.

TB: Didn't you do your residency at Yale?

WB: I went to Harvard first, was interviewed but they would have nothing to do with me. So I went to Yale and they accepted me. But then, I was still interested in many other things.

TB: Like what?

WB: When it came time for me to make a decision on whether or not to accept the Yale appointment, I decided I wasn't going to go; I wrote and told them I was turning it down. I planned to go to Colorado, work in an Emergency Room, ski on the weekends, and finish a novel I was writing. Gene Brody was in charge of Residency at Yale. He wrote me and said, "We've turned down 31 people for this position and if you're not coming, let us know in 24 hours!" I thought it over and figured maybe I could get good material for a novel in a psychiatric residency. So I wrote back and said, "OK, I will come."

TB: What happened to the novel?

WB: I had written half the novel but I never finished it.

TB: Hmm.

WB: After my first day in psychiatric residency, I totally loved it and things moved in a straight line from then on. I came close to not going into psychiatry.

TB: It seems you did. You were interested in writing.

WB: I was and I ended up doing a lot of writing. I have written over 365 scientific papers and edited seven books. I have also written a lot of poetry.

TB: So you are still writing?

WB: It's on the back burner but some day I will probably do that. All my life, I have written poetry.

TB: OK. So after your first day in residency, you fell in love with psychiatry.

WB: It was love at first sight. I wrote my first paper with Tom Detre who was at Yale at the time. He was somewhat of a maverick back then; he was saying we should treat patients with drugs when the rest of the discipline was saying we should use psychotherapy and psychoanalysis. I wrote my second paper with Danny Friedman who was also there.

TB: What was the work you wrote up in that first paper?

WB: Tom Detre had developed a vibration machine which we tested. His hypothesis was that sensitivity to vibration was perceived differently by schizophrenic patients. So we did a study where we investigated the responses of normal individuals and the responses of schizophrenics and, sure enough, the schizophrenic group exhibited a difference in sensitivity to vibration.

TB: Statistically significant?

WB: Yes. We found significant differences.

TB: And that is what you published?

WB: We published the data.

TB: When was this?

WB: Probably in 1959. I remember that because in 1960 I went to NIH.

TB: What about the second paper with Danny Freedman?

WB: We were interested in Rapid Eye Movement (REM) sleep which was already known at that time. We had one subject we hypnotized, telling her she was watching a ping-pong game. We wanted to see if we could replicate REM sleep with hypnosis.

TB: Did you do the hypnosis yourself?

WB: I did, but this was a very susceptible person. We analyzed her sleep EEG.

TB: By hand?

WB: It had to be by hand back then.

TB: You talked about Tom Detre and Danny Freedman. Was there any other person at Yale you would like to mention?

WB: Another very influential person at Yale was Jules Coleman who was a maverick and taught psychotherapy. His was a brilliant psychotherapist and had a cult among the residents. After that I applied to the NIMH and they hired me.

TB: As a resident what kind of drugs did you use?

WB: We were using reserpine and imipramine. Tom Detre was supportive; everybody else thought he was far out.

TB: What about ECT or insulin?

WB: When I took my psychiatry rotation for a month at Henry Ford Hospital they were using insulin. Every severely sick patient was treated with insulin coma or ECT. In the course of ECT some patients were regressed down to diapers and bottles. So, these grown people would be put in diapers and given baby bottles. It was amazing.

TB: So, they did regressive ECT.

WB: I don't think Henry Ford Hospital was very progressive at the time.

TB: What was your first assignment at NIMH?

WB: I was in Lyman Wynn's branch in Jim Moss' section, in charge of the depression ward. David Hamburg was branch chief at the time.

TB: Was Joel Elkes there?

WB: Yes, and also Fritz Freyhan as well as Seymour Kety. Kety and Lyman would argue all the time. Bob Cohen was there; he was the person who did everything. He and John Eberhardt hired everybody, they were a team. (See Cohen in Volume 1; Elkes in Volumes 1 & 10; Kety in Volume 2).

TB: Were your activities connected in any way with the research in Joel Elkes' group?

WB: Totally separate. Joe Elkes was at the St. Elizabeths Hospital. I went there on occasion, but not more than ten times.

TB: Were you one of the first hired for a new program?

WB: Jack Durrell had one ward and I had another, Jack was a little more senior. He was at Yale with me and when he came to NIMH he worked with Kety. He had a biological ward and my ward was transitional, not completely biological.

TB: Didn't you work with David Hamburg?

WB: Dave Hamburg and I wrote a paper about a rating scale paper that ended up as a citation classic. It also laid out how you develop and run a research ward. So it was a methodological paper that probably set criteria for developing research wards around the world.

TB: Where did you publish it?

WB: In the Archives.

TB: So, that was an influential paper?

WB: I think it was. After that paper was published for the next ten years scientists who wanted to develop a research ward came and visited us.

TB: Could you tell us about the research you were in charge of?

WB: We collected cerebrospinal fluid, urine and blood samples and analyzed them for cortical steroids and metabolites of the neurotransmitter-related compounds we were interested in. Collection of those samples went on 24-hours a day. We also developed a rating system in which the nurses rated the patients every hour, 24 hours a day. So we had behavioural

ratings and biological data we could correlate. We developed an informed consent system that was as good as any developed since. The process involved patients in a group meeting, hearing about the procedure before deciding whether to participate. A patient would say, "I'm supposed to have a spinal tap?" and someone in the group would say, "Oh no, don't do that, it was so painful," and three other patients would say, "I didn't even notice it." That was informed consent! Everybody sitting there talking about the process, giving individuals a chance to make up their mind. Most of them went along with it and some of them would say, "No, I don't want to do that." It was totally different than reading a piece of paper and signing your name. That was a long time ago, before anybody even thought about Institutional Review Boards (IRBs) or informed consent forms.

TB: Yours was a depression ward?

WB: We got the most severe depression cases in the entire metropolitan area. These were really sick, very depressed patients, many suicidal. I remember one research subject, a physicist whom we had on constant urine collection. Whenever subjects left the hospital, they would take their specimen bottles with them. One winter day this individual went to a bridge of about a 150 feet elevation and jumped into the water. He left his specimen bottle at the point where he jumped; there was a note, "Please return this to Dr. Bunney at the NIH." Fortunately, he was saved because there was a man in a rowboat who saw him jump, got him out of the ice flow and saved his life.

TB: The research was a kind of group activity; everybody participated?

WB: Right, it was a research team and, in particular, the nurses felt they were a part of the team. There was no question about that. They would argue about the ratings and try to get them right.

TB: Were you using your own rating scale?

WB: We used the scale Dave Hamburg and I developed. A lot of researchers used it.

TB: Could you tell us something about your publications in those years?

WB: In one of the papers we reported our findings on urinary 17-hydroxycorticosteroid levels in 90 patients. In 4 patients who committed suicide or made a very serious attempt 17-hydroxycorticosteroid levels were highly statistically significantly increased. We always said that should be used as a screen when thinking about whether one should discharge or send a patient out on pass. It was a valid test. It was replicated in three or four studies.

TB: Any other publication you would like to mention from that period?

WB: One early publication was the catecholamine hypothesis paper that also became a citation classic. It was written at the same time Joe Schildkraut

wrote his catecholamine hypothesis paper; so there were two papers which were somewhat different.

TB: Any other publications?

WB: Another paper we wrote early was a report on a double blind placebo controlled lithium trial in which we had one patient whom we took off lithium seven times and each time had a striking relapse. The findings of that study had an effect on the whole field. Our paper came out about the same time as Mogen Schou's. It was a product of the research methodology we used; we had ratings every hour every day. We could see patients receiving placebo got worse and, when put back on lithium, got better within a few days.

TB: Wasn't it one of the first papers on lithium in the United States with favourable findings?

WB: Before my paper, Sam Gershon and later Ron Fieve did work on lithium.

TB: Who were your primary collaborators in those years?

WB: Dennis Murphy, Fred Goodwin, and John Davis. I hired all three at NIMH as clinical associates.

TB: How long did you run the depression unit?

WB: Ten years maybe. Later, I was in charge of the Biological Psychiatry branch. Chris Gillin worked with me in those years.

TB: Any other research before you became branch chief?

WB: I did some work with Jack Durrell. Keith Brodie, who ended up being President at Duke, was working with me at the time, before he went to Stanford.

TB: What did he do?

WB: Keith participated in many of our research projects. He published a record number of papers for a clinical associate and still may share the record with Dave Kupfer. It was a very productive period in my life time. There were many people working with me in those years. I once put together a list of scientists and there were 72 collaborators over a period of ten years.

TB: 72 people!

WB: There were a lot of clinical associates.

TB: Would you like to mention a few of them by name.

WB: The key ones, Goodwin, Murphy, and Davis I already mentioned. Dave Janowsky was another one who worked with me.

TB: Then you became Section Chief?

WB: I became Section Chief, and, then I was on vacation when I received a call. Burt Brown said I want you to be Director of what became NIDA. I went back, talked with him and decided to do it. So for three and a half years, I was director of Division of Narcotic Addiction and Drug Abuse, as

it was called. During that time my budget went up from \$44,000,000 to \$240,000,000. I had about one thousand people working for me including the staff at Lexington. That was my PhD. in administration because I was in charge of education, research, development of the clinical programs, and of all the international interactions. We funded Sol Snyder when he did his opiate receptor work and. I participated in the news conference where he and Candace Pert announced the discovery of the opiate receptor.

TB: Where did you move after NIDA?

WB: I had made an agreement with Burt I would be able to go back to the Institute if I wished and he honoured it. Just about the time I went back Lyman Wynn left the Institute and I took over his Branch. I hired a bunch of basic scientists including Dorothy Gallagher, John Tallman, and Candace Pert who did outstanding basic work. I also negotiated so that I could develop a child program and I hired Judy Rapoport. Judy came to head up the child program and did a spectacular job. I had a sleep study program with Chris Gillin and a genetic program with Elliot Gershon. So we put together a genetic program and Judy put together a child program. We had Will Carpenter on the schizophrenia ward before he went to head up the program at the Maryland Research Institute.

TB: What about Bob Post?

WB: Bob Post was there. When I took the job at NIDA, Dennis Murphy was made a Branch Chief and Fred Goodwin was also made a Branch Chief. Then John Davis went to work with Danny Freedman in Chicago.

TB: As branch chief you created several programs. Could you tell us something about the research in the different programs?

WB: Looking at dopamine metabolites and schizophrenia was a hot area in those years. There were small drug trials that we did. In depression we tried cocaine, and we used naloxone to see if we could turn off hallucinations but could not replicate the Scandinavian findings. We did some work on dialysis in schizophrenia trying to replicate others findings. We published a number of negative papers. We looked at GABA agonists in schizophrenia and they didn't work; that still stands. We gave high-doses of diazepam and that did work in some really sick schizophrenics but it had side effects that made it unusable.

TB: Then you were promoted?

WB: Yes, I was appointed Deputy Clinical Director under Bob Cohen and during the last period before I left the NIH, I was Acting Scientific Director of the entire Intramural NIMH Program.

TB: Why did you leave NIMH?

WB: I felt I needed a new environment, new stimulation. There were a lot of things going on at that point in my life. UCI made me an outstanding offer, and it had as good neuroscience as almost any place in the world. That was very intriguing.

TB: What year was that?

WB: That was 1982.

TB: So, you moved to California and became chairman of the department of psychiatry at Irvine. Did you take anyone with you from NIMH?

WB: Earl Usdin and Monte Buchsbaum.

TB: So you had in mind to continue with your work in imaging?

WB: I got a PET scanner within a year and I still I think it is one of the few PET scanners in a department of psychiatry anywhere in the world.

TB: You have been involved very actively in PET scanning for many years.

WB: Yes. Monte Buchsbaum and I had done the first human PET scan work at the NIMH and, when we went to UCI, we continued that.

TB: What was Earl Usdin doing?

WB: Earl was a master at organizing meetings and editing books. Then he got lung cancer and died.

TB: When did this happen?

WB: Very soon after we went to Irvine. And that was very sad. One hundred and fifteen of the top scientists in the world came to show their respect for Earl before he died.

TB: Can you tell us about your activities after your arrival to Irvine?

WB: It was a learning process. In the beginning, I got a MacArthur grant. That was fine, I was not doing a lot of research but running the department and that's a big job. After that, I stopped running the department for a period and, about three years ago, I picked it up again. I didn't have any NIMH funding until about twelve years ago. Then I got a Center Grant with Ted Jones who is probably the best neuroanatomist in the world today and we did a series of ten papers together. We started out by collaborating with other brain banks, and then developed our own and Steve Potkin helped. For the last ten years we have had a brain bank funded by the NIMH. They funded us to do neuroscience research but we also developed the brain bank. The work that came out of that was quite significant. We showed a decrease in GAD 67 mRNA in schizophrenia. As you know, nothing is ever replicated in schizophrenia but this has been replicated by David Lewis, and subsequently by three other groups. We did a lot of research with the NMDA receptor and also showed that the subplate cells which move from the ventricular zone to just below the cortical plate were maldistributed in schizophrenia. So, something went wrong during the second trimester of development. We don't know what but those cells

did not migrate to the correct spot. That was done on our Center grant ten years ago with Ted Jones and Schahram Akbarian.

TB: Did you continue with that research?

WB: We continued and then, three years ago, applied for a Silvio Conte Center grant and received one. For a Conte Center, you are supposed to put together a group of top people. So I got Huda Akil and Stan Watson from Michigan, Ted Jones from UC Davis, and David Cox from Stanford. Cox went to the Perlegen Company so his co-chair, Rick Myers, of the Human Genome Center came on the grant. The research is going on right now and we are two years into a five-year grant. I have been very interested in genetics for the last four years. I am not a geneticist but I decided the only way to learn it was to teach it. So I started teaching a course to residents and faculty. In order to prepare a lecture you learn a tremendous amount including a lot of the language. I am very impressed with microarray technology and had a session here on that. I have developed a major microarray facility, and so has Michigan. Our initial study involved five males and five females. People said you can't run microarrays twice in your own lab and get replicable results. But out of 4,600 genes, we were able to come up with six significant genes and five of those were replicated in all three centers. Then we did RT-PCR that validated it. I presented this at a neuroscience meeting and had a poster there; a scientist came up to me and said, "I spent my life working on mice in terms of male-female gene differences and you've come up with the same genes." We were really excited about that and now have a couple of papers we are working on. Just this month we finished our first cohort of depressed patients and we have some very interesting genes. We have another couple of months to go because we have to put our three groups together, we have to go through the various cluster analyses of these, and we have to figure out what these genes do. That's just for openers but within another couple of months, we will be able to look at all 40,000 genes on two chips. It is not out there yet, but we spent four hours talking with Steve Fidor who is president of Affymetrix and he says they are definitely going to have this technology. So we will be able to survey 40,000 genes in the future. We've got a second cohort and Blynn Bunney reviewed about six hundred papers to try to figure out which areas of the brain are implicated in depression. From lesion studies, tumour studies, and a large number of brain imaging studies we came up with twenty-four areas in the brain. We all get together and work around the clock for about 36-hours to dissect these areas out. So we have about six thousand pieces of brain tissue from our cohorts which are labelled with bar codes and frozen at -80 degrees Fahrenheit. I hired Bill Byerley, an outstanding geneticist.

You look at the animal models and see what genes are implicated there. Then you factor in what you understand and know about pathophysiology. I call it quadrangulation of information. We screen and validate with microarrays. Let's say you have eight schizophrenic genes, four of which were in hot spots of the genome, three of which were implicated by a drug model of schizophrenia like PCP and happen to relate to dopamine. It's not going to be that simple but that's the idea.

TB: Sounds like cutting edge science.

WB: It is a very exciting time right now. You could not have done this before the mapping of the human genome plus the development of microarrays. We have a superb team working on this.

TB: You put together a new team and you were able to generate the necessary funds.

WB: The department is doing very well. Every year, the contracts and grants people publish the amount of money all the departments have in terms of research. In terms of total research dollars, our department ranks #1 out of the 23 departments, above medicine. I am very proud of the people in our department.

TB: You should be. Besides all this, you have been involved in all kinds of international activities during the past twenty years. Would you like to talk about that?

WB: I have been interested in international research all my life but it started with the World Health Organization (WHO) group that Norman Sartorius put together. It was a group of collaborative research programs originally involving about eight countries. We would meet once a year and plan programs. We did genetic and clinical studies, as well as biological studies over a period of approximately ten years. It was quite successful, we all contributed funding and everybody worked pro bono. I really enjoyed getting together with everybody. There were scientists from Russia, England, Belgium, India and Morocco. Alec Coppen, Hans Hippus, and Sol Langer were in it. We would rotate and meet in the various countries to plan research programs.

TB: Would you like to mention some of the studies?

WB: There was this color blindness genetic marker we studied. We did a variety of medication studies, published in top journals. It took a lot of effort because you had to standardize everything and to translate everything into the language of the country studies were conducted in. If you had rating scales, they had to be translated, and then you had to get together and test their reliability.

TB: Did all this start in the mid 1970s?

WB: Yes, and it went on through 1984.

- TB: Among your different activities, you also served on many advisory boards. Would you talk about your experience?
- WB: I served on the Board of the Max-Planck Institute. I have been on NARSAD (National Alliance for Research on Schizophrenia and Depression) from the day they started and that has been an incredible success story. Three weeks ago I reviewed this year's applications, and there were 500 from Young Investigators. NARSAD is an amazing organization. The Manic Depressive and Depressive Association has survived lots of problems and is also going strong at this point. I was also on the IBM Medical Advisory Board and the Merck Advisory Board.
- TB: What would you consider your single, most important contribution to research?
- WB: I would list the lithium studies, the norepinephrine hypothesis, and the one that is in press right now. It is a molecular genetic study in which we have a cohort of fourteen schizophrenic patients, individually matched with controls.
- TB: Could you tell us more about this study?
- WB: I went a number of years ago to Paul Greengard and said let's look at DARRP 32 in schizophrenic patients. He asked me why, and I said that DARRP 32 is regulated by the two neurotransmitters most implicated in schizophrenia. It is reciprocally regulated with glutamate and dopamine and its downstream effect on protein pump inhibition (PPI) is critical for ion channels, neurotransmitters, and transcription factors. He said, "That's great, I have somebody to work on this." It only took us about eight years to do this study but it is impressive, and it will be published in Archives of General Psychiatry. We found low levels in the dorsal lateral prefrontal cortex and not in other areas and not in other proteins, and they weren't changed by animals chronically on neuroleptics and weren't differentially affected in a couple of patients who were not on neuroleptics. We had a control group of eight Alzheimer's patients, eight on and eight off neuroleptics; there was no difference and they were matched. I think it was a really nice study and took a long time to do.
- TB: So, you think these are your three most important contributions?
- WB: These were important contributions and I'm sure there are others. Another major contribution is the switch process.
- TB: You've received several honours and awards. Would you like to mention a few?
- WB: I would say election to the Institute of Medicine-National Academy of Science (IOM/NAS), the Presidency of four organizations: Psychiatric Research; The West Coast College of Biological Psychiatry; The American College of Neuropsychopharmacology (ACNP), and the Collegium

Internationale Neuro-psychopharmacologicum (CINP). The highest honour was certainly the ACNP presidency. I was asked a year ago to be editor of a new neuroscience journal and that is an honour. The most recent award I received was a month ago from NARSAD.

TB: Aren't you a recipient also of the Anna Monika Award?

WB: Yes, I had the Anna Monika Award.

TB: What did you get the Anna Monika Award for?

WB: That was for the write up of the switch process. It was 35 years ago in the late 1960s.

TB: You are still active.

WB: I have the Della Martin Chair of Psychiatry, but I am Co-chair of the Department of Psychiatry also. And I also have a Distinguished Professorship at UCI.

TB: Is there anything else you would like to talk about we did not cover?

WB: I don't think so. Science has always been exciting and could not be more exciting than right now.

TB: You mentioned at the beginning that you have always been involved in poetry. Are you still writing poems?

WB: Yes, I still write poems.

TB: Have you ever published any?

WB: No, I've received a lot of rejection slips. At one point in my life I submitted poems to the New Yorker, New York Times, and Atlantic Monthly. You know, the first time they just send you a stamp informing you that you are rejected. Then they send you a note saying, "rejected." And then they send you a note saying, "Well, we liked this but we didn't like" I got to the last stage but I never got to the acceptance stage.

TB: We talked about your papers, but we didn't talk about your books.

WB: I have seven edited books. I may have written one or two chapters in them.

TB: Could you tell us something about the books?

WB: A couple of them were on substance abuse. Jack Barchas and I did one for Earl Usdin.

TB: Is there anything that you would like to see happen in the future in psychiatry and in neuropsychopharmacology?

WB: It's too bad that probably only 40 of the 125 departments of psychiatry have science programs. It would be great if there was a granting system to get them started. I think research is so important for the education of young residents. I would like to see distinct mentorships worked out. Residents don't have to become scientists but they should learn to read a science paper and know how to evaluate new treatments, new thoughts about diagnosis; science is the way to learn that. There is currently a

lack of clinical researchers, the NIMH is very concerned about this, and I share their concern. I have been very active with the Institute of Medicine (IOM) and I am currently chairing a committee on suicide which has been neglected. You have about 5,000 more suicides than homicides in this country, so we are doing a full report on this.

TB: Anything else you would like to add?

WB: I think we've covered a lot. I have enjoyed the interview. I think you have done a superb job, Tom. You are an excellent interviewer.

TB: Thank you. Thank you for sharing all this information with us.

WILLIAM T. CARPENTER, Jr.

**Interviewed by Thomas A. Ban:
San Juan, Puerto Rico, December 10, 2002**

TB: This is an interview with Dr. William Carpenter* for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. We are at the Annual Meeting of the College in San Juan, Puerto Rico. It is December 10, 2002. Let's start from the very beginning; where and when were you born? Tell us something about your education, early interests and activities.

WC: I was born September 15, 1936, in Jacksonville, Florida. Before long, my family moved back to North Carolina, where both my parents came from. I grew up in a small town in western North Carolina called Rutherfordton. I went through the public school system and then to college. I selected one of the colleges that offered to pay scholarships for football and basketball. I enjoyed sports as a nice way to work my way through college. I went through the Wake Forest University Medical School and interned at the North Carolina Baptist Hospital in Medicine. I trained in Psychiatry at the University of Rochester. John Romano was in his heyday and it was a fantastic place to learn how to be a physician-psychiatrist. I finished training in 1966 and went to the intramural program at NIH. Biff Bunney had started a Depression Unit and I worked with a very exciting group of people for the next two years on that Unit, and then stayed on in the NIMH Intramural Research Program (IRP), working with the World Health Organization International Pilot Study of Schizophrenia.

TB: How did you get into psychiatry?

WC: I went into psychiatry and medicine because I took aptitude testing and the psychologist looked at my histogram and told me "you have no talent in music", which is true, but I don't know how he knew that. He then said, "It means you want to go into medicine and specialize in psychiatry". You can't get that information from tests, but that is what he told me. So, that's how I decided to go into psychiatry.

TB: I see.

WC: So, I went to college knowing I was going to be a psychiatrist. It was almost the same when I went from Rochester to NIMH. I knew I wanted to get into academic medicine and need to do some research first. That was no doubt Romano's influence. One wished to be something that Romano would approve of and it seemed like the way to do that was to go get your

* William T. Carpenter, Jr. was born in Jacksonville, Florida in 1936.

feet wet in research and do some publishing. I published one paper from work I did in Rochester, but that was just a case study.

TB: When was it published?

WC: It was probably published in 1967.

TB: What was the paper on?

WC: There was an old gentleman I saw in the emergency room who had become psychotic and ended up in a nursing facility. He had incipient dementia but was well adjusted at home. He went for an eye exam and became psychotic. So I looked into what drug they put in his eye and found there had been old reports of people having a psychotic reaction if a concentrated solution of that substance was used. There were no reports of psychosis with the dilute solution he received. So, I wrote it up as a first case of psychosis at the approved concentration.

TB: What was the drug?

WC: I don't remember. It was used to dilate the pupil. The reason he didn't recover was that his adjustment to dementia was so frail he wasn't able to go back to living independently. I sent the paper to the Archives of Ophthalmology and they accepted it.

TB: Could you tell us more about Romano? It seems he had a great impact on your career.

WC: Romano was a towering intellectual figure in psychiatry. He took a great interest in his residents, met with all of us regularly. We each had a chance to bond with him and model after him. He was very particular about our training, our program and the people in it. George Engel was the other major influence in Rochester at that time. He espoused the bio-psycho-social model. But, with Romano it was a relationship that I was able to keep up over the years and in his later years saw a lot of him. He was a very influential person, and more than anything, he was a critical thinker, open to all things in psychiatry as long as you thought critically about them. So, it was truly a broad education, very patient centered. Rochester did not have much strength in research at that time although Bob Ader was there, launching the field of psycho-immunology. George Engel's group looked at developmental issues. There was a strong interest in certain psychological issues in terms of vulnerability to different diseases.

TB: So, this was your background before you went to NIH?

WC: Yes.

TB: So you arrived to NIH and started in the Intramural Research Program.

WC: I started off in a fairly large office occupied by Dave Anderson, Fred Goodwin, John Davis, and Dennis Murphy, and David Janowsky came the next year. That was the group working together on that unit. William Bunney was head of the program and Jim Maas head of the section. Jim

moved to Chicago a few months later. Lyman Wynne headed the Adult Psychiatry Branch. I went originally for two years but I wanted to stay on and shifted over to work on schizophrenia in a project with the World Health Organization. I worked in that with Lyman Wynne, John Strauss and John Bartko.

TB: Before you moved to work on schizophrenia you said you worked with Biff Bunney.

WC: I spent two years on Bunney's Depression Unit. I had asked to work with Biff Bunney, because George Engel was very impressed with the work Biff was doing. Lyman Wynne had given a talk in Rochester and I had asked to be in Biff Bunney's group.

TB: What did you do?

W.: Well, there were two main lines of work Biff was interested in that Dennis Murphy, who arrived at the same time, and I should be doing. One was on lithium and electrolytes. This was before lithium was on the US market. The other one was on the hypothalamic-pituitary-adrenocortical axis. Biff assigned Dennis to lithium and electrolytes and off they went. I was asked to run the clinical unit and work on the hypothalamic-adrenocortical axis. This was a nice choice for me. I enjoyed the clinical unit; I wasn't really prepared to be a researcher. Jan Fawcett preceded me in working with Biff, and Jan and Biff had written a blueprint for working up the HPA system in depression. With the blueprint in hand it was not difficult to figure out a series of studies. Other studies involved suppressing the HPA axis with dexamethasone. We had negative results on the hypothesis that depression was associated with failed dexamethasone suppression of adrenocortical release. When I presented the data, Barney Carroll was in the audience and pointed out we dosed at midnight instead of at eleven PM. He was right; this probably explained our negative result. We looked at the circadian rhythm of cortisol and I found some alterations in the daily rhythm. We found a burst of increased cortisol levels around REM sleep, but the lab values were difficult to believe and we did not report this finding. It was right about that time that Ed Sachar reported the episodic bursts in cortisol release. I'm almost sure we were actually seeing those episodic bursts. We also did metabolic clearance rates. This was an interesting series of studies, but we were not able to confirm an abnormality in the HPA axis in manic or depressive disease, except the alterations in circadian rhythm. I think we did not do the dexamethasone suppression test correctly. The main impression these studies made on me was they could not address causation. Almost any alteration in this stress sensitive HPA axis could be secondary to depression rather than a causal pathway. It didn't suit me to continue in these projects. I

don't know why, but my interest was more in schizophrenia. So I talked to Lyman Wynne to see if there were any other positions in the Branch. I had actually asked Lyman about working with him on his family studies and extend it into depression to see whether there was evidence of thought disorder and communication deviance in families of people who were vulnerable to depression with psychosis. I remember Lyman saying, "Well, sure, that would be real interesting. We can do that in the context of the International Pilot Study of Schizophrenia (IPSS)". Of course, we never did. My assignment was to work with John Strauss. Lyman asked John to head up our group. That was in 1968, and it turned out to be a remarkable experience.

TB: Could you tell us something about the IPSS?

WC: In 1968 it seemed everybody in the world knew how to diagnose schizophrenia except American psychiatrists. The comparison of US and UK had made clear that in the United States there was over diagnosis of schizophrenia. The difference may have been overestimated since the US sample was from the New York City area. Paul Hoch's influence with concepts such as latent schizophrenia and pseudoneurotic schizophrenia were in vogue. Diagnostic patterns were different as you moved south and west, but European psychiatrists had a lot more interest in specific approaches to diagnosis. The IPSS was set up using John Wing's Present State Examination (PSE), based on identifying nuclear schizophrenia, using Schneiderian first rank symptoms. So, I'm a young person working on this study. John Strauss is two or three years older so you've got these two young Americans, and Lyman shepherding us. We learned how to do a systematic interview, but John and I thought schizophrenia too complex to be characterized by symptoms. We did not understand the postdictive and predictive power attributed to the nuclear schizophrenia construct; or how special diagnostic symptoms achieved a classification with such robust reduction in heterogeneity. We argued, no doubt inadequately, for the inclusion of developmental, social, and other behavioural assessments. We were not persuasive enough with our international collaborators. There was little interest, no time for added measures and they didn't see any need. If you knew how to diagnose nuclear schizophrenia they insisted you picked up the background pattern that predicted the future course. So, we quickly put together a prognostic scale based on work by Norm Garmacy, Joe Stephens and George Valliant. These prognostic data were only collected in the US cohort. The IPSS plan was to do two year and five-year follow-up studies, but eventually Ann Pulver and I did an eleven-year follow-up on the US cohort. We argued that in assessing outcome you need to assess occupation, social outcome and things other than psychotic symptoms we thought were important. And, again, the investigators from

other countries believed mapping symptom course with the present state examination was sufficient. That was an era when, in clinical trials, the only things measured had to do with the psychosis. You might measure a time to discharge or a time to readmission in a maintenance study, or just measure symptoms. The whole concept was that if you measure the psychosis you're pretty much capturing the disease. So, for studying the US cohort, we developed the Strauss-Carpenter Level of Functioning Scale to assess a variety of functional outcomes in addition to the measures included in the original protocol. Schizophrenia is not good for anybody, but it's not a uniform or a progressive deterioration in most patients. With the developmental data, the symptom data, and the outcome data we collected, we identified three domains of psychopathology in people who have a diagnosis of schizophrenia. Each of these different domains had its own history and its own future. The past predicted the future within each domain, but told almost nothing about the other domains. Even the best measures of psychosis told us nil about the social or occupational course of the disease. If you want to know whether a person is likely to be employed in the future you get their past work record. You don't measure psychosis in order to predict function. Based on our observations we proposed that within the schizophrenia syndrome, individuals have different combinations of pathology. Those different domains are relatively independent from each other. We don't understand why they are co-occurring, but it may be that they have a different etiology and pathophysiology. We also observed that almost all schizophrenia patients had reality distortion such as hallucinations and delusions but not all patients had dissociative thought disorder. You could meet criteria for nuclear schizophrenia without having thought disorder. Some patients had negative symptoms and others did not. We focused on negative symptoms by identifying six pathologic features first, then reducing the six features to a three component model comprised of positive psychotic symptoms, negative symptoms and pathology observed in the interpersonal context. We treated these three domains of psychopathology as independent. We were quickly learning a lot about Schneiderian first rank symptoms extensively used in Europe and the rest of the world in diagnosing schizophrenia and about Langfeldt's system in which true schizophrenia and schizophreniform reaction were separated, seemingly validated by poor outcome in the former and good outcome in the latter. We were able to test these systems, at the time when DSM III was being formulated which, influenced by Washington University, has placed heavy emphasis on reality distortion symptoms and ego boundary disturbances emphasized by Schneider and Langfeldt.

TB: Could you tell us about Schneider's "first rank symptoms"?

WC: Schneider posited that certain psychotic symptoms, referred to as “first rank symptoms” were pathognomic of schizophrenia if they occurred with a clear sensorium. Helm Sterlin described that Schneider, when interviewing, asked the patient about these first rank symptoms. He would say, “Are you hearing your own thoughts aloud?” Or, “Are voices talking about you in the third person?” In our work, in the context of the nine-nation study, we found that first rank symptoms occurred in other disorders as well. Our findings challenged the dominant single disease paradigm, and introduced a new conceptual approach to schizophrenia pathology.

TB: Would you like to say something about the Flexible System Criteria you developed for diagnosing schizophrenia?

WC: We derived empirically the most robust system, the Flexible System, for distinguishing between nuclear schizophrenia and broad-based schizophrenia by analyzing the data from our US Center, then from all nine participating countries, to determine the most discriminating symptoms. John Strauss, John Bartko and I did a discriminate function analysis in half the patients and derived the most discriminating symptoms among cases with psychotic features, and then tested the derived system in the second half of the cohort. The results were basically the same and we reported our findings, the Flexible System Criteria (FSC), in *Science*. Seymour Kety referred to the FSC as the first empirically derived and validated diagnostic system for schizophrenia. Our findings are once again disproving the nuclear schizophrenia hypothesis. Three of the most discriminating symptoms were poor rapport, poor insight, and restricted affect. We argued for their inclusion in DSM-III, but the response was that DSM-III was being based on evidence. Much of the evidence was a belief that the Schneiderian approach defined Kraepelinian schizophrenia which we had disproved in our follow-up studies. The DSM-III approach seemed destined to enshrine first rank symptoms as the way to diagnose schizophrenia, and, by doing that, it transformed schizophrenia into a reality distortion syndrome. DSM-IV-R has attempted to correct this with negative symptoms included in the diagnostic criteria.

TB: What would you say we learned from your studies?

WC: Our studies led to an appreciation there are different components of schizophrenia that run different courses, that prognosis is not based on the ascertainment of special psychotic symptoms, and that reality distortion symptoms, even special forms of it, are common in psychosis and not of much prognostic significance. These data, and the conceptual framework that evolved from them, have profound implications for clinical trials and the assessment of therapeutic efficacy. It has been slow coming, but there is now general recognition that antipsychotic drugs are not

anti-schizophrenic. They have efficacy for psychosis, the reality distortion and disorganization domains, but not for negative symptoms and cognition impairments.

TB: What are the implications of your findings?

WC: If you look in the literature even today, virtually every post-mortem, neuroimaging, treatment or genetic study is designed as though schizophrenia is a single disease. At the Maryland Psychiatric Research Center, a group of us have divided schizophrenia according to the presence or absence of primary negative symptoms, referring to the two groups as deficit schizophrenia and non-deficit schizophrenia, and we got remarkably robust differences between the two groups with functional and structural neuroimaging. Kraepelin classified dementia praecox as a single disease despite observing “two groups of maladies”, and Eugene Bleuler established the single disease paradigm with his concept of the dissociative pathology being fundamental to all cases. The field has been slow to break with this dominant paradigm, but we see increasing interest in the domains of pathology paradigm. For example, the current interest in treatment of negative symptoms and cognition impairments as two separate components of the illness.

TB: Could you say something about the people involved in the IPSS?

WC: Mort Kramer at NIMH was a terrific influence in the field of schizophrenia from an epidemiologic and public health vantage. He had been involved in the US-UK study which suggested that schizophrenia was similar in New York and London, but diagnostic practice was quite different. The findings prompted the World Health Organization and NIMH to determine if schizophrenia was similar or distinctive in various cultures and John Cooper was the PI of that study. Mort Kramer and Marty Katz were important on the NIHM side, and Lyman Wynne was asked to advise and organize the US site. Dr. Lin from Taiwan was then at the World Health Organization, and was initially PI of the IPSS. Norman Sartorius succeeded him as PI. The nine centers were; London, Aarhus, Moscow, Cali, Agra, Ibadan, Prague, Taipei, and the US Center at NIMH. John Wing, author of the Present State Exam, was important in initiating and conducting the study.

TB: When did you leave the NIMH intramural research program?

WC: I was in the intramural program for nine years, leaving in 1975. We had a series of studies with several collaborators, and were beginning to address the heterogeneity problem of schizophrenia at the level of biology, psychophysiology, and clinical phenomena. When Lyman Wynne had left to take the Chair in psychiatry at the University of Rochester, Biff Bunney had come back to head the Adult Psychiatry Branch.

TB: Where did you go?

WC: I went to Einstein in the summer of 1975 and came back to Maryland in the winter of 1977. I did not accomplish much in research during the brief New York time, but did begin to address the confound between primary and secondary negative symptoms.

TB: Primary and secondary negative symptoms?

WC: That concept we published in 1974. We reduced symptom pathology to three components; positive psychotic symptoms including reality distortion and disorganization of thought; negative symptoms described in Jacksonian terms; and pathology that was best seen in a social context, such as poor rapport. This new paradigm was based on the semi-independence of these components within individuals and within domain consistency between developmental history, episode presentation, and future course. Then, in 1982, two papers came out that were very influential. Andreasen had done an analysis with two very important observations, one wrong and one right. She and Olson found that hallucinations and delusions segregated together, and were separate from disorganization, forming two separate pathologic domains. This observation is correct and has been replicated many times. But, Andreasen and Olson also found an inverse relationship between negative and positive symptoms, and proposed these as two subtypes. This was a mistake, because this inverse relationship between negative and positive symptoms has not been observed in most studies. Classifying on the basis of positive and negative symptoms is too state dependent. For example, on admission with florid psychosis a patient would be classified as positive schizophrenia and at follow-up, with psychosis reduced and negative symptoms more apparent, the same patient would be reclassified as mixed or negative. Tim Crow proposed Type I and Type II schizophrenia as two diseases in 1982. This was also very influential; the two types were distinguished by the presence or absence of primary negative symptoms. This approach was similar to our proposal. Crow also hypothesized certain treatment response and pathophysiologic differences between the two types but that has not been validated. According to his hypothesis Type I schizophrenia was associated with dopamine pathophysiology and response to antipsychotic drugs whereas Type II was based on structural pathology and was not responsive to antipsychotic drugs. Empirical studies have reported more evidence for reduced volume of structure in the hippocampus in Type I schizophrenia than in schizophrenia with primary negative symptoms. Our approach to it would be to say that the positive psychotic symptoms occur in both and, in both conditions they are responsive to antipsychotic drugs. The really unfortunate aspect of

the negative symptom story is that the field has made a complete mess of the concept by non-valid ascertainment procedures. A person with schizophrenia may have negative symptoms such as restricted affect, alogia, anhedonia, and low motivation and social drive for many reasons. If they are a direct result of the schizophrenic pathology, these are considered primary. But a patient may be socially withdrawn if paranoid, or if enthralled with reality distortion symptoms. Restricted affect might be the result of drug-induced akinesia. Anhedonia may be a result of depression or demoralization. The rating scales commonly used in psychopathology studies or to measure change in clinical trials do not distinguish negative symptoms based on cause. Anhedonia was an important pathologic feature of schizophrenia as put forward by Rado and by Meehl. But the construct involved a diminished capacity for reinforcement, reward and experience of pleasure. It was not a temporary loss of ability. Normal humans in grief have a reduced ability to experience pleasure, but not a trait loss of capacity. On rating scales, depressive anhedonia would not be differentiated from schizophrenic anhedonia. This failure to differentiate primary from secondary negative symptoms has resulted in today's debate as to whether antipsychotic drugs have efficacy for negative symptoms. If you get a group of depressed paranoid patients on high doses of Haldol (haloperidol) then you have depressive anhedonia, akinesia, psychotic withdrawal and paranoid guardedness resulting in high negative symptom ratings. If you treat the psychosis effectively, especially with a drug that does not induce dysphoria or akinesia, the negative symptom ratings will be substantially reduced. This is the case whether or not the person actually has any primary negative symptoms. So, with all the first generation antipsychotic drugs, the negative symptom ratings would suggest we've got a good treatment for negative symptoms just like we do for psychosis. And with second generation drugs being less likely to cause secondary negative symptoms, they sometimes appear to have superior "efficacy" for negative symptoms. But this is a pseudo-specificity problem that the FDA is keenly aware of, with the result that no superior efficacy claim has been granted for negative symptoms. So, we worked out a method for distinguishing primary from secondary negative symptoms. Some argue that researchers cannot determine whether negative symptoms are primary or secondary. The answer to that is, if a patient comes in with a flat emotionless face, you need to figure out if he's got Parkinson's disease, if he has drug induced akinesia or if it is depressive anhedonia, because we have differential treatments for these conditions. Brian Kirkpatrick led the work in preparing a schedule for the detection of the deficit syndrome. We did a series of studies that relate to

the validity of splitting schizophrenia, according to presence or absence of primary negative symptoms. The question is whether you would get differences between the two groups. Should I go into that?

TB: Yes, please.

WC: At the Maryland Psychiatric Research Center, we found that we could divide schizophrenia into deficit and non-deficit groups reliably. Doing so resulted in interesting clinical differences. For example, the non-deficit group was more likely to be involved in substance abuse, more likely to experience depression, and more likely to be suicidal. Brian Kirkpatrick, who has done a lot of work on this, observed that while the two groups were similar in having delusions, the group with primary negative symptoms was less likely to have a social content to the delusions. Bob Buchanan did a series of neuropsychological studies which suggested these two forms of schizophrenia may have different etiologic pathways. The deficit patients with restricted affect are less likely to experience distress. Another important step involved glucose PET imaging. Carol Tamminga used this technique to identify the involvement of anterior cingulate anatomy in the psychosis domain. We then separated patients into deficit and non-deficit schizophrenia. Most regions of interest did not distinguish schizophrenia subjects from normal controls, but the anterior cingulate differences were present in both schizophrenia subgroups. However, the remarkable finding was the robust reduction in resting glucose metabolism in inferior parietal and prefrontal cortical areas in the deficit subgroup. Non-deficit schizophrenia was similar to normal control values in these regions. This was a categorical, not a quantitative difference, and did not appear related to severity. More recently, Adrienne Lahti and Henry Holcomb, as well as Carol Tamminga and I, have been able to repeat these studies using Oxygen 15 in the presence of a discrimination task and it looks like deficit and non-deficit schizophrenics use their brain differently in accomplishing the same task. The difference is seen in the involvement of inferior parietal and prefrontal cortical areas. A number of other neural integration measures also separated deficit from non-deficit schizophrenia. With this evidence, and support for several aspects from other investigators, we made the provocative claim to have met the hundred year old challenge to determine whether schizophrenia is a syndrome comprising more than one disease. In any case, we summarized the evidence supporting the hypothesis that deficit schizophrenia is a separate disease in the Archives of General Psychiatry. We are involved in determining if this subgroup is distinguished using post-mortem gene expression data. It is clear that the domains of pathology are critical at the treatment level. This is especially important in drug discovery, because

fifty years of creating antipsychotic drugs has not resulted in drugs with therapeutic efficacy for impaired cognition or primary negative symptoms. Even with clozapine, all studies that have separated primary negative symptoms have failed to document efficacy. In cognition, beneficial effects may be more apparent than real.

TB: So, you are saying that clozapine is not superior on primary negative symptoms?

WC: Not on primary negative symptoms. The drug may show superior antipsychotic effects but the negative pathology is not treated. To put it bluntly, fifty years of antipsychotic drug development has not resulted in efficacious treatment for the aspects of schizophrenia that account for poor functional outcomes. Our domain of pathology paradigm predicts that across domains efficacy is unlikely, but drug development has been dominated by the single disease paradigm with psychosis the focus of drug development. From the domain vantage it seems evident that a different developmental model is needed for discovery within each domain. It is good to have drugs with a more favourable effect on negative symptom ratings. But this is quite different than having efficacy for what Kraepelin described as the avolitional component of the illness, and what we refer to as primary negative symptoms. And, I would use a parallel argument with cognitive impairments in schizophrenia. Cognitive advantages of second generation antipsychotic drugs are importantly dependent on excessive dosing with haloperidol in the comparator group and/or commercial sponsorship of the study. We need new models for developing novel treatments! I could be wrong, of course. But if I'm wrong, I'm only slightly wrong. No one thinks there is a robust difference between old and new drugs. So, from the standpoint of drug development, it really calls for new ways to discover molecular targets for drug development to benefit cognition and primary negative symptoms. The psychosocial treatments, incidentally, and this is not our work, have been proven efficacious in schizophrenia. It seemed to work at the level of psychotic symptom reduction and prevention of relapse, in the same areas that are best affected by antipsychotic drugs. Psychosocial treatments are not documented as efficacious for cognition or the primary negative components of the illness. Hogarty has the most promising and comprehensive approach in this regard.

TB: What would you suggest?

WC: We do need new approaches. First, take the domains model seriously and determine domains of interest for drug discovery. Each domain lends itself to developing partial animal models. Etiologic information can also be used to create animal models and determine what domains are manifest.

Greg Elmer, Jim Koenig, and Michael Vogel are doing this at the Maryland Psychiatric Research Center. Jim has used the mid-trimester insult epidemiologic data to create a model in the rat. Relevance to schizophrenia is validated with a number of behavioural, physiologic, and genetic variables. Second, reduce the heterogeneity of schizophrenia in genetic, neuroimaging and post-mortem studies with the domains approach or with the application of genotype data. This can increase the robustness of any hypothesis testing. If there are several pathophysiologic pathways in the schizophrenia syndrome, we can expect neuropathologic findings to relate to some, and not to all, cases. We have been encouraged in this approach by increasing the robustness of neuroimaging findings, and by identifying subgroups with gene expression data. Third, reduce the heterogeneity of genetic studies by linking each involved genotype with a phenotype. Any drug developed, based on genotype information, can best receive proof of concept testing in the involved phenotype. Testing in a schizophrenia cohort with mixed phenotypic make-up, risks type II errors. Fourth, many elements of cognition are impaired in schizophrenia. These elements are dissociable and are good leads for animal model development.

TB: What is your current research?

WC: At present I am PI on a four center, NIMH funded clinical trial, with Bob Buchanan, Dan Javitt, Steve Marder and Nina Schooler. We are testing negative symptom efficacy hypotheses and cognition efficacy hypotheses for an agonist and a partial agonist at the glycine site on the NMDA receptor complex. I am involved with programs establishing design and assessment procedures for testing cognition and selecting suitable candidate drugs for testing.

TB: Could you tell us something about the Maryland Psychiatric Research Center?

WC: Al Kurland, I think a charter member of the ACNP, headed a research unit at the Spring Grove State Hospital. He founded the MPRC as a state mental hygiene administration facility. This included basic science labs and office space. The program opened in 1966. I accepted the appointment as Director in 1977. After a very vexing start, this has become a labour of love. At the outset, there were no clinical facilities, and the scientific staff, was not prepared for a future in schizophrenia and neuroscience research. It had been over five years since an MPRC scientist even applied for a grant. The decision to focus on schizophrenia was easy, for that is what I knew and what the program needed. I believed I could not attract good clinical scientists without a strong neuroscience program, and vice-versa. I also wanted people to be independent scientists

and to reach for their own farthest star. Rather than one or several of us determining the entire scientific agenda, I felt we could rely on a group of scientists in a geographically isolated center to provide synergy and integration, as opportunity occasioned. This seemed the ideal formula for translational research and creative productivity. I have been very surprised with how well this has worked.

TB: Could you tell us about your activities in ACNP? When did you become a member? What would you consider your most important contribution to the organization?

WC: I became a member around 1978 or 1979, after coming to the MPRC. I became a fellow in 1981. Prior to that, my work in psychopathology would not have been viewed as central to neuropsychopharmacology. The first grant I received related to psychopharmacology, was for a clinical trial of hemodialysis, a hot topic in the late 1970s. The results were negative, and publication in the *New England Journal of Medicine* was influential. Since then I have done clinical trials with NIMH support on carbamazepine, diazepam, mazindol, targeted antipsychotic treatment, dose reduction with fluphenazine injections every six weeks compared to biweekly, and the current study with glycine and d-cycloserine. I enjoy the meetings and have served on several committees, but don't know if I contributed much. I have now started serving on Council, and this work seems very important. I am particularly interested in how we manage relations with industry, address conflict-of-interest issues, and how we establish credibility as an independent source of expertise on neuropsychopharmacology issues.

TB: What would you say is your most important contribution to science?

WC: I think the Maryland Psychiatric Research Center. I started with a building on a state hospital campus, and have been able to attract terrific people whose collective contribution to the science of schizophrenia is very substantial. As for specific research contributions, I think the paradigm shift with domains of pathology, defining deficit schizophrenia as a putative disease entity within the schizophrenia syndrome, and distinguishing primary negative symptoms and getting the field to focus on unmet treatment needs.

TB: Is there anything else you would like to add?

WC: No, if you think we've covered everything.

TB: I think we did. This concludes our interview with Dr. Carpenter. Thank you very much.

BERNARD J. CARROLL

**Interviewed by Leo E. Hollister & Thomas A. Ban
Las Croabas, Puerto Rico, December 17, 1998**

LH: Today is December 17, 1998. We're in Las Croabas, Puerto Rico for the annual meeting of the American College of Neuropsychopharmacology. We're interviewing Barney Carroll,* who has been part of this organization and of the history of psychopharmacology since he arrived from Australia. Barney, welcome to Puerto Rico and the ACNP. I'm Leo Hollister and this is Tom Ban; we are going to jointly interview you.

BC: Thank you, Leo. Thank you, Tom.

LH: Around 1973, I was refereeing a paper for the journal, *Clinical Pharmacology and Therapeutics*, on monoamine precursors in psychiatry; it was a very good paper but I had never heard of the author. He was some strange Australian named Carroll, and just to check things out, I called up Dave Hamburg, Chairman of psychiatry at Stanford who had just been in Australia and said, "Who is this fellow, Carroll"? Dave's reply, without hesitation, was "Topnotch", and, so, without any further hesitation, I enthusiastically felt the paper should be published. But it was only later that I got to know Barney Carroll. Tell us, Barney, how did you decide to go into medicine?

BC: It's one of those accidents of being some place at the right time. Leaving high school, I thought I would be a lawyer but then switched to thinking about medical school. The system in Australia is that right out of high school, you enter professional school; you don't have to do four years of college. Medical school was a six year deal but I knew, if I didn't like it, I could switch to a science degree. The person responsible for getting me into psychiatry and pharmacology is Sam Gershon because, in 1959 and 1960, when I was a second and third year medical student, Sam was our lecturer in psychopharmacology and he impressed me so much that I took a year out of the regular curriculum in 1961 to work full time in his lab. We published our first paper from that work. Parenthetically, one of the drugs that I used in 1961 is a drug that has been resurrected, namely tacrine.

LH: Tetrahydroaminoacridine. The anesthesiologists used that to wake people up, didn't they?

BC: I'm not sure they used it as an analeptic, but they certainly used it as a cholinesterase inhibitor. The interest in Australia at that time was because farmers were getting themselves poisoned with cholinesterase inhibitor

* Bernard J. Carroll was born in Sydney, Australia in 1940.

insecticides, so there was a lot of interest in cholinergic pharmacology. So that was my first research project with Sam Gershon, funded by the US Army and the CIA.

LH: That was part of their behavioural program?

BC: It was to develop antidotes to anticholinergic hallucinogens. In the Cold War, the feeling was the Russians might spray American troops with anticholinergic hallucinogen drugs. Ditrane was the drug we studied and my job, as a research student, was to give it to dogs, watch the behavioural syndrome, and develop a rating scale for that. It was about a two hour period of what today we would call anticholinergic delirium and then give putative antidotes; Tacrine was the main drug we worked with to reverse it. We ended up recommending to the US Armed Forces that Tacrine would be a very good drug if the Russians came. Twenty odd years later it resurfaced as a new old drug to treat Alzheimer's disease. I had a good laugh when I saw that happen, believe me!

LH: I guess it coincided with the notion of cholinergic deficit in Alzheimer's.

BC: Yes.

LH: I never knew you had a Gershon connection. Sam was also using another drug, yohimbine. Did you have anything to do with yohimbine?

BC: I didn't work directly with yohimbine, but that work was going on in the lab while I was there. I remember those dogs standing up in their harnesses after being injected with yohimbine and going into a panic attack.

LH: Extrapolating from the evidence of fear in the dog?

BC: That's right.

LH: Working with Sam was a defining experience then?

BC: That was. And the next main step at the end of that twelve month period in Sam's lab was to spend the summer in John Eccles' laboratory at the Australian National University in Canberra on a three month summer studentship. Eccles was soon to receive in 1963 the Nobel Prize for discovering chemical neurotransmission within the central nervous system. I was very fortunate to get a chance to spend three months there before returning to medical school. When I arrived in Canberra, after having met Eccles some months earlier and set this up, Eccles had completely forgotten who I was or why I was there, and abruptly said, "Well, alright, you're here now. You go down the hall and you work with David Curtis". Now, David Curtis and Jeff Watkins, at that very moment, were defining the excitatory neurotransmitter role of glutamate and aspartate, so I was in their lab for three months, pulling multibarrel microelectrode pipettes, putting in glutamate, GABA, strychnine and so on. All of that early excitatory amino acid pharmacology was being worked out right there. So I had a great introduction to very fundamental neuropharmacology through

that experience. At the end of all of that I was due to complete three more years of medical school and then residency. I remember telling Sam I was worried about wasting all that time on medical school, because so many really great new drugs had just come along. This is 1962 we're talking about. Amitriptyline, imipramine, chlorpromazine were new agents, and we had lithium from John Cade, right there in Melbourne. I said to Sam Gershon, "Maybe, I should go directly into psychopharmacology and bypass medical school", because, I said, in the way young people do, "By the time I get through three more years of medical school and residency, all the major questions will already be solved".

LH: That's the optimism of youth.

BC: Sam, in his wisdom, said, "No, go on back. There'll be plenty to work still by the time you get done". Of course he was right.

LH: That really was a flying start in neuropsychopharmacology. I guess you were one of the few people who began before going to medical school.

BC: I did. After I completed medical school, Sam had moved to the US. I signed up for a residency in Internal Medicine, not in Psychiatry. I did two years of Internal Medicine, thinking I would have a career as a Clinical Pharmacologist, not specifically in Psychopharmacology. It was during the second year of medicine residency I had back to back rotations in Endocrinology and Psychiatry, and I put together the idea of using Pharmacology and Endocrinology to test the theories about antidepressant drug action. In other words I articulated the strategy of using neuroendocrine dependent variables to test ideas about neurotransmitters in psychiatric drug action and by extension in the pathophysiology of psychiatric illness. That was how I got back into psychiatry; I left the medicine residency and signed up for three years of psychiatric residency. I had a very good Chairman, Brian Davies, an Englishman who trained at the Maudsley, so he had a very sensible approach to psychiatry.

LH: He was a long time Chairman there, wasn't he?

BC: He was, and I like to say one of the benefits in my training was that my mind was never corrupted by psychoanalytic psychiatry.

LH: That wasn't too popular in those days in Australia?

BC: No, it wasn't.

LH: Psychoanalysis was riding pretty high in the US.

BC: It was dominant. So, Brian arranged I could be affiliated with his research program while I completed my residency. Out of that came the first of my clinical studies, done in collaboration with Brian Davies and with a very good endocrinologist, Skip Martin, in Melbourne. We began a systematic survey of hypothalamic pituitary function tests in psychiatric patients and the idea was to get baseline measures, give the drugs and see what they

did. That all took a right turn, because, when we were getting the baseline measures, one of the procedures we used was a low dose dexamethasone suppression test and already there were ideas cortisol was elevated in depression.

LH: You were doing the clinical test used for Cushing's disease?

BC: That's correct; the low dose DST with a single early morning blood sample and a single overnight administration. I was running the protocol, drawing the blood, processing the blood samples and running cortisol assays through the spectrophotofluorimeter in the hospital biochemistry department.

LH: You were a general factotum!

BC: We had post dexamethasone cortisol levels coming back from depressed patients that were sky high. It finally dawned on us we had something important so we pursued its ramifications for many years afterwards.

LH: Why, with those high cortisol levels, did patients not show signs of hypercortisolism?

BC: That's true. Even back then we said to ourselves, they should look Cushingoid but they don't, and maybe there's a receptor deficit. That has been another fairly extensive line of research. But so far it's been inconclusive in the endocrinology of depression.

LH: That opened a whole new approach. For a long time people thought the endocrine system would be a window to the nervous system, and especially to some of our illnesses.

BC: Like a lot of things, this was an innovation in experimental design waiting to happen and we were not the only people to stumble into this new approach. Gerald Besser in London was doing it at the same time, unknown to us. At NIMH, in David Hamburg's old unit, they were also doing it. Jan Fawcett and others were running dexamethasone procedures then. Peter Stokes in New York was also doing it at the same time.

LH: How about the chap at Columbia who died early in his career? I can't remember his name.

BC: Ed Sachar, at Montefiore Hospital in New York who later moved to Columbia. He was doing intensive studies of baseline cortisol secretion, but Ed had not taken it to the point of interventional probes. He was doing very detailed blood sampling across the day and night cycle of cortisol secretion in not just depression, but psychotic patients.

LH: He was more interested in the daily cycle secretion.

BC: Ed, at that time, was very focused on correlating the endocrine elevations, with what he called, in his psychoanalytic orientation, indices of ego disintegration. He had this elaborate rating scale for ego disintegration in psychotic patients and his primary theme for a long time was that

elevated cortisol results from ego fragmentation and the attending anxiety that induces in the psychotic patient. It was not until he got his night-time cortisol values back and looked hard and long at them that he finally said this is something else, because, even while these people are asleep, the cortisol values are elevated. It was at that point Ed Sachar began to shift away from the psychoanalytic interpretation of psychoendocrine data.

LH: Well, insight comes to everybody.

BC: Right.

LH: Well, I noticed that your second publication was on Lack of Sensitivity to Dexamethasone Challenge. Is that one of the citation classics?

BC: Yes, that's a citation classic.

LH: I should imagine so. Another paper that I reviewed was on the Precursors of Monoamines; tell us how that got started, because I gather that's another citation classic.

BC: A lot of people know me for DST research, but not everybody knows I have worked in quite a few other areas of our field as well, and some of those studies have had a major impact. The study you just mentioned was one. This was a review of monoamine precursors as antidepressant agents. That came about because, in the late 1960's, Alec Coppen in England published an article in which he claimed L-tryptophan was as good as ECT in the treatment of depression. On the face of it, that seemed like an astounding claim.

LH: Certainly, if you were trying to verify it.

BC: So, Brian Davies, Bob Mowbray, our Reader in Clinical Psychology and main statistician, and I set up this study. Bob designed a very elegant sequential trial design where individual patients were matched to receive either L-tryptophan or ECT. You track the winner in each pair and when the cumulative line crosses the predetermined boundary set by the statistical power, you have your answer.

LH: Sequential analysis.

BC: Right. So, in a very economical way, we were able to demonstrate a clear superiority of ECT over L-tryptophan in treatment of depression, and that was in 1970, 1971. In the course of running the trial, I immersed myself in the clinical pharmacology of tryptophan, L-dopa and all of the potential monoamine precursors. Based on that I wrote this review article that has been very highly cited ever since.

LH: That's a pretty good batting average; two citation classics within a few years of each other and in a completely different field. After you went to medical school, did you feel the need to go into psychiatry, neurology or endocrinology?

BC: I was tempted first to go into clinical pharmacology and that's why I went into a general medicine residency, but I put this neuroendocrine idea together in the course of my medicine training and that was when I switched then to psychiatry. I've been very happy with that choice ever since.

LH: You should be. Now we're up to 1973; when did you come to this country?

BC: I completed my medical and psychiatric training and PhD in clinical psychobiology in Melbourne. Then, on my thirty first birthday in 1971, with my wife and two young children we flew to the United States for what was to be a two year Research Fellowship in Philadelphia and, now, twenty seven years later, we're still here.

LH: Did you ever go back?

BC: I never went back to work in Australia. The deal was that the Medical Research Council in Australia had obliquely hinted they would be setting up funding for a psychiatric clinical research unit in Australia and when I came back, with the benefit of Fellowship training in Philadelphia, I would run that unit. But, as the two years came to a close in Philadelphia, priorities changed. They decided against it but said, come back, we'll support you for one year and then you're on your own. Meanwhile, several people, John Davis in Chicago and Al Silverman at Michigan, were asking me to join their faculties. So, with this news from Australia, I went, in 1973, to Ann Arbor as an associate professor and stayed for ten years. That was my first real job; I had nine years of Fellowship and residency, between graduating MD and my first real job.

LH: You must have been getting tired of living on Fellowship stipends.

BC: It was great and when I talk with young people now, I make a point of telling them they have to pay their dues.

LH: That's a long time to pay!

BC: It was two years of medicine residency, three years of psychiatry residency, two years of Fellowship to complete my PhD in Melbourne and two more years of Fellowship clinical research training in Philadelphia. That adds up to nine years.

LH: At thirty-one, you did pretty well with all that training behind you. Now, how did you get to Duke? Was that when Keith Brodie was Chairman and quitting?

BC: I spent ten years at Michigan and we should come back to talk about that, because that was a great period, but in 1982, Michigan was looking for a new Chair, Duke was looking for a new Chair and I interviewed for both positions. I ended up going to Duke at the time where Keith Brodie had been Chairman from 1973 and was moving to being Chancellor.

LH: And, ultimately, President.

-
- BC: And, ultimately, President. So I came in as the next Chair of Psychiatry at Duke in 1983.
- LH: Was the Mental Health Institute at Ann Arbor founded while you were there, or was that already in operation?
- BC: I owe a great deal to the Mental Health Research Institute at the University of Michigan. It was founded around 1962, and I think in embryonic form from 1958. Jim Miller, the general systems theory person, and Ralph Gerard founded the Mental Health Research Institute at Michigan and Gardner Quarton from Mass General became its director around 1968 or 1970. Al Silverman came as Chair of Psychiatry around 1970, and I came in 1973. I owe a great deal to Al and Gardner Quarton for making it possible to function as a junior faculty investigator within the resources and infrastructure of that Mental Health Research Institute.
- LH: You mean, they allowed you enough free time from teaching?
- BC: They sure did and they gave me seed money to get going, so I could get grant support. When I look at what young people now have to cope with to get started on a research career I say to myself, you were very fortunate to start your career in that era and today.
- LH: Other than being trained at NIH, which has sort of unlimited resources, it's very hard for somebody to come up through the ranks in most schools because they can't provide either the free time or the seed money.
- BC: Right. But I had a unique position at Michigan. I like to joke I was brought in as the obligatory biological psychiatrist. It was a heavily psychoanalytical department. Al Silverman's mandate, which he succeeded in, was to change that and I was one of the frontrunners to effect that change and, within the Mental Health Research Institute, I was also a pioneer. The Mental Health Research Institute was occupied mainly by full time research scientists, either in basic laboratory studies, people like Bernie Agranoff and Norman Radin or social scientists; Anatol Rapoport was there, the game theory person, and a group of psychologists. But they had never, in the fifteen year history of Mental Health Research Institute, had a practicing clinician as one of the Institute's research scientists, so when I was given that Institute appointment, the level of paranoia was unbelievable.
- LH: You were a threat.
- BC: I was a threat and my given role was to be an agent of communication between this very powerful, but isolated, pure research group and clinical problems in psychiatry. One of the ways that I did that was to establish, within an annex of the building, the first lithium clinic in Ann Arbor; suddenly, these people saw patients coming in and out and that increased their paranoia even more.

LH: On the other hand, it sounds like ideal training for Chairmanship because a good chairman has to be a symphony conductor.

BC: Absolutely. I learned a lot watching Al Silverman as Chairman. He went through a number of crises in chairmanship and administration in Michigan and I paid a lot of attention to what happened, what the faculty did, how he handled it, and how the administration responded. When I finally left the Chair at Duke in 1990, there were similar political and administrative pressures. I was glad to be stepping out of the Chair. In the beginning it had been a very rewarding time. I built the department from very low research productivity and research funding, somewhere around 1.8 or 2 million dollars a year. Within the space of seven years, I built it up to around 12 or 13 million dollars, recruited a lot of investigators who are still there and are the reason for Duke's strength today.

LH: Today, Duke's Department of Psychiatry would certainly be in the top ten.

BC: In terms of funding it's in the top five and I take a lot of pride in that, but the administrative warfare I endured got to be not worth it. So, I left the Chair in 1990.

LH: You were still pretty young though.

BC: I was not even fifty by the time I left, so I've done a lot of things early in my life. I was Chairman at the age of forty two at Duke and I left it before age fifty. Then I went back to being a professor.

LH: That's the way we do things, isn't it?

BC: It was wonderful.

LH: The thing about an ideal Chairman, has to be a great sense of altruism, because you have to spend so much time fostering other people's careers at the expense of adding more to yours; you must have spent a lot of time to get funding multiplied so fast.

BC: Part of the job description is to be a generative presence within the institution or department and I could point to many protégés I helped get established. One, in particular, I'm very proud of is Ranga Krishnan who I brought on as a junior faculty person in 1984 and he is now the new Chairman at Duke. It's a great pleasure to see my own protégé as Chairman of the department.

LH: What have you been doing since you've become a professor again?

BC: I rediscovered being a professor is the best job in American university life. That's the first thing.

LH: You're your own boss?

BC: Right. And I made a very successful transition back to a funded clinical investigator. Since leaving the Chair in 1990, up until now, I've had more federal research funding than at any other time in my life. As of 1998 I had a mental health clinical research center grant for studying geriatric

depression. I had an RO-1 to fund a longitudinal study of geriatric depression, which is the back half funding of the CRC. Then I have my neuroendocrine RO-1, which I've had since 1976. We're doing some interesting new work on that. So, after being Chairman, I've been able to get back into the clinical investigator research life and I'm very pleased I could do that. The last year I've been giving away these grants, because I'm making a further change in my life at the end of this month. I will go emeritus at Duke and will be moving to California to a new foundation, Pacific Behavioural Research Foundation. I will be the Scientific Director, and will function as a full time research consultant. I'm very excited about this.

LH: This is located in Carmel, California?

BC: It is.

LH: That sounds wonderful. The Dexamethasone Suppression test has had its ups and downs. Where do you think it stands now?

BC: The DST was a very important development for psychobiology, not just because it was a marker of melancholia, but because in the process of examining the DST, the field learned a great deal about how to think about the whole topic of biological markers in disease. The DST gave a "hands on" model to think about issues of sensitivity, specificity, and Bayesian probability theory. Within clinical psychiatry research, those were unused concepts, even as late as 1980. People simply didn't think in those terms. They thought in terms of correlations between biological and psychopathologic variables, or they talked in terms of group mean differences; elevated serum cortisol in depression vs. mania for example, but the idea of using biologic measures as discriminating or diagnostic tools was brand new. I will take the credit for introducing that whole new field of language and terminology, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic efficiency. We did not invent that, we found it in clinical laboratory medicine and statistics, where the concepts were first developed, but we educated the psychiatric community about them. We also educated people about the nuances of iterating between the dependent and independent variables in psychiatric research. For example, if you have a hypothesis abnormal DSTs occur in mood disorder, and you find patients you think are schizophrenic with abnormal DSTs, how do you interpret that? The face value way is to say the DST is no good because it's non-specific. The iterative, most subtle and eventually productive way it is to say let's follow the schizophrenics and see what happens to them, which I had done in some early work. But the best example is Bill Coryell's work from Iowa and his report, which he still stands by, that patients thought to be schizophrenic with abnormal neuroendocrine markers like the DST, followed over time with blind

re-evaluations at two and five years, were eventually found to have affective disorder. The significance of the original marker was our diagnostic assessment was not as strong as we thought it was. That, of course, is what we would predict if we have valid psychobiologic measures. I am not saying that explains all abnormal DSTs but it's an illustration of the way we have to approach diagnostic nomenclature as provisional, testing against the biology, going back and forth in that iterative way.

LH: Some people even propose we abandon all diagnostic terms, and follow markers like the DST, regardless of the diagnosis and see how they respond to different treatments.

BC: There may be some validity to that. Certainly, across all diagnostic groups, but especially within mood disorders, having an abnormal DST is, by and large, a pretty bad thing for longitudinal course. The data show it predicts an eight fold excess risk of suicide. It predicts a switch from unipolar to bipolar status, a remarkable prediction within the population previously thought to be unipolar depressed, and it predicts an eight fold excess in health services utilization of inpatient days over a five to seven year follow up period. Those are Swedish data. So, having an abnormal DST is not a good sign.

LH: Have you ever written this up?

BC: It's been written up.

LH: It gives a different perspective, because so many people think the DST is valueless now. It's part of history.

BC: The DST is practically dead because work that other people and we have done on dexamethasone kinetics and plasma levels has signalled there's a major confound in abnormal dexamethasone metabolism in some cases of nonsuppression. To have valid DST research nowadays, you must control plasma dexamethasone levels. The average clinician is not going to get dexamethasone plasma levels and there's no consensus on the valid plasma concentration windows, like the old idea of an antidepressant therapeutic window. There's no consensus on what that should be at different times of the day for dexamethasone suppression. Because of that, it has fallen into disuse and even I never think about using it these days. Some of the younger people come up to me and say, I want to do a DST on this patient, and I say, if you want to do a DST, go ahead, but I never think of doing a DST on my own patients. We've moved beyond that.

TB: All through your career you did clinical work beside research, right?

BC: I've always kept my hand in as a clinician. In fact, the motivation for the DST work was we were dissatisfied with clinical nomenclature and wanted to go to biology to break through the Gordian Knot of the intermi-

nable debates about endogenous and reactive depression, melancholic and neurotic depression, from the 1960's. They were going nowhere.

TB: Did you treat exclusively patients with affective disorders?

BC: At Michigan we had a predominance of depressed patients. When I started the clinical studies unit at Michigan it was basically a mood disorders program. We would admit patients with other diagnoses, because we wanted them as control subjects, but two-thirds of the patients were mood disorder. I became very skilled at clinical work with recurrent unipolar and bipolar patients and I like to think I'm a very good diagnostician. In the last seven years, since I left the Chair, my clinical life, aside from grants, has been as Director of a hundred bed inpatient geropsychiatric service at John Umstead Hospital. In that setting, I do clinical teaching on all the patients that come along. We have a combined mood dementia service, because so many of our patients have co-morbid Vascular Dementia or Alzheimer's disease with depression.

LH: I think vascular depression and dementia is underrated. Neuropathologists have been telling us for years if you look at the brains of patients diagnosed with Alzheimer's, a viable number have a mixed disorder. They have Alzheimer changes plus vascular changes.

BC: You know more geriatric psychopharmacology than anyone else in the room, Leo, and you're right.

LH: No, that's your field.

BC: One of the great innovations I introduced at our state hospital was to insist our dementia protocol included an MRI brain scan. Not only that, I insisted the radiology department at Duke send us copies of the scans when the patient returned from the procedure. Then, on a regular basis, we would have MRI rounds on my geriatric service. We would all look at the scans then discuss them and the clinical aspects of the case. In a bootstrap kind of way, I taught myself a lot about neuroradiology through doing that. You're completely right, co-morbid small vessel disease appearing as subcortical vascular lesions is extremely common in Alzheimer's and many cases of dementia NOS turn out to be vascular in origin. Also, many cases of late onset depression turn out to be vascular in origin. This is one of the key contributions coming out of the Mental Health Clinical Research Center at Duke. Ranga Krishnan gets most of the credit for this. It goes back to an old idea of Felix Post in the 1960's in London, this idea of vascular depression. Felix Post was right, but he didn't have MRI's to prove that, so in the 1980's and 1990's, we rediscovered it and now have essentially a new clinical entity, late onset vascular depression that people are recognizing as a valid clinical entity.

TB: Is there anyone else, other than Ranga, who you trained?

BC: We had a big group of fellows we trained in Ann Arbor. Elizabeth Young, who is one of the members of the College, Meir Steiner, who is now in charge of a clinical research program in Hamilton, Ontario; Thanasis Zis, who is the Chairman of Psychiatry at the University of British Columbia in Vancouver; John Greden trained in research methodology under me and is now a member of the College and was my clinical lieutenant on the inpatient unit at Michigan; Michael Feinberg, now with Hahnemann Medical College in Philadelphia; Roger Haskett, with the University of Pittsburgh in Tom Detre and David Kupfer's department, and some others, as well. Those are the principal fellows I trained at Michigan and at Duke but Dr. Krishnan was my primary protégé there. When he came on the faculty at Duke, I handed over the day to day running of my neuroendocrine RO-1 and we published many neuroendocrine studies together which gave him the support, freedom and funding he needed to get established as an independent investigator.

LH: That's the altruistic chairman. Are you sad that you passed up a career in clinical pharmacology?

BC: No, clinical pharmacology as a separate discipline hasn't gone very far and many departments of clinical pharmacology have closed in medical schools around the country.

LH: It has an identity crisis.

BC: It sure has! It began with correlating pharmacodynamics and pharmacokinetics and that played out very well with some early classes of drugs, but gradually they did lose their identity.

LH: You have certainly had a tremendous career and now you're entering a new phase and we'll hear more of you.

BC: One of the things I will be working on in the next period of time is psychometrics. I have always been pretty particular about that. One of my early Citation Classics was a paper published in 1973 in the Archives, a critical review of depression rating scales which came out of a clinical study. We had the opportunity to study patients across a broad spectrum of clinical settings, general practice in primary care, a day hospital and an inpatient setting. So, we looked at Max Hamilton's depression rating scale. That was our standard instrument and right around the same time the Zung self rating depression scale had come into vogue in the late 1960's. Bill Zung, who later was a very dear friend of mine at Duke, sent us copies of the scale and we checked it out in a number of studies in Melbourne. In the study across treatment settings, Hamilton's scores went step wise upwards, as you would predict, but Zung scales were exactly the same in the primary care patients as in the really sick inpatients. Alarms went off in my head and when I took a very close look at the Zung scale I realized what

was going on; the scale had a fatal flaw. It asked people the frequency rather than the severity of their symptoms. So, people with persistent but mild symptoms rated themselves as high as people with persistent but extreme symptoms and the scale was unable to discriminate a primary care population of depression from an inpatient group who were mostly getting ECT. I said there has to be a better approach so I designed the prototype of what has become the Carroll Depression Scale and the first field testing was in Melbourne. I brought it to Philadelphia with me. In Ann Arbor, we set it up as a standard clinical scale and it was picked up in the CRC at Duke. Now I have a vast amount of data on this scale. We published it in 1981 in a series of three consecutive articles in *British Journal of Psychiatry*. I first offered that triplet of articles to George Winokur, for his new *Journal of Affective Disorders*, and George, who I love dearly, said, "Barney, it's great, but I'm not going to publish three articles, that's too much". So I persuaded the *British Journal of Psychiatry* to accept all three. After they were published in the other journal, George came up to me and said, "Barney you know, I really made a mistake."

LH: He sure did.

BC: Because that scale was another citation classic and lately I have put a lot of work into new analyses of its performance. That was my poster session here and I've designed a new version of the scale, adding additional statements to cover the melancholic and atypical features of depression. This scale is the only one that has built into it a direct crosswalk to DSM-IV for all the diagnostic symptoms of depression, melancholic features, atypical features and dysthymic disorder with algorithms built in to the scoring. I hope people will pick it up and use it. And, then, I want to develop one further personal line of work, which is to take a fresh look at this entire topic of Suicide in Late Life. This comes out of my work in geriatric depression over the last seven years and I will be working mainly on the internet, getting into national and international databases on Late Life Suicide and trying to get new insights into the correlates of that and the basic motivations of people. The numbers are staggering. The population base rate of suicide is around twelve per hundred thousand per year. In certain western states of the US, among men in their seventies and above, that figure of twelve rises to about ninety, so it's a very, very significant increase.

LH: Well, Australia's loss was our gain. We're so glad you came here and made a great many contributions. There aren't too many people who have that many citation classics.

BC: I've been extraordinarily fortunate. I've had very good mentors, people like Sam Gershon, David Curtis in Canberra, Brian Davies and Bob

Mowbray in psychiatry in Melbourne and Skip Martin in endocrinology. These people helped me a great deal and gave me the modeling of what it is to be a mentor and I have really tried to carry that through in my relations with Fellows and junior faculty over the years. I still have two junior faculty people I'm mentoring, Frederick Cassidy at the hospital and Eileen Ahearn in the department and with them, we are working on yet another field I think is going to be extremely important. It's another combination of nosology and psychometrics. We have a model of mood disorder, a model of bipolar illness. It's called the Carroll-Klein model and it's my extension of Donald Klein's original thoughts on the fundamental biologic dimensions of mood disorder, reward disturbance, central pain dysregulation and psychomotor dysregulation. We have taken that to bipolar illness and looked at it with the development of some new scales. We have a new scale for manic states. We published, January of this year, a very big and very important factor analysis of manic symptoms in Archives, showing for the first time what is the factor structure of manic symptoms and it's nothing like the conventional wisdom that derives from the old Beigel-Murphy studies. Now, we have developed a specific visual analog rating instrument for the patients to tell us where they are on these three orthogonal dimensions of illness and we have some very exciting studies coming along with that. One of the payoffs is a new paper we've sent in proposing, from an actual database, what should be a revised set of diagnostic criteria for mixed bipolar disorder.

LH: A very important group.

BC: The existing criteria for mixed bipolar are that you must have the full depressive syndrome. When you look at the performance of individual depressive symptoms in the context of a manic episode, that's not an effective way to do it, so now we have, from our own data, a way of refining that definition.

LH: That will tie into your interest in suicide prevention.

BC: That is a very high risk group. It's been a great twenty-seven years since I came here and a great time in Australia before that, and I'm extremely grateful to have had as good a shot at things as I have had.

LH: In knowing the history of Australian neuropsychopharmacology from early on did you ever have occasion to meet the most famous Australian psychopharmacologist, John Cade?

BC: John Cade was one of my teachers in psychiatry.

LH: Did he teach at the medical school?

BC: He did. I knew him well. His son, David, was in my medical school class and his other son, John, was two years ahead of us in medical school. I knew the Cades and I knew John; in clinical psychiatry we were taught

at the Royal Park Psychiatric Hospital, the inner city State hospital where John Cade was director of. We would go, as medical students, to the auditorium on Saturday mornings where John Cade would teach us psychopathology and his style was very Kraepelinian. He was up on stage with two chairs, one for the patient and one for him. An assistant would be hovering around and the patients would be lined up off stage. He would signal to stage right for a patient to be brought in and would say, in a very Edwardian authoritarian manner, "Ladies and gentlemen, I'm now going to demonstrate a patient with schizophrenia". The patient would be brought and John Cade would put the schizophrenic patient through his hoops, send the patient off stage left, signal again to stage right and say, "Ladies and gentlemen, I'm now going to demonstrate a patient with mania so you should pay close attention to the differences between them". His style was very autocratic and old fashioned, but in many ways, effective.

LH: Better than learning from a textbook.

BC: Much better. Then, in my psychiatry training, I had more encounters with Dr. Cade. I learned he had what can be called a divergent manner of thinking, a cognitive style with lateral and not always linear thinking. He published a paper in the Australian Medical Journal, on his theory of the etiology of schizophrenia. This, is in the late 1950's, was that schizophrenia was a disease that resulted from a deficiency of stone fruit such peaches and plums. An epidemiological study in the State of Victoria found that most acute schizophrenics were admitted to the receiving hospital from the densely populated parts of the city. They had the lowest density of fruit trees. That's very similar in style to the thinking that led to his discovery of lithium. He had this weird idea that some toxin in the urine of manic patients was responsible. He thought it was a urate salt. Needing a soluble urate salt, he got onto lithium urate. And his one good scientific question was to ask was it the urate or was it the lithium? And the rest is history.

LH: When he was teaching you had he already made that discovery?

BC: He had.

LH: Why did it take so long to catch on? Was it because he had a reputation of being a wild thinker and nobody believed him?

BC: No. Australians are very pragmatic and all through the 1950's, lithium was widely used in Australia and was picked up in England through Mogens Schou in Scandinavia and later in Europe in the 1950's and the 1960's. The resistance to lithium as a clinical agent was centered mostly in the United States.

LH: That was due to its earlier use as a salt substitute for congestive heart failure and deaths due to toxicity before blood levels were available.

BC: Exactly, and that's all being written up in Frank Ayd's book, *Discoveries in Biological Psychiatry*. I now have in my possession glossy photograph copies of John Cade's original case notes of the first patients he treated with lithium and I will donate them to the ACNP Archives. They are very, very interesting.

LH: How was he lucky enough to pick the right dose?

BC: The dose was known, because lithium had been used for epilepsy and gout, so people knew that lithium was safe. John's description of his IND process, shall I say, was that after he'd completed his guinea pig experiments he did a Phase 1 clinical trial on himself and the determining factor, when he treated himself with lithium for two weeks, was whether his wife, the long suffering Mrs. Cade, noted any difference. She did not notice, so he proceeded to treat a group of patients who were essentially chronic residents of the hospital. Today, we would call those patients, looking at the case notes, rapid cycling bipolar. They were in and out of manic and depressive phases of bipolar illness and to everybody's astonishment, they were all discharged within about four months of starting on lithium, so they truly were stabilized. John had complete freedom to do whatever he wanted in those days. There was no drug regulatory agency.

LH: He was the superintendent of the hospital.

BC: He lived on the hospital grounds. I remember going to his house to visit with his sons, who were in medical school with me, going in by the back gate from the hospital grounds to the superintendent's house. There was a basket on the gate that was replenished every day with vegetables from the patients' garden for the consumption of the superintendent and his family.

LH: This is really old style, isn't it?

BC: He was a beloved figure in the hospital and a very conscientious clinician.

LH: That's a new element to your Australian training.

TB: So, you were in medical school about ten years after his publication on lithium, in the late 1950's?

BC: I entered medical school in 1958.

TB: Just ten years after.

BC: That's correct.

TB: Some clinicians had already picked up lithium?

BC: Sam Gershon was using lithium in Australia and in the pharmacology department in Melbourne a number of basic studies of lithium kinetics and distribution were under way and were published during the 1950's. Sam Gershon was already publishing his work on lithium.

LH: I think Gershon came to this country around the early 1960's.

-
- BC: Correct. I was with him in 1961 and he came to America in 1957-1958, came back in 1959-1961 to Melbourne and in 1962, returned to the United States.
- LH: Sam would talk lithium to the sceptics over here. I remember saying, "Lithium, that's a good thing to kill you", because I had fresh in my mind toxicity in cardiac patients.
- BC: The last time I saw John Cade was at a very important event. It was the 1979 International Conference on Use of Lithium in New York and John was the featured person at that meeting, along with Schou. I remember being at the hotel, walking across the lobby the day the meeting was getting underway, and I saw John wandering around in a dazed and confused way. I knew immediately what the problem was. He was in his late seventies and terribly jet lagged. I went up to him and I said, "John, how are you"? And, he said, "I'm alright, Barney, leave me alone". That was his usual style but I went on, "John, you look as though you're not very well". He replied, "All I need is a little sleep". I asked "Where have you been"? and he said, "I just got off the plane from Australia". So I said, "John, do you mean to tell me you didn't break the journey anywhere between Melbourne and New York"? He said, "No, I just flew straight here". I admonished him but he was in a travelers' delirium with severe jet lag and disorientation. So we got him to his room and he slept that off was back to his happy self for the rest of the meeting. I take credit for helping to get John settled down in time for his public appearance.
- LH: Well, that's an interesting side light on an aspect of major importance in the history of psychopharmacology. Thank you, then.
- BC: Thank you.
- LH: I'm glad we caught that.

GUY CHOUINARD

Interviewed by Andrea Tone
San Juan, Puerto Rico, December 10, 2003

AT: My name is Andrea Tone and we're at the 42nd Annual Meeting of the ACNP in San Juan. I'm interviewing Guy Chouinard.* Why don't we start from the beginning? Where and when were you born?

GC: I was born and raised in Montreal in 1944.

AT: Could you tell me a bit about your education?

GC: There was a different system of education at the time in Quebec. Before starting medical school, one had, after four years of grade school, an eight years "classical course" which included both high school and college, during which we studied mainly Latin and Ancient Greek. I did that from 1956 to 1964.

AT: How did you get interested to become a psychiatrist?

GC: My destiny was written quite early in childhood and adolescence. It all started during my eight years of high school and college, which I did in Verdun, a suburb of Montreal, with Heinz E. Lehmann's son François. In the early 1960s, François Lehmann organized a visit to the Verdun Protestant Hospital, today called the Douglas Hospital, where his father, a world famous psychiatrist, led the visit. (See, Lehmann, volume 1.) I remember visiting those wards with long term patients and noticed two features; their autism and their walk. When I saw some patients reading I asked Dr. Lehmann whether he thought they understand what they were reading. He answered, "No. They are too much in their own world". Secondly, the patients were not walking like normal people. Later, I spent 20 years of my investigating those abnormal movements induced by anti-psychotics which are mixed with the abnormal catatonic movements and mannerisms of schizophrenic patients. Also, in the early 1950s, my family lived near a mental hospital, Ste. Anne de Bellevue, in Senneville on the outskirts of Montréal. I recall that the patients were all dressed in light blue gowns; it was always a shock for me to see them. Later, when I became Director of the Schizophrenia Follow-Up Clinic at the Allan Memorial Institute, I recognized a man I'd seen in a blue gown as a child because he had a small malformation of his lips but I never told him this during the many years I treated him. When I succeeded in his treatment with a new generation of atypical neuroleptics, he no longer looked like the person I used to see in that blue gown.

AT: Why did they dress them like that?

* Guy Chouinard was born in Montreal, Quebec, Canada in 1944.

GC: Everyone was afraid of the mentally ill in those days. The hospital wanted them to be easily recognizable in the village; it was a modern mental hospital so the doors of the wards were open.

AT: So, you always wanted to be a psychiatrist?

GC: Initially, I was interested in both philosophy and medicine. My mother was ambivalent about philosophy; a bit concerned about earning a living. Then, I got more and more interested in medicine, and biological medicine became a passion, especially concerning the mysterious mental illnesses. I thought I would return to philosophy later in life, but by then, I had discovered molecular pharmacology and became fascinated by it. However, I kept an interest in philosophy, which in some ways drew me to psychiatry. Philosophy was like a gateway into understanding disorders of the mind.

AT: How did you get interested in psychopharmacology?

GH: When I started medicine there was a well-known pharmacologist, Léon Tétreault who had trained at John Hopkins with Louis Lasagna, the founder of clinical pharmacology in America. Dr Tétreault was a clinical pharmacologist, not a psychiatrist; who was interested in the placebo response and involved in research on narcotics. In 1965, at the end of my first year in medicine, I obtained a student award in pharmacology and worked in the summer with Tétreault; I did my first clinical trials on hypnotic drugs. I was studying the effects of nitrazepam, a benzodiazepine drug initially introduced for the treatment of petit mal epilepsy and myoclonus. I remember being anxious to find a difference from placebo. Dr Tétreault said the only thing I needed to do was to be rigorous and ask questions according to the sleep questionnaire we used. He told me if the instrument was sensitive and the drug had a hypnotic effect I would find it. I did what he said and had no idea which patient was taking what substance in a double-blind placebo-controlled study with secobarbital. I recall expecting, with apprehension, the results from the calculating machine before there were computers. The results were positive and differentiated active medication from placebo. The study was published in 1966; I was a co-author and it was my first publication. Interestingly, it was also the first clinical trial carried out in St Jean de Dieu hospital, now named Louis-H Lafontaine. I had to wait until 1970 before I became involved again, during my first year of residency in psychiatry, in my second and third clinical trials. The drugs I studied then were pimozide and fluspirilene at the Douglas Hospital with Thomas A Ban and Heinz E. Lehmann. Thomas Ban taught me psychiatric semiology; it was a pleasure later on to use his diagnostic scales. I followed what I learned from him when I developed a Rating Scale for Psychotic Symptoms, published in 1999 in *Schizophrenia Research*. Ban

and Lehmann complemented each other well. From them I learned how to do research in psychopharmacology and how to write a paper. They served as my mentors.

AT: How did psychiatry at the time you started compare to psychiatry today?

GC: It was dominated by psychoanalysis.

AT: Were you involved in psychoanalysis yourself?

GC: After my first year of residency in psychiatry at the Douglas Hospital, I continued my training in psychiatry at the Allan Memorial Institute (AMI), one of the most famous North American centers for psychoanalysis. Except for my training with Lehmann and Ban my training at McGill University was in psychoanalytically oriented psychiatry. Throughout my training at the AMI I was always with psychoanalysts, group and family therapists so I learned psychoanalytic principles, which I still apply in my psychopharmacology research.

AT: What did you do after you completed residency?

GC: I returned to the University of Montreal with a Medical Research Council Fellowship for training in clinical pharmacology under Dr Léon Tétréault. I developed my hypothesis that schizophrenia is a dopamine deficiency disease, like Parkinson's disorder, affecting the prefrontal regions and leading to affective negative symptoms, and inducing dopamine over-activity in the basal ganglia and sub-cortical regions producing psychotic or positive symptoms. I still work on this dopamine deficiency hypothesis of schizophrenia that I published in the *Lancet*. In studying schizophrenia and the effect of drugs on the disorder the most important objective is to measure their effect on the dopamine systems by the assessment of both psychiatric and extrapyramidal symptoms (EPS). Psychiatric symptoms were much more difficult to measure than EPS because instruments to measure EPS or drug-induced movement disorders (DIMD) from antipsychotics were not sufficiently precise or sensitive. Therefore I developed, in 1979, a scale with Dr. Andrée Ross, the Extrapyramidal Symptom Rating Scale (ESRS), to measure the four drug-induced movement disorders: Parkinsonism, akathisia, dystonia and dyskinesia.

AT: Could you tell us something about the ESRS?

GC: The ESRS is now used in 30 percent of clinical trials on antipsychotic drugs and has been translated into at least 13 languages. Using my scale I became a specialist in drug emergent effects of psychotropic drugs.

AT: So, you were involved in studying side effects of drugs?

GC: My hypotheses most often start from clinical observations or from trying to understand results from my double blind placebo controlled studies. My initial observations are usually made through direct contact with patients and knowledge about the mechanism of action of drugs they are

taking. Obviously, my observations have to be confirmed in controlled studies. The idea of “supersensitivity psychosis” originated from simple observations but my first paper on it was based on data from three controlled clinical studies.

AT: What was the clinical observation that led to your hypothesis of “supersensitivity psychosis?”

GC: One of our outpatients was not regularly taking his antipsychotic medication, and had one or two relapses every two years. After he started on long acting antipsychotic injections every two weeks, his psychotic symptoms almost immediately come back if he missed an injection. The course of his illness changed. I concluded the brief psychotic episodes after missing an injection were a rebound effect. I called this phenomenon “supersensitivity psychosis”, knowing the terminology was not perfect. I reported the syndrome in two papers published in the American Journal of Psychiatry. So the concept is recognized in some textbooks, but was not sufficiently studied. It is difficult to study rebound syndromes during withdrawal from drugs that are needed by patients. Supersensitivity psychosis has its equivalent in tardive dyskinesia and shares some of its clinical characteristics.

AT: You mentioned you developed a scale to study psychotic symptoms?

GC: I collaborated with people at the Montreal Neurological Institute (MNI). The parents of a patient with schizophrenia donated a new cyclotron to the Institute and Gjedde was interested in studying drug naive schizophrenia with MRI and PET scans. I was responsible for doing the ESRS and the PANSS before patients were scanned, and for confirming the diagnosis of schizophrenia. It was then I realized the limits of the PANSS rating scale. So, I asked Robert Miller to come to Montreal from New Zealand and during that year we developed a dimensional new rating scale for schizophrenia, the Rating Scale for Psychotic Symptoms (RSPS). We published our scale in 1999 in Schizophrenia Research. I purposefully avoided using the term schizophrenia because, in my opinion, psychosis can exist in several disorders, not just in schizophrenia.

AT: Could you say something about your research in the 1980s?

GC: From 1980 to 1990, I was involved in research with the anticonvulsant, clonazepam and antidepressants. I did also studies to see if precursors of neurotransmitters, such as tryptophan and lecithin have therapeutic effects in psychiatric disorders but found little beneficial effect with either unless given in combination with recognized therapeutic drugs. I also did research with levodopa in combination with decarboxylase inhibitors in schizophrenia and drug-induced abnormal movement disorders, but did not find significant effects.

AT: Could you elaborate on your research with tryptophan?

GC: I got interested in tryptophan because it was not understood why a precursor of serotonin had variable effects in affective disorders. There was a controversy about its role in the human brain and efficacy in affective disorders. I collaborated with Ted Sourkes and Simon Young who had published a hypothetical explanation on the variability of findings with tryptophan in depression. They hypothesized if we blocked the liver metabolism of tryptophan, some would penetrate the blood brain barrier, and be converted into active serotonin. We started clinical investigations funded by the Medical Research Council (MRC) of Canada. In double-blind controlled studies we gave large amounts of tryptophan together with nicotinic acid to block the liver metabolism and found therapeutic effects which were more prominent in mania than in depression. These findings led me to research with clonazepam, a serotonergic anticonvulsant. Based on our findings with tryptophan I thought mania would be a better target for treatment with clonazepam than depression. This was at the time people became interested in using anticonvulsants in mania and bipolar affective disorders.

AT: Can we get back for a moment to tryptophan?

GC: Yes. We thought at first we needed to block tryptophan's metabolism in the liver to get it into the brain. However, this didn't turn out to be exactly so. Later, we found tryptophan potentiated both the antimanic and mood stabilizing effects of lithium. These findings led to the approval of the indication for tryptophan as an adjunctive medication to lithium in Canada. But contamination of tryptophan in the US led to decreased use of tryptophan in psychiatry even in Canada though we did not get any cases of the eosinophilia-myalgia syndrome caused by contamination.

AT: When I interrupted you started to talk about clonazepam.

GC: I carried out a crossover study with a small sample under double blind conditions in which I compared clonazepam with lithium in acute mania. It wasn't easy because there was no funding available, and no one was interested in the idea at that point in time. I found clonazepam at least as efficacious as lithium in acute mania. After this first study, the MRC of Canada funded our subsequent studies on clonazepam. Publication of the results in *Biological Psychiatry* led to a new approach in the treatment of agitation. Shortly after we published our findings Lennox published similar results in agitation with lorazepam. Both clonazepam and lorazepam became widely used in acute agitation in combination with a neuroleptic. I believe this is one of my most practical contributions for patient care. Since then clonazepam or lorazepam have been frequently used in combination with the antipsychotic haloperidol in the emergency

treatment of agitation. There was a large-scale study in the US, published in Emergency Medicine, comparing haloperidol alone, benzodiazepine plus haloperidol and benzodiazepine alone, which showed combined treatment was significantly superior. Around the same period of time I was asked to investigate alprazolam in anxiety disorders, probably because of its serotonergic properties. At the end of the 1970s the DSM II diagnosis, anxiety neurosis, was still in use and this permitted me to include not only patients with generalized anxiety disorder but also panic. This was how the antipanic effect of alprazolam was first discovered.

AT: Could you tell us more about your study with alprazolam?

GC: I had a colleague in Montreal who referred me all his panic patients treated taking MAO inhibitors because he was moving to Vancouver. I did not like the MAOI treatment of panic disorder and thought these patients would be excellent candidates for the alprazolam trial. The concept of panic disorder was introduced by Donald Klein, whom I admired, by identifying a group of imipramine responsive patients. I was interested whether alprazolam would work in these patients and in my study 50 percent of the patients had generalized anxiety disorder and 50 percent had panic disorder treated with MAOIs before the trial. We found alprazolam significantly better than placebo in the treatment of panic disorder and comparable to MAOI. Our results were confirmed in several multicenter placebo-controlled trials, which led to approval of the first antipanic agent by the FDA. But the story was not finished because I found patients were getting too dependent on alprazolam. So I decided to do a clinical trial with clonazepam in panic disorder in which I showed clonazepam also had antipanic effects. Our findings with alprazolam and clonazepam contradicted Don Klein's findings and theory that antidepressants are the treatment of panic attacks and not benzodiazepines.

AT: So, the problem with alprazolam was that people became dependent on it?

GC: There was an interdose rebound effect; Rosenbaum's group was the first to describe this phenomenon which they called the "Clock Watching Syndrome". Patients were looking at their watches, waiting for the next dose of alprazolam. When I saw this effect I tried to avoid prescribing the drug and was looking for an alternative that would have the same therapeutic effect without interdose rebound. I decided to use clonazepam instead of alprazolam to block the panic attack, and it worked with less rebound anxiety on drug withdrawal.

AT: Did you work with any other serotonergic drug?

GC: Following my work on tryptophan and clonazepam I was asked to study fluoxetine. I accepted the proposal hoping to find an antidepressant that

would not affect cognition adversely. My work with fluoxetine lasted 12 years until it got final approval from FDA in 1988. In my first clinical trial, I used high doses of up to 80 mg daily and compared fluoxetine with amitriptyline. A few months after clinical investigations began there were several unexplained deaths with fluoxetine and post mortem examination found abnormally high levels of fluoxetine and norfluoxetine in tissues. But when we looked at samples from patients in Montreal there was no accumulation of fluoxetine with long-term administration. So we decided to do animal studies which demonstrated that delay measuring fluoxetine in tissues after death was responsible for the abnormally high post-mortem levels found in those patients with unexplained deaths.

AT: Why did it take FDA so long to approve fluoxetine?

GC: One of the problems was that in animal studies fluoxetine caused phospholipidosis.

AT: What is phospholipidosis?

GC: Phospholipidosis is the deposit of lipids and phospholipids in the eyes, white blood cells, liver and lungs. We designed a study with three different groups, one with patients who received long-term fluoxetine, a second with patients who received an approved drug which causes phospholipidosis in animals but not in humans, and a third group of patients who received amiodorone, an anti-arrhythmic drug which causes phospholipidosis in animals and in humans. The FDA approved the protocol, perhaps thinking there was little hope of doing such a study. But by chance, at the Institute of Cardiology of Montreal, there were more than a hundred patients treated by amiodarone who could serve as controls for the whole study. This was not easy to carry out, because at the Allan Memorial Institute, where we did the study, there was no elevator and the cardiac patients treated with amiodorone had to walk up three floors. Finally, we completed the study and were able to show no evidence of phospholipidosis after several months treatment with fluoxetine. And with these data the drug was approved in 1988.

AT: Any other antidepressant you studied?

GC: I did pivotal studies with bupropion, sertraline and fluoxetine in indications other than major depression. I carried out the first placebo-controlled study of sertraline in OCD and very early studies of fluoxetine in OCD.

AT: Could you tell us about your research in the 1990s?

GC: In 1990, I went back to clinical investigations with antipsychotics and was involved in the development and rapid registration of risperidone first in Canada, then in the US. I participated in the designing of the pivotal multicenter trials with placebo-control in Canada and the US, and without

placebo-control in the rest of the world. At the request of Paul Janssen, I also undertook a trial of risperidone in a patient with severe Tourette's syndrome and recorded the results with videotapes so he could see for himself the effect of the drug on his multiple tics. My idea for risperidone's clinical development was simple; we needed to know if it has an effect on both positive and negative symptoms. We wanted to see if risperidone would have a similar effect as clozapine in terms of an atypical antipsychotic effect, mostly on the negative symptoms of schizophrenia. On the basis of my placebo controlled trial, I was not in favour of using the drug in acute schizophrenia and wanted to have a trial in schizophrenic patients with a sub-chronic illness. In that population, after three or four weeks, the drug showed atypical effects by normalizing the blunted affect of patients so I was convinced we had an atypical antipsychotic, but waited for the statistical analyses of the multicenter trials for confirmation before reporting it.

AT: Were you involved in studying any of the other atypical antipsychotic drugs?

GC: I was involved in the two North American early trials of clozapine in the mid-1970s. The first patient I included in our clozapine study developed an "atropinic psychosis," which led me to keep doses low to avoid serious complications. Then, the drug was off clinical investigation for many years, and I had to wait until it was approved for treatment resistant schizophrenia before I used it again. At the time I was working with clozapine I was in charge of a Special Follow-up Clinic (SFU) at AMI that included more than 300 outpatients with schizophrenia. In addition, I was responsible for a 30-bed unit for patients with treatment resistant schizophrenia at Louis H. Lafontaine Hospital.

AT: When was that?

GC: After I graduated from medical school. It was about the time Maurice Dongier was appointed Chair of Psychiatry at McGill and director of the AMI. Before I took over the clinic a psychoanalyst was in charge and, during my first week, two patients committed suicide. I decided to reorganize the clinic so I could be sure patients were taking medication. In the late 1970s and early 1980s it was difficult to treat schizophrenic outpatients because of compliance problems, limited efficacy of "classical antipsychotics," and, above all, because of the EPS produced by the old drugs. I decided to use only one antipsychotic because there was no evidence that one "classical antipsychotic" was better than another. I had chosen fluphenazine because it was available in oral and two long-acting parenteral formulations. Using fluphenazine I noted how tolerance developed to its antipsychotic effect. I had to increase the doses slowly but continuously to have the same effect and since I was using an injectable form, I

was sure compliance was perfect. This was how I discovered supersensitivity psychosis. I learned that the average patient who stopped taking oral medication relapsed after 16 months without medication, whereas patients on IM long acting medication had a brief relapse every time they missed an injection. The pattern of illness had changed so I tried to understand what was going on. I noticed that patients who relapsed if they missed an injection responded immediately to resumption of treatment whereas patients who relapsed after 12 to 15 months of stopping had a “natural relapse” and remained hospitalized for 2-3 months after treatment restarted.

AT: So you used fluphenazine only at the AMI follow up clinic?

GC: After doing a pivotal study with Haldol Decanoate, I switched our 300 patients from fluphenazine to haloperidol. In the course of this process, about 30 % of patients, most of those who were on high doses of fluphenazine, relapsed. This gave me an opportunity to see many cases of supersensitivity psychosis. About that time I had a visit from the head of the EEG laboratory of the Montreal Neurological Institute (MNI). He told me they had been using chlorpromazine at low doses to uncover epileptic activity and would prefer to use another antipsychotic that had less sedative effect. I recommended the use of haloperidol. Following this meeting it occurred to me that supersensitivity psychosis was somewhat similar to the kindling effect produced by epileptogenic drugs in animal models. Thus, I thought one way to correct and prevent supersensitivity psychosis was to give anticonvulsants in conjunction with antipsychotics. I first tried phenytoin with success, but I didn't like its numerous side effects. I also tried carbamazepine, but it had the disadvantage of numerous drug-to-drug interactions. Then, Harrison Pope invited me to participate in a symposium on anticonvulsants and psychiatric disorders at the APA meeting of 1988 in Montreal. He proposed I do a presentation on clonazepam while Pope would present on carbamazepine and his group on valproate. I asked Pope if I could also present my results on schizophrenic patients with supersensitivity psychosis I had treated with valproate, and he agreed. So I presented my findings on antipsychotic and anticonvulsant combinations in the treatment of schizophrenia. Several years later I learned that up to 30% of schizophrenic patients in the State of New York had been treated with anticonvulsant and antipsychotic combinations.

AT: Were you involved in the development of any other anticonvulsant for psychiatric indications?

GC: Gabapentin. My final contribution was the introduction of gabapentin, an anticonvulsant, in psychiatry as an antianxiety agent and for low back pain. Initially, I used the drug in psychiatric patients as a mood stabilizer

and for the prevention of supersensitivity psychosis. In those patients I discovered its antianxiety, hypnotic and analgesic effects. Based on my unpublished data, I was involved in the initiation of the first clinical trial of gabapentin in panic disorder, published in the *Journal of Clinical Psychopharmacology*. Gabapentin became one of the most prescribed drugs in the United States. I devoted much of my research effort to investigating off label indications for psychotropic drugs and many of those later became official indications.

AT: We should probably wrap it up now. Do you have anything else to add?

GC: My main goal in research has been to improve the immediate treatment of patients. I was always interested in studying side effects of drugs because by studying them we learn to better understand the mechanisms involved in their therapeutic effects.

JOHN M. DAVIS

Interviewed by David Healy
Las Croabas, Puerto Rico, December 15, 1998

DH: Today is Tuesday, the 15th of December 1998. I'm David Healy and I'm interviewing John Davis* on behalf of ACNP at the ACNP annual meeting in Puerto Rico. John, where were you born?

JD: In Kansas City, Missouri

DH: In what year

JD: 1933

DH: What kind of schooling did you have and why did you go into medicine?

JD: I had intended to be a writer, but I am very inarticulate and not a good speller, so I was afraid I would fail freshman English. I took a senior course at Princeton, where I did my undergraduate in Creative Writing, but to get in you had to write a creative piece. So, I wrote a short story and submitted it and I was chosen. It turned out my teacher was Saul Bellow.

DH: Oh, really!

JD: If there was time left over in class, he would read the book he was writing and I would make a few comments. He was writing *The Adventures of Augie March*.

DH: Fascinating.

JD: When he missed a session, as a substitute we had Delmar Swartz and he told me that there were too many writers who are English professors and I should choose another field. I was interested in science, also, so I switched.

DH: So, you, then, took medicine.

JD: I didn't decide that until later. My parents were brought up on farms in Missouri and they took a narrow view of academia. But they would pay my way thru medical school so I went to Yale and became interested in Psychiatry.

DH: How or why?

JD: Because it was partly unexplored, and it interested me a more. I published four or five papers as an undergraduate in a Psychology major. Then I went on with Psychiatry, which was largely psychoanalytic. I did my internship at Massachusetts General Hospital and then went back to Yale for residency.

DH: This was when?

JD: 1960 was when I graduated from medical school. I did my internship at Mass. General in 1960-1961, and residency from 1961 to 1964. It was in

* John M. Davis was born in Kansas City, Missouri in 1933.

the psychoanalytic era and drugs were just coming into use. Everybody was treated with psychoanalysis and there was no formal training in drug treatment, only a few informal seminars. Generally, patients were treated with medication, sub-rosa. If you did so, you would often not mention it at a case conference. And, schizophrenia was very widely diagnosed. I had intended to become a psychoanalyst, but because I was interested in medication and my teachers didn't believe in it, I reviewed the literature on psychotropic drugs and published it in the Archives of General Psychiatry.

DH: This is the paper with William Bunney back in 1965?

JD: That came later. This was earlier and it was me alone. Then, I went to NIMH and worked with Biff Bunney which was one of the happiest periods of my life, because I had great respect for Biff. And, he assigned me to work on the biochemistry of depression. Biff had the basic idea that there might be something to be learned by putting together the clinical effects of drugs and their biochemical pharmacology. So I read the pharmacology and wrote the nuts and bolts of the original biogenic amine theory of affective disorder. At the same time Joe Schildkraut was working on the same theory at a different unit. Joe had done previous work in that area, so he deserves greater credit than we do. It was close to a simultaneous discovery, because we submitted our paper to Science but it was rejected, which allowed him to get his paper out a month earlier.

DH: Let's just go back to about 1963 when you began to work on all this. How did the amine field look at that time? Did you guys know what the amines were? What did you have to go on?

JD: Well, we knew that. Actually, a lot of people were not sure the antidepressants worked but Jan Fawcett and I, in my junior role, we were getting good results with them. We thought they were very effective and that made Biff more enthusiastic. But most of psychiatry was sceptical. The basic paradigm was that you looked for common mechanisms in drugs which helped a disease or which made it worse. The clinician's job was to show what happens in man and the basic scientist's was to find the mechanism of action in animals. Julie Axelrod was close to us at NIMH, so we could walk to his lab and talk with him. It was shortly before I started that he discovered the biogenic amine uptake pump.

DH: When did the coin drop that all these pills were doing the same thing?

JD: It happened about the same time. The time was right; Schildkraut said it and we said it. It helped change the way people thought about the mechanism of action of antidepressants and bridged the gap between basic and clinical science.

DH: Did reserpine seem to be a useful tool because it made people depressed?

JD: Very definitely.

DH: It seemed to lower amine levels. Are you sure it made people depressed?

JD: Absolutely. There was a doctor at NIH, studying the biochemistry of hypertension, and he saw depression in reserpine and in α -methyldopa treated patients. I went over his case records and interviewed patients with him. He was very sceptical of psychiatry and psychiatrists, so he did most of the interviews and I just sat with him. He didn't want to let me loose with patients! But he asked all the right questions and there's no doubt they were depressed. A lot of these patients had previous depressions, so the drug was aggravating a predisposition.

DH: So, you actually saw the patients involved?

JD: Yes.

DH: You say Joe and you came up with the idea at much the same time. You both were in the same lab, but you had very little contact?

JD: We were in different labs. He was in a more scientific lab and we were in a more psychoanalytic lab, run by Lyman Wynn who was interested in family therapy.

DH: How did Biff end up in that lab? .

JD: Biff went to NIH three or four years before me, when Dave Hamburg was laboratory chief, but Lyman Wynn took it over when he left.

DH: What else were you involved with?

JD: Sam Gershon came to give a lecture on lithium, and I was assigned to treat the first patient with lithium at NIH. Fred Goodwin came the next year and took over the lithium project while I went on to work with Axelrod and Kopin in the lab. It was a marvellous experience to try a new drug that nobody had experience with.

DH: To bring you back to that article, can you recall writing it? Were you at a point where you felt you had all the ingredients for formulating the catecholamine hypothesis of affective disorder?

JD: We didn't know what a catechol was, so my first question to Biff was, "What's a catechol?" And, he didn't know either. So, I went to the library and looked up articles on the pharmacology of antidepressants. I also went to seminars people gave, like Axelrod, and listened to them talk about it before I wrote the article. I felt privileged to work with Biff, who was a fine scientist.

DH: David Hamburg, you mentioned; it seems people say he was wonderful. Do you agree?

JD: He had a broad vision, a really intelligent guy.

DH: It seems he was not the one who actually did the work but he set up groups of people to do it.

JD: He was a gifted person, and he went on from NIH to be Chair at Stanford. When I had a research ward at the State Hospital, the legislature intended to cut our budget fifty percent which would have destroyed research and training. The cut passed the House of Representatives in the State of Illinois, 141 votes to 3. I had Dave Hamburg call the President of the House and the Senate and he succeeded in getting our budget restored.

DH: He was the kind of man who could talk at the top levels?

JD: Yes, he could.

DH: How about Biff Bunney? What was his background?

JD: His father was with Squibb and his brother is Chair at Yale.

DH: A few years after publishing the paper of the catecholamine hypothesis you had a book on Psychotropic Drugs.

JD: At the time the academic community was all psychoanalytic and they thought that using drugs was bad. Profoundly depressed patients would get better on antidepressants, they would go back into the community and the first thing their doctor did was take them off the drugs. The leading psychiatrist of the young generation at the time was Don Klein, who discovered panic attacks. So, I asked if he wanted to write a book with me; I would do the scholarship and he could provide the depth of clinical understanding. So we wrote it although we'd hardly met. I think we had dinner once, but it was entirely done by correspondence. I think it was a very fine textbook which influenced a lot of people.

DH: That came out when?

JD: 1969. It was written from 1966 to 1968, and had a complete review of the literature with a lot of good clinical information as well.

DH: It needed that to turn things around, didn't it? The kind of book where readers got a feel for how to practice psychopharmacology.

JD: How to think about diagnosis and the fact there was a lot of evidence that supported the use of drugs. There was no other good textbook, in my opinion, so a lot of clinicians said they learned psychopharmacology from it.

DH: I can see that.

JD: I worked with Julius Axelrod and Irv Kopin in the lab, where I did a number of experiments, some with my own hands, so I have a feel for the lab. We did experiments to study the effects of drugs on transport of amines by the norepinephrine or serotonin uptake pump in rat brain or synaptosomes and did parallel experiments with amine uptake in man with platelets. Dennis Murphy was working with platelets and we would do it in synaptosomes, as we tried to bridge animals and humans.

DH: You said the first draft of the paper went off to Science?

JD: We were rejected, but never knew why.

DH: When Joe Schildkraut's article came out a month or so before yours in the American Journal, how did you feel?

JD: I was mainly worried about my career. I was afraid if there was too much controversy I might get into trouble. Psychoanalysts wanted people to study sleep because sleep had to do with dreams and Freud. At that time I looked at a couple of jobs where they had a sleep lab and wanted to hire a sleep researcher. They weren't interested in biogenic amines and depression. Eventually, after I had a couple of years in the lab, I got a clinical job at Vanderbilt, where they had a very fine Chair of Pharmacology, Alan Bass, who had a vision and got us a state hospital unit. When I went it was just empty space in an old state hospital ward, and the first thing I had to do was buy furniture. But there wasn't enough money in the budget to hire nurses and nursing assistants. So I hired young radicals, right out of college, who wanted to do something good and would work for ten dollars an hour. I recruited David Janowsky, a member of the ACNP, and we did a couple of things of interest. (See, Janowsky, in this Volume.)

DH: Could you say something about those projects?

JD: We knew that most biologic systems are controlled by more than one transmitter and we knew of the balance between acetylcholine and norepinephrine. So, we thought we would manipulate acetylcholine and gave physostigmine, which raises acetylcholine. By inference, from my prior work, one would think acetylcholine would help mania and make depression worse. We found when you inject acetylcholine or physostigmine mania would turn off in a couple of minutes and patients would go into a neutral mood. In fact, they would get a little bit depressed. It was a very dramatic effect and depressed people would get more depressed when given physostigmine. This was greeted with some scepticism. A very sceptical group in New York, led by Sam Gershon, invited us to demonstrate our findings. So, we got informed consent from a patient and injected placebo; nothing happened, and then we injected physostigmine. This was a wildly manic patient who thought he was a multi-millionaire and claimed he owned his own private 747 jet, making billion dollar deals around the world, although he was homeless. Immediately after the physostigmine, he began talking about paying us a fee of a hundred thousand dollars for the consultation, but when the physostigmine started to kick in he reduced the fee to ten thousand, then to one thousand, and, as he became depressed, to a hundred, ten and zero. Finally, he said we should pay him for being an experimental subject.

DH: Given that was so powerful, why have we not made more of the role of the cholinergic system in affective disorder?

JD: My job as a clinician is to test the systems in man so we know which drug works and which systems might be involved. We also studied the dopamine theory of schizophrenia. Several basic scientists worked on it in those years, including some Europeans. The person who particularly got me interested in it was Sol Snyder who found a good correlation between potency of dopamine blockade and antipsychotic effect. We thought we would test this by raising dopamine and seeing what it did to schizophrenia. What we found was that a small injection of dopamine, amphetamine or Ritalin (methylphenidate,) which releases dopamine, doubles the intensity of the psychosis. These drugs work only when patients are psychotic; the psychosis gets worse for about twenty minutes. It's often, in some peculiar way, beneficial. I remember a patient who had an elaborate delusional system about being in the Garden of Eden where some of the staff were angels and others were devils. As soon as she got Ritalin, she said "My God, I'm back in the Garden of Eden and you are an angel and you are a devil." When the experience was over she said, "Oh my God, you know those ideas are really crazy and that drug brought them back." We kept her in the ward for another week but since she was not psychotic we discharged her.

DH: Without an antipsychotic?

JD: Yes.

DH: That's extraordinary, isn't it?

JD: I'm not sure whether that is the kind of thing you could do for treatment.

DH: But it opens up fascinating perspectives.

JD: It's an interesting case.

DH: Absolutely.

JD: It's interesting from the historical point of view, because the work we did with dopamine agonists it's been reactivated now with PET-Scans. There's a question about how we know anti-psychotic drugs work by blocking DA receptors. We know that drugs like methylphenidate which release DA make schizophrenia temporarily worse and we think this is because they may increase DA synthesis or produce super-sensitive receptors. The question is whether we can find out what is happening with brain imaging in the living human when we give a dopamine agonist? There are several groups trying to do that just now by injecting amphetamine. The schizophrenics get more psychotic for a few minutes after the injection and they can calculate dopamine release during that time; it seems schizophrenics have increased DA release. By and large, those people don't know Dave Janowsky and I did the same thing at Vanderbilt. It's just undergone a reactivation with a different technology.

DH: Did you ever look at 5HT?

- JD: I regret we didn't when we did the original biogenic amine theory. In the first draft I mentioned that what we said for catecholamines applied to serotonin but both Biff and I were so sure it was norepinephrine (NE) we cut that segment out of the final paper. We made a mistake and I regret it.
- DH: So, you think you ought to have left the serotonin possibility there?
- JD: Yes. Joe Schildkraut was caught up with NE as well and made the same mistake.
- DH: In a sense, it's odd. How come you guys became so NE oriented when five or ten years before Brodie at NIH had been very 5HT oriented?
- JD: Well, I actually worked with Brodie.
- DH: Could you say something about him?
- JD: It was a different type of work in Brodie's lab. Brodie was a night worker. He would come in the lab in the afternoon and often talk to people until the late evening or early morning. Sometimes he would call me into his office in the early afternoon and talk till five or six. You had to be a person who got along with four hours of sleep to get the most out of working in his lab. Brodie was interested, also, in plasma levels of drugs and drug metabolism. He had a pharmacologist, Steve Curry, who developed assays for chlorpromazine and he another guy from Sweden, doing drug metabolism with tricyclics. Steve Curry and I did the first plasma level studies in psychosis, measuring the relationship between plasma levels of chlorpromazine and clinical response. We didn't know enough to do mathematical modeling or anything like that. But we found if you want to treat effectively somebody who is very psychotic you give them chlorpromazine intramuscularly. When I was on duty for the first night as a psychiatrist without any training in how to use drugs, I was called to the emergency room to see a man who was breaking up the furniture and was very psychotic. I knew from the telephone call I needed to bring some nursing assistants with me. When we took the patient to our unit he was fighting and the nursing assistants were holding him down. Then, a nurse said, "Doctor, you want to inject him with Thorazine don't you?" That is how I learned what was state of the art.
- DH: You learned from necessity what worked?
- JD: It turned out plasma levels after injection are much higher than after oral administration. We didn't know enough, as I said, to mathematically model it. We also found that phenobarbital induced liver microsomes, the enzymes that metabolized chlorpromazine. When I went to Vanderbilt we discovered that after adding chlorpromazine to successfully treated hypertensive patients' guanethidine no longer worked. We discovered three or four drug-drug interactions while I was at Vanderbilt. Today, with new drugs, the companies thoroughly investigate a drug's metabolism,

so a lot of interactions are discovered in animals before the drug is used in man.

DH: But this was not the case at the time.

JD: Correct.

DH: Things have changed; they have become much more rational.

JD: When I was a resident, it was very dangerous to talk about drug treatment and if you did people thought you were a second rate psychiatrist. It was a failure for a therapist to use drugs. There was a lot of hostility between those using drugs and therapists. Most of my professional life I worked in state hospitals where you don't have much contact with residents.

DH: You hint things haven't changed completely and people who run the training programs still lean towards the psychological approach? Why do residents, when they enter a training program, lean towards psychological approaches?

JD: A new generation will come along and when they see drugs they are using are efficacious that will help. Part of my professional life has been reviewing the literature and in 1975 I published a review based on meta-analysis. I started to use meta-analyses in 1971 or 1972 when I did the first meta-analysis in psychiatry; it may have been the first in general medicine before the term, meta-analysis, was used. We were using the right statistics and showed there was massive evidence that anti-psychotic drugs prevent relapse. There was also massive evidence that anti-manics and antidepressants prevent relapse. I did not do the original work on maintenance treatment but we showed in our analyses that the prophylactic effects of these drugs are really massive and beyond any reasonable doubt.

DH: How did you get into all this? It is a long way from English literature.

JD: I had a half term of statistics, but I became confused in the elementary course, so I stopped. Before stopping I asked my teacher what should I read and he told me there was a good article in *Biometrika*. So, I read it. When I was looking, some years later, at the results of all the studies on maintenance medication, I remembered that article and it struck me that the technique could be used for an analysis. It's the same technique people use in the Cochrane Institute.

DH: Let's go back to 1971 while you were at NIH and became involved in a huge program on the psychobiology of mood disorders that ran for years.

JD: I was a member of that. But the clinical part of the study died after five or six years. They got good data, but the group disbanded and the study wasn't carried on.

DH: The idea was to test the amine theories properly and look at MHPG and 5-HIAA.

- JD: The goal was to find to what extent findings in the periphery reflect what goes in the brain. MHPG in the urine didn't reflect the brain, whereas 5-HIAA is a very valid thing to measure in the periphery. I also think there's low 5-HIAA in depression and there's also a group of depressed patients with low HVA. Some patients have psychomotor retardation and they have low HVA. They might have a kind of Parkinsonian retardation. I have data from that study which are still being analyzed.
- DH: It looks like what happened was, in that huge complex set of data, the role of the amine metabolites was lost.
- JD: Partly because it's hard to do human studies. But there's more evidence for the biogenic theory than ever, because all the new drugs in the treatment of depression work via NE and/or serotonin. It applies even to lithium.
- DH: You are referring to the work of Claude de Montigny and Pierre Blier? (See, de Montigny, in this Volume.)
- JD: I've been very impressed with their work, so, I'm a believer in what they found.
- DH: Well, the newer drugs for depression actually act on NE.
- JD: There is a revival of NE, but I've thought from the very beginning that both norepinephrine and serotonin are involved. Maybe, there's an involvement of dopamine as well. There's also a chance that acetylcholine may be involved both in schizophrenia and affective disease. The problem is how to prove it and what will it teach us. Actually, the same transmitters are involved in drugs of abuse, too. I did some work with Bob Schuster and Murray Fishman on IV and intranasal cocaine, measuring plasma levels, euphoria and heart rate. We got a pretty good correlation between plasma levels and the clinical variables, except the clinical variables dropped off faster. We discussed the data at a research meeting and I had the idea if give cocaine by intranasal injection, wait an hour until the subjective effects and rapid heart rate dissipate, and then give a booster IV dose we might overcome the dissociation. But, when we gave the booster dose, very little happened. The patients had rapid tolerance or tachyphylaxis to cocaine. I think that's part of the cocaine story; people start taking cocaine and they have to take more and more because of rapid tachyphylaxis.
- DH: Let me switch to another area. You must have joined ACNP pretty early on, as you were the kind of person they needed. When was it?
- JD: I have forgotten which meeting was the first I attended. It could be the third or fourth.
- DH: At that time the group was really outside the mainstream.

JD: There was no establishment for mentoring in those years. Now, when young people come, they often get assigned a mentor to smooth the way. There was nothing like that then.

DH: What were the meetings like?

JD: They were very exciting. Since then the ACNP has changed tremendously and I don't think in a good direction. Back in the early days there were about a third of basic scientists, maybe a third were psychologists and a third psychiatrists. But, some of the psychiatrists were involved also in basic science. There was pretty much of a mixture; clinicians may have been in the minority, but they were plenty attending. It's changed quite substantially; mostly basic scientists are attending. My feeling is that unless they make an effort to involve more clinicians, ACNP is going to change to a basic science organization. It's very hard now for clinicians to get in. If somebody makes a basic science discovery it is considered to be important and people think the person needs to be a member; there is a bias in the selection committee.

DH: When you were meeting here first, psychiatric disease was not considered to be biological. DSM-III changed all that, didn't it?

JD: Discovery of the biochemistry of mental illness would decide who is right and who is wrong. In the meantime much of the basic science work is trivial and a waste of money.

DH: You feel that strongly about it?

JD: Definitely. I fault the federal authorities for not supporting clinical research more vigorously and supporting a lot of trivial stuff, which is worthless. When I started the diagnostic criteria for depression were very vague and there was no distinction between psychotic and non-psychotic depression. Then, a group at Pittsburgh showed that depressed patients needed both an anti-psychotic and an antidepressant for good response. Sandy Glassman had the insight that psychotic depression did not respond to tricyclic antidepressants alone, and I thought that was a major discovery. Psychotic depression is a different animal than non-psychotic. Recently, we did a metaanalysis of the DST test and found there's a much higher incidence of the cortisol abnormality in psychotic depression than in non-psychotic depression. The division between psychotic and non-psychotic was more relevant to the cortisol abnormality than the division between endogenous and non-endogenous. In schizophrenia and depression, I bet if you counted, there would be ten thousand abnormalities reported in the literature, most of which died of old age, just like old soldiers fade away. And, the federal authorities never set up a requirement in basic research to prove your findings with blind analysis. People are looking for an abnormality, they find something promising, and they report it.

-
- DH: We have not talked about when you moved to Chicago from Nashville. How long were you at Vanderbilt?
- JD: I was three years at Vanderbilt and, then, in the mid-1970s I was recruited to Illinois State Hospital in Chicago. I did the work we talked about with Bob Schuster on cocaine in Chicago. I did a number of studies here in the state hospital.
- DH: And currently you are working on reelin. Tell me about that.
- JD: I'm working on reelin with Dr. Erminio Costa, a great scientist. He's an order of magnitude above me. When I talk to him, I know there's a difference in intellect. He had the thought that schizophrenia was a neuro-developmental disease and we might want to look at things involved in development with the reeler mouse where there's abnormal development, particularly, in the cerebellum. Reelin is a protein, which is absent in the reeler mice; it helps cells get to where they are supposed to go. And reelin is substantially low in the brains of schizophrenics. This is really Dr. Costa's work.
- DH: When was the first paper on this published?
- JD: It was just presented to Neuroscience. It's not out yet.
- DH: So, it's hot off the press?
- JD: Just a couple of weeks ago, we found reelin in plasma, so it is just hot off the press.
- DH: That's going to be very interesting.
- JD: We don't know yet whether it'll be true or not. The federal authorities should have a way to prove, in a blind manner, that the finding of low reelin in the brain is true or false before people move on with research in this area.
- DH: It's one of the things that hold us back. We haven't really had any drug which is a big improvement over the ones before.
- JD: I want to talk about that. Clozapine came along and if you look at the original data from Europe, it was better than the standard control. I've done retrospective meta-analysis, and it's better. Clozapine was only put on the map when John Kane and the drug company did a control clinical trial to show it was better. I would give credit, partly, to Paul Leber for insisting on a good trial. FDA played a major role and it was a creative act by FDA, industry and academia. Sandoz took the gamble to spend the money for the trial and they also deserve a lot of credit. John Kane did the trial. It established that clozapine is better. Independent of that Paul Janssen and his coworkers developed risperidone which has both anti-serotonin and anti-dopamine effects. It is better, more efficacious and safer than standard anti-psychotics. But this is not widely recognized. I've analyzed a good deal of the risperidone data base independent of Janssen funding

and paid for out of my own pocket. They wouldn't let the data out of Janssen, so I went to Belgium. It cost me money, because I had to pay my travel. If you combine several studies, the percentage improvement with risperidone is double. The amount of change on the standard rating scale is double; risperidone lowers the PANSS eighteen points, Haldol lowers it nine, massively statistically significant. Now, the PANSS is a rating instrument made up with positive and negative symptoms on theoretical grounds. When we did factor analysis, on all five dimensions of the scale, risperidone was better. So it really is a substantially better drug. I reanalyzed the data of Lilly on olanzapine and it is also better on all five dimensions. So, I think these drugs are better anti-psychotics than the old ones.

DH: What about the antidepressants?

JD: The antidepressants are more controversial. I think they're all about the same. There's a hint that those which act on both NE and serotonin may be more powerful, but it's not established beyond a doubt.

DH: The point I was trying to make was that what we lack is real breakthroughs. We had the big one with chlorpromazine in the fifties.

JD: We still don't know whether clozapine is better than risperidone or olanzapine. As soon as we had risperidone and it looked better than haloperidol, NIMH should have moved with a definitive study. Now, they're talking about it; I think they should move rapidly.

DH: You don't think that once we get a real breakthrough drug, there won't be any need for NIMH to get involved, because it'll be so clear.

JD: Lithium was a real breakthrough drug and it took twenty or thirty years for it to spread. Schou read about it in the Medical Journal of Australia and started to use it and Sam Gershon came from Australia.

I told you about my paper on maintenance medication. It showed a fifty percent effect, a doubling of the percentage of patients who did not relapse. That's roughly the same as you get with antibiotics. When penicillin was discovered, sulfa drugs were the standard medication for infections. The death rate with sulfa drugs was twelve percent. Penicillin reduced it to six. When streptomycin was discovered, the British did the first multi hospital study. It was back in the days when double blind studies were just coming on line and they did a multi hospital study. Streptomycin helped sixty-nine percent of patients, whereas bed rest alone helped thirty-three percent. It was a doubling of efficacy. If you use antibiotic prophylaxis in intensive care, you can decrease by about fifty percent the incidents of infection. So I feel the maintenance effect of lithium or anti-psychotics and antidepressants is in the realm of antibiotics. I once gave these results in a lecture and an elderly GP said the antidepressants had

a much greater effect in his practice. In terms of antipsychotics, there was a considerable effort funded by NIMH, which was social and psychoanalytically oriented by funding radical lawyers, who tried to make it illegal or put impediments to using anti-psychotic drugs, arguing that they were burning out the brain and doing bad things to patients. The lawyers who were trying to stop people from using drugs were making their living from NIMH funds!

DH: You think there is major ambivalence about this within NIMH?

JD: Yes.

DH: Besides reelin, are you working on anything else these days?

JD: Drs. Costa and Guidotti found neurosteroids in the brain and certain neurosteroids will stimulate γ -receptors. So, I'm trying to see whether we have a neurosteroid abnormality in depression, in pre-menopausal dysphoric disease (PMDD) and in panic disorder.

DH: So you are working on PMDD?

JD: I think it is a major disease. I'm just done a meta-analysis, presented at this meeting, and the probability that serotonin uptake inhibitors help PMDD is established beyond reasonable doubt. Patients with this disease are supersensitive to injections of benzodiazepine when they have the symptoms.

DH: When they get benzodiazepines during this period they are much more likely to go to sleep, is that what you mean?

JD: They are much more sensitive to benzodiazepines and they are helped by SSRIs beyond any shadow of a doubt.

DH: Did David Garver work with you?

JD: He did. We started working with lithium in schizo-affective disease. He took the idea and carried it on using lithium and sub-dividing schizophrenia. First, it was lithium response vs. non-responsive, but now David Garver is using CSF to look at reelin in sub-dividing schizophrenia.

DH: Would you like to say something about people who worked with you.

JD: Joe Hiblan is a young investigator. He trained with me as a medical student and is now at NIAAA. He has found abnormalities in Omega Three Fatty Acids and depression. And, there may be something cooking with that. Eddie Fann was working with me in Nashville, who is a member of ACNP. He is doing a lot of drug trials through all of medicine, as a psychiatrist at Baylor. When Maurice Diskin was a young psychiatrist at University of Chicago I got him started on doing studies in geriatrics. We injected physostigmine in elderly people to see if it improved mental function, and he is now head of the Geriatric Research program at Minnesota. Regina Casper worked first on an Eating Disorder program under me. Dave Ostrow did work on lithium transport. Then, he switched into AIDS

work. Pandy was working with me. He is now an ACNP member. Phil Janisak worked with me on plasma levels. I have also done drug development work with Francis Summer. We had a monkey colony and were trying to get animal models for schizophrenia. I have had four students who have become Chairs, one of whom got into serious trouble.

DH: These things happen; in many ways your greatest contribution is the people you train.

JD: Mentoring is how science should work, but sometimes, it's problematic. Some people are good mentors and some are not. In mentoring you share the credit with your young people. In some cases mentors try to steal the credit from their young people. It's not a trivial issue.

JD: Yes.

DH: At the other end, often your offspring can try to conceal the roots of their inspiration.

JD: The senior investigator should have the responsibility of developing the career of the younger person. When I see the younger people are ready to leave I assign them to write a grant, so when they leave they can take their own money with them. Some of the friction that goes on is when people are ready to leave and want to go on their own. Sometimes it's very much like a family, with adolescent rebellion. I think it's good to give them the credit so they can leave on their own without too much fuss. And, I have a good relationship with everybody I've trained. Another thing one can do is what Axelrod did. He didn't have much space in his lab; there were only four little modules. Sometimes you would see him doing an experiment, often a very simple experiment, with just a few tubes, maybe twelve or sixteen tubes, and if he proved the principle, he would pass it on to one of his many people, like Dick Wurtman or Sol Snyder. I remember meetings with Brodie when he would say "take a flyer on this." The other thing he said was, "If it's not working out, give it up, go on to something else". I try to pass on some of these general principles that come from people like Axelrod to people in psychiatry; to work on important problems, not to fool around with minor stuff.

DH: We are coming toward the end of this tape and we ought to take a break for lunch.

JD: Yes.

DH: It's been great. I'll take you to lunch.

CLAUDE DE MONTIGNY

Interviewed by Andrea Tone
Paris, France, June 22, 2004

AT: My name is Dr. Andrea Tone and we are here at the CINP Congress in Paris in June 2004, and it is my great pleasure this morning to be interviewing Dr. Claude de Montigny.* Thank you for agreeing to be interviewed. I want to start by asking you how you became interested in the particular kind of research you are involved with.

CD: When I was at college I thought that the ultimate science was psychoanalysis. After reading Freud's work I thought there were two ways to become a psychoanalyst, by studying medicine or psychology. Then, I thought that learning about the brain, during medical training, would help me become a good psychoanalyst. To my great surprise, I was very interested in the science of medicine; I discovered myself, and my interest in the brain sciences. So, at that point, I decided to go into psychiatry and see how it works. But I was disappointed that psychiatry was dominated by psychoanalytic theory; everyone could say whatever they thought without being bothered how they came to one or another conclusion. So, I decided I'd do something else for awhile.

AT: Can I ask where you went to college, and when?

CD: This was in the 1960s. I studied at Jesus College, in Montreal, Quebec and medicine at the University of Montreal. I thought neurology would provide me a good foundation for trying to understand the dynamics of different mental illnesses. I loved neurology and did my residency in it. But I soon realized the cerebrovascular accidents I saw in the emergency room, would not tell me anything about the dynamics or the biology of mental disease, such as schizophrenia. The alternate way was to get a PhD in neuroscience. I enrolled at the Neuroscience Center of the University of Montreal that has a worldwide reputation, fell in love with basic science and was very excited about it. At the time I received my PhD, I had to choose between psychiatry or neurology, and I opted to finish clinical training in psychiatry. I found it very difficult to go from the liberty and creativity of a basic research laboratory to residency in psychiatry. Then, I looked for a post-doc position and was extremely lucky to be accepted by Dr. George Aghajanian at Yale University. It was at that point I started my research activities towards my goal in life and then returned to Montreal to start my independent venture with a research unit. I gave myself five years to decide whether I was good at it or not. It went very,

* Claude de Montigny was born in Montreal, Quebec, Canada in 1945.

very well and I decided to start a second clinical unit in a hospital affiliated with the University of Montreal. I was trying to see both-sides of the coin, how the brains of animals react to antidepressant medication, and how this translates into the effect of antidepressants in depressed patients.

AT: What are you focused on in your research? Is it depression?

CD: It has been mainly depression but we did do some work outside of depression and antidepressant treatment.

AT: What got you interested in depression?

CD: At the time I became involved in this area one of the theories among US scientists was that endorphin was responsible for major depression and that different treatments for depression were additive on the endorphin system. The theory had several shortcomings and I decided to study the effect of antidepressants on a neurotransmitter called serotonin, a metabolite of tryptophan. To the surprise of everyone, I found antidepressants dramatically enhanced neurotransmission in the brain that was using serotonin. We were also able to confirm that antidepressant treatment produced improvement in patients by enhancing function in the 5HT system. This happened not long before the introduction of Prozac (fluoxetine). As a result of our findings drug companies started to look at their selective 5HT reuptake blockers.

AT: Were you involved in research with Prozac before it was marketed in 1987?

CD: We had a chance to work with it when it was referred to by a number, before it received its brand name. We studied fluoxetine along with other antidepressant drugs. It was very effective clinically and increased serotonin neurotransmission. Our findings played a role in Eli Lilly's decision to go ahead with marketing the drug.

AT: Did you have a sense at the time your research would revolutionize the treatment of depression?

CD: Yes, I did. Some people say that even if the introduction of Prozac has not revolutionized the treatment of depression, the selective serotonin re-uptake inhibitors represent a significant advance over the "dirty drugs" we had before. By "dirty," people mean old drugs with many actions on the brain leading to severe side effects.

AT: Are you referring to the MAO inhibitors and tricyclic antidepressants?

CD: Yes, the two main classes of antidepressant drugs used before. Most people, and I'm among them, believe the SSRIs represent a true revolution, because they are effective and almost totally devoid of side effects. Patients are more willing to take drugs for years which don't produce the kind of side effects the old antidepressants do. During the seventies, the most frequently prescribed drugs in the treatment of depression

were the tricyclic antidepressants and all of them were inducing obesity and weight gain. People, after gaining eighteen to twenty-five pounds, decided that it was not worth proceeding with treatment.

- AT: Wasn't Prozac discovered, initially, to be helpful for weight loss? Not only did it not cause weight gain, but in the short term it could be associated with weight loss. I remember reading Lilly toyed with the idea of marketing it as a dietary supplement. Is there any truth to that?
- CD: Weight loss occurred in some but not in the majority of patients and the idea of marketing Prozac as a dietary supplement was abandoned by Eli Lilly.
- AT: What would you say your other accomplishments are in the field? What would you single out as your most important contribution?
- CD: The one which was well received by the scientific and clinical community was related to treatment resistant depression, the enhancement of serotonergic transmission produced in antidepressants by other drugs such as lithium. There are more than two hundred papers showing lithium can potentiate the effect of antidepressant drugs in treatment refractory depression.
- AT: That's wonderful. Thinking about your contributions to administration and the organization of the CINP, how did you end up at McGill and how did you become so involved with CINP? You were President from 1996 to 1998 and responsible for hosting the CINP meeting in Montreal. Tell us how that came about.
- CD: I was attached to the people at the University of Montreal. I liked them, had fun working with them and, in the middle of my career, the Dean of McGill, made an offer I accepted. I had in mind creating a research group in the Department of Psychiatry at McGill that I could not do at the University of Montreal. It was a difficult but good decision.
- AT: McGill's Psychiatry Department in the fifties was the center of biological psychiatry in North American and, then, with the controversy surrounding Cameron, biological psychiatry fell out of favor.
- CD: I would like to mention Heinz Lehmann at this point. I loved this man and everybody in the CINP knew him very well. He contributed tremendously to the acceptance of biological psychiatry when psychoanalysis was the main stream in the field. He had a hard time but he was very successful. Heinz Lehmann was the pioneer in getting chlorpromazine accepted by physicians in North America. I was very lucky to know him. His office was near mine in the research and training building of the Department of Psychiatry at McGill, and I was able to drop into his office and ask for advice. He was a very intelligent, very sensitive man, appreciated by everyone.

AT: Tell us how you became involved with CINP. Lehmann was president, at one point, and you were president, as well.

CD: I became involved relatively early with the CINP, in the seventies, when I realized the science at meetings corresponded with my interests. I was asked to become a councillor first and later on a member of the executive. I was very surprised when I chosen to be president elect, which meant two years later, I became president. At the time CINP had many difficulties and I was able to recruit a few extraordinary men, who did a wonderful job in solving the problems of the organization. CINP now is a healthy, financially sound and efficient organization. I don't know to what extent people realize that. One of the people who helped was Benny Lerer. When I was president, I created a journal for CINP and the members voted for me to become editor-in-chief. Instead I asked Benny to become the editor in chief and he did an excellent job. We learned, a week ago, that our journal ranks fourth among scientific journals; that is very high for a specialized journal. My primary reason for creating a journal was to increase the feeling among members that they belong to the organization. So, many members of CINP now submit their best papers to the journal.

AT: That's wonderful. Is there anything you would like to add to the interview that I haven't asked you about?

CD: There would be plenty of things. But I think we covered the central elements.

AT: I'm sure they will want to interview you again. Thank you very much.

JAN A. FAWCETT

**Interviewed by Frederick K. Goodwin
Waikoloa Village, Hawaii, December 9, 1997**

FG: This is the ACNP Task Force and I'm Dr. Fred Goodwin. I have with me Dr. Jan Fawcett,* who is, not only, a long standing colleague, but a very good friend, but I won't let that bias the interview. Jan is considered by most of us as one of the pioneers in psychopharmacology and I'd like you to help us record how that got started and how you first got interested in this. You came into the field at the beginning of the psychopharmacology revolution, when in residency, it wasn't the main focus.

JF: Exactly.

FG: I know how you got started, but let's not assume everyone else does.

JF: After getting some early experience with research at Yale Medical School with John Davis, we did some stress research and I found myself, after residency, going to NIMH. I ended up in the Clinical Center on William "Biff" Bunney's inpatient depression unit. This was at the height of excitement with the pharmacological revolution. The antidepressant, imipramine, had been out for a few years. Chlorpromazine had been discovered and the catecholamine depletion hypothesis, from Axelrod's work, had just hit and we believed, for the first time, that we had a biochemical theory of depression. It was an amazing time; there was almost a delirious excitement at the NIMH and I was infected by it. Before I got there I had just started using some of the new medications. But, in my residency, there were very few people who even knew how to supervise me. The young faculty wasn't very knowledgeable or interested in them, to tell the truth. They thought the drugs were sedatives you gave people while you were doing psychotherapy.

FG: There was no hypothesis about how they acted.

JF: They weren't even considered primary treatments. They were something to quiet the patient down so they would accept psychotherapy.

FG: While you worked up the psychodynamic formulation.

JF: Exactly. So, I found myself on this island of excitement and turbulence around the catecholamine hypothesis; Biff and John Davis were writing a review paper about a biochemical hypothesis of depression.

FG: You and John arrived in the same year?

JF: Yes, we were classmates at Yale but took our residencies at different places. I went to Langley Porter for two years and, then, a third year with John Romano at the University of Rochester and ended up, by chance,

* Jan A. Fawcett was born in Jamestown, New York in 1934.

at NIMH. And so did John. We met again after doing stress research together as classmates at Yale.

FG: It's amazing how many people ended up in that program.

JF: The word was they only were taking graduates from Harvard and places like that, but they had shortages once in a while. I was in the Public Health Service Career Development program and they wanted to send me to some God forsaken place to treat alcoholic seamen but, all of a sudden, this opening at NIMH came up, so I went for it. I can't even describe what an exciting experience that was and how fast we got involved in the research. As associates we were supposed to do clinical care, more or less glorified residents so not many of the associates participated in research. But because of our interest John and I got very involved and found ourselves tremendously committed. Those two years were some of the most intense I ever spent and the experience hooked me for life on clinical research in psychiatry.

FG: What was it that hooked you?

JF: The possibility a disorder of brain metabolism might be the cause of severe depression was very stimulating; at that time it was catecholamine and corticosteroid metabolism. Those were the two areas Biff was interested in. We weren't initially using medication on the patients, so we had a chance to observe the severity of their symptoms. In fact we had a revolution when we insisted on treating the patients after a few weeks, because we had Chestnut Lodge supervision and were expected to treat them with psychotherapy. Dexter Bullard, from Chestnut Lodge, was my supervisor and I would see my patients every day, sometimes seven days a week. They were extremely sick, psychotically depressed and highly suicidal manic depressive patients.

FG: Would you agree there was something you had with that intensive clinical contact that's lacking now in clinical trials?

JF: Nobody's getting anything like this now. The experience of feeling the patients' pain, day in and day out and seeing them suffer, had a tremendous impact on my determination to find more effective treatments. Then, to see the effects when we eventually put them on medication was mind boggling. Biff was fairly open to us working with data, much of which had already been collected. He didn't have time, so he assigned me to work with data to do with elevated steroids in patients who committed suicide. We had had a couple of suicides on that unit, and were collecting daily 17-hydroxycorticosteroids. So we had banks and banks of frozen urine.

FG: There weren't sophisticated statisticians who massaged the data before you got to them.

- JF: No. Biff just gave me the data and said make some sense of it, there's something important there.
- FG: Make some common sense out of it!
- JF: I got intensely involved in that data, very intensely. I worked day and night on it.
- FG: It was so different from today, you were immersed in the patient's care, you knew the patient's background; and you knew the data. You weren't looking at some extraction of it.
- JF: They hadn't been analyzed; they were very raw data that hadn't been crunched. Sophisticated statistical analyses and computers were not available at that time. So, we were very, very close to our data, doing it by hand and learning statistics as we went. So, that's what occupied me and I got interested. I had done research for my thesis at Yale with Dr Bondy, Head of Endocrinology, and knew something about steroid metabolism. When I found Biff was studying this, it was a nice fit and I got very excited. I couldn't think about anything else for two years. Then, to find patients that committed suicide had elevated steroids prior to their death was the original discovery of hyper-adrenal function preceding suicide. This was in the late sixties and we published it about 1965. People thought we were nuts; trying to predict behaviour by studying metabolites in urine. They couldn't relate to it, it seemed so far out.
- FG: Were you in contact with Jim Maas in the Intramural Research Program?
- JF: Jim was the section head at NIMH. Technically he was Biff's superior.
- FG: He was a renaissance man.
- JF: He loved good wine; he loved race cars; he loved to live like Hemingway; he was a very colourful guy. I hope we have a tape on Jim. He took over Percival Bailey's job as Director of Research at the Illinois State Psychiatric Institute. That job was a big plum back then, because the institution got all the money and it went into a fund that could only be used for research.
- FG: Wasn't there money from cigarette taxes and alcohol taxes?
- JF: Maybe so, the fund had at least ten million dollars in it. That was a lot of money back then. The Institute had been built by Percival Bailey with money raised in the hope prefrontal lobotomy would be a cure for mental illness. It had a very modern surgical operating suite in the center which I don't think was ever used, because, by the time the Institute was built, the procedure had been discredited. The research was mainly physiologic under Bailey. Jim Maas, when he moved from NIMH, changed the whole program to one of biochemical research. He was interested in the catecholamine theory, and a metabolite, MHPG. He took me to Chicago to run the clinical side of his program because I was very clinically oriented. So, two years out of residency, I had my own inpatient unit, my

own laboratory, my own secretary, my own lab assistant, and all on hard money!

FG: You experienced two extraordinary environments back to back, the intramural program and the Illinois State Psychiatric Institute, ISPI.

JF: Not only that, but when I went to Chicago, I'd had lots of experience treating very ill patients with medications while working on the catecholamine theory. And I moved into a city that was committed to psychoanalysis, the Chicago Psychoanalytic Institute was totally dominant.

FG: Jim Maas had analytic training, didn't he?

JF: At the Washington Institute.

FG: And Biff had analytic training too?

JF: That's right, and I had been advised on very high authority, by Fritz Redlich, my Chairman as a medical student at Yale, that if I didn't have a training analysis, I wouldn't go anywhere in academia. I had to make a decision. If I was going to invest energy in research, I could not spend time earning money to pay for a training analysis while studying at a psychoanalytic institute. So I didn't follow Dr Redlich's well meant advice.

FG: At Bethesda you said you thought about nothing else but research.

JF: Exactly. When I got to Chicago, I was very adept in psychopharmacology, especially of depression. Nobody in the city had the faintest idea how to use these drugs. They were giving them in homeopathic doses and weren't using them when they should. Gradually, some of the analysts started sending me patients that were not doing well, who were very sick. I would put them on a routine dose of imipramine and they did better. It was like shooting fish in a barrel. And, suddenly, I was doing a great deal of the psychopharmacology treatment in Chicago.

FG: This wasn't clinical trials, it was treatment.

JF: Right, I was treating these patients but it was also giving me access to a lot of potential research subjects. I opened up a treatment-research unit at ISPI, because of the suicide research we had done at NIMH, and I wanted to see if that was replicable. I selected patients who had made serious suicide attempts, people who had jumped off buildings and survived; very sick patients. We collected twenty-four hour urines, looking for MHPG. That was also what Jim wanted; he needed clinical samples to test the catecholamine depletion hypothesis of depression. He developed a double isotope dilution technique and we found a pattern of decreased MHPG in a large subgroup of depressed patients, supporting the hypothesis.

FG: You were elegant and advanced for the time.

JF: It was amazing. So, we were collecting samples for both Jim Maas and for my research. He was interested in the MHPG data principally and

I was interested in the steroid data. In addition to replicating our steroid data in suicide I became interested in how you might predict which patients respond to amitriptyline and which respond to imipramine.

FG: At the time you started we had only MAO inhibitors and imipramine.

JF: Lithium wasn't approved when I went to Illinois.

FG: I remember that, in the early intramural days, we were against the catecholamine hypothesis with lithium.

JF: That's true.

FG: It wasn't supposed to work in depression.

JF: Right, all the interest was on norepinephrine at that point while people in England were interested in serotonin.

FG: There was still no interest in serotonin in the US at that time.

JF: When we studied lithium we only used it in bipolar patients.

FG: They weren't called bipolar then.

JF: I'm sorry! They were manic depressives. But all severe depressions were called manic depressives by the Washington U group, at that point.

FG: That's right.

JF: You didn't need to have mania to be a manic depressive.

FG: To go back to ISPI. When you started you put a lot of people on imipramine, and then amitriptyline came along.

JF: Right. I was interested in how to predict antidepressant response, because not everyone responded. The one drug that rapidly released norepinephrine, that had an immediate action within a few hours, was dextroamphetamine. If I gave depressed patients dextroamphetamine, about half would feel remarkably improved, in a couple of hours. The other half wouldn't feel anything. I became very curious about that, so I started doing amphetamine challenge tests and found people who responded were the low MHPG excretors. They were also the ones who seemed to respond to desipramine. So, I had a theory I could give amphetamine and predict the desipramine responders as well as the MHPG level. It all came together, it was beautiful.

FG: One thing that has characterized your research has been theoretical elegance and practicality. Clinicians could relate to it regardless whether they cared about the MHPG part. It was something clinicians could appreciate and use.

JF: Right. And, it was okay to do clinical research back then. There was no molecular biology; neurochemistry was in its beginning and molecular genetics was relatively undeveloped. There was no functional brain imaging in those years.

FG: And you were getting fresh patients, you weren't advertising in the newspapers.

JF: These were the sickest of the sick who were very happy to come for treatment. I had a patient who survived a suicide leap from eighteen stories, and lived by landing on a Toyota. You don't see patients like that very often.

FG: What happened to the amphetamine challenge story?

JF: It got bypassed when the serotonin reuptake inhibitors came out and the whole serotonin story became the focus.

FG: But it did get used in the sixties and seventies.

JF: It went from that to amphetamine as a diagnostic test for augmenting antidepressant effect in poor treatment response.

FG: Did you do augmentation trials with the tricyclics?

JF: I did a lot of augmentation trials in my practice with both tricyclics and MAO inhibitors in treatment refractory patients. I developed a very large practice, and I used it to develop my ideas when I got more and more treatment resistant patients, as time went on. I found myself using a lot of amphetamines, especially Dexedrine (dextroamphetamine), to augment tricyclic and MAOI antidepressants.

FG: Did you ever report your findings?

JF: First, I reported the use of Dexedrine to potentiate MAO inhibitors. It's the largest series in literature. There's only one other paper on the subject; John Feighner's, published in 1990. It took me about seven years to gather a sufficiently large series. These were patients who were at high risk of suicide; many of them ECT failures. You may remember there are three reported deaths with antidepressant amphetamine combination and a big black box warning regarding its safety. I only did it when the patient was at high risk for suicide and had failed ECT.

FG: But, it turned out to be safe?

JF: It has turned out to be safe for the last ten or fifteen years.

FG: There were some animal data published that supports its safety.

JF: And there was evidence that adding a tricyclic like amitriptyline made the amphetamine and MAOI combination even safer.

FG: Is it your impression that people who are doing trials without your extensive clinical experience are missing something?

JF: I think they do. We are also missing something because of our new and improved diagnostic system, the DSM. When we went from the RDC or from DSM-II to DSM-III there could be no longer an undiagnosed category.

FG: You had to force fit everyone into a diagnostic category in the DSM.

JF: This was no longer a research diagnostic system, but a real world system for use in categorizing illness and billing for services. That was one loss, and the other, which I think was bigger, was you gave up assessing the severity of symptoms as they were rated by the SADS, which yielded an

RDC diagnosis. Today, people don't understand what we have lost. When a person has insomnia, it's a symptom toward DSM-III major depression but there is no discrimination of severity. Patients could have a little trouble sleeping or they could be up all night and it still counts as insomnia. The difference in severity of symptoms probably is more important than the difference in diagnosis. I think that's what's been lost. People use the SCID derived from the DSM-III in research with symptoms present or absent without severity measures.

FG: The SCID is standardized and used now in research.

JF: The SCID is much easier to do than the SADS and much less time is required. You can teach inexperienced clinicians to use it with little training in psychiatry or even psychology regarding assessment of symptom severity. So you can create diagnostic categories without assessing severity, but how valid are they? The alternative is difficult because you need raters, trained to be reliable and that is very expensive. You have to bring raters together, show them the same tape, and argue over whether something's present or not, and how severe it is.

FG: I wonder if, for a drug company, it would pay off in the long term. It might be less expensive to do it right than to end up with trials that are uninformative.

JF: That's a question that has come up at this meeting.

FG: Some of the people in industry are beginning to see that.

JF: Right.

FG: Bill Potter at Eli Lilly is thinking about it. Clinical trials have become so mechanized to do them fast and easily. Another thing I feel has been lost is the longitudinal look at patients. The DSM provides a cross-sectional diagnosis. It trains residents by giving them five minute video snippets and you know what happens if you're supposed to make a diagnosis in five minutes. At the NIMH and in the ISPI you had experience in observing patients longitudinally over time.

JF: When I left ISPI and went to Rush, I was involved in the collaborative study with a twenty year follow-up of patients.

FG: Wasn't your role in the collaborative study primarily suicide prediction?

JF: As far as the data analysis is concerned, that's right. We were one of the five centers that collected clinical data.

FG: When did you move from ISPI to Rush?

JF: I went to Rush as Chairman in 1972. Rush had just opened a medical school.

FG: Are you the longest surviving Chair?

- JF: I don't claim to be the longest surviving Chair. I don't know if I am or not, but it's been a long time. This is my twenty-fifth year.
- FG: I wouldn't be surprised if that isn't the longest.
- JF: It's possible, but I don't consider that a particular distinction. The question is, what did you accomplish?
- FG: Of course you're still active in research.
- JF: Right. And the wonderful thing about going to a small department, as opposed to a well established one, is you have a chance to develop your own shop and can afford to do research and teaching yourself, because it's not a huge behemoth where you have to spend all your time wheeling and dealing in administrative matters. I even continued to practice, I saw patients, and I got clinical experience. That has been the most satisfying aspect of my career, being able to see patients, being able to teach, being able to do research and run my own show. That doesn't happen very often.
- FG: It doesn't and a lot of people, who are involved in matters related to health policy and are considered experts, have very little clinical experience. It's scary!
- JF: Up until a year ago, I spent twenty-five hours with patients every week, sometimes thirty. I ran the department, did my teaching, and did my research. Last year, I had to modify that; I'm down to about ten hours of seeing patients. I do consultations.
- FG: At your max, how many hours a week were you working?
- JF: I got up to over a hundred hours. I did collapse at one point, my hypertension was out of control, and I was told I was going to die if I kept it up.
- FG: Maybe you had a little hypomania!
- JF: I was once accused in court of being hypomanic when people didn't like the testimony I was giving in a divorce trial on behalf of a manic depressive woman I had treated. The fact is I drove a red Porsche, made rounds at midnight and got up at six in the morning. I don't think I was ever clinically hypomanic but I was certainly excited about my work.
- FG: So was Biff. Biff's excitement was infectious, wasn't it?
- JF: There's no question about it. It was Biff's excitement that hooked me on this career. I blame him for my being hooked on research in psychiatry. I always said research is like an addiction. You get the highs from new data. It's like a gambling addiction, you imagine you're going to make some discovery that might make a difference and change things. That's a grandiose thought because we know that most findings don't change anything. Many don't even survive, and most don't make a huge difference. But there's a chance. A chance you can find something that's going to make a difference someday, and that's exciting!

- FG: People get cynical about research. They say we select data, crunch it and then back the findings into a hypothesis based on what the data looks like.
- JF: It wasn't crunched data I worked with at NIMH. It was hand done.
- FG: It was hand done and we've lost something by not having that any longer.
- JF: You didn't need a complex data set, because you had a very small sample of patients.
- FG: You didn't have to use a computer. If you look back at innovations, wouldn't you agree a lot of new directions came from pretty small data sets?
- JF: I think so.
- FG: How do you feel the current grant system is working, in terms of innovation?
- JF: I've been very disappointed after participating on three or four review committees. I've watched the deliberations and usually felt myself to be in the minority. The committees tended to be much too concerned with details about the adequacy of scientific aspects of the protocol but the creativity of the ideas has been lost. New applicants with an idea that's not in vogue are subject to more scrutiny and criticism. This is true of publications, too. People have a new idea, a new finding that doesn't fit, that goes against the grain, which is what science is supposed to do, are subject to much more criticism. New ideas get much more intense scrutiny and criticism and are much less likely to be funded. So young investigators learn, after awhile, to apply for grants that are in vogue and will be funded, when it's innovation that moves science.
- FG: You had the experience of starting in the intramural program where you didn't have to worry about that. Then, you had a similar situation at ISPI.
- JF: Right. ISPI had its' own funding and you didn't have to get outside grants. In some of the most creative research I have done since I have been supported by money from endowments. Now we're funded by the collaborative study and I got to analyze the data on suicide outcome.
- FG: Those are important data.
- JF: The collaborative study is the most important research I've been involved with.
- FG: Why don't you explain what it's all about?
- JF: We're in our twentieth year, the collaborative study started in 1978. It used the SADS, and the RDC; it measured the severity of symptoms in RDC diagnoses from just under a thousand patients at five of the admitting universities. We followed our patients at six month intervals for the first five years and yearly after that. And we stratified for different types, such as major affective disorder, unipolar disorder, manic depressive disorder,

schizoaffective disorder and we were interested in the differential outcomes. We also interviewed about twenty-five hundred relatives of those patients.

FG: What was the number of patients?

JF: Nine hundred and fifty-four was the exact number and everybody staked out the areas they wanted to analyze. At the New York Center Jean Endicott was interested in the nosology, because she and Spitzer had worked together so she took over that. Washington U was interested the family from a genetic point of view, and so was Iowa. I was interested in suicide from the days I worked with Biff. At that time all the data was from retrospective studies. Here it was a prospective study with a very high risk group of patients of which eighty-five percent had been in hospital with severe affective disorders. So I knew a certain percentage was going to die from suicide. The question was which ones? Nobody knew. So we followed those patients and we waited five years. I didn't write a paper from the collaborative study for about six years. I just looked at the data and, at the end of five years, there were twenty-five suicides across all the centers. We pulled those patients out and looked at their SADS scores and every item we thought might relate to suicide risk. There were about a hundred and forty-two items we thought relevant to SADS from out of about twelve hundred.

FG: To be able to do that shows something about the importance of your very extensive clinical experience. You didn't just let the computer crunch all the items.

JF: We included items like the patient's marital status, religious participation, as well as the severity of symptoms. And, an astonishing thing happened when we analyzed that data. We found none of the traditional predictors of suicide, except for hopelessness.

FG: In the five year prediction?

JF: In the five year prediction nothing but hopelessness was traditional. Not having a child under eighteen came out as a predictor. Some sort of psychotic turmoil, a depressive turmoil came out as predictor. Abuse of alcohol was significant. None of the standard suicide risk factors, such as prior attempts, suicidal ideation, came out as predictors. I was just astounded that none of the usual risk factors were significant in the suicide group. I couldn't figure it out; not even severity of prior suicide attempts was significantly different. Then I told the statistician to look at the time of suicide after assessment, because these suicides had occurred over five years and I figured, maybe there'd be a difference as whether the patient suicided within a few months of the interview vs. several years later. I had to wait another year, because we didn't have enough subjects. Finally, we

found the predictions of suicide in the first year were not the usual ones. They were severe anxiety, panic attacks, alcohol abuse in a moderate level and global insomnia.

FG: And anhedonia.

JF: Yes, very severe anhedonia. So we found the traditional suicide risk factors, such as suicidal ideation, suicidal attempts, hopelessness, were significantly associated with one year follow-up and all the items we originally found were long term predictors. So by doing a prospective study, we separated long and short term predictors.

FG: Would you put that number one among your contributions?

JF: Yes, I felt nobody had done this before. Nobody had even talked about acute vs. chronic predictors of suicide. All the previous predictors came from retrospective studies.

FG: This is a very fundamental contribution to the field.

JF: I don't think it's been accepted very broadly, even now. I don't think a lot of people even know about it, because it's only been reported in two or three papers.

FG: I show your findings on a slide when I talk about depression.

JF: You do? What I'm saying is it hasn't permeated the field. It's just started to be reflected in chapters of books.

FG: Fundamental observations, when you look back historically, are often not accepted in the first ten or fifteen years.

JF: When I first saw the findings in which we took the time factor in I felt like the mountain climber who reached the top of the mountain first and put his name there or his flag. I just couldn't believe it. But, in my clinical experience, I'd been seeing it all along. I just didn't realize it.

FG: You, probably, had some sense of what you were looking for more than you give yourself credit.

JF: I looked at a review I'd written several years before these data were analyzed and I had said something about acute factors in suicide and I had mentioned something about "perturbation," a term used by Schneidman. He liked to make up neologisms.

FG: But he didn't think it had to do with depression.

JF: No, he didn't. He thought it had to do with perturbation, interestingly enough. I also found a paper he wrote with his collaborator Farberow.

FG: Farberow was an analyst.

JF: He was a psychologist and did a VA study in which he found that anxiety predicted suicide, but he didn't even report it in his paper.

FG: It didn't fit the prevailing notion.

JF: He didn't even mention it in his conclusions, but I found it in this paper, published ten or fifteen years before our study.

- FG: The point you've made about anxiety as a predictor of suicide is a powerful justification for using anxiolytics, at least temporarily, in some patients with depression.
- JF: It would save lives by treating the patients' agitation and anxiety, the best way we can. Maybe benzodiazepines are not always best, but we are going to get new agents and end up with CRH inhibitors that are going to save lives.
- FG: Let me jump ahead. What do you see coming down the pike in the future in pharmacology?
- JF: We're going to sub-type depressions like we'll sub-type schizophrenias and even bipolar disorders by using PET scan findings and functional MRI. We'll sort cases into different sub-types and be able to make rational decisions about their pharmacologic treatment, based on which circuitry is involved. And we'll find other neurotransmitters that are targets for treatment. Right now, we've got serotonin, norepinephrine, and dopamine as major targets. The monoamine theory has survived the test of time, but I don't think it's enough to explain the heterogeneity of the illnesses we treat. We still have a lot of people who aren't fully responding to treatment and patients who don't respond at all. I think we'll learn more about dopamine and have more dopaminergic drugs so we won't have to use stimulants.
- FG: Do you think that progress is going to continue to be incremental from new advances in basic neuroscience or do you think it's going to be punctuated by things like lithium that came out of the blue.
- JF: We may have more rational advances from basic research, from molecular biology and things like that, but I still feel we haven't got beyond the point where people are going to find a new tool that suddenly changes things like, for instance, an NMDA receptor modulator.
- FG: What about clinical observations by people trying something on a hunch?
- JF: I still think there's room for that.
- FG: There's a need for it, but is it going to happen if we have guidelines and managed care?
- JF: It's less likely, because there will be less room for mavericks. Things are going to be more standardized.
- FG: The question is how will people come up with anything novel in systems that are increasingly regulated? You've got FDA; you've got IRB's; you've got Review Committees all controlling grant funding.
- JF: We're going to have sub-types of disorders; we'll have to rename them something. I don't know what the names will be but I think there'll be more specific treatments.

-
- FG: So, you think the fruit is going to look more like an orange where you have segments than an apple which is continuous?
- JF: They'll be certain common factors that facilitate treatment response; the physician/patient relationship will always be necessary, but I'm talking now about treatments that specifically affect sub-segments. We are doing that blindly now. We have plenty of agents, but they're not differentially dealing with specific mechanisms.
- FG: Currently, what we see in the meeting here, is pharmaceutical development determined by pre-clinical science and marketing with the clinical field in the middle is getting lost.
- JF: Right. We're only around to apply it, to write the prescription, rather than having a real role in development. That has definitely happened.
- FG: Let me go back and ask who influenced your career the most?
- JF: My taste for research started in medical school when I worked with John Davis. I got very interested but I knew nothing; I was totally naive. He was quite sophisticated by the time we met in medical school.
- FG: I should give a disclosure here. You, John, Will Carpenter and I shared a seclusion room as an office in the intramural program!
- JF: Exactly. We ended up being thrown together. And Biff certainly turned me on to research, there's no question about it. Then, I wouldn't have stayed in research if it hadn't been for Jim Maas. He was certainly a mentor who encouraged my clinical and research interests. I was able to bridge my interest in psychopharmacology with the norepinephrine hypothesis of depression, through MHPG which he was working with. So he's been a massive influence. I was influenced in medical school when I had to do my thesis on steroids, go to the lab and come up with an assay for etiocholanolone. My direct supervisor for this project, a young faculty internist was not very interested in what I was trying to do, and insisted I use a faulty extraction method. He insisted I just wasn't doing it right. I learned a lot from that. I spent a whole summer throwing out chemicals I was supposed to extract and measure, because I listened to him. I never did that again.
- FG: What about people you've influenced?
- JF: I have a few people who have been influenced by me. I've influenced David Clark in my department. David is a well known researcher in suicide, a psychologist and a brilliant guy. I've had interactions with John Zajecks, who is up and coming. I think we're going to see great things from John, if he's not going to become so busy he can't focus on research. He's such a good clinician and speaker everybody wants him to do things, other than research.
- FG: Is he working a hundred hours a week like you did?

- JF: He's close to it. I had some effect on Bob Gibbons, who's a masterful statistician by bringing clinical issues to his attention. I certainly interacted with my colleagues in the collaborative study, but I think it went both ways. Jean Endicott was very important to me in the diagnostic issues. I admired George Winokur very much when I worked with him.
- FG: I'd add that you're one of the most effective teachers in CME lecturing.
- JF: I've done a lot of CME lectures and I'm sure that may have some effect on people.
- FG: I think what people respond to is that you're a sophisticated researcher, a real clinician, not somebody who goes and looks at patients to just follow a research protocol.
- JF: And, I won't give canned talks. I present my own data.
- FG: That's not something people get from most CME lectures.
- JF: There's a need to keep the flame alive and the big question is how that's going to happen in the current situation?
- FG: Am I correct that you've been for thirty-three years in the field?
- JF: Well, yes.
- FG: How do you stay so young?
- JF: It's the excitement of the work and it must be some genetic help as well as luck. But, I think the excitement of the field is a lot of it. It's still very exciting and, assuming my health holds, I plan to keep looking into things and doing research as long as I can.
- FG: That capacity for excitement can't be manufactured.
- JF: I agree with you; there's got to be some kind of excitement there. I caught the flame that makes a person do this, makes them willing to put in hours of extra work, lots of time when there's nothing coming back except criticism and turn downs. If a person doesn't have that capacity, I don't think they should try to force it. People should go into research to make a difference, not for another career.
- FG: Not to make a living.
- JF: Not to make a living, no. I don't think it's a good way to make a living. I think you could make a much more secure living doing other things. But, I don't think you'd get the excitement.
- FG: I've known you for all these years and I benefitted myself from the excitement you are talking about.
- JF: It's made for a wonderful career. It's such a privilege to be able to treat patients, make a difference in their lives and do research and teach; to do all those things together and combine them. That's a real privilege and I hope some young people will find a way to do that. That's just a wonderful way to live.

FG: I was very privileged to have been at your Feschrift a few months ago. It was sort of the highlight of the year.

JF: It was wonderful for you to be there with Bob Post and Marty Keller and Bob Hirschfeld. It meant a great deal to me, because I respect the work that's been done by you and all these people. But it was not a retirement party!

FG: That's what I was going to say.

JF: It was a celebration of a wonderful time and if people aren't having a good time in their work, then perhaps, they should do something else.

FG: We could have waited another thirty years to do this interview, but they told us to do it now.

JF: Maybe we'll come back in another twenty years and add some things.

FG: We shall come back and do it again. Thank you, Jan.

ARNOLD J. FRIEDHOFF

**Interviewed by Benjamin (Steve) Bunney
San Juan, Puerto Rico, December 12, 1995**

SB: I am Steve Bunney and I'm interviewing Arnold Friedhoff.* Arnie, how did you get started in psychiatry?

AF: It's an odd story and I'm not sure it ought to be recorded but I'll tell it. I was paying back the army for the educational benefit I got from the Army Specialized Training Program while I was in medical school and they allowed me to finish my internship before I went into the service for two years during the Korean War. My assignment, having just finished my internship, was to be the Chief Medical Consultant on the big army post at Camp Atterbury, where I was getting requests for consults from doctors out in field hospitals, many of whom had boards in internal medicine. So I was pouring through medical textbooks, trying to write consultations about all kinds of complicated medical problems. One day I ran into a friend from Yale who said, "Look, you're the medical consultant here, but sooner or later they're going to find out you don't know anything and they're going to send you to Korea". And then he said, "I work in the psychiatric hospital and we need psychiatrists and if you get assigned there, you'll stay on the post". So, I said, "Well, Korea or psychiatry, it's kind of a toss up, but I'll take psychiatry". So, I went to the psychiatric hospital at Camp Atterbury, stayed for two years and got a year's residency credit. I applied to Bellevue to complete my residency, stayed for two years and decided to remain in psychiatry and do research.

SB: How did you get into the research end of psychiatry?

AF: I'd always planned to do research. Although I trained in psychiatry I also had Seymour Kety as my pharmacology instructor at the University of Pennsylvania Medical School. He was a young instructor, doing very exciting work in human experimentation and asked students to be volunteers. I volunteered for studies on various drugs. He gave me mecholyl, a cholinergic drug, and about twenty minutes later, I went and sat in a corner and laughed for an hour. I couldn't stop. I had some kind of cholinergic reaction and that interested me, the fact there were drugs that could influence how you behaved. When I finished medical school and residency, research seemed a logical thing to do. I picked Bellevue because I thought it would be a place where there would be research going on since it was probably the best-known psychiatric hospital in the world. I got there and decided I wanted an opportunity to do research during

* Arnold J. Friedhoff was born in Johnstown, Pennsylvania in 1923. Friedhoff died in 2001.

residency but there was no research program for residents. In fact, there was no research program at all. I talked to Sam Wortis, the Chairman, who was very interested in research, but they didn't have any research money or any laboratories, except that Lucas Torbery was doing some interesting research on brain lesions, trying to localize functional effects. David Wexler was also there, but already accomplished his monumental work on measurement of intelligence and was now very interested in going on to more physiological kinds of research. However, there was no grant money and there were no instruments. The whole time he was there, (he stayed there until he died,) he spent trying to make a polygraph out of the ringer of an old washing machine. It was the only thing he set out to do he never accomplished, because that polygraph never got built. So, I told Sam I wanted to develop a research program in psychiatry. Wortis, who had an enormous impact on American psychiatry and development of the NIMH, spent a lot of time in Washington, but not much at NYU. He said, "Sure, I'd like you to do research and encourage you to do it, but we have no money and we have no space." So, I asked Torbery but he didn't have any space in his lab and Dave Wexler was occupied with the washing machine. Finally, I found an old kitchen which had some counters and a sink. Across the hall was a linen closet, so we set it up as an office with the kitchen as a lab. At that point, fortunately, Smith, Kline, and French (SKF), gave us a grant of \$50,000 a year for three years to do what we wanted, except we had to study psychotropic drugs, once in a while, if they had an interesting one.

SB: How did you get to them?

AF: Sam Wortis had connections with all kinds of people who were potential sources of funds. It was through his influence with SKF we got the grant. He asked me to do it because he knew I was interested in research and there weren't many other people who were. So, we set up the lab with this \$50,000.00 a year; it doesn't sound much now, but at that time it was an enormous grant. The first thing we studied was the Akerfeldt test. A Swede named Akerfeldt had published papers saying he had a test for schizophrenia; that if you took some plasma from schizophrenic patients and put it in solution with an oxidizing agent, dimethyl phenylene diamine, it would turn blue if you were schizophrenic. I knew this compound wasn't blue, it was colorless, and I understood a little about the chemistry, it was an oxidizing agent. I thought, blue in plasma, sounds like the copper protein ceruloplasmin. I also thought we ought to determine whether this was simply based on differences in activity level between patients and controls. So, we asked for volunteers to do some heavy exercising. One of the volunteers was somebody well known to the ACNP, Murray

Alpert, who was then a student. We asked him to jump up and down fifty or a hundred times, and took a sample of blood before and after. Before, nobody had any blue, after, everybody had blue. Then, we did further experiments with ascorbate showing you could block the appearance of the blue color by using an antioxidant. We published a paper saying that the Akerfeldt test might well be based on differences in activity levels or diet, as patients in state hospitals weren't regularly given orange juice.

SB: What year would that have been?

AF: Around 1958, but I'm not positive.

SB: Well, you started with a blue spot but in your later research you found a pink spot. How did that happen?

AF: Next we got interested in hallucinogens, their effects and their metabolism. We showed that human liver, if you give the right precursor, can make mescaline. If you start with hydroxy dimethyl ethoxy phenethylamine, you can methylate the last hydroxy group, so human liver is capable of making mescaline. We couldn't find any in urine. I don't think we looked in blood; we didn't have sensitive enough instruments. But we started to explore human urine for possible differences between schizophrenics and controls of various types such as medical patients and normals.

SB: So the blue spot adventure got you thinking maybe you could find a marker, even though this was not it?

AF: Yes, we got interested in trying to find a marker for schizophrenia. The idea being, if we found a marker, maybe it would lead to the cause of schizophrenia. This doesn't necessarily follow today but, at that point, it seemed logical. So, we started looking for markers. I always had an interest in hypotheses and I've generated a number of them, but I've, also, always had an interest in how do you look for something if you don't know where to start? We've tried various approaches to that question. One was to use paper chromatography to compare urine from schizophrenic patients with urine from non-schizophrenic patients. We didn't have much problem with drug treatment as a contaminating variable back then, because drugs were not very widely used and we had lots of drug free patients. During that period, because I was interested in metabolites, I went to site visit a grant from a very famous person, who became interested in schizophrenia and who was doing a similar thing, but with gas chromatography, which we didn't have. He was collecting a thousand urines from patients in state hospitals and a thousand controls and running gas chromatographs, comparing them using the principal of averaging, which was very clever, because metabolites consistently present would keep increasing along with the number of subjects. Those which were randomly present would not. So I sat through the site visit for a day

and realized it was going to take three years to collect and run all these gas chromatographs. So I said, "You know, you could achieve the same thing if you took all these urines, poured them in a barrel and ran one gas chromatograph". Never the less we gave him the grant. We were interested in the same subtractive approach looking at urines and developed a new test for studying biogenic amine metabolites, which produced a pink color. Basically, we used aryllic reagents and converted the amines to aldehydes which developed a color. Incidentally I spent a lot of time at NYU, taking graduate courses in organic chemistry. So, we started to consistently find this pink colored spot in some schizophrenics using the reagent we developed, although not in all the schizophrenics, and not in any of the controls. I had an interesting experience which shows how your mind works at night, when you're sleeping. We did the experiments but it was getting very discouraging because we realized we needed to identify what the metabolite was or it would remain just a spot. Unfortunately it did come to be known as "the pink spot". It sounds like a rash. So, we were trying to identify this compound. We didn't have mass spectrometry and we didn't have sensitive instruments so we were using various kinds of chemical procedures. One day, we ran some paper chromatographies and it was very discouraging I threw it in the garbage. I woke up in the middle of the night and I said, "It's on there and I didn't realize it". Then I thought, oh my God, they're going to take the garbage out at Bellevue, so I went there at three in the morning and fished it out of the garbage can. That, led us to identify the compound as 3, 4 dimethoxyphenethylamine.

SB: When was this?

AF: About 1962.

SB: I just want to add to your story. I was a medical student at NYU at that time, and didn't know whether I was interested in research or not. So I asked my brother, who was older and a research psychiatrist, if I was interested in learning about research who should I go to at Bellevue. And he said, "There's only one person, a fellow by the name Arnie Friedhoff". At that time you were giving a journal club for medical students so I signed up for it.

AF: Oh, my goodness!

SB: Not only that, but I'm pretty sure we were holding that journal club meeting when one of your technicians came running in with a piece of paper, showed it to you, and you got very excited.

AF: Quite likely.

SB: You then told us about your research and why you became so excited. Your excitement at making a discovery and the implications you felt it had for understanding schizophrenia probably played a role in why I finally ended up as a psychiatrist doing research.

AF: No kidding! I think the technician probably came in because she confirmed what I had found on the chromatogram in the middle of the night.

SB: I think that was exactly the timing.

AF: Fascinating! So, we did identify the compound. Then, somebody in the Heart Institute, a well known biochemist, confirmed it with mass spectroscopy; the identification of the compound was correct, but it was present in only microgram or sub-microgram quantities. This chemical test we'd devised was very sensitive but then people began publishing articles saying it was secondary to chlorpromazine treatment whereas we found it disappeared when patients were treated. Besides, all our patients were drug free. Somebody else said, it's from cigarettes, so now I was starting to suffer the same fate as Akerfeldt. I realized I couldn't spend all my time answering other peoples' questions so I decided to put this aside and do something less controversial. We did try one other thing which did not work, and that was to see if humans could produce it metabolically from some logical precursor, but we could never find any evidence of enzymatic transformation in vivo. In vitro, yes; in vivo, no! I realized if we couldn't show how it was produced, finding it in urine was just going to result in endless controversy.

SB: So, what did you decide to do next?

AF: I got interested in dopamine. I looked around for an experienced catecholamineologist, found Menek Goldstein at the Worcester Foundation and induced him to come and work with me. Actually, he was more my teacher than a staff member. I learned a lot from him about analytical methodology and what the issues were in the catecholamine business. I had just published some methods for analyzing norepinephrine so we started to work on the dopamine system. We identified a couple of new metabolites of dopamine that hadn't been published before. They were analogues to what had already been published for norepinephrine, so they weren't monumental discoveries although they hadn't been identified for dopamine. Then, in a sort of elliptical way, I probably was the first proposer of the dopamine hypothesis, using what I now consider to be illogical reasoning; if drugs that make you better reduce dopamine, probably dopamine is causing schizophrenia. It eliminated a whole part of the circuitry; that there are compensatory or buffer systems that, even with abnormal genes, attempt to maintain homeostasis and normal function. But we spent a lot of time looking for abnormalities in dopamine metabolites in patients with schizophrenia. We didn't find any, nor has anybody else to my knowledge. We looked in every kind of fluid until the idea came to me that maybe the hypothesis was not entirely logical, and I became interested in buffer or compensatory systems, of which I

am now pretty convinced dopamine is one. My argument was that since dopamine antagonists work in all kinds of psychoses, not just in schizophrenia, it would not be logical to think the etiology of all of them was dopamine excess, “hyperdopaminergic.” Dopamine either was part of a final common pathway or of a compensatory system. I was leaning toward the latter idea so we started to study compensatory systems in rats subjected to stress. We also studied humans using plasma HVA, a marker of dopaminergic activity. While there are lots of arguments about why HVA it’s not a good marker of dopaminergic activity in the brain, it is an excellent predictor of response to neuroleptics, so there’s some basis for maintaining an interest in it. We also started studying buffer systems in rats. In the last couple of years, I was attracted by the finding that all antipsychotic drugs, whether atypical or typical, inhibit the conditioned avoidance response. In fact, that’s the way that almost all of them have been screened. I got interested in the possibility of using the conditioned avoidance response as a way of studying buffer systems in rats. Recently, in the ACNP Journal, we published an article showing if you stress rats, acutely, nothing happens, but if you stress them with mild stress for seven or eight days, it inhibits the conditioned avoidance response. One interpretation is that this invokes a dopaminergic system, particularly the nucleus accumbens one. We couldn’t use genetic stress, because we don’t know what the gene is, so we used mild tail shock stress every day for eight days. It inhibited the conditioned avoidance response in the same way as a dopamine agonist.

SB: Which dopamine agonist, bromocriptine?

AF: Yes, if you give bromocriptine in the prefrontal cortex, you get the same effect. We haven’t published that, but we’ve done it. And, the escape response is not affected, so it’s not a motoric impairment like you’d expect from learned helplessness.

SB: What would you say was your biggest contribution?

AF: I don’t think any of my findings had a major impact up to this point, but my thinking about buffer systems in the brain and their role; that the primary genetic abnormality in some schizophrenics might be a defect in a buffer system. I think most antipsychotic drugs pharmacologically increase the efficiency of or make up for the inability of a defective buffer system to reduce dopaminergic activity. So that’s the thing I’m most enthusiastic about. We’re, also, doing interesting studies using subtractive hybridization with discordant identical twins. One of the big problems of linkage studies in schizophrenia is that schizophrenia is not one disease. The way you can be sure you’re studying one disease, genetically, is to study a set of discordant identical twins with unilateral transmission of schizophrenia

who haven't taken drugs. We found such a set to study gene expression by subtractive hybridization. The other thing combines my interest in the genetics of schizophrenia with my interest in buffer systems. We've studied six sets of discordant twins who weren't taking medication and in every set the well twins had lower plasma HVA than the sick twins, suggesting they spontaneously turned down their dopaminergic system, like the rats did, in the face of stress. One hypothesis is that, in discordant sets, the sub twin has a less functional buffer system. Another piece of evidence is that, in almost every case, the sick twin has the lower birth weight. There's very good family data showing that, in most cases, both twins carry the schizophrenia gene because the transmission rate is pretty much the same. In the sets of twins we've studied, one set of which are very close, the well twin is taking care of the sick one, who has been hallucinating for four years, but has never taken drugs, except for a brief period of four months four years ago. Six genes differentiate them, have a fairly large difference in MRA formation, and we're now sequencing those. We've published one article. We've also studied distribution of the expression of these genes. Three of these six genes are novel but the most interesting thing is that these genes are very prominently expressed in rat brain cortex, in the hippocampus and in the medial geniculate body. It is a very robust expression in the medial geniculate. They may all turn out to be differences in dietary habit or God knows what, but I think there's a remote shot that one or more of them could turn out to be a marker for schizophrenia. So I have come back, by a different route, to my first interest.

SB: You certainly have. You're about as good an example of a self starter as anybody I've ever met. Your formal training, in terms of actually carrying out research, was what?

AF: Was zero.

SB: Zero. That's what I thought. In terms of the course work you took some organic chemistry.

AF: Physical chemistry, organic chemistry.

SB: Maybe in college you took some courses?

AF: I was chemistry major in college, so I knew a little bit, but it was mostly self taught.

SB: That is a remarkable story. I don't know whether, nowadays, one could do that.

AF: I don't think so. Nobody would give you the chance.

SB: That's right. It's a remarkable story. Can we turn to the future; in the next five or ten years, where do you think the payoffs may be in our field?

AF: I'm pretty confident of two things, one is, that if gene therapy ever develops it will be beyond my lifetime and, maybe, everybody who's alive now.

I see that far in the future. What will happen in the not too distant future is better understanding of the regulation of genes which will lead to using transcription factors and other gene regulators as drugs. The big problem we have now is that we don't know enough even to start doing that. When we do, and can get the drugs to their targets, we'll start to use transcription factors as drugs and there will be a big advantage in telling the tyrosine hydroxylase gene to turn itself down instead of using all these indirect ways, blocking receptors and giving instructions to intracellular messengers.

SB: All kinds of compensatory changes; although, they may not be therapeutic.

AF: Exactly.

SB: One last question, how do you feel, in terms of how it turned out in your career? What would you tell somebody who wanted to enter the field now? Is that a good idea or a bad idea?

AF: If you'd asked me that question two years ago, I would have said, fantastic. I've had a career in which nobody ever told me what to do. I could indulge my own research interests without any interference and with adequate support, very interesting collaborators and the ability to develop a large laboratory. But, things have taken such a sad turn now in research funding that I'm not sure how I'm going to feel at the end of my career.

SB: Thank you very much.

AF: Thank you.

FREDERICK K. GOODWIN

Interviewed by Thomas Detre
San Juan, Puerto Rico, December 10, 1996

TD: Good evening. I'm Thomas Detre and I have the privilege of interviewing one of my distinguished colleagues, Dr. Fred Goodwin,* who has played such an important role in the development of psychopharmacology in the United States and in the world. But, before we get to psychopharmacology, I would like to know how you got into medicine.

FG: I was in philosophy and I liked the intellectual discipline but I didn't like how quiet it was, spending time in the library, so I thought medicine would be more active. Also, my mother, who was a psychiatric social worker, always wanted to be a doctor, and had she been born twenty years later, probably would have been a doctor but, in those days, women in medical schools were not very common. Part of her wish to be a doctor rubbed off on me. I went to medical school and was slated to be a surgeon, because I like to work with my hands. But one afternoon, in my senior year, when I was not finishing my work with pre- and post-operative patients sufficiently fast, one of my professors of surgery, the same Ted Cooper who went to the Heart Institute and became Assistant Secretary of Health asked, "What is the matter? You are a good student and you're good in the operating room, so what's the matter"? I said, "Dr. Cooper, I have no idea". He said, "Let me sit in with you and see if we can figure it out". So, he sat in with me and at the end called me into his office and said, "I think you should be a psychiatrist". I was crushed. At that time, psychiatry, at least in medical school, was not very intellectually interesting. It was at the beginning of a transition from the dominance of psychoanalysis into some kind of rough empiricism but nothing intellectually interesting. He explained, "I listened to you and to the patients and you were learning more about them in a few minutes than I did from knowing them for years; you would be frustrated as a surgeon, because you'd never have a chance to get to know your patients. You'd never have a chance to really talk to them". So, I took a mixed internship that gave me exposure to psychiatry. I still did not decide on psychiatry until late in the fall and the residency at Yale was too late to apply to. Instead I applied at Chapel Hill which was a good move because I met Morey Lipton and Art Prange there. And, that was the beginning of realizing there was an intellectual basis to the new psychiatry.

TD: The beginning of biologic psychiatry.

* Frederick K. Goodwin was born in Cincinnati, Ohio in 1936

FG: The very early sixties was just the beginning of the psychopharmacology revolution. What had been an empirical fact these drugs had effects began changing psychiatry with the realization perhaps they were clinically specific and you might make theoretical conclusions about mental disorders from studying their mechanism of action. So I got interested in learning more about them from Morrie Lipton, a distinguished past president of this organization. It was a great blow to all of us when he died a few years ago. Morrie used to give conferences, in which he talked about the brain and the mechanism of action of drugs. Then, I decided to apply for a clinical associate position at the NIH but, at the time, I was still primarily interested in what I had found most interesting during my residency, which was the “family dynamic theory” in the etiology of schizophrenia. Lyman Wynn, at the NIH, was the principal investigator for this kind of work on family communications and how they might contribute to paralogical and psychotic thinking in schizophrenia. So, I went to my interview with Dr. Wynn but, due to a mistake, he was out of town. The secretary felt sorry for me, having come from Chapel Hill and looked around to see who was available. And a young man, named Biff Bunney, was the only guy who had time to talk to me. I went into the interview with Biff and I became very excited because he was bubbling over with enthusiasm and energy. He was interested in me because I had worked in a biochemistry lab at NIH during summers in medical school and published two or three papers. Biff was beginning to convert his clinical interest in depression into an emerging biology and was looking for people who had some background in that area. So we hit it off very well. I was slated to work with Biff and Jim Mass, another important figure in this organization, who also passed away a couple of years ago. Then I got a call from Jim saying, “How would you like to come to Bethesda this July”? It turned out that Joe English, who was a clinical associate at the time, had gone to the Peace Corp and decided he wanted to stay rather than return to Bethesda. So a spot opened up, unexpectedly, and I had to make a decision, did I stay in residency or go to Bethesda. I think I made the right decision when I went to Bethesda without completing clinical training. We learned later that many of the people who came, like Dennis Murphy and Bob Post, before they completed residency, were more likely become full time researchers than those who had already become experts in the clinical field.

TD: Experts, licensed to do something else.

FG: The NIH intramural program has done quite well over the years with people who were not completely trained when they got there, some of us with one year, some like Dennis Murphy, with two years of residency. They’ve

also done well with people who were completely trained. I picked up additional training at NIMH and through programs at George Washington University, and the Washington School of Psychiatry where I continued psychoanalytic training, which was still the dominant intellectual tradition at the time. When I got there in the summer, NIMH was still a part of NIH. It was also before the days Biff had his small group that was to include me, Jan Fawcett, Will Carpenter, Dennis Murphy, and a little later, Dave Janowsky, all of us working in one converted seclusion room. John Davis was there as well, and all of us in that original group stayed in research and are still active. Biff made sure each clinical associate took up a project that was ongoing so they could get the feeling for data, preparing data analysis for publication, mid-stream. We picked up a project that someone else had left but definitely on its way to being completed. Then, he'd give each of us a project that was entirely our own from the beginning.

TD: That you chose or were given to you?

FG: Chosen from a pre-selected list. I later learned, as I became a mentor over the years, that it was important not to leave people totally free floating and undirected.

TD: And each clinical associate was assigned a mentor?

FG: They were assigned a mentor but the group was small enough that Biff was mentor of research for the entire group. The NIH is a very unique organization; you can go down the hall and find an expert in just about anything. So we were all influenced by Julius Axelrod and Lyman Wynn. Bill Polin was doing some of the best twin studies at NIH in those days. There were several distinguished early behavioural geneticists in the laboratory of psychology. And, we had weekly research meetings. They were like Grand Rounds and intellectually stimulating. Jack Durell was there, running a program. There were so many bright people it's hard to say how much you learned from one segment or the other. And everyone was very competitive. The area I chose to do my research was lithium. It was brand new to the United States, and Biff had figured it was going to be of great importance. One of my patient's was on lithium and I felt both the patient's depression and mania was getting better, which was counter to the prevailing wisdom of the time; the amine hypotheses were dominant and it was incomprehensible to have a substance that combined anti-manic and antidepressant effects.

TD: Where did this lead to?

FG: To a double-blind controlled trial to determine whether or not lithium was an antidepressant. We were the first to report, in a controlled study,, the antidepressant effects of lithium, which was used as an anchor for the

hypothesis that depression and mania were different facets of the same physiology. Now, in the light of hypotheses about the role of the phosphoinositol cycle in signal transduction, we are starting to understand how this could happen. At the time, I didn't even know the catecholamine hypothesis that well, because I had come with an interest in schizophrenia. If anything, I was more interested in psychodynamic issues than in biology. Moreover I wasn't trained well enough clinically to completely trust my own observations. Perhaps there was some stubbornness in me that forced me to continue making observations and figure out how to structure a study to test it. So, Biff, Jan Fawcett and John Davis designed a study where we could look at independent blind ratings by nurses and found that lithium had antidepressant effects. They were more often observed in the cyclic patients. We didn't have the bipolar versus unipolar distinction; we had cyclic and non-cyclic depression. Cyclic depression could have been unipolar or bipolar; like the Kraepelinian distinction. We found that cyclic depressed patients, regardless of polarity, responded to lithium. We also found that lithium response occurred over a longer time frame, but by using an intensive on and off design we could rule out spontaneous recovery. That was my introduction to research.

TD: Would you move to the next step in your research?

FG: The next step was driven by the environment in which we lived. Biff became very interested in direct methods for testing the amine hypothesis, so all of us got involved in using probes for testing hypotheses. I became involved in research with L-DOPA and was the main investigator in our first L-DOPA study for which we received the Bennett Award. We used the system that Biff and David Hamburg built to assess patients on a daily basis by trained nurses with inter-rater reliability. We were doing something for which there weren't accepted statistical methods for the analyses of data, but it suited the intramural environment. From L-DOPA, we moved to studies with α -methylparatyrosine and parachlorophenylalanine. Later, when I had my own group, we did, with David Sack, studies using dopamine beta-hydroxylase inhibitors to separate the dopaminergic from the noradrenergic contribution to mania. By using fusaric acid, a potent dopamine beta hydroxylase inhibitor we got findings which indicated that dopamine had more to do with the psychotic element of mania and norepinephrine had more to do with the mood element. So we would do something and move on. But we never moved away from the methodology; the daily ratings and careful longitudinal observation.

TD: There were some changes in your administrative responsibilities in time?

FG: My mother influenced me toward medicine but my father was a career government executive. He was one of Roosevelt's brain trust, who had

a leading role in establishing the unemployment insurance system, so I'd grown up with that culture as well. I had a family connection to policy issues and that, plus my background in philosophy, began to show itself even while I was a working scientist. When Herb Pardes came as director of NIMH, he gave me the opportunity to be Director of Intramural Research and that tended to be a science policy job for NIMH, broader than just directing the intramural program. In that job I became very interested in policy. It was tremendously gratifying to provide leadership for the intramural program; I was able to develop and make laboratories available for many of the people who have gone on distinguished careers, like Steve Paul and a host of others. Judy Rapoport and Danny Weinberger had their own laboratories; Tom Wehr his own branch, and Phil Gold his own section. It was a time of changeover and growth in that program. I was getting very interested in matters that had more to do with national policy. The biggest change was when I left what was the best job in the field to take one that might be considered risky for a scientist, which was Administrator of ADAMHA, a political job. Just like my father, a career executive who had become an Assistant Secretary of Labor under Kennedy and Johnson, and had to step back later, in the Nixon administration. It's the same thing I did, but under different circumstances. When I took the ADAMHA job, a presidential appointment, it was a dramatic change because I was able to bring some scientific background to a position that had been uneven about science after Jerry Klerman's departure. I tried to bring that image back to the ADAMHA by working on special issues.

TD: You were looking into the drug design issue, right?

FG: Right.

TD: You started the drug discovery program?

FG: What has now become the NIDA program. We had Don Klein as my science advisor for a couple of years; it was a very active time and I remained at ADAMHA for a little over four years. I was also able to bring more resources into the fight against animal rights and I crossed swords with the Church of Scientology many times, which I paid a price for later on. It was a wonderful four or four and a half years made special because I had such a fantastic deputy in Bob Trachtenberg, a lawyer, who while not scientifically trained, had a great appreciation and respect for science. He used his extensive experience in government at high levels to nurture science and protect it

TD: And, then?

FG: The low point of my career occurred when I was giving informal remarks to the Mental Health Council, after a night of sleep deprivation. My wife's

mother had a stroke and we were up all night trying to figure out how to get my wife to Minnesota to be with her. And, as I walked into the NIMH Council, Allen Leshner the acting director said, "Would you please talk about the secretary's violence initiative"? I said, "Sure" and gave my normal report. Everything was going fine until I remembered something a colleague, Mark Linnoila, had told me two days before about some very exciting research on primates. I started talking about that and said something to the effect that half the young male monkeys, when put in the natural environment, ended up dead while the half that survived became well functioning adult primates. It was interesting because the least and most aggressive died, while the ones in the middle did well. I hadn't thought about what connections it made, clinically. The people there who heard me didn't think anything was wrong, except for one employee. When it was printed after somebody leaking it to the press, it didn't read right, even to me. I said something like, "It seems what might be happening is we're beginning to lose some of the structure society provides that keeps mankind civilized and maybe, in some of the inner cities, we're losing some of that structure". The comment that really got me in trouble was; "It's not surprising some people refer to the inner cities as jungles" I'd heard Spike Lee on the radio, the day before, talking about the jungle and the problems it represented in the inner city. But I wasn't thinking about race at all.

TD: It was inferred to be a racist comment.

FG: Yes, it was. One of my black friends told me, "You're so color blind you don't even hear that but if you had a trace of racism, you'd be more careful and wouldn't say it." One of my best defenders listened to the tape because he wanted to hear how it sounded, and said, "This sounds like Fred talking carelessly about animals, but when he talks about animals he's always thinking of connections". One of my assets has always been to do that.

TD: You looked on this as an animal model to help understand human behaviour.

FG: Yes, but I wasn't careful. In retrospect, I shouldn't have been thinking out loud in that setting. That's the kind of thing you would do in a lab group but I do think sleep deprivation played some role. Anyway, we don't have enough time to describe what happened after that; essentially a series of events led to my stepping down from ADAMHA. It was not automatic, by the way. It was only when a member of a congressman's staff lied to the black caucus that I had been refusing to take the congressman's calls that changed the outcome. I had already apologized and everything was settled down. I was staying as ADAMHA administrator; Lou Sullivan

and I had agreed that was the best way to go and that's what the White House wanted until that staff member lied. She turned out to be a close friend of the number one anti-psychiatrist in the country. He's a psychiatrist who thinks mental illness is a myth and that all we do is poison people with drugs. He's also affiliated with the Church of Scientology that I had antagonized. This woman also got staffers from Kennedy's and Dingle's office to sign a letter, for which Senator Kennedy later apologized directly. Then, of course, Louis Sullivan the African-American Secretary of Health, a Republican, was in a very embarrassing position. He had been a very good friend and supportive in the animal rights issues and a number of other things. I felt the situation kept him under political pressure although The White House did not want me to resign and I was a presidential appointee. But I realized it was very awkward for Lou Sullivan and knew I was probably going to leave NIMH a few months later with the reorganization already on the books to bring the Institutes back into NIH. So, I decided to step down. Some people say it was a mistake because, when I stepped down, it looked like I was admitting that I had done something wrong. Two or three months later, when I was working with the local DC community and with the DC city council, I visited the DC jail at their request, to talk about how NIMH could help with violence research. I was feeling the thing was behind me when a very favorable editorial in the Washington Post said, "Fred, you know, you've really made lemonade out of a lemon". Sometime later I was sitting in New York with my wife one week-end and when I saw in the New York Times that the University of Maryland was sponsoring a conference on crime I said, "Can you imagine anyone being so naive as to call a conference, The Crime Gene. That's so provocative, particularly, in the environment I stirred up". I turned to Page A6 and there's my picture with my comments quoted by the same anti-psychiatrist, who had been conducting the scientology campaign against me. My remark, of course, wasn't about genetics it was about the environment. That's the first time I felt out of control. And, that's the first time I decided I didn't have the genetic vulnerability for depression because I wasn't getting depressed!

TD: Instead, you started a new career.

FG: I served at NIMH for two more years and contributed a fair amount to the task force on mental health and health care reform. We got out the data on efficacy, but I did feel that with the change of administration and the hangover from that gene conference I was no longer well respected throughout the new department leadership. So that's when I started my new career at George Washington University. I'm dealing with many of the same issues I dealt with in the government, with substantially fewer

resources but with more freedom. The biggest problem in the new position is that, after 34 years of government, with the last twelve spent in high intensity jobs where everything was made to seem urgent, it's very difficult to decide what's important when nothing is urgent.

TD: That's a very interesting point.

FG: I did well in those jobs because I put my own priorities aside and responded to the needs of the organization, its constituencies and the people above me. I was good at that, so all of a sudden, to be in a position where I have to decide what's important has been a tough adjustment. But, I'm getting there. We're looking at managed care issues, how to preserve innovation in the face of guidelines that operate like cookbooks. I testified on the Hill about FDA reform; we got into the issue whether the FDA was pushing too far in considering dissemination of off label information as advertising, if the information was in peer reviewed papers. I have a person with me on sabbatical from the NIH, Suzanne Hadley, who was very much caught up in science misconduct and feels it should be dealt with by pro-active education rather than policing it. We've begun to write some pieces; that it is not wise to create a big science police force, raising the question of how big is the misconduct problem and would it justify a science misconduct apparatus, that once established, had to find problems to justify its' existence. We're holding a conference on that, down the road. We are co-sponsoring a conference with The Media Center in Washington for reporters about brain, science and the biology of behaviour and how the genetics of behaviour translates into something the public can understand but is not frightened by.

TD: There's an old saying that, "The best victor of tomorrow is the victor of yesterdays". You have been a productive person your entire life and your productivity will continue unabated for many years to come.

FG: I'm hoping so and I have a young colleague now who has opened up possibilities for me to continue in my field of bipolar illness. Kay Jamison and I are considering a second edition of our book on manic depressive illness and I am doing some writing for the general public. My wife said I look happier than I have in many years. She gets to see more of me than she did before. And I have two new grandchildren.

TD: Since you were a high-ranking official in government, the role you could play in the ACNP was somewhat limited. But, you've been a very active member.

FG: I joined ACNP quite early and in the late sixties or early seventies became a Fellow. In the beginning, when I was a working scientist, I was active and headed the committee on Problems of Public Concern. I was on the credentials committee and the membership committee and had a couple

of other committee assignments. As it grew up to the point when it might have been appropriate to be on the council or an officer I was in the kind of positions where I didn't feel it was appropriate to mix my government role with leadership in the organization. Now I don't have that conflict I find myself getting back interested in the policy areas of the organization and may see if there are people interested in supporting me for council membership. I've watched this organization grow and get uncomfortable when people say basic science is the source of everything. Much of what we understand about the synaptic connections of the central nervous system came out of efforts to understand how imipramine worked. It was the effort to understand how psychoactive drugs worked biologically that was a major driving force in the evolution of functional neuroscience. The meetings have grown and grown and I worry they are getting too big. But, I've never missed any of the annual meetings in thirty years and I never learn at other meetings as much about my field and the people in it as at these meetings. When I come to the meetings in December, it's also associated with a lot of sadness because of some of the people who aren't with us anymore, like Danny Friedman and Morrie Lipton.

TD: You come partly for the camaraderie.

FG: When I was a young scientist it meant a lot to have drinks with Danny or go out for dinner with Morrie. I remember the enormous influence those men had on me. It was very subtle and it wasn't just about what they taught me about science. These meetings were structured as informal interactions around the pool, in the hallway, at the restaurant as much as what the scientific sessions were about. It's important the meetings don't get so big they become only a place where people sit around listening to lectures because it wouldn't be ACNP any more. I love this organization.

TD: Thank you very much.

JOHN F. GREDEN

Interviewed by Thomas A. Ban
San Juan, Puerto Rico, December 2, 2004

TB: This is an interview with Dr. John Greden* for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College. It is December 2, 2002. I'm Thomas Ban. Could we begin with where you were born, your background and how you decided to go into medicine?

JG: I'm John Greden and I'm honored to join the distinguished company of people interviewed for the historical archives. I was born in Rolling Stone, Minnesota. Jokingly, people give me a hard time about the fact that Rolling Stone was a very small town; when I grew up it had a population of 395 associates and me. I wasn't aware I might be going to medical school but it was probably by mother's influence. She was a registered nurse in a small community with no doctor; she was the person people called for medical advice so I was exposed to this while growing up. Nevertheless, when I started college, I had plans to do something else because I was not even in a pre-medical curriculum. It was in my freshman year I decided to switch to medical school and that was one of the best decisions I ever made. Whenever anybody asked, "What are you going to do," I replied, "I'm either going to be a psychiatrist or a surgeon". This was in the early 1960s, and, when I would say that people would reply, "Oh, be a surgeon." I was aware there was stigma associated with psychiatry. I got my undergraduate degree from the University of Minnesota and after I entered medical school I found myself asking what I would like to do. Probably the most enjoyable course I had in my first year was neuroanatomy. After my first year with an NIMH fellowship I spent my summer vacation on a project interviewing depressed women and published on that project with my mentor. After I finished medical school I did an internship at UCLA's Harbor General Hospital, in Los Angeles, California. It was one year after the Watts riots. At that time my intention was to become a pediatrician. But, during the year at Harbor General, I found myself spending most of my free time reading about psychiatry. And, about two-thirds the way through the year decided to switch from a pediatric residency to psychiatry. Again, that was one of the best decisions that I have ever made. Along the way I had married, Renee; we knew each other from our small community and intermittently dated since high school. So, I already had two small children by the time I had finished

* John F. Greden was born in Rolling Stone, Minnesota in 1942.

internship. There was turmoil because of Vietnam and I was in the last group of physicians subject to the draft under the Berry Plan. After one year of residency in psychiatry at the University of Minnesota, I was called to active duty, posted to Fort Sam Houston in Texas for basic training. From there, I ended up assigned to Fort Lee, Virginia where I was what the army called a partially trained psychiatrist, looking after thirty thousand soldiers with another physician who had just completed psychiatric residency. It was great exposure to psychiatric problems and a wonderful opportunity to learn. We had to handle everything and were perceived as experts. To do the job we had to read a lot and learn fast. Those were the years when the epidemic of drug abuse hit society at large and the military specifically. President Nixon considered it the number one public enemy, and, declared “war on drugs.” I ended up evaluating the scope of the problem at Fort Lee and published my findings in the Archives of General Psychiatry. As time passed I was becoming more and more interested in psychopharmacology.

TB: You mentioned you had one year of residency in Psychiatry at the University of Minnesota. Was Bert Schiele chairman of the department?

JG: The chair was Don Hastings. But Bert, a pioneer in psychopharmacology, was one of my mentors. Faruk Abuzzahab also taught us psychopharmacology. I did not think at the time that was the type of psychiatrist I would like to be; I was interested in a number disciplines and in integrating knowledge from them. I tend to call myself an integrator. I love neuroscience and I love to translate findings from neuroscience into clinical use. I also love the idea of moving forward; whatever project I do I like to move forward with it.

TB: Where did you do your other years of residency and what did you do afterwards.

JG: I finished my residency at Walter Reed. After my residency I was asked to stay on as associate director of research. But I also had an offer from the University of Michigan and I chose to accept that appointment. I was still young and chose a colleague, Barney Carroll, who was the individual probably closest to what I wanted to do, as my mentor. Suddenly, I found myself learning more about neuroendocrinology and spent much of the next ten years trying to blend together my interest in the longitudinal course of depression in a Kraepelinian model, with my interest in psychopharmacology and neuroendocrinology. We used the dexamethasone suppression test, DST, and I began to monitor what happens in the longitudinal course of depression with the hypothalamic-pituitary-adrenal axis. In collaboration with Barney Carroll, Michael Feinberg, Phinasas Isk,

Roger Haskett, Ira Ball and others, it was intriguing to find variables such as relapse, suicide, and others, were related to HPA dysregulation.

TB: Could you tell us about the DST?

JG: The DST was based on finding that administration of a small, 1 mg or 2 mg dose of dexamethasone at night in normals shuts off hypothalamic-pituitary-adrenal secretion, as measured by suppression of the morning rise in plasma cortisol level; but 30% to 80% of depressed patients do not suppress this morning increase. The finding that cortisol “escapes” suppression is an indicator of the dysregulation of the hypothalamic-pituitary-adrenal axis in depression. People initially developed the wrong idea that DST might be just another useless laboratory test. Later it was recognized that the DST reflects what is going on in the brain of depressed patients. The hope that the DST might be the first laboratory test in psychiatry for deciding whether a depressive illness requires medication created a great deal of excitement in the United States.

TB: Did you participate in the development of the DST?

JG: I cannot take credit for that, but I was the first to use it in a longitudinal study.

TB: Didn't Barney Carroll start work with DST while still in Australia?

JG: It was Barney who started it in Australia. From Australia Barney went to Philadelphia before he was recruited to the University of Michigan, a little bit before I arrived. With the approval of Al Silverman, the chair of the department, Barney and I converted 12 beds from a 24 bed inpatient service, into a clinical research unit for affective disorders. We called it the CSU, the Clinical Studies Unit for Affective Disorders and also organized an outpatient clinic to follow patients who participated in protocols in the CSU. For ten years it was like running a GCRC in Psychiatry. It was very productive and probably the most rewarding time in my life. In about 1983 or 1984, Dr. Carroll left, and, there was a short time when we had turmoil in the department. I had taken a sabbatical, published several papers and was promoted to Professor. I was still a young professor when people started asking me to become chairman of the department. I said, “no,” several times; I felt I already had the best job in the country, running the clinical studies unit. But the department started to fall apart and, in 1985, I was asked by the Dean to take over as acting chair. After struggling for several months I decided to accept. Otherwise I might have ended up leaving Ann Arbor because of turmoil in the department. By then we had three children and I loved Ann Arbor and the university. That was long time ago. I have been chairman for about eighteen years. In my early years I set out to build a network for translational research. It was hard to pull things together and more and more I had to leave my specific

laboratory responsibilities to pay attention to how to train a new generation of psychiatrists. I began to focus on trying to recruit young scholars and start people in research careers.

TB: What happened to your laboratory after you delegated some of your laboratory responsibilities?

JG: The laboratory has remained operational. It is in our Mental Health Research Institute, MHRI. The people we recruited were Huda Akil, a past president of this College and current president of the Society of Neurosciences, and, Stan Watson, an internationally recognized neuroscientist. Elizabeth Young, a fellow of this college, is a product of our laboratory training. We all worked together but I was the engine of recruitment in those early years. Operations in the MHRI have continued, but shifted from the traditional search for a laboratory test to molecular genetics, neuroimaging, and the study of proteomic mechanisms. Stan, Huda, Elizabeth and a number of people who grew up in our department have remained. So the lab is very operational and has continued to be extremely productive in working on the basic science-clinical interface.

TB: One of the former chairmen of your department, Al Silverman, was involved in research in psychophysiology. I remember him from the late 1950s or early 1960s. What happened to his laboratory?

JG: Al ran his lab, even as Chair, and I ended up inheriting part of the space when I received an NIMH grant to study Psychomotor Regulation and Affective Disorders. I looked at facial electromyography and reactivated interest in the Omega Sign, a corrugator muscle activity seen in sadness. Now this research is done with fMRI, a far more sophisticated technique than EMG. I was also measuring speech periodicity by voice recordings and monitoring motility. The technologies were all rather primitive but we have come a long way since. But I inherited Dr. Silverman's lab space and used it for about five years. Right now there is a great deal of emphasis in our department on sleep research. But the focus of activities, after Dr. Silverman's retirement, shifted from psychophysiology to stress and the neuroendocrine system, molecular psychopharmacology, and neuroimaging. Now I'm reflecting on it for the first time it is an intriguing and exciting story. I didn't come prepared to go over this and find myself looking back and realizing there have been some very good things that emerged.

TB: You dedicated a considerable amount of your time as chairman to the development of research. Weren't you the chairman also of the faculty group practice at the University?

JG: In 1996 the sixteen clinical departments of the University of Michigan decided to form a faculty group practice. For whatever reason, I was elected the first Chair. When my elected term ended I could have probably

gone off to be a dean. I said, jokingly, to my wife Renee, "I wonder what I want to do when I grow up?" I should have been grown up by then but apparently I was still searching for what I wanted to do. I also had an opportunity to shift from academia to the pharmaceutical industry. Rather than become a dean or take a position with industry, I decided to take a sabbatical, and asked Dr. Schatzberg, another past president of this College and a very close friend, whether I could spend it in his department at Stanford. My idea was to pursue a different dream and, while on sabbatical, conceptualize a depression center. In February 1999, after I returned from sabbatical, I made a proposal to our school of administration to establish a comprehensive depression center. I envisaged a center that would incorporate inputs from many disciplines, not just from psychiatry. I thought we needed input from basic science, cognitive neuroscience, the social sciences, and expertise in epidemiology. By being there for all of those years, I knew a lot of research was going on in the different departments of our University. My idea was to bring all that expertise together. The idea might have been rather bold, but in December 2001, we got approval to establish the center, and, in 2002, we also got approval for the construction of a new thirty-eight million dollar facility to house it. It will have fifty-eight thousand square feet, half for research. The Center has the largest representation from psychiatry and medicine but also includes family medicine, obstetrics and gynecology, emergency medicine, geriatrics, cardiovascular medicine, and a cancer center. In all these areas there are experts very interested in research on depression. The Center has input from the school of public health, social work, pharmacy, nursing, psychology and biostatistics. By bringing all this expertise together, it serves as a research engine that produces a great deal of excitement. Last January, I spent my entire month preparing a proposal to NIH, requesting support to help build the research laboratories. It made it possible for us to expand our new facility beyond what I just described. The fun part for me will be in constructing a new version of the clinical studies unit I had with Dr. Carroll twenty-five years ago, a model for the next generation. I'm very excited about what we can do. I believe we have laid a foundation in our field for future translational research by having an Institute that can move forward treatment, regardless whether it's with CRF antagonists, genetic therapies, or antagonizing neurotrophines. So, for the past five years, my challenge has been to wear this new hat.

TB: Over and above of all your other activities you have been involved in mentoring several people.

JG: I have in the past fifteen years served as a mentor for about 14 Career Development Awardees.

TB: Could you name some of them?

JG: Well, some of the names I've already mentioned. I have been involved with Elizabeth Young's training, once our research fellow. Some of the others include Israel Liberzon, Bridget Tinden, and Helen Kales. There were also people whose primary mentors were Stan Watson, Huda Akil who I was mentoring in collaboration. We have an outstanding young scholar named Heather Flynn, interested to look at women who refuse to take medications because they are pregnant, and I decided to help mentor her.

TB: You have been very successful with your research teams.

JG: When I look back I have a longing that it would have been nice to pursue more research of my own. But currently you need teams to make progress because of the vast array of knowledge required to pursue the work. It is necessary to bring people with different expertise together and that represents a challenge. You end up struggling to manage the teams and need administrative and interpersonal skills to keep people on the same page.

TB: You have also been active in the ACNP.

JG: I have been on the council now for several years and before that I was serving on the advocacy and the publications committee. I was also asked by the council to be a senior administrative editor and help to revise and restructure the college's publications. I was involved in the selection of the right people as editors for *The Fifth Generation of Progress*. We brought in Ken Davis, Dennis Charney, Joe Coyle and Charlie Nemeroff to edit the book and Jim Edward Woodruff in doing the scientific web site of the ACNP Journal. I ended up having Bob Lenox in the role of journal editor. Now Charlie Nemeroff is doing it.

TB: When did you become a member of the ACNP?

JG: It was sometime in the 1970's. I became a Fellow about a decade ago.

TB: Would you like to comment on the annual meetings?

JG: The annual ACNP meetings have always been highlights for me. I remember when the teaching days started. The college has much to be proud of when it looks back on its' past and membership.

TB: Let me switch to another topic. You have been wearing many hats successfully. How much of your time are you spending in clinical practice, seeing patients?

JG: I have continued to try to stay active clinically. For twenty-five years I've had funding as a PI or Co-PI, and, I've tried to have my clinical activity stay relevant to my ongoing clinical research grants. I have averaged

about five to six hours of patient contact a week. In recent years I see mostly VIP's. I am asked to do evaluations of people within our university or community. Some of these people I treat and follow subsequently. If I would not do that I would lose the fine edge of my clinical skills. Five to six hours a week is probably not enough but I've tried to stay involved in clinical practice. As chairman of the department of psychiatry I'm responsible also for the MHRI. I have terrific leaders at the Institute. Stan Watson and Huda Akil as co-directors take care of the day-to-day activities. I am also the founder and executive director of the Michigan Depression Center I mentioned, and I guess it is taking about half my time. You made a nice compliment when you said "I'm wearing a number of hats and I seem to be doing them successfully." I hadn't thought about it that way, because sometimes I worry I'm not doing any of them well. Still, there is one more activity I should add to the different activities we already talked about. I've become a bit of a "philanthropy development officer," as I call it. To make sure the depression center is a success, I set a goal to raise fifty million dollars to help in its' operations. At the time I set this goal, some of my colleagues at the University scoffed. But we have now been moving towards our target for about a year and a half and have raised about 19 1/2 million dollars already. So we are well on course. Many colleagues doubted people were going to donate for research in depression but, in actuality, many people are quite willing to do so. It's been very rewarding to see our region so responsive.

TB: You have been certainly very successful. Are you currently involved actively in any of the research projects at the Depression Center or the MHRI?

JG: I have continued to stay active and participate in our research. I'm the Co-PI on a grant we just submitted on the prevention of suicide that is focused on depression and alcohol use, the highest risk for suicide in our society. We have chosen to develop some programs as part of the depression center that looks at depression in college students and, I'm part of that project also. I have continued to play a role in the Star D project, although, the protocol in that project is followed by others.

TB: Do you have any special research interest these days?

JG: I've developed an interest in depression and pain, and especially in why is it that the SSRI's don't seem to work in patients with physical symptoms and pain; whereas the old tricyclic antidepressants do. We might need to develop other strategies for these conditions, possibly using SNRIs. Many depressed patients are seen by primary care physicians. I believe that we must detect depression earlier, intervene earlier and more effectively to prevent its progression. That is a long-term interest of mine. To

achieve this goal we moved many of our people into family medicine, the cancer center, the cardiovascular center, the emergency room and we are trying to work with people in those centers side by side, in a collaborative model, sharing expertise. Our colleagues at the University of Michigan have been wonderful. They love it. We have already learned people with depression who show up in family medicine and in the cancer center have a whole different array of symptoms than those who end up in psychiatric facilities.

TB: You mentioned that one of your current interests is in depression and pain.

JG: The pain story is like the other stories in depression. What you discover is that it's an orchestra and if something goes wrong you don't get good music. In addition to the endorphins and neurotrophins, traditional neurotransmitters, like norepinephrine and serotonin, play a role in sensitivity to pain. Among the pharmacological treatments, trazodone was considered to be especially useful but many of the old tricyclic antidepressants, like imipramine, amitriptyline and nortriptyline also have an effect on chronic pain associated with depression. When we moved into the era of the SSRI's, seeking for more selectivity, we tossed out anticholinergic side effects, and by doing that we have lost an effect that is relevant to depression. We've made great progress in the treatment of depression during the past decades, but we still have about thirty percent of the depressed population who don't respond at all, and, probably, another thirty to forty percent, who respond only partially. From the total population only thirty to forty percent achieve remission. The group of non-responders or partial responders probably consists of individuals with an alteration in a circuit other than those targeted by selective re-uptake blockers. These are people with lots of physical symptoms, who have pain and are chronically ill. Our challenge is to move into a new era in which we pay more attention to getting people better and keeping them well than to having more and more selective drugs with fewer and fewer side effects. We need to focus on depression associated with physical symptoms. I doubt it, but it's not impossible we need to go back to the tricyclic antidepressants and trazodone. For this population the right medication might be dual or triple reuptake inhibitors or an entirely different group of drugs.

TB: You mentioned that we might have lost something by trying to eliminate the anticholinergic effects of antidepressants. Could you say something about the possible role of the cholinergic system in depression and antidepressant effects?

JG: I became interested in the cholinergic system while working with Dr. Carroll, because of its' apparent role in pushing the HPA axis, probably

by being involved in the release of CRH. At one point in time we were trying to address this by looking at the effects of physostigmine infusions. We became interested in what happens to people when they suddenly discontinue their tricyclic antidepressants, and we were first to describe what we called a “cholinergic supersensitivity pattern” that consists of nausea, nightmares, sleep disturbances and recurrence of depressive symptoms. We also discovered re-instituting the antidepressant with anticholinergic effects would suddenly alleviate the syndrome. I wasn’t surprised when I learned there is also a withdrawal syndrome to SSRIs that is different from the withdrawal syndrome with tricyclic antidepressants. I was, frankly, a strong supporter of the SSRIs when they were introduced because I saw many people with blurred vision and dry mouth on the old drugs. I had to get people to suck grapes or other things to keep them on their medications. But now it’s clear to me that if we pursue developing more and more selective drugs we block scientific development. To move forward we probably need to pick up some combinations and I hope our colleagues in industry will help us do that.

TB: Are you involved in research with any of the newer drugs?

JG: We are involved with some in our depression center. I’m very much interested in the SNRI story and following closely the research with duloxetine, milnacipran, and venlafaxine. Not long ago I completed the chapter on duloxetine and milnacipran for a psychopharmacology textbook edited by Drs. Schatzberg and Nemeroff. The molecular structure of these drugs and their mechanism of action is currently in the focus of my interest, as I said, I am more of an integrator. With the exception of longitudinal monitoring of depression and trying to work out ways to get depressed patients better and keep them well, I never stayed with any research project over an extended period. My latest area of interest is in minimally invasive brain stimulation strategies regardless whether it is with repeated transcranial magnetic stimulation, rTMS, vagal nerve stimulation, VNS, or deep brain stimulation. We have started to move into this area of research. I doubt we will have one magic silver bullet that will hit all depressions because I think we have different pathophysiologies.

TB: We have only a few more minutes left and I’m wondering whether you could say something about your publications?

JG: My first publication that attracted attention was related to caffeine. I could have chosen to pursue that as an entire field, and it would have been fun. If you coin a syndrome like caffeinism as I did, you can be proud. I was member of the team in a series of publications on neuroendocrine strategies, but the paper I’m proudest of is the one on Serial Neuroendocrine Monitoring, Normalization of the DST, a Laboratory

Indicator of Improvement, published in *Biological Psychiatry*. Most people who read it get the point I was trying to make, namely that the DST reflects what's happening in the brain, and it's not just clinical features and phenomenology one should pay attention to. To address the phenomenological and genetic heterogeneity of depressive illness as related to treatment response we would need to deal with the heterogeneity of transporters. My 5-HT transporter polymorphism may be totally different than yours and if we're both given the same drug what are the odds both of us will respond in the same way. It's the same with the norepinephrine transporter, the dopamine transporter, and with a number of other polymorphisms. That'll be a new exciting era to work in. I hope I will be part of that and make some contribution to it. So far, much of the excitement about the gains we've made in understanding depressive illness has been accompanied by frustration. I don't think we're targeting brand new treatments in the right way and that represents a challenge.

TB: So you would like to see novel ways for targeting brand new treatments and using genetic technology for prediction of responsiveness to them.

JG: Very much so.

TB: Anything else you would like to see to happen?

JG: One of my dreams, a comprehensive depression center, has already become a reality. It was also my privilege to testify before the White House Freedom Commission about the state of affairs of our mental health delivery system; I basically said "Depression must be a key part of this". According to the World Health Organization depressive illnesses is the leading cause of disability in the world, and if we are not making progress in the number one disease among the one hundred most important diseases, we need a different strategy. This was partially why I pushed for the establishment of our depression center and advocated we should develop a national network of depression centers. That's my current passion. Unless we bring clinical expertise, basic science expertise and social sciences into the field we're not going to make the difference we seek. All we know now is, if someone has a depressive illness with a constellation of symptoms, we give an antidepressant and, if it does not work after eight weeks, we try another one. I believe science should enable us to be more specific.

TB: If the integration of different disciplines is done properly?

JG: The integration of contributions from different disciplines is the challenge; to bring things together optimally.

TB: On this note, we conclude this interview with Dr Greden, Thank you for sharing this information with us.

JG: Thank you. I remember when this oral history project started I thought it was for senior people. So, when I was contacted to participate, I thought, does that mean I'm there?

ANGELOS E. HALARIS

Interviewed by Leo E. Hollister
Waikoloa Village, Hawaii, December 11, 1997

LH: Today is Thursday, December 11, 1997. I'm doing an interview with Angelos Halaris,* who is the Chairman of the Department of Psychiatry at the University of Mississippi, Jackson, for ACNP's History project. I'm Leo Hollister, the interviewer. Welcome to the project.

AH: Thank you.

LH: Where did you begin life?

AH: Life began in Athens, Greece.

LH: With a name like Halaris, it had to be Greek. Were you born there?

AH: I was born and raised there through high school. I attended a Greek-American school in Athens, so I learned English as my second language very early. But, then, I switched course. After graduating from high school, I went to the University of Munich in Germany on a scholarship awarded by the Bavarian government.

LH: It must have been quite an honor.

AH: It was, but rather unexpected and it allowed me to enter Medical School. European medical schools are a straight six years and the scholarship covered half, what we could call pre-med here; then because I'd done well, I got a second scholarship from the German government that saw me through medical school.

LH: So you got a degree from the University of Munich?

AH: The University of Munich School of Medicine and then I joined the Max Planck Institute of Psychiatry in Munich.

LH: That's another prestigious place.

AH: The idea was to do a doctoral dissertation with the option of a literature review or basic science dissertation, so I opted for the latter. I started with some morphological studies, learned how to use the electron microscope and, at the same time, did lipid research on Tay-Sachs disease as my dissertation. Then I met Dr. Norbert Matussek, who played a major role in my shifting gears and getting me into biogenic amines, studying the biology of depression. He's a wonderful individual and I consider him my first true mentor. He worked at the Max Planck Institute and had just returned from NIMH, where he spent time working with Biff Bunney and the group he had assembled. That was around 1965, the landmark year that saw the publications about the noradrenergic hypothesis of depression. Norbert

* Angelos E. Halaris was born in Athens, Greece in 1942.

was exposed to that thinking, so when he returned to Germany, he set up a laboratory to pursue similar work.

LH: Did you shift from lipids to monoamines?

AH: Yes. It was more exciting; working with Norbert we were looking at the effect of reserpine, on depletion of biogenic amines. Since I had learned to do electron microscopy, we treated rats with reserpine and other shorter acting drugs then looked at the hypothalamus to see if we could visualize the depletion of biogenic amines. We were measuring the level of biogenic amines and correlated the depletion of biogenic amines with the disappearance of dense core vesicles from hypothalamic tissue prepared for electron microscopy.

LH: So you did microscopic structural work, along with biogenic amine analyses.

AH: Exactly. I was doing that with Norbert, while trying to finish medical school, which I did, and everything went very well. Another major encounter occurred in 1970 when I met Daniel X. Freedman at a conference on drug abuse in Zurich, Switzerland. I had been following Danny's work and was fascinated by his theories about serotonin, psychotomimetic drugs and model psychosis.

LH: That's still one of the better explanations for experimentally-induced psychosis.

AH: There have been better ones since that time. Danny helped me get a research fellowship through the Foundations' Fund for Research in Psychiatry. So, I joined him in Chicago in 1971, after completing my military duty in the Greek Army.

LH: You had to do obligatory service in the Army?

AH: I had to as a Greek citizen. I exhausted all of my deferrals when they caught up with me and said, you're going to have to spend time with us before you can go anywhere else. Danny was patient enough to wait for me to get released from the Greek Army and, a month later, I was in Chicago to start my Research Fellowship. I don't know if you remember the Foundation's Fund for Research in Psychiatry. They were offering fellowships in the early seventies. After spending two years as research fellow I had a position waiting for me in the Department of Psychiatry at the University of Munich to work for Hans Hippus. Danny asked me to stay on and work in his department at the University of Chicago. "OK I said, I am honored by the invitation, but I want to do a residency in Psychiatry because I want to become a psychiatrist." Frankly, he wasn't too keen to see me become a psychiatrist stating "Anybody can be a psychiatrist; you can be a successful researcher."

LH: Up till then, you'd been doing laboratory but no clinical research?

- AH: I wasn't even licensed to do clinical work in the United States. So I struck a deal with Danny that I would continue to work in the lab and pursue a common interest he and I had in psychotomimetics, but I insisted I wanted to do a residency. He said, "Well, I'll arrange for that". And he did. So, for a while, I was in residency and working in the laboratory at the same time.
- LH: Jack Barchas and a number of other people combined lab work with their residency.
- AH: I think George Aghajanian did something like that.
- LH: Sol Snyder did it; the first I met him, he was in the lab, but nominally a resident at Hopkins.
- AH: It was a bit tough, especially during the time I had to do my inpatient rotation, which was demanding, but the lab was right next to the ward; I could go back and forth easily and I had technicians trained, so the lab kept running. We had already obtained sizeable grant support and so it all worked out. Looking back, I am very glad I didn't drop research to get specialty training and I didn't drop training to pursue research. I did both and that proved to be a wise decision. I also had to get a license to practice medicine in the United States. That was a tough time, having to study hard while working full time as a resident and researcher. As an international graduate I had to take the FLEX, a gruelling three day examination, covering the entire field of preclinical and clinical medicine.
- LH: And, you were already out of school for several years. That made it really tough.
- AH: Indeed, but it all worked out eventually. The first time I took the test I was totally unprepared and flunked it, but I wised up, studied and passed. Danny wanted me to stay in Chicago, which I did. He gave me a faculty appointment and I became an Associate Professor toward the end of the seventies. I began to pursue other research interests which I had started in Munich with Norbert Matussek; that was on the role of serotonin and norepinephrine in the action of antidepressants. By that time I had begun to suspect that dopamine might also play a role.
- LH: In depression?
- AH: In depression. As a matter of fact, Danny and I wrote a chapter in one of the books he edited.
- LH: That was before the days of bupropion.
- AH: When bupropion was ready for clinical trials I linked up with Burroughs Wellcome and Dr. Warren Stern, who was the organizer of the clinical trial program, to develop bupropion as an antidepressant. I jumped at the idea, because people thought bupropion acted through dopamine.
- LH: Did you join the company?

AH: No, I just did studies for them and I'm proud to say I did the first open label study of bupropion in depression. I was very impressed with the response I saw in the first six or eight patients I studied, so I called and said, "Warren, you've got a potential winner here". As you know the drug eventually came on the market.

LH: Is it proven how bupropion works via dopamine?

AH: I think it's a dual dopamine and norepinephrine uptake inhibitor. Its major metabolite, hydroxybupropion, inhibits norepinephrine reuptake whereas bupropion itself inhibits dopamine reuptake. I was excited because it confirmed my idea dopamine is involved in some aspects of depression, and drugs that enhance dopaminergic transmission can exert an antidepressant effect. That work started while I was still in Chicago. In 1980 I moved to UCLA and was given the opportunity to set up a laboratory at the Brentwood VA.

LH: At the VA Hospital affiliate?

AH: Right. I was given an inpatient ward to run and support to build a laboratory underneath the ward, so I was able to do much the same thing I had done during residency. The ward was upstairs where I was Ward Chief and the laboratory was in the basement where I was Lab Chief, so I could ride two horses at the same time.

LH: If you didn't mind running upstairs, it was ideal. There were a number of other labs at that hospital, weren't there?

AH: Ed Geller and Ted Van Putten. Phil May's laboratory was down the hall from my laboratory. Steve Marder is still there and Art Yuwiler is probably still there.

LH: I think they were there about the same time as Sam Eiduson was.

AH: I don't know if he's retired or not. Art was very active in research. I spent almost five years at UCLA and during that time I made a major change in my research approach. I began to look for a marker for depression and because of my interest in dopamine I wanted to develop a blood test and measure dopamine or HVA in blood as an index of central dopaminergic activity. However, everybody was looking at MHPG and measuring it in urine or CSF and CSF wasn't easy to obtain. We wanted to have something that anybody could do easily. So I thought, how about a blood assay for MHPG? I was fortunate to hook up with a young biochemist, Ed DeMet, who had come to work with me while I was in Chicago. We set out to develop a gas chromatographic technique for measuring plasma MHPG and we succeeded, although it took over a year until we had a method we could apply to studying depressed and manic patients.

LH: It's the one still in use, isn't it?

- AH: Actually we've replaced gas chromatography with HPLC. It's simpler, cheaper and faster, but we started out with a huge gas chromatograph, an old model but it worked. It was a cumbersome method but I'd draw samples from manic patients and, lo and behold, MHPG was very high and then got some depressives but that was variable, sometimes low and sometimes the same as in healthy subjects, much like everything else in depression.
- LH: I remember the MHPG era. Mostly, the determination of MHPG was done at twenty-four hour intervals and I was curious what the reliability was. I didn't think very much of it.
- AH: If you measure twenty-four hour output you can't assess what happens from hour to hour. We needed something that would allow us to do that.
- LH: To get it right.
- AH: If the amount of blood isn't large one can sample more than once a day and we were able to do that, especially after we switched to using HPLC. I was disappointed I couldn't get a clear picture about how high, low or normal MHPG was in depression. Then I thought maybe it's not a matter of too much or too little, maybe there is dysregulation in the output of norepinephrine by the nervous system. That was a theory Larry Siever and others had put forward. I modified that theory to start talking about desynchronization, got into biological rhythms and discovered a diurnal rhythm for plasma MHPG in normal volunteers by sampling six or eight times during a twenty-four period.
- LH: The endocrinologists pioneered techniques where you could do continuous sampling.
- AH: That's right. But we needed ten ml of blood per draw, so the most we could do was sixty to eighty ml in a day. That was the limit, but it allowed us to construct a diurnal curve, using sophisticated statistics called the cosinor model. We applied that to our measurements and came up with an impressive sinusoidal curve we described and published on a few times. Then I said, "Okay, now that we know there's a normal rhythm, if our desynchronization theory is correct and we applied the same methodology to depressed patients, we should not see that nice sinusoidal curve." And that was exactly what we got, nothing like the clean sinusoidal curve we had seen in healthy subjects. So we can say now that MHPG production is desynchronized in depression, but what that means I don't know.
- LH: Nobody knows what changed rhythms in depression mean; whether they're a secondary phenomenon or of primary importance. You stayed with the catecholamines for quite a long while. Did you go into the HVA?

AH: No. We tried to simulate our plasma MHPG method and develop a plasma HVA method. We had, for some reason, more trouble getting consistent results with HVA and there were serious questions about how much plasma HVA reflected brain dopamine activity. So we dropped that approach altogether, believing we had gone as far as we could. Then we got excited by the α_2 receptor theory and began to work with platelets. I started that in 1983-84, while I was still at UCLA. Then I moved again, at the end of 1984, to Case Western Reserve University in Cleveland, Ohio. I took a Medical Directorship and Vice Chairmanship with the stipulation I could have a laboratory. So I packed up the equipment I owned and moved the laboratory to Cleveland.

LH: People get hustled into administration too early.

AH: Probably a bit too early, but I was determined to pursue research at the same time. I was fortunate to find a young scientist, Dr. John Piletz, who I recruited at UCLA. He had just finished his fellowship in molecular biology, had expertise I lacked and wanted to do research in neuroscience. That was a good marriage and he's still with. So I made the transition from plasma MHPG to platelet α_2 receptors, hoping this might prove to be a reliable marker for depression. But when we reviewed the literature the findings were discrepant. There were studies that showed α_2 receptor up regulation in depression, studies that showed no difference, and studies that showed fewer α_2 receptors; so everything was possible. We couldn't sort this out until one day, by serendipity, one of our technicians made a mistake by mixing up the buffer for incubation of platelets that made a ten-fold difference in the magnesium concentration. That mistake resulted in resolving two binding sites on the platelet when we constructed the Scatchard plot, a very positive finding. After at least a year we figured out assays people had been using to measure α_2 adrenoceptor on the platelet were two binding sites lumped in one. If we changed the concentration of the buffer, we could separate these two sites. One was the α_2 adrenoceptor, but the other was something else. Eventually, we identified it as an imidazoline site that also binds clonidine and clonidine-like compounds, but it is not an α_2 receptor binding site. What struck us was that depressed patients showed very clear, consistent and statistically significant increases in this binding site.

LH: Which were not α_2 receptor binding sites.

AH: The α_2 continued to show increases of a minor degree, not always significant, but the imidazoline binding site, was always unmistakably elevated. Encouraged by this finding, we launched several studies of depression. We now have a total of five studies and more than one hundred patients, some of which were done in Cleveland, and some in Mississippi. And, we

have consistent results. So we now have an imidazoline receptor theory of depression.

LH: And you think it's a fairly reliable marker?

AH: It has been confirmed in five studies by us, by Garcia Sevilla in Spain, and probably others working on that story. It looks true and reliable.

LH: The trouble about depression these days is that it's not clearly defined what kind you talking about, psychotic, melancholic or whatever.

AH: We use DSM-III and DSM-IV diagnoses.

LH: So your findings are in major depression?

AH: Major depression, non-psychotic, unipolar, but even this group is a mixed bag. But we've consistent information from this patient population. We treated the patients for six to eight weeks, in the first study with desipramine, and at the end of treatment, we saw a normalization of the imidazoline binding site. Patients who respond to treatment show the normalization. Then, I thought, maybe a non-adrenergic antidepressant might not show us this effect, so we did another study using fluoxetine and got the same thing after eight weeks of treatment. Then I said, "How about doing a third study and use a different antidepressant drug". So, we picked bupropion. Of course, bupropion has mainly a dopaminergic effect, but it's a very different molecule.

LH: I think of it as a tamed down amphetamine.

AH: Absolutely. And, bupropion gave us the same result. So, that's been our focus for the past seven or eight years, now. I moved from UCLA in 1993 to become chairman of Psychiatry at the University of Mississippi, and moved my lab from LA with me. I feel like a turtle who takes his house and belongings with him.

LH: Your gypsy life began in Greece, went to Germany, Chicago, Los Angeles, Cleveland and, then Jackson.

AH: That's probably the last stop. In Jackson I was given lots of resources by the medical school and set up ten laboratories where there was nothing before. I was given, very generously, an entire floor in the brand new Research Building the University built in 1993; it was opened as I was arriving. Psychiatry has a sizeable basic science operation at the University of Mississippi and I'm very proud of our accomplishment.

LH: And, your clinical facilities are in the University Hospital?

AH: The laboratories in the new Research Building adjoin the Hospital and the medical school, it's clustered together nicely so I can walk back and forth easily.

LH: In recruiting faculty you are research minded?

AH: Yes. We have ten PhD basic scientists in the department.

LH: That's pretty good.

AH: They each direct their own laboratory. A lot of them choose to work on different aspects of depression, but I leave them alone. They can do as they wish.

LH: That's the way to do it.

AH: They've been very successful, all but one has independent funding from NIMH and NIDA.

LH: That's tough to get these days.

AH: Yes and I'm pleased I continue to have an RO1 myself; I got my renewal grant application funded two weeks ago.

LH: You recruited one of the residents from Houston, Peggy Pazzaglia, who spent time with Bob Post and then came to your place.

AH: Yes, she came to Jackson.

LH: Then you got a fellow a travel recipient award.

AH: For Craig Rush, he came from Hopkins and had done a fellowship with Higgins. He is a behavioural pharmacologist. One of the things I wanted to set up was drug abuse research so I recruited Bill Woolverton from Chicago. He trained with Bob Schuster, was an Associate Professor and very successful. He's from Alabama and wanted to come back to the South.

LH: There's something about the South that's attractive, especially when you've lived in Chicago for a while.

AH: Bill brought fifty monkeys with him so we set up a drug abuse laboratory and I said, "This is fine for basic animal research but we need to add two more components to complete the picture". We needed to have Human Behavioural Pharmacology of the kind Bob Schuster and Uhlenhuth set up in Chicago. I learned a lot in Chicago and a lot of my models go back to the Danny Freedman era. We recruited Craig Rush from Hopkins and he set up a wonderful, very successful laboratory. Now we're looking for someone to do the third component, which is a patient based program.

LH: Sounds like you've got a good blueprint.

AH: It's been a good twenty-five or so years starting in Chicago and, before that, in Germany.

LH: It's nice to hear Danny Freedman played a pivotal role in your career. He was such a remarkable person.

AH: He taught me an awful lot and, not just in psychopharmacology and "aminology."

LH: He was always fun to be around, too. After he became editor of the Archives, I said, "Danny, just because we've been friends, I want you to treat every manuscript I ever send in as objectively as if you didn't know me at all. Otherwise, my Presbyterian conscience would bother me". He

- turned to me and said, "So would my Jewish conscience." I understand his wife died very soon after him.
- AH: Yes, a few months later.
- LH: You were probably at that seventieth birthday party for him that was in Washington?
- AH: Yes, that was in Washington, and you know he moved to UCLA. I preceded him by about a year. We overlapped for a year and a half and then I moved to Cleveland. He did quite well at UCLA, then one morning, shortly after I moved to Jackson in 1993, I got a call from Steve Pacht, Danny's right hand since the Yale years. Steve was a lab technician, who had administrative skills that Danny appreciated tremendously. He said, "Danny just died last night in his sleep".
- LH: Did he have a cerebral hemorrhage?
- AH: It looks like it.
- LH: I remember, after Danny died, writing to Mary and saying how great a time that seventieth anniversary party was. But within a year he died. Well, you've got a lot of future ahead; you shouldn't be part of a history project yet. We ought to interview you again twenty years from now!
- AH: I hope so. I don't feel I'm anywhere near, even pre-retirement. I hope I can be active for, at least, another fifteen years.
- LH: How old are you now?
- AH: I turned fifty-five last month.
- LH: Another twenty wouldn't be bad; although we do die. No question about it.
- AH: We become wiser with age. We don't jump as quickly at what appears to be a hot idea as we used to in our youth.
- LH: Was it Oscar Wilde, who said, "Experience is the name we give to our mistakes"? So, I think most of us develop a lot of experience over the years!
- AH: I don't know much about this History project.
- LH: The project was Oakley Ray's idea. He thought that before it becomes lost we ought to recover the history of this organization, because after thirty-five or thirty-six years it's getting a little old to remember. This is one facet of the bigger project, but the idea of doing video tapes is attractive, because it's easy and it gives any future historian a source of direct quotes. I try, in our interviews, to elicit information about people as well, who the interviewee knew, but who are now dead and try to let the dead speak through them.
- AH: Right.
- LH: So, the idea is to get older people. That's why I said you're almost too young for the project, because the idea was to get people before we lose

them; you have to be realistic, nobody's going to last forever and you want to get things on record before it's lost. Already, we've missed a few chances, but you're much too young to be part of history.

AH: I hope I've offered insight into Danny's mentorship. I see myself as being his brainchild, he raised me. What I learned from Norbert Matussek in Germany was useful and very good, but Danny really shaped me so I have a lot to thank him for. And, he was patient with me.

LH: We're blessed to be in a field where you get so much intellectual satisfaction and are paid for it. That's hard to beat! It's been very nice talking with you.

AH: I enjoyed our conversation, too.

LH: Yours is the classical success story in every respect, and I hope it will continue that way.

AH: I hope so, too.

DAVID S. JANOWSKY*

Interviewed by Leo E. Hollister
Nashville, Tennessee, May 9, 1997

LH: Today is Friday, May 9, 1997. I'm Leo Hollister and we are videotaping one of the interviews of people involved in the early development of Psychopharmacology, a series sponsored by the American College of Neuropsychopharmacology. We are in Nashville and talking to a wonderful person. Welcome, David.

DJ: Thank you Leo. I'm very happy to be here.

LH: I'm always interested in why people decided to go into medicine and, particularly, psychiatry. Can you tell us how that happened?

DJ: I came from a background that had nothing to do with medicine. My father was a symphony violinist and a music teacher in the public schools, and my mother was an artist. I didn't know what I was going to be when I grew up. However, in the 9th grade I took the Kuder Interest Inventory and it showed I was a social do-gooder and liked science. One of the options was to become a physician, so that is how I decided. My grades had been adequate, not great, and in 7th grade my dad had to pull strings to keep me from being put in a vocational track, after scoring poorly on some selection test. I mostly got straight A's after that in high school. No one in my family had been a physician and my parents were not encouraging that, at least to my face. I went to San Diego State College. It wasn't a university then, and ultimately I went on to UCLA, and then to medical school at UC San Francisco.

LH: Good school.

DJ: Right. I did that after 3 years of college and enjoyed it relatively well, although I didn't really love it, especially the preclinical years. I enjoyed the clinical years a lot better and always liked psychiatry. However, it was not particularly "in" to become a psychiatrist at that time. There were social pressures against being one from my classmates, such as the idea all psychiatrists are "crazy and weird," and not "real doctors."

LH: Anyway, you got exposed to psychiatry?

DJ: In bits and pieces. Two things got me into psychiatry. Until my third year, I had no particular interest in psychiatry, but on our clinical psychiatry rotation, they sent us to the San Francisco General Hospital and threw us onto the admitting wards, which were quite wild.

LH: Front line battle.

* David S. Janowsky was born in San Diego, California in 1939.

DJ: Front line battle and you were supposed to see a patient each day, talk to them, get to know them, write them up and then talk to the attending psychiatrist and course director, Dr. Jerome Motto, who ran the service. I loved it and thought, “This is great.” It was so interesting to learn about these strange peoples’ lives, especially, amphetamine addicts, schizophrenics and suicidal people. It was raw and very exciting.

DJ: It was the county hospital?

LH: San Francisco General Hospital was the county hospital. But, I was also good in pediatrics and while on that clerkship at San Francisco General Hospital, I had written a conceptual research paper for Moses Grossman, head of the Pediatric Department. I got an A on my research paper in which I created a novel way to treat neonatal jaundice, which I later learned had been published by someone else and ultimately applied to patients. Of course, it wasn’t my technique, but by logic, I had figured out how to do it. It consisted of giving albumin to babies to bind the bilirubin. Dr. Grossman was impressed, encouraging, and treated me very well. So I decided to become a pediatrician, and ultimately an intern. But in our 4th year, as our psychiatry experience, we were assigned to one or two cases and told to follow them as outpatients for six or eight weeks. We’d see them once a week and my supervisor was Marty Horowitz, who later went on to great fame as a psychotherapy researcher. One of the cases was a gay person, who was having tremendous conflicts in terms of sexuality. I was working with him and felt I did a good job; people’s stories just interested me. Another experience in my senior year, other than seeing outpatients, was an elective on one of the wards. The unit was a milieu therapy ward, a creative situation. My job was to hang out there, participate in patient activities and interview them. I was there for 4 weeks and really enjoyed the experience. But it was very unacceptable in our class to want to be a psychiatrist. Those who liked psychiatry and planned it as a career were thought of as not medically oriented, not practical and not “with it”. This was at least the image. So I went on with what was “in,” and I took a pediatric internship at UC San Francisco’s Moffitt Hospital in San Francisco. I liked it, but after a while found it routine and/or sad when someone died. I kept thinking that I really did love psychiatry; I felt it was a forefront area. The whole dynamic direction was very strong and intellectually stimulating, and drugs were just getting to be popular.

LH: This was what year?

DJ: I graduated medical school in 1964, so I was a student from 1960 to 1964.

LH: That was the time when psychiatry was swinging from the dynamic to the pharmacologic?

DJ: It hadn't yet swung, at least in most programs. It was still very dynamically oriented, but with medications. People would give them apologetically and as an afterthought. I thought these people's stories are interesting, you have a whole world of dreams and dynamic psychiatry, and also this biologic approach and especially drugs. I was very practically oriented and believed maybe we could combine all this. I felt the field of psychiatry would move in the biologic direction and it was wide open. Internal medicine or Pediatrics were more closed. And so, at some time in my internship, I said, "I'm going to take a psych residency." I finished my Pediatric internship and went to UCLA to begin psychiatry residency. They started us off in the inpatient rotation and assigned me to a fellow named Rod Gorney, who was a very interesting guy. He was interested in philosophy and a very good psychiatrist. He still is. He set up a ward as a therapeutic community, similar to the one I rotated on in San Francisco but called it a milieu therapy community. Residents could treat patients who might be on that ward for a year. This was at the UCLA Neuropsychiatric Institute; the program was extremely psychodynamically oriented and I found it very interesting. There were also a few biologic psychiatrists, like Arnold Mandell and Bob Rubin.

LH: That was when Norm Brill was the Chairman.

DJ: At UCLA the dynamically oriented types were the heroes. But, Bob Rubin was a young assistant professor and Arnold Mandell was there; they were very biologically oriented and I hooked up with both to some extent. Rod Gorney and I began to talk about doing some work in the area of premenstrual tension, because some patients would come in very psychotic, then they would have their menstrual period and get better. So I did some work looking at mineralocorticoids and menstrual cycles and published in Archives. Dr. Gorney, being a big picture guy, had us do some work looking at premenstrual tension from an anthropologic point of view, across species. But I should go back a step. My interest in research came out of the experience in paediatrics, thinking about albumen and neonatal jaundice. It also came out of the fact that in my third year of medical school, I had a summer clerkship with Werner Rosenau, a pathologist. It was a way to make money to start with. He asked me to try to isolate white cells from blood using different sugar solutions and trying different techniques. By accident, one night, I put my test tubes in water to let them soak and went home. When I came back there were only white cells in the bottom of the test tubes. We discovered that we had developed a technique for isolating living white cells. It was serendipity, but they were alive. The red cells had been lysed but the white cells were there. We perfected that technique over the summer and published it in JPET. Werner Rosenau put

me as first author on the paper and it received more reprint requests than I've ever had since.

LH: Was this Edward Rosenau?

DJ: No, his name was Werner Rosenau; he was German and probably an associate professor of pathology at UCSF at the time. So that whetted my taste for the glory of research. But, I didn't think I was going to be a researcher, I thought I'd be a clinician. Anyway, when I got to UCLA, Rod Gorney and I did some research on premenstrual tension. I also was very interested in psychotherapy, which I did a lot of with patients, the sicker the better. I didn't want to treat healthy people.

For the second year of psychiatric residency, some of us went to Harbor General Hospital, a big county hospital in LA. This was a slam bam kind of place led by a famous psychiatrist, Pietro Castelnuovo-Tedesco, a brilliant dynamic psychoanalyst. That year I had to make a choice about what to do next. One choice was to finish my residency, do a child fellowship, go on to the Berry plan, be deferred and then spend 3 years in the Air Force. I thought I was going to be in the Air Force as a military child psychiatrist and I figured it would take a few years. The other choice was to apply to NIMH to be a clinical associate at the Clinical Research Center in Bethesda. I had a very strong interest in milieu therapeutic communities, as opposed to pyramidally structured medical model wards. At NIMH Jack Durell wanted to compare a therapeutic community oriented system with a regular system to see which worked better. I interviewed to run the therapeutic community ward and was accepted. At that time, if you joined NIMH, you went after two years of residency. After two years you got credit for a third year residency. You also had your military obligation out of the way all at once. Basically, for putting in one extra year of my time, I would become a psychiatrist, be in the Public Health Service, avoid the draft, and not have to go to Vietnam. So I decided to go to NIMH.

LH: A good deal.

DJ: It was a wonderful deal. I was going to be with this therapeutic community but when I got there Jack Durell must have had a political fight with somebody; they'd stripped him of his unit, so they assigned me to Biff Bunney. I literally walked in the door thinking I was going to be with Durell, but they said, go see Dr. Bunney. So I ended up on Bunney's unit. Everyone knew he was a famous and a very distinguished psychobiologist/psychopharmacologist and I was supposed to run his ward. There were a number of now very notable people in his group, in the group next door, and on the floor above us. These included Herb Meltzer, John Davis, Will Carpenter, David Kupfer, Richard Wyatt, Fred Goodwin, Dennis Murphy

and Keith Brody. I'm sure there were others. It was a very high powered clinical research group, but all of us were just getting started. We were either clinical associates, like I was, which essentially was a Fellowship, or a little above that. And we were all crammed into a very small amount of space. My job was to run a bipolar ward and I did that for about a year. I wanted to convert it into an egalitarian therapeutic community, but Bunney didn't like that because it would leave things too loose and not controlled enough. Basically, I did as best I could setting up the ward the way I wanted. I wrote a paper with Richard Epstein, called "Playing the Manic Game." It ended up being a very popular paper that people have quoted ever since and used to train residents. It has to do with how manics interact with others. We had many manic depressives on this ward, three or four at a time, and they would drive everybody up the wall. So we wrote a paper about that and it is now a classic.

LH: So far you've been talking more about clinical activities. How did you get into biologic research?

DJ: John Davis was at NIMH and I think we both felt alienated from the power structure. He was working with Bob Colburn, who was a pre-clinical person involved with the actions of drugs. John inspired me and invited me to work with them. I was very interested in premenstrual tension, which I mentioned, so we did some work in rats looking at monoamines, their release and uptake as affected by progesterone and estrogen. I was also involved at NIMH under Dr. Bunney's supervision giving L-DOPA to depressives to see if we could turn off the depression. This was following the Bunney-Davis and Schildkraut catecholamine hypothesis. In the cases we studied, L-DOPA seemed to convert patients either into hypomania or help their depression. But overall it didn't work over time, although we did have one of the first papers on that subject. In another paper Mike Paul and I were the first to show increased urine cyclic AMP in manics. I wrote another paper looking at the dynamics of how people in research think they are helping the patient, but actually are doing it for research glory, and maybe to the patient's detriment. This was a paper about rationalization and self-deception so you can imagine how popular that was! At the end of the second year at NIMH, in 1969, I had finished my military obligation, and I wasn't sure what to do next. Nobody was begging me to stay at NIMH, or even asking me to. I had been rejected by Stanford, so I found myself looking for another job. I went to California and took a job at UCLA, again at Harbor General Hospital, setting up a crisis emergency service. I did no research for a year. This was 1969. At the end of that year, John Davis called and said he had been asked to take over the clinical part of the Tennessee Neuropsychiatric Institute in Nashville.

A preclinical unit had been there, but the whole clinical research unit, maybe 10 beds, was to be developed at Central State Hospital. He asked if I would come and run the ward. John and I had been good friends, my wife didn't like LA and Nashville sounded exotic, so we thought, why not give it a shot? I went out to Nashville, interviewed and became a member of the Psychiatry and Pharmacology Departments. I was paid by a Center grant run by John Oates, an internist and a clinical pharmacologist.

LH: So you came to the Tennessee Neuropsychiatric Institute.

DJ: In 1970, and we set up a research ward very quickly. I came in September and by January we had the research ward up and running and had hired people. We set it up to be extremely therapeutic as well as research oriented, with many of the principles of a therapeutic community. This was quite unusual in that day and age. So we tried to help patients clinically, but at the same time to do research. It did work. We set up a system that was designed to interact with the preclinical people in terms of ideas, if not studies. A lot of the preclinical studies that were going on were involved with monoamines. For example, Fridolin Sulser and his group were looking at chlomipramine and its effect on serotonin. There were people working on drug interactions and others on marijuana and how it affected cell biology. All that inspired us. So our unit looked at a lot of things and I was clinically running it. But I was also one of the main investigators and contributors to the research directions it took. Several major findings came out of that unit. We were one of the first to show, in controlled studies, that methylphenidate activated pre-existing psychotic symptoms. Thus, we supported the dopamine hypothesis of schizophrenia. In addition, via a combination of luck and serendipity, we were giving physostigmine, a cholinesterase inhibitor which causes central acetylcholine to increase. We were using it to see if we could turn off antidepressant-induced confusional states, thinking these could be an anticholinergic syndrome. I also had the idea maybe physostigmine could turn off mania. The concept was that, like the heart, there could be a balance between adrenergic and cholinergic factors in mania and depression, with mania being too little acetylcholine and too much norepinephrine or other monoamines and depression being the converse. Indeed, we found that mania in several patients was turned off rapidly and dramatically by physostigmine. Over a period of minutes depression was induced. From that I proposed the adrenergic-cholinergic hypothesis of mania and depression, published first as a letter to the editor in *Lancet* and later as a hypothesis paper. It was probably the first, or at least one of the first, multi-neurotransmitter hypotheses, and it set the tone for future ones.

- LH: That was a very novel hypothesis at the time. What ever happened to that?
- DJ: That's an interesting question I pursued after I left the Tennessee Neuropsychiatric Institute. In 1973, I went to the University of California San Diego where I also pursued our Ritalin schizophrenia work. We looked at Ritalin's effects on projective tests in schizophrenics and found it increased the pathology as it increased growth hormone. We kept plugging away at that until I left San Diego in 1986. Craig Risch, Leighton Huey, Louis Judd, Chris Gillin and I did a number of neuroendocrine studies looking at hypersensitivity to acetylcholine. Reactivity to physostigmine appeared to be more intense with respect to behaviour in people with a history of depression. We then tried to look at mechanisms, such as what happens to neuroendocrines when all this is happening. We looked at cortisol, ACTH, prolactin, and epinephrine which all increased dramatically with physostigmine, and abstracted the neurochemistry from the neuroendocrinology. That also led us to propose an acetylcholine hypothesis of stress regulation. Acetylcholine was proposed to be a master neurochemical that turned on many others such as CRH, β Endorphin, cortisol, prolactin, epinephrine, etc. What has happened to the hypothesis and the work over time is interesting. It is still there but you don't hear as much about it. It is in most of the psychiatric textbooks, but the serotonergic hypothesis has become the theory of the day.
- LH: We always have to be suspicious of a fad.
- DJ: I don't know if it's a fad. I've been studying and thinking about how the cholinergic system might interact with the serotonergic system. In 1986 I left San Diego and became Chairman of the Department of Psychiatry at the University of North Carolina in Chapel Hill and my life stopped as a scientist for the next 8 years.
- LH: Do you have any regrets about taking on a chairmanship too early in your career?
- DJ: I was 46 at the time. I don't regret I took it on too early, I just regret I took it on at all. I did an okay job as a chairman, maybe even a fine job, but it was at a price of being focused so very much on the job and not doing much research. It also took an emotional toll. I think my style was not to be a dictator. I did great in small groups but it was very hard for me to deal with large groups of people, as a boss. So I regret I ever bothered to do it, because, while I went into something which had positives, for the most part it was negative.
- LH: When you become a chairman you have to look after your people and forego your own ambition.

DJ: That was part of it, but what was worse was that there are so many agendas you can't make everybody happy all the time. There's always somebody who isn't happy and it's a very adversarial relationship at times, at least that was what I felt. When I came to UNC, even though this wasn't an area I specialized in, I was assigned to be head of a center for alcohol studies. It was a package deal. So I was going to be Chairman of Psychiatry and head of the Center for Alcohol Studies. Alcoholism wasn't my field of research even though I had done some work in the area. I figured if they wanted to give me this as a way to keep my research going, why should I say no. So I took over the UNC Center for Alcohol Studies while trying to be effective as a Chairman. In that format I tried to do some research. Actually, it worked out fairly well. I was able to do research indirectly through people such as David Overstreet and Amir Rezvani. Do you know David?

LH: I've heard of him. I don't think I've met him.

DJ: He came to San Diego for several months in the mid 1980s. This was a few years before I left for Chapel Hill. He developed a strain of hypercholinergic rats and I said, David if these animals are hypercholinergic maybe they're also depressed. From that we spent the next 12 or 15 years working on an animal depression model, using Flinders sensitive hypercholinergic rats. So he came to Chapel Hill in 1990 and I put him in the Alcohol Center. We did some work with the rats with respect to alcohol, but kept pursuing a pre-clinical mood/depression direction. Around this work and that of several others, we set up a fairly strong pre-clinical behavioural pharmacology section. Dr. Amir Rezvani was studying the ability of the calcium channel inhibitor, verapamil, to block alcohol induced hypothermia, a physical effect. This was going on before I arrived so I said why don't we see if verapamil also blocks alcohol consumption? This was a very simple minded thing to do, but it changed Dr. Rezvani's research from a physiologic to a more clinically relevant behavioural direction. So I had a preclinical operation going in the alcohol center, done somewhat by remote control.

LH: But you lost track of the cholinergic hypothesis of depression.

DJ: Mostly, except for the Dr. Overstreet connection.

LH: Has anybody tried to use the cholinesterase inhibitors to actually treat mania or depression. Has anybody tried Aricept in depression or mania?

DJ: People haven't tried it for mania that I know of. But you asked whatever happened to the hypothesis, and what's happened is interesting. Over the years people have given choline as a precursor to treat mania.

LH: We did that.

DJ: Did you do it for mania? I thought you did it for schizophrenia.

- LH: No, we were interested in Huntington's and tardive dyskinesia.
- DJ: I remember now. Very recently, a pretty convincing paper came out of the McLean group, by Bruce Cohen and his collaborators. They gave choline to rapidly cycling bipolar patients on lithium and it seemed to help. Their paper came out in the last few months and it quotes our cholinergic hypothesis. Then, there has been some work using pupillometry to reflect cholinergic tone; when you give a muscarinic agonist like pilocarpine you get greater constriction of the pupils of patients who have affective disorder. There's been other work recently with brain choline uptake, using NMR Spec, showing that depressives pick up more than non-depressives. This phenomenon goes away when you treat the patient with Prozac (fluoxetine). There's also been work like we did by Bob Rubin, showing hyper-reactivity of ACTH and cortisol when a low dose of physostigmine is given. Bob Rubin gave such a low dose it didn't cause behavioural effects or nausea, which is theoretically very important. If you look at the data as it comes out, there is almost nothing that doesn't fit the cholinergic hypothesis. The only piece that doesn't, and this is very important, is a lack of an antidepressant effect of anticholinergic agents such as scopolamine. It doesn't help depression but it should, yet, on the other side, centrally active cholinesterase inhibitors increase depression, especially in depression prone people. So the hypothesis still is there, but it doesn't get much play at meetings and very few people are doing research other than I just described. It is gratifying to know that this cholinergic direction might have a clinical application, such as using cholinesterase inhibitors to turn off mania. Indeed, there has been talk you could give physostigmine in the Emergency Room to turn off mania, but that would be difficult in terms of side effects.
- LH: It's tricky because it has a biphasic action.
- DJ: It also has a very steep dose response curve. By the way, over the years I have kept up a general interest in the area of ovarian hormone linked psychiatric disorders. I think some of the work I did, where we were looking at serotonin and norepinephrine release with ovarian hormones was groundbreaking. In 1972, we proposed monoamine changes might be the cause of premenstrual syndrome and predicted how drugs such as SSRIs, which at that point had not been used clinically, might be good treatments for premenstrual tension. People don't quote that paper but it was in the Archives of Sexual Behaviour. With our pre-clinical work and hypothesizing, we predicted what has turned out to be the recent treatment for premenstrual tension and what the main direction of premenstrual tension research is now. We also put together an aldosterone-angiotension hypothesis of premenstrual tension, the concept being

that angiotension and aldosterone, stimulated by monoamines, caused the dysphoria. When I stopped being Chair in 1994, I decided to stay in Chapel Hill and not become a Chair or faculty member somewhere else. Mostly this was due to family considerations. Since 1994, what I have done, aside from seeing a lot of patients clinically, is I have developed an interest in the relationship of one's core personality to psychopathology. Around 1992, I took an American Association of Medical Colleges course on how to be a university medical school administrator. Part of it was to take a test called the Myers-Briggs Type Indicator. You may know that test. It is used a lot in the "real world." It divides people into extroverts or introverts, sensing or intuitive types, thinking or feeling types, and judging or perceiving types. This test is widely used in management circles and very little studied in formal psychiatry and psychology. Anyway, I took this test as part of a management course. It said that I was not a "natural manager," which by then I had already figured out. Managers have profiles, for example that are either extroverted or introverted, sensing, thinking or judging. Mine was extroverted, intuitive, feeling and perceiving. I got very interested in the test because it is uncanny in describing one's personality. It struck me as amazing you could take this test and it could tell what you are like. During the course they had us play games in which we would, for example, take the three highest feeling people in the room and the three highest thinking people and the goal was to have them decide what to do if one has a Little League team and needs to send it to the finals, and there is only enough money for 15 of the 17 kids. The thinkers quickly said, "Let's get the best players", and the feelers said "Everyone has to go, let's figure out a way to do it." I even said I would write a check. The thinkers were quite judgmental, and said we would never succeed in getting any money. Anyway, I thought this was an amazing psychologic tool, because it is talking about people's basic personalities and what they are like. So, I began to study the Myers Briggs Type Indicator. I've been giving the Myers Briggs Type Inventory and Cloninger's Tridimensional Personality Questionnaire, which measures harm avoidance, novelty seeking, reward dependence and persistence. I gave both to anybody I could find on the inpatient units as a starting point. I've discovered the patients who have unipolar depression have profiles that are very distinctive. For example, one that shows up often in depressives is being introverted rather than extroverted, sensing rather than intuitive, feeling rather than thinking and perceiving rather than judging. Social phobia patients are extremely introverted, more so than the depressives. They are also highly judgmental. People who try to commit suicide are usually highly introverted, but I found they are also highly feeling oriented, which

means they care very much what people think of them, and are subject to being crushed if people are down on them. They are also very judgmental, meaning they are likely to be hard on themselves and others. So, I've been pursuing this direction in some depth. I've given the tests to a number of alcoholic and other substance abusers in a community detoxification center, and followed them to see who relapsed who didn't, and who went to AA meetings, who didn't and so on. I found some results that have been very interesting. People with low persistence on the Cloninger TPQ scale relapsed much earlier than those who have high persistence. Introverts tended not to go to AA meetings. There is a study by Fritzi in Germany who gave 10 normal doctors physostigmine and looked at their neuroendocrines and their personalities and coping mechanisms. He showed that the ones who became withdrawn, give up, or use denial under stress were the ones who had the most physostigmine reactivity, both behaviourally and in terms of neuroendocrines. I've been thinking I might want to get people who are not clinically ill and categorize them by personality profiles. For example, a combination of introverted, sensing, feeling, judging, qualities could be those prone to depression if you give them physostigmine. So I want to begin to define the biology of personality as it underlies psychopathology.

LH: The Millon test is geared to pick up personality disorders, isn't it?

DJ: I'm not sure I know that test.

LH: He's a psychologist who developed a widely used test, primarily for diagnosing personality disorders. But, what you're talking about is normal personality, what is also called temperament, which we never hear much about.

DJ: Right. I've never figured out how to tell the difference, but I'm making the assumption or hypothesis that these temperaments, under certain environmental or stress conditions, are predisposing to depression and related symptoms or illnesses. For example, who is to say a gene for depression isn't some combination of introversion and basic temperament types. If you take bipolars and unipolars and give them the Myers-Briggs Test bipolars are over-represented as being intuitive, which correlates with being creative, as in a dramatist or artist. Unipolar depressives tend to be sensing rather than intuitive. They deal with the here and now and what is in front of them. They're not particularly open to new experiences and are not overly creative. This test might be particularly good in differentiating pre-bipolars from pre-unipolars. One of the most genetically determined Myers Briggs scales is the intuitive-sensing scale. It correlates very highly with the Neo-PI openness to experience scale which has been shown to be highly heritable in twin studies. Some day we may find an intuitive gene

or genes which are highly prevalent in bipolar disorder patients. Similarly, depressed bipolars are more extroverted than equally depressed unipolars and, conversely, unipolars are more introverted. Extroversion is also a highly genetically determined personality characteristic. My hypothesis would be that a lot of things we are calling a disease, such as alcoholism or bipolar disorder, are actually a cluster of genes regulating temperament or personality. These, under the wrong conditions like stress or too much alcohol, could lead to a given pathologic outcome.

LH: How stable are these profiles? If you do the test today and two years from now, are they stable?

DJ: They're pretty stable. I'm doing a study now trying to follow up after patients leave hospital. I was wondering if their profile changes when they get out of the hospital. At least for normal people, they're pretty stable, maybe a correlation of $r=0.7$, after six months on the Myers-Briggs test for a given dichotomy like extroversion and introversion. My preliminary results suggest there is quite a bit of stability in the personality profiles of psychiatric patients, even if their depression alleviates. There is also some evidence that temperament changes over the years. Older people, for example, become less extroverted and more introverted. There's undoubtedly an environmental part to this. So that's the study I'm doing now. I'm following people in the hospital and at one month, three months, six months and a year afterwards to see what happens to these personality variables and if they predict outcome.

LH: It's an interesting approach to research. As you say, there are not very many people into the personality area with respect to diagnostic nosology. Larry Seiber has made a career out of it. I have the greatest trouble deciding which of the personality disorders to call somebody, because there's such a tremendous overlap.

DJ: That's something I've been thinking about. I believe there is also a tremendous overlap between personality disorders and Axis I disorders, and what we are seeing is clusters of temperament. One of the interesting thing, relevant to the cholinergic hypothesis, is that Larry Seiber and his group have given physostigmine to borderline patients vs. other kinds of personality disorder patients. The borderline patients show behavioural hyper-reactivity of the cholinergic system and get more depressed than other people when receiving physostigmine, just like the depressives do.

LH: The emphasis on diagnoses came from the St. Louis group, the whole idea of DSM from I to IV has been a medicalization of psychiatric disorders. It is nice in defining what we're talking about, but it doesn't help to understand it.

- DJ: Not only does it not help to understand disorders, but when you get right down to it, the question is why is it that Prozac works for obsessive-compulsive disorder, minor depression, anxiety, major depression, premenstrual tension and who knows what else. You have to ask, isn't that interesting, are we missing something by splitting instead of lumping?
- LH: To deduce what relationships are between psychiatric disorders, based on a specific drug, gets difficult with the DSM-III or IV model, but, if you could identify the personality characteristics common to all of these, that would be a drastic change in our whole nosological approach.
- DJ: In one study Robert Cloninger and his group gave people chlorimipramine vs. desipramine, and also the Tridimensional Personality Questionnaire. From the results of the Tridimensional Personality Questionnaire, one could determine who was going to be a chlorimipramine responder vs. a desipramine responder. In a related set of studies in the 1980s we gave a variety of inpatients methylphenidate on one occasion and placebo on the other. We then administered the Barrett Leonard Relationship Inventory. This test shows how you perceive a significant other, i.e. are they empathetic, accepting, unconditional, genuine, etc. We found if you are depressed you tend to perceive an interviewer as low in all of those therapeutic qualities. After a rapid infusion of methylphenidate, the individuals who were depressed then perceived their therapist as wonderful, warm, accepting, giving and so on. Here you are turning on dopamine or some system in the brain and in minutes changing the perception of a significant other. To me, that has to be important. So, I've had this ongoing interest in the interaction of biology and personality.
- LH: It sounds like it will keep you rolling till retirement.
- DJ: It could.
- LH: But, it is, as you say, a frontier. The book, *Listening to Prozac*, has been the biggest hype for that drug you could imagine, but the assertion about how it makes you a new person, in terms of your personality, would be something to look at.
- DJ: It would be. The question is whether or not you can change things that used to be thought of as fixed in stone. They probably aren't.
- LH: If you thought it was fixed in stone psychotherapy would be totally useless, because most psychotherapy is for personality change. That's an interesting career you've had and I want to thank you for coming and sharing it with us. It will be interesting to see what you come up with in another 10 years from now.
- DJ: Thank you so much.

SHITIJ KAPUR

Interviewed by Elizabeth Bromley
San Juan, Puerto Rico, December 13, 2005

EB: This is an interview with Dr. Shitij Kapur* for the archives of the American College of Neuropsychopharmacology. It is December 13, 2005. We are at the annual meeting of the College. I am Elizabeth Bromley. Please tell us where you were born and about your upbringing.

SK: I was born in Montreal, Canada where my father was doing his graduate work but while I was very young we returned to India and grew up in there. When I finished medical training I was trying to figure out a way to obtain further training and turned to the States. And, as for my family, my father is a professor of engineering, my mother teaches and I have a brother.

EB: Where in India did you grow up?

SK: I grew in Chandigarh, which is the capital of the state of Punjab and went to medical school in Delhi, which is the capital of India.

EB: Is your brother younger or older?

SK: He is the younger brother.

EB: What did your mother teach?

SK: She started off teaching kindergarten and got a diploma in Fine Arts. She already had a degree in Fine Arts, so she started teaching Fine Arts and décor from our home but, when we came back to North America, none of her qualifications were transferable. So, she now teaches kindergarten, after some early child care retraining. My brother was an engineer, who also trained as an economist, and now works for a bank.

EB: Tell me about your schooling.

SK: In India you go to a ten year school system, and then you can enroll in a two year pre-medical course before going to medical school. You don't attend college and, in grade 13, you're in medical school. My school was run by Irish Catholic brothers; it was a fairly western education tailored after the British system. At the time I grew up careers weren't individual choices, they were more cultural stereotypes. If you were a member of the upper middle educated class, you tried to become an engineer or a doctor. It's very different from the way things are in America, and even the way things are now in India. But, in the 1970s, you didn't give much thought to it. It was a given you would go to college; otherwise you didn't have a future unless your parents were independently rich. Almost everyone was striving to do exactly the same thing and the only real choice

* Shitij Kapur was born in Montreal, Quebec, Canada in 1964.

was, did you want to be an engineer or a doctor? Being a lawyer was not an option so those who couldn't get into engineering or medical school did a degree in commerce. So, the real choice was engineer or doctor.

EB: Did your parents have expectations about that?

SK: They would have been OK with either. I grew up in a part of the city where there's a big engineering college and a very big medical institute. Almost everyone living around us were either faculty of engineering or the medical school. That was the world I knew and I started off, after high school, going into pre-engineering, but I realized that's too close to what my dad does, so I switched to pre-medical.

EB: Did you have any mentors or teachers that were particularly important?

SK: I was particularly influenced by Dr. Wahi, a leading cardiologist, who was a family friend. He was a man of great personal presence and social prestige and I was probably influenced by his confidence, success and position; I wanted to be like him. The other important medical person was Dr. Wig, Chairman of the Department of Psychiatry in the Medical Institute. At the time I grew up people didn't talk about psychiatry, it was a highly stigmatized profession. People viewed Dr. Wig as an interesting oddity. Psychiatry was associated with asylums which was called "pagal khana" which literally translated meant "mad house." But Dr. Wig was also a charismatic person who served on WHO panels and was involved in an international study comparing the incidence of mental illnesses around the world. These early influences formed my reasons for going into medicine and affection for psychiatry.

EB: You went to medical school and in the third or fourth year decided about the specialty?

SK: Everything was determined by written exams in India. Psychiatry used to rank just above forensic medicine. Medicine and Surgery were at the top, followed by pediatrics, followed by psychiatry in the pecking order. But, I didn't do psychiatry in India; instead I applied, blindly, for a residency in the US after doing the ECFMG. The Indian government would not allow me to take the exam in India because a lot of the young doctors were leaving for the United States and they saw that as a brain drain. One way of stopping them was not to allow them to take the exam in India because that meant they had to leave the country to do so. Although the exam was offered in Pakistan, one could not get a visa so Singapore was the nearest place. Twenty years ago, getting a visa to Singapore for a young medical student was a big undertaking so parents had to come up with a substantial sum of money to make it possible. Then you had to get a sufficiently high score in the exam to get into a residency program in the US.

EB: And you wanted to get in psychiatry?

SK: Yes.

EB: So, you decided to leave India, go through all this to do psychiatry. How did you decide on psychiatry?

SK: I don't really know, but there was a singular case that fascinated me. I was doing my psychiatry rotation, it was probably the first week or so, when an actor in the National School of Drama, who was playing a leper in a play, took a boiling cup of tea and spilled it on his face intentionally, because he wanted to have a scar to make his role real; it would give him the feeling lepers have. The scary part is this went on for sometime while the other actors thought this was just identifying with the role. Instead he was going through the first break of a psychotic illness. I was just fascinated and spent all four weeks of my rotation with him. By the time I left, he recovered. In those days they were probably using chlorpromazine, because none of the newer medications were available. When I applied to be a psychiatrist in the U.S. I knew very little about the way psychiatry was practiced.

EB: Were you surprised when you got here?

SK: I applied to a number of schools; like other foreign medical graduates I had no less than fifty applications and every program probably threw it in the garbage. But, interestingly enough, Dr. Wig, who I mentioned, was attending an international conference in Egypt where he recommended me to Professor Juan Mezzich, a professor at the University of Pittsburgh. And Mezzich brought my case to the attention of their residency director. This was 1988 and if you were a prestigious medical school in America, you didn't take foreign medical graduates. Foreign medical graduates served in inner city hospitals in large cities so nearly half of New York's city hospitals were run by people with ECFMGs. But the University of Pittsburgh agreed to interview me and they offered me a position which I accepted.

EB: Did you have a career objective you were able to communicate to the people interviewing you?

SK: I wanted to study psychosis and schizophrenia and the relationship between brain and behaviour. In one of my summer vacations in India I had created an elective to study iodine deficiency. There was a very good professor involved in iodine replenishment programs in the Himalayas, where many people are iodine deficient and hypothyroid. The adults compensate by having a big goitre, but their children are born with cretinism. What needs to be done is to add a little iodine to the salt. So, in this huge public health program, all they were doing was iodizing the salt and reducing dramatically the people with cretinism, also leading to

cognitive enhancement. The kids were getting smarter by putting a little iodine in the salt. It was an amazing program and I worked in their lab for sometime. And next summer I wanted to look at stress responses. This was a project I developed on my own; I was in third year of medical school and I collected urine samples from first year medical students before they were going into a very stressful exam. My hypothesis was we would find high levels of stress hormones in the urine. By the time I got in psychiatry I had become attuned to this neuroscience side of psychiatry, brain imaging was just beginning and, in psychiatry journals, some of Nancy Andreasen's findings were out and the first reports of looking at dopamine receptors with PET. So I came to my interviews interested in the neuroscience of psychosis. But, I hadn't done any research into that.

EB: Where do you think you get your ideas?

SK: By reading.

EB: Reading what?

SK: As much as I can. I've thought about this a lot, because now, as I do research and research administration, I don't do much with my own hands, I have fellows. They know the technologies better than I do, so I ask, what value am I bringing? The main value is the ability to conceptualize and decide where to go next.

EB: Reading the literature?

SK: Reading the literature.

EB: Reading science?

SK: Reading science.

EB: What about conferences?

SK: You sit here and see someone else describing something and, whether you like it or not, you're thinking how does it relate to what I do? I don't consciously do that, but I am spontaneously trying to make connections, how can I experiment with this or how would this change the experiments I'm doing? Of the thousands of idle thoughts one has, a few make a connection and lead to some action. When you come to a conference you're exposed suddenly to many people doing things that are, to you, novel. For me that's been very important.

EB: Do you read the history of science or psychiatry?

SK: To get ideas?

EB: Yes.

SK: I signed up to a service by the National Library of Medicine which scans all the world's literature for anything to do with dopamine, PET or schizophrenia and it drops about a hundred and fifty articles in my e-mail every Friday and I scan them all. Remarkably, it doesn't take very long. In thirty minutes you can scan a hundred and fifty abstracts, because most of

them, I don't need to follow up. I single three to five papers out, get copies and read them. I'm particularly interested in some of the historical articles. Rather than having discovered some new gene no one knew about, much of what I have found has given meaning to the observations smart clinicians have made. Such people have observing eyes and you don't need a microscope, a PET or rating scales to see behaviour. I would argue people who are uncontaminated by scales actually see behaviour. Often we don't see behaviour any more when we are obsessed with rating scales.

EB: Can you talk about the role of technological innovation and the development of your ideas?

SK: I'm totally dependent on technology, because what I do is brain imaging and the technology came to life about the same time I entered psychiatry. I'm also dependent on a lot of people who don't have much to do with psychiatry, but they're the experts in technology. These are chemists, physicists and people who run cameras. What I have tried to do is use technology to focus on the phenomenon of psychosis and, increasingly, on how antipsychotics work. Most of what I do utilizes technology at the rodent or human level.

EB: What kind of technological innovation do you think would be helpful?

SK: We could see chemicals in the brain if we could increase the temporal and spatial resolution of our instruments. We can see chemicals in the brain and I can measure, let's say, dopamine-D₂ receptor levels in a large area of the brain called the striatum. But to neuroanatomists, talking about the striatum is not specific at all. They want to know which parts of the striatum. Lately, with the newer scanners, we can break the striatum into three distinct areas or five regions; whereas, if you talk to the neuroanatomical scientists, they're working at the micron level, looking at individual neurons. If we want to understand behavioural phenomena in living human beings at the level in which they're initiated, at the level of neurons, our spatial resolution has to improve. The second is temporal resolution. Currently, we do a PET scan and get an answer that dopamine levels are "X" as measured over a ninety minute period; whereas some people talk about electrophysiology modeling at the level of a sub-second. So the big game from an imaging perspective would be to get closer to nature, which would be enhancing our spatial and temporal resolution. What worries me is that this is an endless chase, because even if I got to the level of a single neuron, people would say each neuron makes ten thousand connections with other neurons. My concern is that level of information might just be overwhelming. What would I do if I knew all your ten million neurons and their supposedly two hundred billion connections? At

one level there is this quest for ever faster, ever smaller. At another level information complexity would become endless unless we develop some different way of conceptualizing it. My sense is, as technology improves, it will feed us data of such staggering dimensions that mathematicians and bioinformatics folks will jump in to help us so we will be looking at derivatives of the data that are more useful.

EB: It's interesting to think about the ultimate utility of imaging. Let's say we know things happen at certain spots in the brain where behaviour originates, where would that lead?

SK: That worries me a lot. The general public conception is that if you're imaging something you'll be able to see something and do something about it. That is why the public is fascinated by it; they relate imaging to the fact they have a chest X-ray, someone looks and finds a hole and gives a treatment. In a perfect world, imaging would do that too, but it doesn't. The ultimate hope and goal of imaging would be three fold. One would be to advance the understanding of brain function as pure scientific curiosity, just as humans want to understand all aspects of our reality. In that respect imaging is an indispensable tool and I'm very confident about its contribution. The second would enhance therapeutics so that imaging can help develop better drugs for everyone, not help choose which one to give which patient; we have made progress there for sure. At this point, imaging is increasingly used to guide in selection of the kinds of molecules we want to use. The final frontier would be helping you make decisions about treating individuals. Psychiatry doesn't have a good track record there, yet, but that would be the hope.

EB: Like a chest X-ray.

SK: Like a chest X-ray. If you're depressed, you would have a PET or fMRI scan that would predict what would happen in the course of this illness and so make decisions. Now I don't believe that it would make any sense to diagnose depression on a scan.

EB: Can I ask you about funding?

SK: I'm fortunate because I work in Canada where the model is different. Salary comes from your base institution. In the US, if you devote time for research or you're not a tenured professor at the university but are working in a hospital, your salary comes from NIH grants and if you don't get those repeatedly, you have to do more clinical work. I'm fortunate that I'm in Canada where my salary is secure. It's not endlessly secure, but it's not from my grant. For grants, I look to the Canadian Institutes of Health Research, which is the Canadian equivalent to the NIH. Fortunately, a lot of work I do has implications for drug development, so we often get grants from drug companies or partnerships, which help. We also go to

foundations whenever we can; NARSAD and the Stanley Foundation have been good to us. The first thing one has to worry about is conflict of interest and whether one can be persuaded into taking positions on data one would not have taken, otherwise. Fortunately, I have not found myself in that position though one can never be too sure, so one should always have others judge that.

EB: How would conflict of interest in your work come up?

SK: What makes my situation easier is that in the work I do, efficacy and side effects of drugs are not the main variables of interest. So, there hasn't been any kind of a pressure and it has been a very positive experience for me. I would hope it's been positive for the people who funded my research on the industry side. It's an example of where academic and industry collaboration has worked well. What are some of the drawbacks? First is that their process of funding is a very nebulous one. It's not as if you put in a proposal and they let you know by a certain date it'll go up on the website if you get the funds or not. How they decide funding is a very complex mixture of money available, competing projects and things like that. So, as a scientist, it's always nebulous. One takes on projects and realizes later their ultimate scientific value is limited, but one has committed to them and that takes up a lot of time and energy.

EB: You go into the project, thinking there may be more interest from a scientific point of view?

SK: Yes, then you realize it isn't, but it's a contract. You agree to do something, so you have to do it. There's a fine line, because there's only so much time and energy and if one starts doing too much of this work, it can keep one from doing more independent hypothesis generating work, which is not about compounds. I constantly have to struggle with how much time I devote to the study of compounds, which tells you a lot about one compound but not about the general class and how much you might want to study. The companies are rarely interested testing their compound against another unless they're sure they're going to win. They are never interested in working with an outsider unless they feel confident they can demonstrate something by using the technology the outsider has. Otherwise, they'd rather do it in house.

EB: Do you feel you can set up relationships so you can, in the future, compare compounds?

SK: Absolutely. Those relationships are much more genuinely possible, because the calibre of scientists in industry is as good as in academia. It's the same people but they have more access to the latest technology and to compounds you don't. The relationship with people working in industry has been very valuable over time in getting access to compounds

and their latest data. Interestingly enough they have a lot of competitive data, which they don't always make public, which is very important when you're trying to understand an entire class of drugs from a mechanistic perspective. Their scientists have done a lot of due diligence on these compounds and what works and what doesn't work, especially in the pre-clinical area.

EB: What's the part of your job you like the most?

SK: Three things; seeing fascinating patients who get better with antipsychotics, talking to them and finding what changed. The second part I enjoy on a day to day basis is working with Fellows who are struggling and being able to guide them. The third would be when you find something and present it, not write a paper, because that is such an anonymous process. You write a paper and it goes out to the journal and you don't know to whom. Then one day, you get an e-mail saying it's accepted or rejected but you don't know who liked it, accepted or rejected it, but they always say slightly critical things, even if they accept it. Presentations are more alive, because your audience is there and you get feedback. You can have detailed discussions with people in the audience, so those are things I like the most.

EB: Is there a part that you dislike?

SK: No. This is a very good way of making a living.

EB: Is there something that we should talk about that we haven't touched on, yet?

SK: No. I'm very satisfied with the advancements in our science. Yet, I'm a bit disappointed, about how far we have come in making a difference in the lives of our patients because I still feel that our science has not, as yet, changed the practice of psychiatry. It has done a lot of good; it has changed the public's conception of mental illness and had a tremendous impact on removing stigma. If the NIH has put an equivalent amount of money into some kind of anti-stigma program it wouldn't have worked as well as the neuroscientification of psychiatric illness has towards erasing stigma. That isn't the only reward from neuroscience. Hopefully it should lead to individualized better outcomes for our patients although it hasn't happened so far.

EB: Where do you think it is breaking down? What's not working?

SK: Complexity. We have tremendous ability to understand neuroscience if we isolate a problem and totally constrain the limits surrounding it. You can do a very constrained working memory experiment in an fMRI on a schizophrenic patient and predict many things. But the models we're working with are too simplistic, given the complexity of the reality which gets expressed. That reality is not just neuroscience, but neuroscience,

culture and society including economic and political forces; that's what makes the whole patient.

EB: Is there a solution to that?

SK: I think about it often and ask myself how I can be constructively critical. What would I do differently? If someone suddenly said tell us where to spend the money the general answer would be, if the incentives were structured to make more differences for patients, the brilliant scientists would change science to gain the incentives. I'm encouraged by AIDS where we've made such tremendous progress because the incentives were to do better neuroscience. But I can't say follow a specific receptor and it'll get you there, although history has shown when the incentives are structured in a way that all the bright minds put themselves in one direction, tremendous things happen. For the last ten years in the "decade of the brain", incentives were structured to understand the brain with the hope once we understood the organ we could logically understand things like depression and anxiety. That hasn't happened, but the understanding we've gained is tremendous and rather than another call for more understanding of the brain, the call can be modified for more understanding with a higher likelihood of an impact. Many people disagree with that and say you can never do it. They say you can never predict and we should let people follow their curiosity because that's where the best answers come from. Maybe that's right, but there must be something one can do more than random curiosity.

EB: I'm trying to think of a scientific project that is trying to realign the incentives.

SK: AIDS, in many ways, was about that. In AIDS, it was not more biology for the sake of biology. It was biology in search of a cure. Bill Gates is doing that with his vaccine program. That is not just more vaccine science, but he has, through his Gates Foundation, set clinical goals.

EB: Motivated patients, active patients, a social movement.

SK: If you look at breast cancer it's not an accident the biggest advances have been made there. There were social movements and with those it was not just money, it was that the area became respectable, it became important. That's what people wanted and that's where the brightest in science wanted to go. I hope that can happen elsewhere.

EB: Thanks very much. Excellent.

SK: This was wonderful. I got a chance to reflect on my career, so I probably learned something about myself. I'll have to figure out later what it was!

ALFRED J. LEWY

Interviewed by John M. Davis
San Juan, Puerto Rico, December 11, 2006

JD: This will be an interview with Alfred Lewy.* It is December 2006. I'm John Davis. What sort of training did you have in Psychopharmacology?

AL: In addition to getting a medical degree, and, of course, I went on to become a psychiatrist; I also got a PhD in psychopharmacology under Lewis Seiden. He was a great role model in a number of ways. One of the things I liked best about him was his sense of humor. It's very important when you're picking a dissertation advisor to choose somebody who is a nice person, who you can get along with and who is supportive, and Lew Seiden was all of those for me. My dissertation was published in *Science* in 1972. Next, I did my internship and psychiatric residency at Mt Zion Hospital. I then came to the NIMH where I got further psychiatric residency and research training. It's the perfect place to be trained as a clinical researcher. I became interested in circadian rhythms, because I took care of a ward of manic-depressives. Ahead of me in the program was Tom Wehr, who became my next mentor along with his mentor, Fred Goodwin. They were following up on some ideas that the biological clock was possibly involved in timing of manic and depressive episodes. I'd worked there for about a year hoping to make an original contribution to this area, and I thought a melatonin assay would be important. I had become interested in melatonin in mid-1976 when Julius Axelrod gave his Nobel Laureate lecture at the NIH auditorium on a day when I was stuck on the ward taking care of patients, so I couldn't attend. But Tom and Phil Gold, who were a little ahead of me in the program, both attended this lecture. Between the two of them, they were able to recite it to me, almost verbatim. I don't know whether I was more impressed by the lecture itself, or by their ability to remember it so well. In any event, I was impressed, so decided to work on melatonin. In my literature search I found there wasn't a good way to measure melatonin in humans, so that was my first task. Because I had worked in Lew Seiden's lab I knew some biochemistry. Together with S. P. Markey I developed what became "the gold standard" assay for measuring melatonin in humans. It was published in *Science* in 1978. For the last ten years, we haven't used it much but it has led to the development of very good radioimmunoassays. Now there are a lot of people measuring melatonin in research laboratories. Measuring melatonin will probably become a clinical test soon. I remember calling my father

* Alfred J. Lewy was born in Chicago, Illinois in 1945.

when I was in the mass-spectrometry laboratory. I was injecting samples into the gas-chromatograph column, watching the chart recorder pen move while the melatonin was coming through. I remember saying to him, “I feel like I’ve just put the finishing touches on a rocket ship that’s going to take me into the unknown. I don’t know where it’s going to take me, but I’m sure it’s going to take me some place very interesting”. He said, “Well, let’s celebrate. Your godfather has just been named the Governor General of Australia. Let’s go experience the Vice Regal life”. We went there for two weeks. When I returned to Washington, DC, I measured my jet lag by measuring my melatonin levels each day at 9 a.m. To my surprise, my levels in the morning were very low. They should have been high, because that was the Australian night, and it should have taken several days for them to come down as my body clock adjusted. I figured maybe sunlight was suppressing my melatonin production, so with Tom, Fred, S.P. Markey and David Newsome, in 1980 we published in *Science* a paper that showed bright light, like sunlight, can suppress human melatonin production. This paper had a number of important implications that I, and others, have been following for the last twenty-six years. One was that you might be able to use bright light to manipulate biological rhythms in humans as bright light therapy. This thinking led to our discovery of seasonal affective disorder (SAD) and bright light therapy, which is now the treatment of choice for SAD. Another implication from our 1980 paper was that blind people had another form of light deprivation resulting in abnormal circadian rhythms. This implication, along with the work I did with Bob Sack, led to the development of melatonin as the treatment of choice for abnormal circadian rhythms in blind people. That paper in *Science* led to two different treatments, bright light and melatonin, for two different disorders that really weren’t known before 1980.

JD: I just want to be sure; seasonal depression had not been described before?

AL: Tom later found case reports in the literature describing depression in the winter but we were not aware of them at the time of our entry into this area.

JD: Yes, many things have historical precursors. So, you discovered a disease and its treatment?

AL: I discovered the treatment, and then I looked for a disease to apply this treatment to.

JD: That’s an interesting twist on it. You discovered a biologic mechanism.

AL: I figured out two types of circadian disorders that might be related to light deprivation, SAD and total blindness. The discovery of SAD was very serendipitous; a patient, Herb Kern, called me in 1979, who had

read about my work on melatonin, and told me he got depressed every winter. He had been to five other eminent psychiatrists up and down the east coast who refused to treat him, because they didn't think there was such a thing as winter depression. Apparently, they weren't aware of the past literature, either. I invited him to come to the NIH. He had requested I measure his melatonin levels, since he thought he had some atavistic response similar to the reproductive cycles of mammals where melatonin is involved in seasonal rhythms. Instead, I told him we had just discovered that bright light could suppress melatonin. I said, "Maybe bright light can do something to your seasonal rhythm," and he became the first patient treated with light for winter depression, which started the field. If it wasn't for Herb Kern, I don't know if we would have discovered seasonal affective disorder or light therapy. Light therapy is now the treatment of choice for winter depression.

The other two important implications from the 1980 *Science* paper were that melatonin was probably a very good way of measuring biological timing, but that you had to reduce the light levels to get it accurately measured. That led to what is now the standard marker for biological timing in humans. It is called the dim light melatonin onset (DLMO). And, it should be a widely available clinical test by 2011-2012. It will hopefully be a standard clinical test, perhaps with insurance reimbursement. These were the major implications of the 1980 *Science* paper. Melatonin treatment, especially as the treatment of choice for blind people, also resulted from that paper.

JD: Was it recognized, at the time, that blind people had a problem?

AL: In general, no, although, now it seems so obvious. You can go back into the literature and find some hints here and there, but in those days scientists thought that social cues were predominant for humans so it didn't matter if a blind person didn't have light perception, because they were exposed to the same social cues as everyone else. This is why it wasn't thought blind people would have any rhythm abnormalities. I did work with Bob Sack on blind people, giving them melatonin, which reached an important point in 2000 when we published a paper in *New England Journal of Medicine*; Bob was the lead author.

For the light treatment of winter depression, an important year was 1998, when our group and two others published papers in the *Archives of General Psychiatry* on morning light being more effective than evening light, and that supported our circadian rhythm hypothesis for winter depression, published in *Science* in 1987; this paper was entitled "Antidepressant and Circadian Phase-Shifting Effects of Light". Then, just last year, we published a paper in the *Proceedings in the National*

Academy of Sciences, "The Circadian Basis of Winter Depression". This was based on our discovery in 1992 that melatonin is a chemical darkness signal for the human biological clock. In treating winter depression, we found, just as morning is the best time to give light exposure, afternoon is the best time to administer melatonin, at least for most patients with SAD. Our paper provided proof of the phase shift hypothesis (PSH) for winter depression. So, we now have two phase-shifting tools, light and melatonin, which make up the biological mechanism. Now the question is: what disorders could they benefit? I don't think that schizophrenia is a biological rhythm disorder, but it might have a circadian component. Certainly other types of depression and sleep disorders could have circadian components.

JD: And, also, mania?

AL: Yes, mania. I'm hoping in the next few years we'll be seeing a lot of work using the DLMO to assess bright light and exogenous melatonin's therapeutic efficacy for a variety of psychiatric disorders, especially affective disorders.

I think the last thing I might mention today, unless you have some other questions, is an unexpected finding. I wouldn't necessarily call it serendipity, but it certainly is an interesting finding. When we began to study blind people more intensely, we found that non-photoc social cues may be important in humans after all. This idea stems initially from the received wisdom in 1979 that social cues were the predominant time cue in humans. In order to test whether social cues affect human circadian rhythms, we had to study people who didn't have exposure to the light/dark cycle, that is, blind people. They offer a unique experiment of nature, controlling for the confounding effect of light, so that we can see what else the human clock might be responding to. When we studied these blind people very carefully, we found that they don't drift at the same rate each day. If you're free-running at the same rate each day, it means you're impervious to any other time cues, but if your rhythms are speeding up on some days and slowing down on other days, then some environmental time cue is affecting them.

JD: Free-running would be like if you put a person in a cave, away from all light clues for many days or weeks, their rhythm seeks its natural course?

AL: Right. The natural rhythm is around 24½ hours. It's usually longer than the 24-hour day, so you drift later each day. But, blind people don't drift the exact same amount each day. When the melatonin onset is moving across the day, they drift fast, and when it's moving across the night, they drift slower. So, other time cues, possibly social cues, are speeding up the clock as it's drifting across the day and slowing the clock as

it's drifting across the night. We published that in 2005. Jon Emens was the lead author on that paper. We figured out that the speeding up and slowing down response can be quantified and is a direct proportional measure of the sensitivity to social cues. And, we found a robust gender difference. Guess which gender is more sensitive to social cues? Women, of course, because men are from Mars and women are from Venus!

JD: Yeah!

AL: So, women have twice the response to social cues. Free-running blind women seem to have twice the response to social cues as males and they're so sensitive we found that about twenty-five percent of women are entrained to the social cues, so not all totally blind people free-run. Out of twenty-five males, we've yet to find one male who is entrained. This is a very robust gender difference. It seems to start at puberty. In fact, before puberty, in this very preliminary study, all five of our pre-pubertal boys were so sensitive to the social cues that they were entrained to them. It's as if little boys have to be on extra good behaviour to get along with their siblings and parents, because once testosterone mucks up their brains, they become less sensitive to social cues, like adult males. Alternatively, the rigid routine of childhood may be why younger blind people tend to be entrained; once they leave school, more of them start to free-run. In any event, we're now going to follow up to see if we can identify a third type of a time cue for the human biological clock, which might be a social cue.

JD: It's interesting there was a level of serendipity, but some treatments are discovered by chance by clinicians, and it may be many years later the mechanism is understood. But, in this case, you were dually trained, but you hit the mechanism first and, then, found the disease, or maybe I should say you found the diseases.

AL: That's right. A lot of our work grew out of the animal scientific literature and applying it to humans. It's a little tricky, because humans are different than animals even in their biology so you have to know when to generalize and when not to generalize, and that's a bit of guesswork. But, it was basically an obsessive and tenacious focus on melatonin in all of its circadian rhythm possibilities that led to the work I've done over the years. Incidentally, I've been involved in many instances of "reverse translation" where our work with humans stimulates neuroscience studies in animals.

JD: But, you got hooked at NIH on rhythms.

AL: And, melatonin.

JD: You were inspired by a lecture that you didn't hear but that was described to you.

AL: Right. And, I never knew whether or not melatonin was going to lead anywhere, but happily it led to a lot of interesting things. I've done a lot of light therapy studies and a lot of winter depression studies, but I've always returned to my focus on melatonin, and that brought me to other new applications for the blind people, jet lag treatments and treatments for shift work maladaptation, and certain kinds of sleep disorders, advanced or delayed sleep phase syndrome. All those can now be treated with light or melatonin, except light can't treat blindness.

JD: In terms of the diagnosis for winter depression, you were mentioning something about how you might expand on that?

AL: We have a tool, the DLMO, to determine whether the type of winter depression you have is the typically phased-delayed type with the later dawn in winter, or the phase-advanced type with the earlier dusk of winter, the atypical type of winter depression. Depending on which direction your body clock is shifted you need the light, either in the morning as most SAD patients, or in the evening for the atypical subgroup. It's the same with melatonin, although it is given at times opposite to light, since we have discovered that melatonin is a chemical darkness signal.

JD: How did you get onto that?

AL: Immediately after my colleagues and I discovered winter depression and light therapy, we did think it was a seasonal rhythm, and you should use the light, both in the morning and in the evening to change day length. That is how we treated Herb Kern the first patient, but when I came to Portland, I began to wonder if that was a fruitful approach, because humans don't really have a lot of seasonal rhythms. We certainly don't have seasonal reproductive cycles; we have the menstrual cycle. However, we do have a lot of twenty-four hour (circadian) rhythms and there was a theory for non-seasonal depression, a diagnostic concept that Tom Wehr, Dan Kripke and some others developed whereby they thought there was internal misalignment between the temperature rhythm and the sleep-wake cycle, like jet lag. It was a mismatch in circadian rhythms, and I guessed that was going on with SAD and it seems that's the case. Now, if there's a mismatch between circadian rhythms, there are logically two types of ways that mismatch can occur. Your body clock can be phase advanced with respect to the sleep-wake cycle or it can be phased delayed with respect to the sleep/wake cycle. I needed to think this through.

JD: To think it through?

AL: Yes. It's important to think through what the implications are of any thought you have. To try to take it to the next step. It's also important to challenge your own fundamental assumptions and I do this frequently. Being your own worst critic is crucial since you know your strengths and

your weaknesses better than anyone else. You know the work of your lab better than anyone else. You know its potential pitfalls, so being your own worst critic is very helpful.

JD: Do you try to be your own worst critic in some regular way?

AL: Not so much regular, as often. So, the future work is now going to be devoted to identifying the social cues that might affect sighted people, as well as blind people, but I've still postponed the final question I've always wanted to answer, which is, what is the function of melatonin in humans? We know it's a good marker for the biological clock. We know we can give melatonin to shift the biological clock and to treat biological clock disorders, but what is the function of endogenous melatonin production? I think that is going to be related to the births of my two boys, which occurred in 2003 and 2006. The theory I'm going to try to test in the next few years is that the function of endogenous melatonin production is for the pregnant woman, through her blood melatonin levels, to communicate biological time to the third trimester fetus and then the nursing mother, through melatonin in her breast milk, to communicate biological time to the nursing infant, until the infant is about 3 months old, when the retino-hypothalamic tract starts to function and the infant can entrain to the light/dark cycle. Before that, they're like a little blind person. They can see, but they can't entrain to the light/dark cycle. I'm sure you know many similar stories of people who are new parents. Whenever I mention to somebody that I'm a recent dad, they always ask, "How's your sleep?" It may be that we can use melatonin to help infants sleep, so that their moms get more sleep and can be better moms. That'll be a new area I'll be working on in the next few years. Perhaps melatonin from the mother is important for optimal early development in her offspring: I call this the maternal ontogenic melatonin (MOM) hypothesis for the function of melatonin in humans.

JD: How would you fit in the melatonin story in an evolutionary sense about how rhythms develop? You mentioned several: seasonal rhythms, 24-hour rhythms, possibly, menstrual cycle rhythms.

AL: Well, melatonin has always been the chemical darkness signal, even in unicellular organisms, for many, many millions of years. A seasonal breeder will use this chemical darkness signal to time seasonal rhythms, but if you're not a seasonal breeder, melatonin is more likely going to be used to time 24-hour rhythms. I think humans have retained the melatonin rhythm and the suppressant effect of light on melatonin, because melatonin does have a function in humans, which may have been disrupted over the last million years, since the invention of fire, because levels in breast milk, for example, are lower in light exposure and the

only way that it could really be high enough to affect the suckling infant would be if there was no light exposure at night. There are some other factors that need to be thought through. In any event, with high definition TV emitting bright light, and if mothers are watching TV at night and suppressing their melatonin, they're probably not getting enough melatonin into their breast milk for the infant to be much affected by it. So, we might think of artificial light as an uncontrolled experiment on our human biology. Perhaps another implication of our 1980 *Science* paper is that it got people thinking about the difference between sunlight and indoor light. As an example, architects are now building houses with more sunlight coming through the windows.

JD: Is there anything we haven't covered that we should?

AL: There are probably a few disorders out there that could be treated with melatonin that may be serendipitously discovered. For example, if you have a lot of people taking melatonin and an astute clinician notices the difference in some disease, that's another condition that is possibly benefited by melatonin. That's not in my approach thus far, but I might start trying to figure out if there is some other use of melatonin, one that may not even relate to circadian rhythms.

JD: Is everything explained clearly enough so that it would be obvious to a layman, because a tape like this could be edited and they could pick something out and put it back where it belongs?

AL: Is there anything more I can do to explain this to the layman?

JD: Did we explain it clearly? And, I know that you want to define free-running.

AL: Before I do, I just want to add to that last thought about the medical uses of melatonin. My guess is a lot of people are going to be taking melatonin because it's safe. There are no toxic side effects, especially at the low doses we have found it effective.

JD: And, that would be?

AL: 0.5 milligrams. We've entrained some blind people to 10 micrograms, a very low physiological dose.

JD: And, in what dose is it marketed now?

AL: Most people are taking 3 milligrams at bedtime.

JD: And, some may be taking higher doses?

AL: Yes.

JD: Sometimes 10?

AL: Yes.

JD: Is there anything wrong with, say, 10?

AL: It won't hurt you, although it may not be any more effective than 3mg for helping sleep. Actually about 30 percent of the population gets sleepy on

melatonin, so they use it for bedtime sleep. We can't predict who these people are in advance.

JD: Does it hang around long enough so it may be too much?

AL: If it hangs around too long it won't shift the clock very well. Low doses seem to work better for clock shifting, because they are more discreet time signals. That's another point that probably should be mentioned. A few people report feeling "hangover" after taking high doses at bedtime.

JD: And, there's a significant difference between, say, 0.3 and 3.0.

AL: That's a ten-fold difference.

JD: And, that's something people need to know.

AL: So, low doses of melatonin may work better than high doses for phase shifting. Melatonin is a chemical darkness signal. It works opposite to light. The way you shift the body clock earlier is to give morning light or melatonin in the afternoon or evening. The way you shift the body clock later is to give evening light or melatonin in the morning. Between these two regimens we've described over the years, you can shift the body clock in either direction and correct either type of body clock disturbance.

JD: I'm just picking the things we may have omitted. Describe what Seasonal Affective Disease is.

AL: Seasonal Affective Disorders is quite common. For some reason, it occurs more in females. The further away from the equator you live, the more likely you're going to have it. It has some of the characteristics of depression, but there is increased appetite, weight gain, preference for carbohydrates, increased sleep and fatigue, despite the increased sleep.

JD: Laymen may still not understand what seasonal depression is.

AL: It's similar to non-seasonal depression, in that you feel sad, hopeless and helpless. There's social withdrawal but rarely thoughts of suicide. There is indifference to things that normally give you pleasure. But sleep disturbance in winter depression is different than in non-seasonal depression. In non-seasonal depression there is often early morning awaking. In winter depression, people want to sleep all the time, which is why we first thought it was some kind of atavistic form of hibernation, but I discarded that idea when I adopted the circadian rhythm theory.

JD: So, it's different from typical depression in that they are sleeping more?

AL: And eating more.

JD: Sleeping more, eating more.

AL: With non-seasonal depression, there's generally a lack of appetite and weight loss. Bipolar depression seems to be similar to winter depression. And, like bipolar depression and some forms of unipolar depression, it's recurrent. That's another hallmark of winter depression. It recurs every winter.

JD: And, what are the behavioural consequences in blind people of not having a rhythm?

AL: When a blind person's rhythms have drifted 12 hours out-of-phase with their sleep/wake cycle, they're sleepy during the day, they can't sleep at night and they're depressed.

JD: They can't sleep at night and they're depressed?

AL: Yes.

JD: I mean their quality of life is adversely affected?

AL: Absolutely.

JD: And, you discovered the disease?

AL: We discovered that melatonin rhythms are abnormal in blind people and when they're most abnormal they're very symptomatic and this is their worst burden, second only to not being able to see. Fortunately we can treat virtually one hundred percent of them with a tiny dose of melatonin, taken every day.

JD: It's a fascinating story. You discovered several diseases and it's interesting from the point of view that you were a clinician and a basic scientist. You discovered a mechanism and, because you were a clinician you went on to discover a disease. It's also interesting that a patient with the disease came to you and you both discovered the disease.

AL: I think that being a clinician and being a scientist were helpful in allowing me to do what I've done.

JD: And, having a setting like the clinical center.

AL: Yes, my experiences at the NIMH were indispensable.

JD: Yes.

AL: And working with great people (there and here in Oregon), particularly with Bob Sack for twenty years.

JD: Let's think for a moment if anything we've missed.

AL: I think we've covered it.

JD: OK, great.

AL: Thanks.

HERBERT Y. MELTZER

Interviewed by Stephen H. Koslow
San Juan, Puerto Rico, December 10, 1996

SK: Today we have a great opportunity to meet with Herb Meltzer* and talk about his extensive and successful career in Psychopharmacology. He is a leading member and past president of the ACNP. He is currently at Vanderbilt University as a Professor of Psychiatry and Pharmacology and Director of the Psychopharmacology Center. Herb has had such a rich career that it's hard to know where to start. Probably the best place is what's the most exciting thing you're working on now and if you could elaborate on where you think this is going to take us.

HM: The most exciting thing I'm doing now is looking at the new antipsychotic drugs in the treatment of schizophrenia and their many applications, and, having the continuing opportunity to integrate my basic science interest with the clinical. They've always been an important part of me. It's why I went into this field; because I couldn't decide between the two of them and it's one of the unique fields in medicine, where I could really do both. We're having a tremendous amount of fun, seeing how good these drugs really are, what their strengths and limitations are, where the new drugs, the olanzapines, risperidones, sertindoles and ziprasidones, fit into treatment strategies, as well as understanding the basic mechanisms and trying to push ahead to the next generation of antipsychotics, using these drugs as tools to understand what schizophrenia is all about.

SK: When do you think there will be the next generation of antipsychotics?

HM: Well, the most immediate thing you can see are some drugs that are antipsychotic without directly blocking the dopaminergic system, drugs like MDL 100907 and finanserin, which are serotonin_{2A} antagonists with little or no effect directly on the dopaminergic system. What I'm really passionate about is trying to get a way to intervene in schizophrenia before the psychosis begins. We know this is more a developmental disorder and I have found, it's not a unique finding, but certainly confirming it, that the core cognitive deficit in schizophrenia, the problems in attention and executive functioning, in memory and learning are present at a fairly significant level before the psychosis emerges. These deficits, much more than the delusions and hallucinations, set a limit on how people with the illness function in the world. So what we're trying to do is identify people through syndromal characteristics. I'm sure, in the next five years, we're going to have genetic markers for this and, once we've got them, we will

* Herbert Y. Meltzer was born in Brooklyn, New York in 1937.

be able to develop new pharmacologic and non-pharmacologic means to prevent the emergence of the psychosis and the progression of the cognitive deficit. On the pre-clinical side we would have animal models of schizophrenia as a way of understanding the development of the disease process and getting into cognitive studies in animals will help understand the cognitive deficit. One of the most exciting findings I discovered with clozapine was it is the first antipsychotic drug which can improve some but not all cognitive function; it improves semantic memory, attention and certain kinds of executive function. Fascinatingly, it also worsens, in a transient way, working memory.

SK: Let me ask about what you said, in terms of the future, and then go back a little bit. It's unclear to me when you say prevent the psychosis, or treat some of the cognitive functions early on, which you think is more important in terms of recovery and outcome?

HM: For years clinical trials were based on, if you had a drug that treated delusions and hallucinations, that's all the FDA wanted to know; and all clinicians also neglected what was happening in other part of people's lives. In effect, these are very independent measures. What I consider really important are the cognitive deficits that affect quality of life, work and social function. If it was a forced choice between cognitive deficits vs. the delusions and hallucinations I'd pick the cognitive deficits. Let me give you an example. When I was the clinical director of the Illinois State Psychiatric Institute, there was a very schizotypal person, at least on the surface, who ran the clinical lab, and after we got to work together for a couple of years she came to me and she said, "I've never told anybody this, but I hear voices all the time, do you think I should get treated"? From the point of view of work and social functioning, it wasn't the voices that created the problem but that she was cognitively impaired. If you looked at the work, social function and quality of life of the average schizophrenic, doing well on Haldol (haloperidol) in the sense of no delusions and hallucinations, it was as bad as anybody with AIDS. You can treat those positive symptoms but your impact on the person's life is very small and it's the cognitive deficit you need to change. I've been recruiting neuropsychologists to work with me at Vanderbilt on that and I've been lining up grant support for that. When I made this finding on the effect of clozapine on cognition, a very distinguished neuropsychologist said this doesn't work. He had much more solid credentials in this area than I did, but our data showed what it showed. We published it, it's been replicated across the board, industry has really got onto this and it has become a new area of research; the impact of cognitive deficit on social functioning and its treatability. We're getting a lot of people who have

never looked at schizophrenia in the field of cognition, coming back to it. That had been a dead field for a long period of time.

SK: From a career perspective, you mentioned one of the highpoints in your career was the capability to go between basic and clinical research. If you were advising a younger person, pursuing a career in psychopharmacological research, how important would you make this and what types of things have you found helpful to make your career successful?

HM: Everything today is so complicated and competitive. To advise anybody to be as diffuse as I have been, might be foolhardy, but I wouldn't trade that. There's a real advantage in the breadth of being into basic and clinical research that compensates for the loss in depth. PhDs will continue to have a major impact on how our field develops and so will MDs who also have a PhD. I felt tortured about whether to go into Chemistry and do Organic Chemistry, which I loved passionately, or be a doctor, that was also terribly important, and I couldn't decide. I bounced back and forth between graduate and medical school until I discovered psychopharmacology and psychiatry on Tom Detre's ward at Yale, and within a few weeks I knew what I wanted to do. I wanted to continue to do lab work, which I had been doing in Dan Freedman and Nick Garman's lab and get training in clinical psychiatry to do the things I saw Tom Detre and other people doing. I'll never regret that choice. If I'd done only one thing, the other part of me would always have felt I'd made a mistake.

SK: You named some pretty significant names in this organization and in psychopharmacology, Tom Detre, Danny Freedman and others. Did these people have a major impact on you?

HM: Tom, unquestionably, was the person who made me want to be a clinical psychiatrist. I don't think I was thinking about that until I had the chance to work with him. Jack Durell was crucial to me in that when I went to NIMH for research training, I found through his example, a terrific model for treating schizophrenia, totally different from what I learned as a resident at the Mass Mental Health Center, which was supposedly the Mecca for treating schizophrenia. It was a very psychoanalytically based therapy model while Jack had this milieu, multidisciplinary approach and was very comfortable with the use of medication. At Mass Mental Health Center we were made to feel second class physicians if we used anti-psychotic drugs rather than psychotherapy. So, I give Jack a lot of credit for what I learned at NIMH. Arvid Carlsson was very important to me. I never had the opportunity to work with him, but I wrote this review article on the *Dopamine Hypothesis of Schizophrenia* with Steve Stahl for the *Schizophrenia Bulletin* and when I met Carlsson at a meeting, he said, "This is the best article I've ever seen on this, I want to commend you".

At that point I was just beginning to get started and that kind of feedback was just immensely gratifying and encouraging. Hans Hippius, the leader of European psychiatry for many years, was also important to me. When I was at NIMH in Durell's group, Jack left while I was there so I had an opportunity to do anything I wanted. I remember looking around for a project and Hippius had this paper about muscle enzymes in schizophrenia that he discovered in large quantities in acutely psychotic patients. That was the year when Seymour Kety was debunking just about everything in the literature, so there was no real logical starting place. So I picked up that finding by Hippius and replicated it. It was a bizarre finding but I took it one step further fairly quickly. Hippius thought CPK was coming from the brain of schizophrenic patients. I began to read about CPK and realized I could quickly answer where it came from by determining which isoenzyme it was. I discovered it was the skeletal muscle enzyme, which made it an even more puzzling problem. So I went through a series of studies to show the increase of CPK was not the result of trauma or activity. Then I began animal research to figure this out, to find an animal model, and that led me into psychopharmacology on my own for the first time. I'd done psychopharmacology as a medical student in Danny's lab and in Jack Peter Green's lab, but this was my first solo project. One of the interesting things was that I found that PCP and stress in combination was the best model for elevation of CPK muscle enzymes. That led me to be the first person to report PCP was an indirect dopamine agonist and I got an RO1 to study that when I left the NIMH. Then, all of a sudden, they discovered the PCP receptor and that PCP is a partial NMDA antagonist, so I could never get the dopamine aspect of PCP refunded. The interesting thing now is that Bob Roth's lab at Yale is showing the dopamine aspects of PCP in primates; the dopaminergic action is controlling a lot of the behavioural effects of PCP in animals. When I got to Chicago I was still caught up in the PCP finding and Phil Holtzman and I were able to do studies administering PCP to volunteers and also ketamine, which is an analog. This was long before the current wave of interest in ketamine, and we made some fascinating findings which are still very relevant. So, I'm thinking of going back to some of the PCP work with what we now understand about it.

SK: You mentioned the importance of dopamine in schizophrenia. Everyone would agree with you on that, but also you mentioned that perhaps the next class of drugs won't involve dopamine. Is the theory of dopamine finished in schizophrenia?

HM: It's not finished. It's still an element, but that question allows me to talk about our main pursuit in schizophrenia at the moment, which is the

serotonin story. Going back to Durell's era, there was a serotonin hypothesis related to Woolley and Shaw and the notion that endogenous methylated indoleamines have psychotomimetic effects. My involvement with serotonin and schizophrenia began by being one of the first investigators to use fluoxetine (Prozac) clinically. The first person we gave it to at ISPI developed a dystonic reaction as if I'd given him IM Haldol. I thought the nurses had inadvertently used the wrong medication but we found Prozac in his blood and no Haldol. I spent months writing up this case report and although people look down on case reports, Floyd Bloom was editor of *Journal of Neurotransmission* and he published the report intact, in which I reviewed in depth what we knew about serotonin-dopamine interactions. That was probably in 1973 or 1974. Ten years later I found these amazing things about clozapine in treatment resistant schizophrenia while everybody was still talking about dopamine and acetylcholine. There were a few ideas about serotonin in relation to clozapine, but not very much. So I thought of the possible dopamine and serotonin interaction and went back to the laboratory to work with animals, using in vitro binding after looking at the affinities of thirty-seven different drugs with the notion the serotonin-dopamine ratio was critical if you want a drug for the treatment of schizophrenia which produces few extrapyramidal side effects. Paul Janssen and the Janssen group came up with the same theory independently, developing risperidone. After my article was published a lot of other companies became involved and that led to working with olanzapine and ziprasidone, etc. We've taken the story a lot further. I still think those $5HT_{2A}$ receptors are critical but we have seen that $5HT_{2C}$ and $5HT_7$ receptors are also relevant to the clinical effect of drugs in schizophrenia. The story about the relationship of dopamine to the effect of drugs on psychosis is also interesting because they are exciting new drugs which are antipsychotic without an effect on dopamine- D_2 receptors. The dopamine- D_4 receptors might also be involved but I'm not convinced. Attention may be influenced by drugs with an effect on the dopamine system, but when you talk about influencing various kinds of memory and executive functions you've got to be thinking about effects on glutamate and GABA. I work now at Vanderbilt and have a team of clinical and pre-clinical people that have a good shot at trying to sort things out.

SK: Let me ask you a career question. You have lived through an exciting period in which psychopharmacology and rapid technological advances in basic research have changed the way mental disorders are looked at. There were great changes and, then, suddenly, there was a screeching halt. People are fearful to do clinical research because of the way medical

care is handled today. Money available for grants is scarce and people are worried about their ability to get funded for a research career. Is there encouragement for a young person to come into this field? Is there something left to do for them and can they do it?

HM: There's an enormous amount of work left. Treatments for schizophrenia are, at best, on a scale of one to ten, at three or four. Would the old models that I used years ago work? No, but that does not mean that there are no new models. I've only been at Vanderbilt for a few months but, to my astonishment, I find it possible to do research in a managed care environment. They're so desperate for expertise to handle the responsibilities they greedily went after that they're turning to people with experience to come up with ways to use the new drugs. I'll give you an example. The medical director of one of the biggest pharmacy benefits management company said to me, "I'm sure doctors are underutilizing these new anti-psychotic drugs, particularly, clozapine. We want doctors to use more; give us data that show the outcomes and I'll make sure the drugs get used." That was before I went to Vanderbilt; now I'm being given research opportunities in managed care in the VA and the public sector.

SK: What would you say the top elements are to create a successful place for someone who wants to pursue research?

HM: First, you have to work with heads of systems and to have their commitment to let you to do your thing. And, when you lose that you have to move on. If I made one mistake in my life it was staying in a job too long. If you're trying to do something in clinical research it's almost impossible to do it on your own; you have to have people to work with you. If I have to spend, as I did when I first started out, thirty hours a week taking care of the patients, I couldn't get it done. Today, if you want to keep up with all the new developments in molecular biology or brain imaging, you have to be part of a team that will do the rest of what you need to do. You have to think about state regulations; I just found out that Georgia won't allow you to use clozapine or any of the new drugs, so you don't want to waste your energy fighting city hall.

SK: Another career choice you've made is to stay in research. Many successful people in research are siphoned off as to become department chairs. You haven't done that, you've stayed in research. Can you shed light on that?

HM: There are many people who want an upward projector so I want to tell young people my career has not been at the expense of a decent income. I've been recompensed, not at the level of a chairman, but I've made a good salary. Secondly, I love what I do and it's hard to imagine, as long as I'm breathing, that somehow I won't be involved in research. It's

become very easy today to turn down opportunities to be a chairman. It wasn't so clear cut some years ago but I didn't have the aspiration a chairman should have, caring about child psychiatry or caring about medical school teaching to the point where that was equally important. Research is what's most important to me. I've also turned down jobs in industry. People have come to me when NIMH directorships have been open and said, why don't you apply, but I had no interest. I wanted to keep doing research. There's nothing more satisfying than coming up with something in research, applying it clinically and seeing the results. I've had such wonderful experiences with patients and families, learning from them what a difference clozapine, or something else I did, made in their lives.

SK: So you would say any person who's interested in research can create the right environment without having to have a big department they're in charge of. They can create the space and get the things they need to stay on the research path.

HM: Here I want to put a pitch in for the center grant mechanism. It's going to be a great tragedy if people cut that out because it enables you, if you get a five year renewal on a center grant, to develop the infrastructure that supports work with funds from different places. With the RO1 mechanism you get a grant for work you've already largely completed and you know the answers. It produces a lot of fine, but somewhat dated work.

SK: What are some of your fondest memories of ACNP activities you've been involved in?

HM: It's going to sound like an advertisement, but it's a fantastic group and it's getting better; the quality of the science and interaction between people.

SK: Anything you would like to say about your contributions to ACNP?

HM: I started the poster sessions when I was chairman of the Program Committee. I had to fight for two or three years to get them to accept posters and you know what's going on in the poster room now.

SK: You've had a very rich career. Is there anything you would like to add we haven't touched on?

HM: It's a privilege to have had this career in psychopharmacology; having the opportunity to understand brain and behaviour, from the molecule to the mind. There's nothing more exciting and it's great to be part of it.

SK: It's a great frontier that's challenging us and you have made significant contributions. It's been great fun knowing you and having the opportunity to do this interview. Maybe we'll do another in ten years.

HM: I hope so. I hope we'll both be around.

SK: We will. Thank you.

GREGORY F. OXENKRUG

**Interviewed by Thomas A. Ban
Waikoloa Village, Hawaii, December 9, 2001**

- TB: We are in Waikoloa Village in Hawaii at the annual meeting of the American College of Neuropsychopharmacology. It is December 9, 2001. This is an interview with Dr. Gregory Oxenkrug* for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Please tell us where and when you were born, something about your early interests, and education.
- GO: I'm very glad to have this interview and especially that you are my interviewer because it was your textbook and monographs I read first when I entered psychopharmacology. I was born 60 years ago, in 1941 in Leningrad, in the Soviet Union. It's now called St. Petersburg in Russia. During the Siege of Leningrad during World War II it was my Mother who saved my life. There were only two kids on our street who survived.
- TB: Could you say something about your family?
- GO: My father was a pharmacist and almost all of my relatives, including my aunts and uncles, were doctors on both sides. I knew from an early age I would study medicine and I was also dedicated to chemistry to the extent that in high school I took a college course in it. I was admitted to medical school at 17 and my interests were in endocrinology and genetics. Then, in the fifth year, I became intrigued with psychiatry and attended all the lectures and rounds by Professor Khvelevetskiy at the Bekhterev Psychoneurological Institute.
- TB: Who was professor Khvelevetskiy?
- GO: Professor Khvelevetskiy came from a family of famous physicians, lawyers and musicians. He was Chairman of the Department of Psychiatry at the Bekhterev Psychoneurological Research Institute and a very gifted psychopathologist.
- TB: Were you involved in any research as a medical student?
- GO: I was interested in fingerprints and would have liked to do some research on that under Professor Khvelevetskiy but he didn't let me.
- TB: How did you get interested in fingerprints?
- GO: I was interested in genetics and learned that fingerprints are unique for each person; they are formed in the first trimester of pregnancy, and the pattern of fingerprints is different in schizophrenic patients than in normal subjects. I reviewed the literature and although Professor Khvelevetskiy liked my review he did not want me to do research.

* Gregory F. Oxenkrug was born in St. Petersburg (Leningrad), Russia (Soviet Union) in 1941.

TB: Why?

GO: Because in 1948 the Communist Government closed genetic schools and many people involved in genetic research lost their job and, sometimes, freedom.

TB: So, you were not allowed to do genetic research?

GO: But Professor Khvelevetskiy liked my review; he used to call me “Mendel” and after my graduation from medical school in 1965, he tried to get for me an appointment in his Institute. But, his request was denied, mainly because I was Jewish and they did not want to appoint a Jew in a medical research position. Fortunately, in 1964, an Institute of Endocrinology was built outside Leningrad. It was a huge facility and I got a job as a senior technician in one of the laboratories. It wasn’t a medical research position, but it made it possible for me to do some research and Professor Dilman, who was in charge of the laboratory, was a genius.

TB: What was his special field?

GO: Professor Dilman was very interested in the mechanisms involved in the aging process, and he had a unique theory that still holds up. He was the first to suggest that hyperinsulinemia plays a role in the etiology of cancer and high blood pressure, and is one of the major mechanisms in the aging process. He published many books and some were translated into English. After he published his last book he moved to the United States. Later on he developed cancer and died about seven years ago in New York.

TB: Could you say something about your research in his laboratory?

GO: I was involved in studying the endocrine changes in breast cancer patients by measuring hormones in the urine.

TB: What did you find?

GO: The levels of estrogen like compounds and cortisone remained high even after ovariectomy. In 1966, in collaboration with oncologists, I published my first paper on the findings.

TB: When did you move from the Institute of Endocrinology to the Bekhterev Psychoneurological Institute?

GO: In 1967. Slava Lapin, the Head of the Psychopharmacology Laboratory at the Institute was looking for somebody with experience in measuring cortisone and I was accepted in their three year PhD program.

TB: Did you have any contact with Professor Khvelevetskiy after you joined the Institute?

GO: Very much. We worked in close collaboration.

TB: Could you tell us about the history of the Laboratory of Psychopharmacology at the Bekhterev Institute?

- GO: It was the first psychopharmacology laboratory in the Soviet Union, established by Slava Lapin in 1960, at the initiative of Professor Boris Lebedev who was Scientific Director of the Institute.
- TB: Was this the Professor Lebedev who was later director of the Mental Health Unit of the WHO?
- GO: Yes. He was Scientific Director first then the Director of the Institute before he was appointed, in 1964, as an officer in the Mental Health Unit of the WHO. By the time I arrived he was in Geneva.
- TB: He was the one who hired Slava Lapin to set up the laboratory?
- GH: Yes. Initially the Laboratory was on the third floor of the building with animal quarters on the first floor. By the time I arrived the Laboratory had eight rooms on the second floor designated for pharmacological screening and behavioural pharmacology, and four rooms on the third floor for biochemistry. Lapin's first research collaborators were Rebecca Khaunina and Eugene Schelkunov. Then, Yuri Nuller, a psychiatrist, Irina Prakhie, a veterinarian, Maya Samsonova, a neurophysiologist, Irina Kiseleva, a medical doctor and I joined the team.
- TB: So your laboratory was in the Institute founded by Bekhterev. Could you tell us something about Bekhterev?
- GO: Bekhterev was a very prominent neuropsychiatrist. He was professor and Chairman of Neuropsychiatry at the Military Medical Academy in St. Petersburg established by Peter the Great in the 17th century. Among many other things he did some work on conditioning, similar to Pavlov, who was a physiologist. There was some kind of strife between them; Pavlov would never allow Bekhterev to become a member of the Russian Academy of Sciences. At age 50 Bekhterev had to retire from the Military Medical Academy and, in retirement, with private donations he founded a Neuropsychological Institute. He was personal physician to the Czar's family, so they gave him the land where the Institute was built. At the time the Institute was on the outskirts of the city, but now it is in the center of St. Petersburg.
- TB: When was the Institute opened?
- GO: In 1907. Then, in 1917 the Institute was taken over by the government of the Soviet Union.
- TB: But Bekhterev stayed active, didn't he?
- GO: He did, but apparently he dabbled in Stalinism and was poisoned with mushrooms in 1927. He was never officially condemned but the Institute was converted temporarily into a hospital.
- TB: So, Bekhterev was poisoned. What was the official report of his death?
- GO: According to the newspapers he was in Moscow, presiding over meetings, and went to a ballet in the evening before he died at night. The

rumor was that it was his second wife who poisoned him on the orders of the KGB. But, as years passed, he was rehabilitated. By the 50th anniversary of the Institute, in 1957, the hospital became a Research Institute again with Bekhterev's ashes in an urn in the middle of the huge room he used as his study. They were buried in the cemetery next to Pavlov's grave. The burial was a big celebrated event but I guess Pavlov wouldn't have liked it!

TB: Could you tell us about the research in the Laboratory?

GO: One of the ongoing projects was on acetylcholine esterase inhibitors, the antimuscarinic drugs, some of which were used as insecticides. This was well before my arrival. I understand the first compound Slava Lapin worked with was β -phenyl-GABA that he called originally phenigama but was to become known as Phenibut. In the initial preclinical studies Lapin conducted in collaboration with Rebecca Khaunina and Irina Prakhie, phenigama was found to have a similar pharmacological profile to meprobamate and diazepam. Then Khaunina and Maslova showed the substance passes the blood brain barrier. In clinical trials conducted by Professor Khvelevetskiy, Phenibut was found to be an anxiolytic drug with hypnotic and antimanic effects. By the mid-1960s the first paper on Phenibut was in print and a monograph was written by Lapin and Khaunina on The Role of GABA in the Nervous System. It was published by the Leningrad University Press.

TB: When you joined the Laboratory in 1967 what was your first research project?

GO: Lapin and Schelkunov were interested in the mechanism of action of antidepressants. I was involved in endocrinological research before, so I was given two to three months to orient myself about the state of art in psychopharmacology and especially in antidepressants.

TB: Was any research going on in the Laboratory with antidepressants at the time?

GO: Yes. In 1964 Lapin published the first review in the Soviet Union on imipramine and Schelkunov was studying the role of cholinergic structures in antidepressant effects. By the time of my arrival there was a battery of tests in use, developed by Lapin in collaboration with Schelkunov, Khaunina, Prakhie and Samsonova, for screening potential antidepressants. By 1968, one year after my arrival, there was sufficient information to report the results of seven years of systematic research on screening for antidepressants.

TB: Where was it published?

GO: In Russian in the Proceedings of the Bekhterev Institute under the title "*Experimental Studies on Antidepressants.*" The report focused on the

fact many screening tests, considered to be predictive of antidepressant effects, such as reserpine antagonism and amphetamine potentiation, are non-specific because they confound sympathomimetic action and stimulation of motor activity with antidepressant effects. Many drugs, including amphetamines, cocaine, and anticholinergics are active in these tests without necessarily having mood elevating effects in depressed patients.

TB: In 1969 Lapin and you published a paper in the *Lancet* that turned attention to the role of serotonin in the antidepressant effect of drugs.

GO: The title of our paper was, "*Intensification of the Central Serotonergic Processes as a Possible Determinant of the Thymoleptic Effect.*" We followed up our first paper in 1970 with another entitled "*The Frog as a Subject for Screening Thymoleptic drugs.*" Apparently, the frog brain contains predominantly serotonin (5-HT) whereas the rodent brain contains predominantly norepinephrine (NE); Lapin found in frogs that reserpine's sedative effect was potentiated by tricyclic antidepressants, instead of being reversed in rodents. Subsequently, we also found in rodents, like rats, it was L-DOPA and not L-hydroxytryptophan that antagonized reserpine induced sedation while in the frog, it was 5-hydroxytryptophan and not L-DOPA that potentiated the sedative effect of reserpine. Our results corresponded with Arvid Carlsson's finding that in rats one could prevent reserpine-induced sedation with L-DOPA, but not with 5-hydroxytryptophan. It was mainly on the basis of these findings we assumed the mood elevating effect of antidepressants is related to serotonin. It eventually led to my appointment as Director of a Biochemical Laboratory in the Laboratory of Psychopharmacology. We had the capability to measure 5-HT brain tissue as well as the uptake, and inhibition of uptake, of 5-HT in blood platelets. About that time we proposed to use the "frog test" in screening for potential serotonergic antidepressants in the Soviet Union. Our proposal was rejected by the Soviet equivalent of the FDA. Our paper was also rejected by the Russian psychiatric journal. Our request to publish our "serotonin hypothesis" in the January issue of the *Lancet* in 1969 was, however, approved by the Ministry of Health, after a lengthy delay by the KGB.

TB: What about Carlsson's paper?

GO: It was published a few months later.

TB: So, your paper with Lapin was published first?

GO: Yes. This whole area of research was opened up by Lapin's findings that imipramine did not reverse, but potentiated the sedative effect of reserpine in frogs. After that we conducted a series of studies in frogs.

TB: Was it you who carried out those studies?

GO: Lapin did the first study which showed imipramine potentiated the effect of reserpine in frogs and my task was to find out why. A major part of my PhD Thesis, dealt with the “frog.” It was my finding that frog brain contains mostly serotonin, and has no noradrenaline or dopamine at all. In reserpine reversal by tricyclic antidepressants in rodents what we actually saw was that the effects of the noradrenergic system mask those of the serotonergic system. But, in the frog, you can study pure serotonin effects. About that point in time, a pharmaceutical company in Switzerland developed a drug that in rodents showed antidepressant effects, but did not seem to work clinically. We tested the substance in frogs and found it did not work as an antidepressant; it had a strong noradrenergic effect without any serotonergic properties. Based on the findings of our test it was clear the substance had potent noradrenergic effects, but, without serotonergic properties, it was not antidepressant. Our paper in the *Lancet* was very well received; it ended up as a citation classic. Our hypothesis was frequently referred to as the “serotonin hypothesis of depression” which we formulated prior to publication. In our hypothesis the emphasis was on the role of serotonin and tryptophan in the mechanism of action of antidepressants and not on the etiology of depressive disease. The two may or may not be related.

TB: Did the work with serotonin continue in the Laboratory after these two important publications?

GO: Yes. Simultaneously with our research, Samsonova, in our laboratory, was studying the pharmacology of the antidepressant effects of tryptophan. Serotonin, as you know, is a metabolite of tryptophan, and Lapin became interested in kynurenine, another metabolite of tryptophan.

TB: Is the “frog test” still in use for the screening of potential antidepressants?

GO: I think the “frog test” was used in the identification of both zimelidine and fluoxetine. But, in Finland, a researcher found it works in winter but not in summer. In summer you have to keep frogs in the refrigerator for a couple of weeks and then you can work with them.

TB: You said that it was not introduced in screening for antidepressants in the Soviet Union. Why?

GO: I suggested it for screening in Russia but a very prominent psychopharmacologist told me not to do it, and he would not help me because, “I don’t want to be accused of promoting mental depression in the frog.” It was the same fear from 1948 to 1950, when the Communist Government closed genetic and physiological studies.

TB: Before leaving Russia what else did you work on?

GO: I worked with serotonin uptake in platelets and with the dexamethasone test, especially in alcoholics. We found alcohol did have an effect on

serotonin uptake similar to antidepressants and that the escape of cortisone from suppression after the administration of dexamethasone at midnight is not present in all depressed subjects but is also present in other psychiatric diagnoses.

TB: In spite of the restrictions it seems you were in contact with many psychopharmacologists in the West.

GO: I went to the library regularly and asked colleagues for reprints from the West. Professor Lapin established and maintained contact with Western colleagues. We had many guests in the Laboratory including Sam Gershon, Joseph Knoll and the late Jerry Klerman. We also actively corresponded with Bill Bunney, Barney Carroll, Arvid Carlsson, Alfred Pletscher and Bernard Brodie. Merton Sandler's and Irv Kopin's visits left an indelible mark on my life.

TB: So, in 1979, you left?

GO: I arrived in Boston in December 1979 and invited to Duke University in Durham, North Carolina where Prof. Schanberg was kind to offer me a postdoctoral position for two years with the understanding I would get my medical license. I told him I would be happy to work as a PhD, but he strongly suggested getting my MD. Prof. Schanberg remained my guardian angel for many years, and chaired the credentials committee of ACNP in the year I was accepted as a member. From Durham I went to Boston and from 1980 to 1982 was a clinical Associate Professor at Boston University and a postdoctoral associate in the Department of Brain and Cognitive Sciences at the Massachusetts Institute of Technology. In Boston, it took me a year to get my medical license. Just about that time Sam Gershon moved from New York to Detroit, to become Chairman of the Department of Psychiatry at Wayne State University, and Lapin wrote him about me. So I applied and spent .six years with Sam. They were the happiest years in my career and during them serotonin was at the center of interest in the US.

TB: We are talking from about 1982 to 1988?

GO: Yes. Many of the things we did in Leningrad were redone here but with much better techniques. By that time we also knew that both serotonergic and noradrenergic mechanisms could be involved in the mechanism of action of antidepressants. It was in those years I became interested and involved in research with melatonin. I remembered from my research in Leningrad that, after injecting frogs with reserpine, the animals lost their righting reflex and then started twitching. As a third step we saw a yellowish-brown discoloration in their skin. It was not until I came to the United States I realized the discoloration was the result of melatonin and, if you give melatonin to a frog, you get this discoloration. I started to

think about the role of melatonin in the serotonin-norepinephrine balance and hypothesized it might be melatonin that's responsible for the antidepressant effect of drugs. To prove our hypothesis I collaborated with a fellow Sam hired in Australia, Dr. McIntyre. He was very talented chemist and we found that administration of melatonin has similar pharmacological effects seen with antidepressants. Then, after we demonstrated that clorgyline, an MAO-A inhibitor, stimulates melatonin production, Dennis Murphy and his group at NIMH became involved in studying the effects of selective MAO-A inhibitors in monkeys, and we became involved in studying the same drugs in humans. In addition to stimulating melatonin production, MAO-A inhibitors also decrease blood pressure. We were the first, in 1985, to prove the hypotensive effect of MAO-A inhibitors is mediated by melatonin. About ten years later melatonin's hypotensive effect became a very popular object of investigations. We then found the hypotensive effect of MAO-A inhibitors was mediated not only by melatonin, but also by its immediate precursor, N-acetylserotonin. Furthermore, we found not only melatonin, but also N-acetylserotonin, behaves as an antidepressant in some pharmacological tests. I started to study the pharmacological properties of N-acetylserotonin and found it prolonged life in mice. Then, we showed it decreases lipid peroxidation and production of tumor necrosis factor- α . So, the focus of my research moved from serotonin through melatonin to N-acetylserotonin.

TB: Are we still in the 1980s while you were in Detroit?

GO: Yes. Then, in 1988, Sam left and I was invited to Brown University to become a Professor of Psychiatry there. So I moved to Providence, Rhode Island and spent six years there. Then, in 1994, I moved to Boston to become Professor of Psychiatry at Tufts University and Chairman of Psychiatry at St. Elizabeth's Medical Center, a teaching hospital of Tufts University.

TB: It seems that during the years your activities shifted from pre-clinical to clinical. Did you do any clinical work in Russia?

GO: Some, but I was never an attending physician, except for the first years when I was in endocrinology. I was doing some clinical research in the Laboratory of Pharmacology with MAO-A inhibitors, tryptophan, and worked with alcoholics. After my arrival in the United States, while in Boston, I worked for two years as an attending psychiatrist in a State hospital. My position with Sam Gershon was looking after patients on the inpatient unit, and only in my spare time, after regular work, would I go to the laboratory because that was not what I was paid for. At Brown University, I was Chief of Psychiatry at the VA Hospital and seeing outpatients. When I was appointed Chair to the Department of Psychiatry at

St. Elizabeth's Medical Center, I gave up clinical work because I couldn't do everything. I inherited a residency program that was on probation and I had to attend to that immediately.

TB: How many residents do you have?

GO: Twenty. Clinical work today requires a lot of paper work and it wouldn't be proper use of my time.

TB: You said in Detroit you were in a clinical position.

GO: Right, but I also had an NIMH grant to study the dexamethasone test in Alzheimer's dementia. By the time I left Detroit we already had one paper published in Psychiatry. What we found was that only in women was there a correlation between the DST test and the clinical state. I would have liked to follow up those findings in Providence but at the VA hospital we only had male patients. So my grant was terminated but we got another from the VA to study the effects of benzodiazepines on melatonin and cholesterol, because benzodiazepines have a significant effect on lipid metabolism.

TB: What is your current research?

GO: We're studying the effect of N-acetylserotonin on aging. We found that it prolonged life in male but not female mice. These are long-term studies; it takes about two years to do them because one has to wait until all the mice die. We found that N-acetylserotonin decreases the oxidation of lipids and, recently, we started to study the possible antioxidant effect of some of its analogues.

TB: Any other research project you did or are currently doing you would like to talk about?

GO: We used light therapy for winter depression and also tried it in narcolepsy. We are participating in the CATIE project that is a very interesting project I feel very good about.

TB: Could you tell us something about the CATIE project?

GO: It is a multi-center comparative study in which some of the new antipsychotics are compared with some of the old ones.

TB: How many centers are involved?

GO: Thirty-five centers; all in the United States.

TB: Are all new atypical antipsychotics included in the study?

GO: We are using risperidone and olanzapine.

TB: What about the old drugs?

GO: Trilafon. But this is not just another comparative study of old and new drugs; we are also studying the effects of social factors on treatment.

TB: Who is the principal investigator of the project?

GO: Jeffrey Lieberman. The project is supported by an NIMH grant.

TB: Is it a placebo-controlled study?

GO: No. It's a double blind, parallel group design. It's a long-term study; patients who fail to respond to treatment in the first phase are moved into the next phase.

TB: What dosages are used?

GO: We have flexible doses with an upper cap.

TB: What would you consider your most important contribution to the field?

GO: The serotonin studies we conducted in the Laboratory of Psychopharmacology.

TB: Your early work?

GO: Yes, my early work because it attracted attention on the role of serotonin in the mechanism of action of antidepressants and stimulated research. I don't want to take full credit myself, of course, for that work. I also think the recognition of the role of melatonin in the action of antidepressants and that the antidepressants effect is related to their acute pharmacological action and we don't need to give them beyond two weeks to get optimal effects.

TB: Are you saying the duration of a clinical trial with an antidepressant should be no longer than two weeks?

GO: What I am saying is that we are dealing with an acute pharmacological action and not with chronic effects on receptors. If I fly from Boston to London, at the time I arrive in London my endogenous system is still "on Boston time" and would not produce melatonin until my endogenous cycle became adjusted. If I give an antidepressant that stimulates melatonin production it would help the endogenous cycle to synchronize with the new environmental day/night schedule. In our studies we found that for the first four nights after arrival there was no melatonin production and then it started up gradually. But, if you give melatonin in the first two nights, you help the transition. I see the pathology of depression as a product of the endogenous cycle of melatonin and antidepressants as substances that help correct it. This might not be the case in all types of depression; some patients relapse despite taking antidepressants for years.

TB: You don't think prophylactic therapy is necessary?

GO: Not the way it's done now. We need to follow patients, check them with regularity, and give them antidepressants when they need them. An effective way to use antidepressants is by infusion, but American psychiatrists are not familiar with it. In Europe it is widely used and within two hours of starting the infusion some patients are symptom free. When we stop the infusion the depressive symptoms re-appear and we need to repeat the infusion until the patient remains symptom free.

TB: Did you use antidepressants IV yourself?

- GO: I did, in collaboration with Prof. Khvelevetskiy.
- TB: Do you have any research grant to study antidepressants?
- GO: I have some industrial support.
- TB: So you are currently running a clinical department of psychiatry?
- GO: Right. But I also do basic research and teaching.
- TB: What was the last paper you published?
- GO: It was on the effect of N-acetylserotonin on aging.
- TB: Did your research interest shift from depression to aging?
- GO: Aging and depression have a lot in common, physiologically. In 1979 Dilman, Lapin and I published a chapter on “*Serotonin and aging*” in Essman’s five volumes “*Serotonin in Health and Disease*”.
- TB: So, your research in aging is a continuation of your research in depression?
- GO: Yes.
- TB: How did you get involved with ACNP?
- GO: Sam Gershon invited me to the annual meeting in 1982, and, since that time, I probably haven’t missed any of the meetings.
- TB: When did you become a member?
- GO: In 1999. I’m very proud of being a member. The annual meetings of ACNP are the best meetings I attend.
- TB: Are you active in the College?
- GO: I’m trying to be; I was on a committee and have presented papers and posters at annual meetings.
- TB: Am I correct you are involved in clinical trials as well?
- GO: I spend about two days weekly with clinical trials.
- TB: Where do you get the patients?
- GO: From the community.
- TB: Is there anything else you would like to add?
- GO: No, I think we covered more or less everything.
- TB: Thank you very much for sharing this information with us.
- GO: Thank you very much.

ROBERT M. POST

**Interviewed by Thomas A. Ban
Waikoloa Village, Hawaii, December 9, 2001**

TB: This is the annual meeting of the American College of Neuropsychopharmacology. We are in Hawaii. It is December 9, 2001, and this will be an interview with Dr. Robert Post* for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Where and when were you born? Tell us something about your early interests, education and how you got into neuropsychopharmacology.

RP: I was born September 16, 1942, in New Haven, Connecticut. I always had an interest in psychology and when I was an undergraduate at Yale, Robert Galambos gave us lectures on REM sleep. He told us about all the amazing neural activity that was happening and it turned me on to the whole issue of brain activity and behaviour.

TB: So, Robert Galambos's lecture had a major impact on you. Did you have any contact with him later?

RP: Not really. Even before I listened to Galambos' lectures my interest was tweaked about the brain by being a nurse's aid on the Yale inpatient psychiatry unit.

TB: You were born in New Haven and were an undergraduate at Yale?

RP: Yes. I wanted to go to school any place in the country except Yale, but my internist encouraged me to apply and I got in. I didn't bother applying to other places, so that's how I ended up there. I was a psychology major and that continued to stimulate my interest. Galambos came by for these lectures and, all of a sudden, I realized that everybody knew how the heart and the kidney worked, but the brain was a virtual mystery. Anything you found out about it, like REM sleep, was going to be new. That's how I got intrigued by neuroscience.

TB: When did you decide to become a physician?

RP: When I was young a kid with cerebral palsy knocked on the door of our house and I was shocked and distressed looking at him. Based on the image of that person and his suffering, I wanted to help people in some way, as a physician.

TB: Where did you go to medical school?

RP: At the University of Pennsylvania and then I had a mixed medical, neurology and pediatrics internship at Einstein in the Bronx.

TB: Where did you do your residency?

* Robert M. Post was born in New Haven, Connecticut in 1942.

RP: I had one year of psychiatry residency at Mass General Hospital when Biff Bunney, at the NIH, called and said, “We just had a researcher drop out. If you want to come as a clinical associate to the NIMH, we have a slot for you. If you come after three years, as a full psychiatric resident, we may or may not be able to take you in”. So, I went to the NIMH. Biff Bunney, Fred Goodwin and Dennis Murphy, interviewed me and they asked, “What do you want to do”? I said, “I don’t know, I’ll do anything you want”. They weren’t very impressed so I think they drew straws for who would not have to work with me, and Fred Goodwin lost, so he got me.

TB: How did Biff Bunney know about you?

RP: I’d applied to NIMH several years before but I didn’t pass the FBI background check for some unknown reason. I still don’t know why they said I was not eligible to enter the Public Health Service, but I remember saying when I was told I was not eligible, “You mean, I can be sent to Vietnam but I’m not good enough for the Public Health Service”? They said, “Yes”, I said, “Why”? And they said, “We can’t tell you”. I had my brother-in-law, a lawyer, who was in the Civil Liberties Union, start talking to people but he could never find out what was wrong. However, he stirred up enough Senators and Congressmen to confirm there wasn’t anything bad enough to disallow me from being in the Public Health Service. So, finally, I did get to the NIMH, but that was a very anxious year for me. They thought I had done some terrible thing, but I had no idea what that might be.

TB: Anyway, you got the job.

RP: I finally got in.

TB: What year did you get to NIH?

RP: In 1970 and I’ve been there more than thirty-seven years. Early in that clinical associate-ship, since I didn’t know in which research direction I should go, Biff and Fred said, “Why don’t you study cocaine? It’s a potent facilitator of the catecholamines and induces euphoria; it should be a good antidepressant.” I thought it was a silly idea, giving cocaine to depressed patients, but I said, “OK, if that’s what you want me to do.” The same thing happened in medical school. Dr. Jerry Smith, in physiology, was assigning topics and said, “You, Bob, should write about the role of the amygdala in the regulation of eating and affect”. I said, “You really want me to write on the amygdala”? I thought that was a really silly idea, too. But from that time forward, the amygdala has been involved in almost all of my thinking about affective illness as well as in bipolar disorder. These assigned topics turned out to be very big influence in the direction of my career. I didn’t choose those two topics, they were given to me, and I took off and ran with them.

- TB: Did you ever resume formal training in psychiatry?
- RP: I got one year of residency credit for the two years at NIMH and I needed another year to finish. I went to George Washington Hospital, and took seminars, particularly in child psychiatry. After two years working with Arnold Meyersburg I got another year of credit. That was at a time when they could approve three years at three separate places. They don't allow that any more.
- TB: Were you involved in seeing patients and clinical work all through the years at NIMH?
- RP: Yes. The first year, when I was a clinical associate, I worked with Joel Kotin, who has gone on to do psychoanalysis in Southern California. He was the ward chief and I was the person who was responsible for screening patients. Dr. Kotin was very skilful with those very difficult patients and extremely helpful in terms of getting my clinical career off the ground. I was very anxious about how to manage severely ill patients in the complexity of a clinical research environment. It was quite an education. Between Kotin's friendship and support and Fred Goodwin's mentoring, my research took off in the area of bipolar illness.
- TB: Could we get back to your research with cocaine in depression?
- RB: It turned out cocaine was not a very good antidepressant in serious depression. However, I got very interested in the acute and long term effects of cocaine, and found it paradoxically produced behavioural sensitization, rather than tolerance. Animals showed increased amounts of activity and stereotypy on repeated treatment and rats started having seizures on the same dose of cocaine which they previously tolerated well. So, what I observed was kindling-like phenomena.
- TB: You observed kindling-like phenomena with cocaine?
- R: Graham Goddard had just discovered, in 1969, electrical kindling of the amygdala. There was evidence that cocaine and lidocaine, as local anesthetics, were activating the amygdala and I began to think these drugs were kindling seizures, just like Goddard was with electrical stimulation. I began to study acute and chronic cocaine administration in animals to figure out why there was increasing response to cocaine over time, in terms of behaviour and seizures, rather than tolerance. That study of kindling focused me on the amygdala and subsequently to the anticonvulsants, such as carbamazepine, which are particularly good in inhibiting amygdala kindled seizures.
- TB: When was that?
- RP: In the early 1970's we got interested in that with Jim Ballenger, and postulated that if we could quiet the excitability of the amygdala, maybe we'd get mood-stabilizing effects. Also, patients with temporal lobe epilepsy

were having positive effects on mood with less depression when given carbamazepine (Tegretol). Based on these empirical data and the kindling notion, we became involved in research with carbamazepine. Just as we were getting started we found out Okuma in Japan had positive data on the mood stabilizing effect of carbamazepine in open studies. From the second patient in our double-blind study we learned that carbamazepine was an effective antimanic agent, because he got substantially better on the active drug, relapsed when it was substituted with placebo and responded again to the active drug. This was somebody who, at baseline, was very psychotic; he was hallucinating, screaming, and had to be kept in seclusion. He was non-responsive to lithium, yet was a really good responder to carbamazepine. From this off-on-off-on trial, we knew it would work for some people, and the only question was on what percent of patients. Currently, there are nineteen controlled studies showing that carbamazepine is effective in acute manic patients and more than a dozen that it is effective in prophylaxis.

TB: So, you were familiar with the Okuma's work in Japan when you started your carbamazepine studies.

RP: We found out about the Japanese work as we were thinking about using carbamazepine as a way of quieting down the amygdala system. We were already onto that idea when we found out they already had preliminary open data before our controlled studies.

TB: But you did the first double blind study using the on-off-on design with carbamazepine?

RP: Yes. In the mid 1970's, we did the first controlled study and published it in 1978. Shortly after, in 1979, Okuma published a controlled study and a lot of other groups followed suit.

TB: Were you looking for an alternative treatment to lithium?

RP: Yes, and it turned out to be very productive territory; now, other anti-convulsants are looking very good in the treatment of bipolar illness, particularly the latest, lamotrigine. Lamotrigine looks like it has excellent antidepressant effects, as opposed to carbamazepine and valproate, which have better antimanic than antidepressant effects. Lamotrigine has a different clinical profile and it may become a very important drug for bipolar depressed patients. In bipolar illness, depression is the most difficult component to treat.

TB: What response rate did you get with carbamazepine in your studies?

RP: About a sixty percent response rate in acute mania in people who failed lithium, so carbamazepine worked in some of the patients we were most interested in treating. Patients who did not respond to what conventional treatment in the community, came to us at the NIMH to participate in our

- research studies. So, a fifty to sixty percent response rate was pretty good in this treatment refractory subgroup of the bipolar population.
- TB: That is a pretty good response rate in this population.
- RP: Yes, and all our studies were double-blind with placebo control, using the off-on-off-on design and in many responders, another round of placebo followed the carbamazepine to confirm individual responsiveness on a double-blind basis.
- TB: Did you work with any of the other antidepressants or anticonvulsants in bipolar patients?
- RP: I worked with lamotrigine and gabapentin. In a placebo-controlled parallel group study it turned out lamotrigine was significantly more effective than either gabapentin or placebo in bipolar illness and in depression.
- TB: Didn't you work at a certain point in time with Irwin Kopin?
- RP: After I was at the NIMH, as a clinical associate for two years, I had the opportunity of going either to Yale, to work with George Heninger and Malcolm Bowers, or to Pittsburgh, to work with David Kupfer, or staying at the NIMH. After much agonizing, I decided to stay at the NIMH and have a third year fellowship with Irwin Kopin during which I did some work in the lab.
- TB: What did you do with Irwin?
- RP: I worked on catecholamine metabolism and the effects of stress, but I didn't become a lab person like most people did. I continued my clinical research work but was very influenced by Irwin's work on catecholamines and stress.
- TB: Is there anyone else you worked with?
- RP: Jerry Smith, the physiologist, back in medical school tweaked me into studying the limbic system.
- TB: With whom did you work after Irwin?
- RP: After the year with Irwin, Biff Bunney offered me a job in his Biological Psychiatry Branch, and I took over running a clinical research unit. On that unit I was greatly influenced by all of the young clinical associates who came to work with me. John Carman and Fred Stoddard were the first. Carman had what appeared to be the ridiculous idea that calcium was important in signal transduction and we studied plasma and CSF calcium, which nobody else did. Now it turns out that calcium is a central player in signal transduction. Carman also had the idea that dopamine was important in depression. At that time everybody else was thinking about norepinephrine and serotonin in depression. There was Schildkraut's catecholamine hypothesis, Bunney and Davis had norepinephrine as the key substance in their theories of mania and depression, and Curzon, Van Praag and others had serotonin as a central player. Then here's this

young kid, Carman, with a big beard and high heel shoes, saying that “dopamine is the critical player”. His ideas directed us towards the role of dopamine in depression and mania, another theme I never really left. With Bob Gerner and David Jimerson we studied a direct dopamine agonist used for Parkinson’s disease, called ET495 or piribedil, which turned out had very nice antidepressant effects. This work helped bring the role of dopamine in affective illness into the foreground. Then, dopamine reuptake blockers came along as antidepressants.

TB: When did you begin with this line of research?

RP: That began about four years after I arrived. During my first year as head of a unit, I was studying bipolar illness. The first two patients were profoundly manic; they left the unit and threatened the President of the U.S. and the head of the NIH. They were running all around before we figured out how to contain them. It was very interesting to learn how to approach and treat patients with bipolar illness.

TB: Didn’t you also work with unipolar patients?

RP: I did some work with refractory unipolar depression but for the last twenty-five years I always had about two-thirds, bipolar patients and one-third, refractory depression patients on our research unit.

TB: You said Carman generated some research projects with calcium and also with dopamine. Did any of the other clinical associates generate new projects?

RP: Each clinical associate who came to work with me brought some novel ideas. We tried to run with those as much as possible and that turned out to be very, very productive. We got into research with the thyrotropin releasing hormone, TRH with other associates. One of the latest associates was Mark George, who started work on our unit using repeated transcranial magnetic stimulation (rTMS) of the brain, with Eric Wasserman and Mark Hallett of the Neurology Institute. We’re the first group to use high frequency, 20 Hz, repeated stimulation of the brain with magnets, over the left prefrontal cortex in depression. Now rTMS is looking promising as an antidepressant modality. We’re currently comparing the effect of high frequency 20 Hz, and low frequency 1 Hz rTMS with Andy Speer on cerebral blood flow, as measured by PET, and we found that 20 Hz produced a long-lasting, widespread increase in blood flow, while 1 Hz decreased it. Individual patients appear to respond preferentially to high or low frequency rTMS, and we are trying to see if we can predict this on the basis of their pre-treatment PET.

TB: So, you got involved after your arrival at NIMH in areas of research you had little or no prior experience with as well as using sophisticated technology.

-
- RP: That was clearly the case. When I arrived to NIMH, learning neurochemistry was like learning a foreign language. I had no idea what the catecholamines were or what the term biosynthetic pathway meant. They were talking rapidly in this foreign language and I didn't know any of the words. I was a complete foreigner, but became totally immersed in the atmosphere.
- TB: You had to learn that new language fast.
- RP: I tried.
- TB: You had to feel as if dropped into another country.
- RP: You had to learn quickly if you didn't want to starve to death.
- TB: But you got involved promptly with bipolar patients?
- RP: Yes, I was taking care of bipolar patients who we had to get better even though lots of them were not responding to lithium. That drove us to look for alternatives and that's how we got to study the anticonvulsant, carbamazepine. It was to quiet down the limbic hyperexcitability, the affective dysregulation, that Papez, MacLean and others postulated.
- TB: Where did you get your patients from?
- RP: They were referred from all over the country and sometimes from outside the US. That's continued to this day, but patients are now even more treatment refractory than they were in early days. They used to come in just non-responsive to lithium. Later, they were non-responsive to lithium and carbamazepine and so we had to try valproate. More recently they are coming non-responsive to lithium, carbamazepine and valproate, so we have started a new protocol with lamotrigine. Lamotrigine worked about 50% of the time in these highly treatment refractory patients and was superior to both gabapentin and placebo. We have been getting more and more refractory patients over time. In the seventies, we used to be able to discharge patients on one drug, and we could do that about seventy-five to eighty percent of the time. We had good success early on, sending them back on one drug. Now we achieve the same positive results, but it takes three or four drugs on average. So it's getting harder and harder to stabilize these patients.
- TB: How much neuroleptics, are you using?
- RP: At NIMH, we had this unique opportunity to try to find treatments without the usual time limits. Since patients then could stay as long as they need, it was possible to use the time to try and figure out what would work, even if the first several drugs we tried didn't help. We were able to explore different treatment strategies, and, as a result, discharged almost all our patients without the need for neuroleptic treatment. Only about ten to fifteen percent of the patients had neuroleptics in their regimen when they left the NIMH. We could deal effectively with manic psychosis and

psychotic depression without neuroleptics, which was important in terms of trying to avoid tardive dyskinesia. We were working largely with lithium, mood stabilizing anticonvulsants, thyroid augmentation and nimodipine, an L-type calcium channel blocker. We tried these and other treatment approaches in order to avoid neuroleptics, and we found we could succeed most of the time.

TB: So, you tried to avoid the use of neuroleptics because of concerns of tardive dyskinesia?

RP: Yes, during the medication free periods, when we were trying to contain patients we used either seclusion or wet sheet packs. As our studies and interventions progressed we began treating the patients earlier and earlier, and the need for wet sheet packs fell by the wayside.

TB: This was in 1970 and, instead of giving them chlorpromazine or haloperidol, you used wet sheet packs, right?

RP: Right.

TB: And seclusion?

RP: Yes, both.

TB: And, you were waiting until lithium started to work?

RP: Lithium or other experimental drugs, like carbamazepine, valproate, nimodipine, and lamotrigine. We got some very excited manic patients through the medication free periods with these measures.

TB: How often did you use ECT?

RP: We used ECT about once or twice a year.

TB: So not frequently?

RP: Not very frequently. But we were always struck with how effective and rapidly ECT worked in patients who failed to respond to everything available at the time.

TB: So, you were impressed with ECT?

RP: Early on I was impressed. It was only in recent years we began to see more equivocal responses in some patients to ECT. Our findings were like those of Harold Sackheim's group, who achieved an eighty percent response rate in patients who are relatively treatment naive, but only a 50% response rate in those who are treatment refractory. Our patients were pan-refractory, so ECT has lost its' halo. We saw some patients become tolerant to the therapeutic effects of ECT, and some patients had severe memory problems. The other problem with our bipolar patients was that many of them were rapid cyclers and even if they had a good response to ECT, we still had to figure out what to do next in preventive psychopharmacology. So, we tried to come up with a pharmacological regimen on which they could go home for long-term maintenance.

TB: Rapid cycling is a relatively new concept. Could you define it for us?

- RP: Dave Dunner came up with the category in the early nineteen-eighties. He defined rapid cycling as more than four episodes per year and found these patients were less likely to respond to lithium. We saw more and more patients who had four episodes per year. We also began to see ultra rapid cyclers who had four episodes a month. With Keith Kramlinger and Mark George, we wrote papers on ultra-rapid cycling and ultradian cycling. We were seeing patients with classic manic-depressive illness switching many times within a single day. It turns out that the cycling spectrum is on a continuum with no distinct cut off at the traditional marker of four per year.
- TB: What was the proportion of rapid cyclers among the patients you had?
- RP: It was fifteen percent in the 1970's and now, at the end of the 1990's, it is seventy-five percent in patients who come to NIMH. This is probably why we have to discharge them now on regimens involving many more medications. Patients in the more recent cohorts have earlier onset of illness, more time depressed and more rapid cycling prior to being included in our studies. So they had all sorts of negative prognostic characteristics.
- TB: So, you are getting more severe patients than before.
- RP: Right. The question arises, is this due to better treatment of patients in the community as a result of which we are getting only the most refractory patients, or is the same thing happening in the community? I think it's a bit of both, as Myrna Weissman and Elliot Gershon have demonstrated a cohort effect. The age of onset for unipolar and bipolar illness is moving earlier and the incidence or prevalence is moving higher in every generation since World War I. Earlier age of onset of affective illness, higher incidence of rapid cycling and treatment resistance are more frequent than before also in the general community.
- TB: How many patients you have on your unit?
- RP: We only have twelve beds; it's a small unit. We had to make a choice whether we were going to try to do acute studies with a high patient turnover or study fewer patients longitudinally. From the beginning we decided to look at the long term effects of treatment. We wanted to figure out what was happening over time, how we could slow the progression of the illness and deal better with people who were treatment refractory. We wanted to see if they didn't respond to X, whether they would respond to Y or Z, or the combination of X, Y and Z. It turned out that treatment with complex combinations, especially in the more recent cohorts, was necessary. Mark Frye wrote a paper showing that we needed more and more poly-pharmacy to get the same degree of efficacy, and this was running in parallel with patients having faster cycling, earlier age of onset and more time depressed prior to coming to NIH.

TB: So, the natural course of the illness has changed?

RP: To some extent there is sensitization or kindling effects in the course of untreated illness. That notion was put forward first by Emil Kraepelin. He noted that recurrences were coming faster and faster with shorter well intervals; that initial episodes were triggered by psychosocial stressors and, then, with enough recurrences, they started automatically. Those two fundamentals of the sensitization-kindling hypothesis were described by him, at the very beginning.

TB: You were trying to get information on the natural course of manic-depressive illness before it was re-named bipolar disorder?

RP: We tried to get descriptions of what the illness was like and how it evolved over time. Since we were looking at the long-term course, we got very interested in descriptions of the illness before there were good treatments available, to define the naturalistic course. We found our treatment refractory patients were having the cyclic acceleration Kraepelin described, which occurred despite the medications they were given.

TB: In which edition of his textbook did Kraepelin describe the cyclic acceleration we are talking about?

RP: His book published in 1921. He described everything anybody could want to know about the natural course of manic-depressive illness. And we have seen everything Kraepelin described. Every time we thought we saw something new, we went back to the book and saw it was perfectly described seventy years before.

TB: Did you find the bipolar population a homogeneous group?

RP: We decided to take a very agnostic approach to see what the illness told us. Kraepelin did some charts on his patients and showed that episodes were totally chaotic and unpredictable. However, as an overall pattern, he found episodes would occur with shorter and shorter well intervals between each successive episode. So we decided that the best thing to do was to adopt a Kraepelinian type of mood charting to more precisely map the course of illness of our patients.

TB: You were charting the mood of patients on your unit?

RP: We did very detailed mood charting, rating patients every day.

TB: What were you rating?

RP: Mania and depression severity based on the degree of functional incapacity; how much they affected patients social, educational or occupational functioning. They were rated mild, low moderate, high moderate and severe, in terms of incapacity associated with their mania or depression. And, with these daily ratings, we could, for the first time, accurately describe the precise course of illness. Bipolar illness is the most pleomorphic illness in psychiatry. You can have all patterns, all frequencies

of both mania and depression. That's one of the reasons bipolar illness is so understudied relative to schizophrenia; the methodology is difficult because of the tremendous heterogeneity. We tried to describe the course of illness and its' variations, rather than arbitrarily deciding an episode had to be two weeks or it wasn't an episode. We saw patients going manic and being in seclusion for one or two days and then being almost catatonic and depressed for another two days. These patients would not meet classic criteria for an episode but it was a clear-cut all or none phenomena.

TB: You didn't stick with DSM criteria?

RP: We did comply with it, but once those criteria were met we followed patients carefully to find what the real variations were. This is like the story of recurrent brief depression, where Jules Angst and Stuart Montgomery pulled the concept together, because DSM wouldn't allow you to diagnose a depressive episode unless it lasted two weeks. They found these recurrent brief depressions, just as we found recurrent brief manias. We also found fast patterns of mood switches, even within a day, tended to occur late in the illness. So, sensitization has been validated in the literature by us and others, just like Kraepelin described them. The best data for validating the episode sensitization effect are from Kessing and colleagues who looked at it in the Danish case registry in more than 20,000 unipolar and bipolar depressed patients. They found the rate of relapse and the latency to relapse was directly proportional to the number of previous depressive episodes. So the notion that episodes sensitize to further and faster recurrences is definitely supported in the literature. The other fundamental Kraepelinian type of sensitization is that initial episodes are triggered by stressors but, after frequent episodes, they can occur on their own, was elegantly documented in unipolar depression by Ken Kendler. In 1992 I did a literature review on all of the studies that looked at stressors as a function of number of episodes. Kendler has shown that over the first 7 to 9 episodes of unipolar depression, stressors are involved as triggers to a successively lesser degree and, after that, stressors don't seem to be necessary precipitants anymore. The relationship between stressors and the occurrence of episodes plateaus after the first 7 to 9 episodes. So, both the stress sensitization and the episode sensitization concepts we derived from the cocaine sensitization rodent models, seem to hold in recurrent unipolar and bipolar illnesses.

TB: The concept of bipolar illness in the German literature is not restricted to manic-depressive illness but includes other illnesses. Did you have any interest in those?

RP: We looked at some of those, for example periodic catatonia Gjessing described, but decided to just take the illness forms and see how they went along with different clinical phenomena and response to treatment. The DSM confused the issue when they used the term mixed states. Mixed states can either be extremely fast variations in mood or more continuous dysphoric mania. You can differentiate which part of mixed states is ultra-ultra, rapid cycling, like back and forth switching within minutes to hours, ultradish cycling, and which is dysphoric mania. The cycling can be between severe depression and either euphoric or dysphoric mania. With our rating instrument, the NIMH Life Chart Method (LCM) you can handle all those concepts descriptively.

TB: So, you collected all the information you could?

RP: We hope we did.

TB: That in itself is a major contribution.

RP: The NIMH-LCM is one of the more important contributions for both prospective research and clinical care. When I see patients I have them do daily life charts. When I do rounds on the patients on the unit every Monday morning, the first thing I say is “Hi, how are things going?” and I ask to see their mood chart. In this way the patient and I can be in synchrony in an instant about where their mood is, how severe it is, and whether they’re improving or not. I don’t need to spend the first ten or fifteen minutes, to interview them for finding out about that information. We know immediately, and then we can get to more important issues in the short time available for rounds. We can discuss and think about what the alternative approaches are and how to deal with a patient’s illness. I ask all my patients to chart their mood on a daily basis and bring that in so we can treat their residual symptoms.

TB: On how many patients do you have data?

RP: The NIMH inpatient cohort we have good retrospective and prospective life charts on is about three or four hundred patients. We now also have a collaborative outpatient project that is another nine hundred patients.

TB: That’s quite a number. How do your findings compare to those of Paul Grof?

RP: Paul Grof was one of the first to show the sensitization phenomena in recurrent unipolar patients, where the episodes got closer and closer together. He also has some unique cohorts of highly lithium responsive patients he’s been able to garner over the years. He studies lithium responsive patients and keeps them, as opposed to the NIMH, where we rarely see them again.

TB: His population and yours are different?

- RP: To some extent they are. I get more and more impressed with the heterogeneity of the illness and that some people are lithium responsive whereas others are not. Some of this is going to get sorted out when we have the right combination of clinical, physiological and SNP profiling for treatment response.
- TB: Paul Grof spent a couple of years at NIMH. Was he working with you?
- RP: He worked closely with Fred Goodwin, but I got to know him later.
- TB: What about Jules Angst and his data?
- RP: Same thing. He chose to look at the illness, both in detail and longitudinally and now has a wonderful cohort of patients in which he has studied all the illness variations. He thinks that some five percent of the general public consists of patients in the bipolar spectrum. It's not just the one or two percent of bipolar I and bipolar II, but there's a whole spectrum of patients he can identify. He counts recurrent brief hypomania in variations of the bipolar spectrum. Angst broadened the concept like Hagop Akiskal did, and has the data to support that. What's so beautiful in his cohort is that he's got longitudinal prospective data.
- TB: What about Mogens Schou, what kind of data did he have?
- RP: Gorgeous data, and when British critics said lithium really didn't work Schou went back and did other studies which reconfirmed lithium's efficacy in long term prevention of manic and depressive episodes
- TB: What happened with his cohort of patients? Who is following them now?
- RP: I don't think anybody is in that same way but Per Vestergaard is following some of his patients.
- TB: What happened to Paul Grof's cohort after he moved from Hamilton to Ottawa?
- RP: I don't know.
- TB: Was David Dunner at NIMH during your time?
- RP: No, he was at NIMH right before me.
- TB: He became known for coining bipolar II disease?
- RP: Yes.
- TB: Was the work you did with John Carman followed up?
- RP: We measured calcium in plasma and spinal fluid and found it was elevated in depression. Ten or twelve years later, with Peggy Pazzaglia, we began to study calcium channel blockers. We were impressed with reports that verapamil, the L-type calcium channel blocker, was effective in mania in many small double blind controlled-studies, but when we saw that no one ever used it in spite of the positive data we thought that there must be something wrong. So we decided not to study verapamil, but instead studied the dihydropyridine calcium channel blocker, nimodipine, which seemed different from verapamil by having an anticonvulsant

action. Nimodipine has effects on dopamine release and blocks cocaine hyperactivity, whereas verapamil does not. Nimodipine is also positive in animal models of depression while verapamil is not. We gave nimodipine to our treatment refractory bipolar patients and found it did have effects in very rapid cycling and ultra rapid cycling cases on both the manic and depressive phases. The dihydropyridine calcium channel blockers are definitely worth a further look in both phases of bipolar illness.

TB: Do you think that nimodipine works also in treatment refractory depressed patients?

RP: Possibly. The problem with nimodipine is it's only approved for subarachnoid hemorrhage; treatment in daily doses as high as 400 to 500 milligrams would cost something like twenty-five thousand dollars a year. We think the other dihydropyridines, like isradipine and amlodipine, may be equally effective and less expensive.

TB: So you think the dihydropyridine calcium channel blockers are more suitable for treating bipolar illness than the other L-type calcium channel blockers?

RP: We've crossed a few patients over double blind from nimodipine to verapamil and they didn't remain well. They'd break through with depression and when we switched them back to another dihydropyridine such as isradipine, they would regain a response. So, even though there are few systematic data, I might try amlodipine, who were nimodipine responders or couldn't tolerate lithium and were switching moods within 24 hours, because it has a long half life and can be dosed on a once daily basis.

TB: Would you consider calcium channel blockers an alternative treatment of lithium?

RP: Yes, particularly for good lithium responders who are intolerant to lithium. Yet, they are typically not high up in the treatment algorithm. I would usually attempt to use several other mood stabilizers and combinations prior to using nimodipine.

TB: So, you would use combinations as a first alternative?

RP: Several drugs in combination or an atypical antipsychotic if needed. I would use mood stabilizers and more mood stabilizers, even thyroid augmentation, antidepressants and atypical antipsychotics and then, somewhere further in the treatment sequence, calcium channel blockers might fit in, but not very early except for those with ultradian-cycling.

TB: Okay.

RP: A patient came to me, who was a flutist, on lithium and doing beautifully, but she had a lithium tremor and couldn't play the flute as well as she would have liked. Every time she lowered her dose of lithium, she'd start to relapse. But now she's done equally well on calcium channel blockers

as a supplement to her lower but well tolerated dose of lithium. It's people, who are cycling in an ultradian pattern or can't tolerate lithium, who are the ones I use calcium channel blockers on.

TB: Was propranolol tried in your flutist to control her tremor?

RP: Yes, and it didn't work.

TB: Do you have data on drug combinations?

RP: No, there is almost no systematic comparative data in the field on drug combinations, and that's a problem. Everybody is now using complex combination therapies, three to five drugs on the average, but it's not like cancer chemotherapy where they know one combination works better than another based on controlled trials. We don't have those kinds of systematic data on combination therapy in this field, partly because of controversy about what's the best methodology. Because of the variability in bipolar illness, it's very difficult to have treatment studies funded by the NIMH. Since Bob Prien's studies twenty-five years ago, Joe Calabrese's on prophylaxis are the first studies NIMH has funded in the area. It's a catastrophe! There is a need to study complex combination therapies and how to put them into appropriate algorithms. There needs to be a methodology to figure out better treatments for patients.

TB: Are you trying to develop a new methodology?

RP: I'm trying to find reliable and valid markers of the illness and ways of evaluating treatment response, so we can confirm what works and what doesn't. We have to start doing clinical trials of combination therapy systematically. That's beginning to be done in our Bipolar Collaborative Network and by a few of the drug companies, who are finally doing add-on studies. All of the new anticonvulsants have been FDA approved as add-on's, for refractory epilepsy. But, in psychiatry, we keep insisting on monotherapy even though it doesn't work well for the vast majority of patients with bipolar illness. That's an area where we need more data.

TB: Would you like to say something about your findings with brain imaging?

RP: We're finding that some unipolar and bipolar depressed patients have the classic frontal hypometabolism on PET scans but others are hyperactive during depression. These two types of patients respond differentially to high frequency vs. low frequency rTMS. High frequency rTMS increases toward normal the low baseline patterns of prefrontal activity, and conversely 1 Hz or low frequency rTMS drives down the pattern of prefrontal hyperactivity. When patients are matched to the right frequency of rTMS, according to baseline activity on PET scan, this may help in prediction of a positive response. That's one thing Dr. Andy Speer is doing, mostly in unipolar patients, but also in some bipolars.

TB: You have recently turned your unit over to one of your associates? Are you still involved in research on the unit?

RP: I am more involved in design, analysis, and interpretation of the studies, but I don't do the rTMS or brain imaging procedures.

TB: What is your position at NIMH?

RP: I went from Unit to Section Chief to Acting Branch Chief and, for the last twenty or so years, I've been Chief of the Biological Psychiatry Branch, the clinical equivalent of a lab chief. The Biological Psychiatry Branch used to be an enormous lab, under Biff Bunney. When I took over it got considerably smaller and now just one clinical focus, on rTMS. We are not doing any animal laboratory work I'd been doing with Dr. Susan Weiss. She'd been doing all the kindling and cocaine sensitization work but that lab is closed, as well as our neurochemistry lab.

TB: So the group has reduced in size?

RP: Yes, and now, it's just a small clinical group with a total of eight people; one physician, a social worker, and several research assistants and secretaries.

TB: What would you consider your most important contribution in the field?

RP: My important contribution, I think, is around the longitudinal view of recurrent bipolar affective disorders; as often following a kindling-like course; the idea that episodes can speed up over time and one can get sensitized to stressors and substance of abuse, such as cocaine; and that if you intervene early with effective prophylaxis, you may be able to ward off the adverse consequences in these otherwise recurrent illnesses. That's what I'd like to do next, treat bipolar illness in kids early, to see if it makes a difference over the course of their life. The notion of affective recurrences initiate a downhill course emphasizes the importance of episode prevention, so early treatment maybe more important than anything else.

TB: Do you mean by starting treatment in children?

RP: It would be good to do in those with childhood onset.

TB: What is the current status in that area of research? Have you done any studies in children?

RP: We designed a study for very high-risk bipolar kids, who have bi-lineal pedigrees. When they become symptomatic, even before they get the whole full-blown illness, one should consider treating them. We did a survey that asked parents whether they would volunteer their kids for that kind of study and they said they definitely would. But, so far, we haven't been able to put the study together.

TB: Is there any other area of research you have been involved with we haven't touched upon?

-
- RP: No. The central theme of my research is how to treat patients with bipolar illness more effectively. This idea of early intervention would be a new territory, driven by patient needs. Early intervention would fit in with the theoretical overview of the kindling hypothesis that the illness can be progressive. If you could treat early, you might save people a tremendous amount of grief, like with malignancy. If you take it out early, before it metastasizes, it's a lot easier to treat.
- TB: Do you remember what your first publication was?
- RP: An article with Joel Kotin in which we reported that most patients with depression who came to our unit were under-treated. The disturbing thing is, even though we do much better now, there are still a tremendous number of patients in the community who are not being treated for serious depression and, even worse, for bipolar illness. In our outpatient bipolar collaborative network, we're finding an average of ten years delay between the onset of first affective symptoms causing dysfunction and the first treatment. The delay has horrendous consequences. Not only are people ill and suffering, but the continuous presence of symptoms may be making the brain more vulnerable to cell dysfunction and further recurrences.
- TB: What was your last publication?
- RP: The last one was a description of the illness morbidity naturalistically treated bipolar patients had. The first two hundred and fifty-three patients in our outpatient collaborative network had considerable morbidity after one year of prospective naturalistic treatment. About two-thirds of patients in this cohort were still markedly impacted by their bipolar illness, despite being treated with an average of four classes of pharmacological agents. In that paper we also examined what were the predictors of who did well vs. who did poorly, and those with earlier and onset and more and more prior episodes fared the worst.
- TB: When did you get involved with ACNP?
- RP: I was very fortunate that Fred Goodwin, early on, brought me to one of the ACNP meetings. I was like a kid in a candy store. I went to every session and thought everyone had new and exciting findings. The ACNP has always been the key meeting in my professional life and continues to be.
- TB: When did you attend the first annual meeting?
- RP: Probably in the late seventies or early eighties. It's a long time ago but it's been a consistently wonderful experience.
- TB: Have you been active in presenting papers?
- RP: I have been a presenter or discussant many times, and always an interested and active participant.
- TB: Have you been active in committees?

RP: I've been totally absorbed in clinical research, so I haven't been very active in the college. I was on one of the training committees getting young investigators to the ACNP, and now I am on the liaison committee.

TB: Weren't you the recipient of one of the ACNP research awards?

RP: I received the ACNP Daniel Efron Research Award a number of years ago, and it's one of the awards I'm the most proud of. To get the award from my colleagues was wonderful.

TB: Any other awards?

RP: I got the A. E. Bennett Award and the Gold Medal Award from the Society of Biological Psychiatry, an award from the American Psychiatry Association, the International Anna Monika Prize and several other prizes like that. It was also very meaningful to win prizes from some of the patient associations; the Klerman Award from the National Depressive and Manic Depressive Association (NMDA) now called the DBSA, and two NARSAD awards, one for lifetime research on bipolar illness.

TB: Do you have a family?

RP: A wonderful family; my wife, Susan, and a daughter, Laura, who married in September, right after the 9/11 catastrophe, and a son, David. Neither of my children wanted to go into medicine. They're both teachers, which is great.

TB: Any other interest beside your research?

RP: I am a golfer. I played on the high school team and on an intramural college team but I didn't quite make the Yale Varsity. but I was close, only two strokes away.

TB: Is there anything you would like to see happen in the field?

RP: I hope we can get over the current controversies about how bipolar illness presents in children so we can treat them earlier and more effectively. A key issue, for both children and adults, is figuring out which medication works for which patient and which combinations work best. It would be wonderful to have systematic data in those areas.

TB: Do you think we have progressed in your area of research during the past 30 years?

RP: In spite of the funding shortfalls in bipolar illness, the field has advanced remarkably from having lithium, neuroleptics and antidepressants to a huge range of options. All we have to do is figure out how to put them into play in the best way.

TB: And, you feel strongly that it would be very important to have better funding?

RP: Oh, yes, better funding for bipolar illness treatment research and somehow getting over the methodological issues so there are more NIMH funded studies. Even at the ACNP, there are four to five times more panels on

schizophrenia than on bipolar illness despite the greater prevalence of bipolar disease. Investigators get discouraged because of the funding shortfalls so I hope that can change.

TB: Thank you very much for sharing all this information with us.

RP: Thank you for asking and listening to all these clinical treatment issues. And thanks to the ACNP for everything they've done for me personally and the field of mental illness research in general.

WILLIAM Z. POTTER

**Interviewed by Thomas A. Ban
San Juan, Puerto Rico, December 8, 2003**

TB: This will be an interview with Dr. William Potter* for the archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College, in San Juan, Puerto Rico. It is December 8, 2003. I'm Thomas Ban. Let's start from the beginning; when and where were you born? Tell us something about your education.

WP: I was born on April 3, 1945 in Charleston, South Carolina. At that point my father was still in medical school, somewhat older than the rest in his class. He had gone back to medical school during World War II after working in the state public health service in South Carolina. My mother's family had come from the south, and my father's family had been from Tennessee and North Carolina. My father did not like the strained race relations in South Carolina and when I was about four years old he moved us to Ridgeville, Indiana, a small town of about a 1,000 people. I was brought up in this small mid-western town, although all my family was from the south. My father was in partnership with an older doctor who died tragically in an automobile accident two or three years after we arrived. So my father became the only doctor for an area of many miles and would rotate back and forth between two county hospitals 15 miles apart. As a child, I would ride with him to visit patients in their homes. My father's office, with my mother's help, also ran a pharmacy because there was no drugstore in the town. He diagnosed and treated patients and was doing lots of minor surgery. The pharmacy allowed him to charge patients very little; many weren't charged at all except for the medicine. He was very much the country doctor. Seeing the way my father lived, both my older brothers decided they would not study medicine, but I picked up the idea medicine was important. The educational system in the town where we lived was very bad so my parents decided it would be good for me to have the opportunity to get a better education and I was sent to a boarding school outside Cleveland, Ohio: Western Reserve Academy. It was a very good boarding school with sixty people in each year. A fifth would do extremely well and it was competitive. A lot of graduates from Western Reserve went on to East Coast schools but I won a full scholarship to school in England for a year. There I studied A-levels in history and became interested in philosophy. In the meantime my father had been ill, so I decided to go to Indiana University on return from England. There, I

* William Z. Potter was born in Charleston, South Carolina in 1945.

was able to do my undergraduate work in a couple of years. About that time the NIMH had been funding MD/PhD programs and I was accepted for one. I had a vision of becoming a well-educated doctor, and I planned to do a PhD in philosophy along with my MD. So I was taking my pre-clinical courses for medical school while attending courses in philosophy. I was a very good student in philosophy but they would not give me a fellowship because they knew I intended to become a doctor; it would be a waste of money. I thought this was not in the spirit of the program and went to my advisor, Lyle Beck, a very nice older gentleman in the Department of Pharmacology. When he learned about my problem he said I could work in his department. So I did, and I earned money washing dishes in the Department of Pharmacology. They also involved me in experiments measuring insulin levels, using a radioimmunoassay technique.

TB: When did this happen?

WP: This was back in the 1960s. Radioimmunoassays had only been out for a couple of years at the time but I got lab experience and handled pipettes pretty well. They suggested I do a degree in pharmacology, so I did. This is how I got into pharmacology.

TB: What year?

WP: In 1966 I switched from philosophy to pharmacology and later received my masters in pharmacology. My early research and first papers were on the effects of hydrazine that was used originally as rocket fuel but there were concerns it might be a hazard for astronauts exposed to it. The research was prompted by reports hydrazine produced dramatic changes in blood glucose in rats. In the course of that research I learned how to cannulate rat arteries. That was not a routine procedure so I had to work out how to do it. I learned you could work things out for yourself in the lab; that you could develop new assays just by reading papers. By the time I received my MD the Vietnam War was on and I had the choice to be drafted or get a NIH fellowship in the PRAT program.

TB: When was that?

WP: In 1971. I remember interviewing with BB Brodie who asked what I was interested in, and I explained some of the research I did and how I enjoyed it. Then he went on an incredible riff about coming back from Australia where sheep were dying of liver failure, and he got to thinking about what might be going on. To make a long story short, his view was there might have been an active metabolite being formed from a substance causing liver necrosis. I said, Dr. Brodie, I don't know anything about liver necrosis. "Good," he told me, and literally picked up the phone to call the secretary of the PRAT program and said "Bill Potter is coming to my

laboratory.” I later became very involved in NIMH’s PRAT Program and learned about the rules for bringing people in. He was highhanded, but if you were BB Brodie, you could be like that. And working in Brodie’s lab on how active metabolites of drugs can cause liver necrosis was an incredible experience. My first decent papers were all related to acetaminophen-induced hepatotoxicity. It was a classic series of articles which are still frequently cited. A group of us with a guy called Jerry Mitchell were involved. Brody’s name was on all of them, and sometimes Jim Gillette. I also remember that under the pressure of meeting presentation deadlines we had difficulty to reproduce acetaminophen induced toxicity in the rat. You could convince yourself the findings were there, but we had to heat up the acetaminophen, which didn’t get in the solution very well, ram it down the rat’s throat, and sometimes you would get results and some times you wouldn’t. This made me nervous, because being new you wanted to have clean results. About that time, and I’m pretty sure it was BB Brody who said, why don’t we look at other animals? I will never forget the experiment injecting acetaminophen in a series of rabbits, guinea pigs, mice and hamsters; on autopsy we saw nothing in rabbits and guinea pigs, but when we opened up the hamsters and mice, the livers were white. Working in Brodie’s lab taught me to make an experiment work one needs a good animal model and very robust end-points. In that lab I would also try to show chlorpromazine might be activated to something that causes hepatotoxicity but that turned out to be due to a different mechanism. During that time I realized I wanted to take laboratory science and apply it to developing new treatments; I also decided to do a residency in psychiatry.

TB: What year was that?

WP: In 1974. After a three year PRAT fellowship, rather than staying in the Heart and Lung Institute I entered psychiatric residency at St. Elizabeths Hospital. I forgot to mention my PhD dissertation was done at the National Heart and Lung Institute with the cooperation of Roger Michael. Indiana University allowed me to do my PhD work at NIH.

TB: You got your PhD from Indiana University but did the work at NIH.

WP: Yes. The public health service also allowed me to start my residency in psychiatry at St. Elizabeths Hospital, and continue doing research at the NIH, which, by that time, became the National Institute of Mental Health (NIMH.).

TB: When was that?

WP: In 1976. So, I did not return to the Heart and Lung Institute but to Fred Goodwin’s branch at NIMH. I was, for the next 20 years, part of the Intramural Program at the NIMH in a number of different roles. First, I

was in Fred's branch, and then I got a section of clinical pharmacology that was created because I was trying to do bridging research from studies in animals into humans. Part of the time my position was supported by the National Institute of General Medical Science. I was coordinating the training both clinical pharmacologists and psychopharmacologists at NIH. So I supervised individuals who were clinical pharmacologists in many of the other institutes as well. But my personal research interest remained in clinical psychopharmacology. That is, how I got involved with the ACNP.

TB: In what year?

WP: 1978 was the first time I came to a meeting here in Puerto Rico. The focus of my work in clinical psychopharmacology covered all of the classic questions in pharmacology, such as how the blood concentration of a substance relates to clinical effects. That has been extraordinarily elusive because, unlike in rats with necrotic livers, our outcome measures for depression, schizophrenia, anxiety disorders, and manic depressive illness are not very precise and do not lend themselves well to looking at simple concentration-response relationships, nor does the time course of effect. I learned that early on. However, during the 1970s, there was a burst of activity hoping that measuring concentrations of drugs would greatly improve therapeutics. Retrospectively, the fundamental lesson learned as we appreciated the variation in drug metabolism, was that many, many patients were under dosed. The general rule that emerged was that it was important to use higher doses to achieve therapeutic effects. This may seem obvious now, but back then a lot of people were being treated, particularly in depression, with sub-therapeutic doses. The lesson of finding the right dose has been well learned, although it is still not well done. Post-marketing experience with many of our new anti-depressants and anti-psychotics indicates the marketed dose is not always the right one. Once I became comfortable with classic pharmacological/pharmacokinetic measurements, I became interested, as did many other people at NIMH heavily influenced by Fred Goodwin, in manic depressive illness, a robust clinically striking condition in which you had multiple phases of the illness. I became interested in the work on catecholamines by Irv Kopin's group and also inspired by Julie Axelrod's research. It provided an opportunity to explore whether the biochemical theories related to mental illness that were very popular could be proven in humans.

TB: Which theories are you referring to?

WP: The biochemical theories then current had to do with an abnormality of catecholamine metabolism, a "noradrenergic depression" or an abnormality of indoleamine metabolism, a "serotonergic depression." It was

thought in that antidepressant effects could be produced with selective serotonin reuptake inhibitors (SSRIs).

TB: What years are we talking about?

WP: Mid to late 1970s. There had already been data coming out of Sweden using a fairly selective serotonin uptake inhibitor called zimelidine, in the treatment depression. The research that led to SSRIs was laid out by people like Arvid Carlsson. Although Brodie and Costa had been focused on serotonin, it was Arvid who first provided solid evidence that tricyclic antidepressants influenced the serotonin system. To make a long story short, we did what was to me the most important formative clinical experiment for my development by comparing zimelidine, from Astra Pharmaceuticals in Sweden, with the most selective norepinephrine reuptake inhibitor we could find. The hypothesis was you would get selective effects on serotonin and norepinephrine metabolism. The results were you could not distinguish very clearly between the two. Each drug, after several weeks of administration, influenced both norepinephrine and serotonin metabolism. Our findings led us to speculate there must be interactions between the nor-epinephrine and serotonin systems that were important in terms of downstream events. It was a very important experiment from my point of view. I learned that one could not follow a relatively simplistic model in psychopharmacology, in which, if you know the pre-existing biochemistry, you would have a specific biochemical treatment for a particular subtype of psychiatric illness. It indicated a simple approach to biochemical sub-typing was not feasible, most important would be to understand the mechanism of action of psychiatric drugs. In the next decade of my career I studied how psychotropic drugs, in therapeutic doses, affect more subtle pathways than norepinephrine and serotonin. I was especially interested in the effects of lithium on signal transduction.

TB: How did you get from NIMH to Lilly?

WP: When Steve Paul left NIMH in the early 1990s he suggested the best opportunity for research from bench to bedside might be in the pharmaceutical industry that has the enormous resources necessary to carry this off. So, in 1996, I went to work in the research laboratories of Lilly. The era we are now entering is going to be putting research at NIH, in large academic consortiums, and in industry together, creating information in data bases with proteomics and of course genetic measures. The American College plays a huge role in providing a forum to bring us together with different ideas about how to achieve this objective. The annual meetings of ACNP provide an opportunity to be in touch with the latest evolving science on a regular basis. It is in these meetings the best conversations

take place in terms of figuring out how to create the ideal interaction between government, industry, and academia.

TB: Let us get back to your research. You entered psychopharmacology by becoming involved in drug metabolism and pharmacokinetics. Could you put that research in perspective for us?

WP: Research in those areas is still extraordinarily important. Controlling your dose in your preclinical experiment is a huge issue, even now. When you give 10 mg per kilogram of a substance you get more or less the same exposure across your inbred rats. In humans, that is not so. Pharmacokinetics is core to controlling for variants, that is a given. One takes that as part of life. What hasn't been so easy is modeling the relationship between pharmacokinetic and pharmacodynamic findings. It has been extraordinarily difficult in the brain to relate concentrations to systematic changes. This has to do with difficulty in understanding changes in interacting systems where you have a time element; when we look at biochemical outputs we are looking at points in time, not at a constant curve where there is stability unless we are looking at something like receptor occupancy. That is the only area where PK/PD works out really well.

TB: That is very important for neuropsychopharmacological research.

WP: It is. When we worked at Lilly on antidepressant potentiation with pindolol we had difficulties interpreting our findings because nobody had defined appropriately in humans the relationship between pindolol concentration and occupancy of the serotonin_{1a} receptor. The hypothesis was that blocking serotonin_{1a} receptors would potentiate the effect of serotonin uptake inhibitors. When people looked at the findings they concluded the doses of pindolol used in those clinical studies probably only hit receptors. The doses used only achieved 25, 35, or at most 40 percent occupancy of the serotonin_{1a} receptors, instead of full or at least 90 percent occupancy. Despite the tens of millions of dollars spent in that research the hypothesis has not been properly tested. I can give multiple examples of similar cases. If we do our experiments right we will be able to greatly increase our success rate. We should be able to do that now with the employment of brain imaging technologies.

TB: Do you think it is feasible?

WP: It is becoming increasingly feasible with ligand development. We have already developed ligands for the norepinephrine transporter with people in Uppsala, Sweden, and we are moving ahead with ligand development so we should be able to use PET or SPECT in our drug development programs. An exciting aspect of this research is that it is done in collaboration with the NIH. We are co-grantees with both Columbia and Hopkins in developing ligands for novel targets. We are finding ways to

work together and I am convinced this will greatly improve our hit rate in developing novel therapeutics.

TB: So you hope to develop collaboration between government, industry and academia in this crucial area of research?

WP: Right.

TB: Earlier you said one of your important findings was that norepinephrine and serotonin reuptake inhibitors might not be as selective in their mode of action as we think.

WP: Yes, and we have to approach questions very differently from the rather simplistic model we had been using. At the time I did that research the prevailing theory of antidepressant action was β -receptor down regulation, and Fridolin Sulser was one of its great champions. We were all trying to show, using peripheral lymphocytes or whatever, to find indirect ways of measuring β -receptor down regulation in humans. All that was far too simplistic; eventually it became apparent we have to understand the full cascade of events, including the coupling of receptors to G-proteins and second messengers. During the 1980s it became possible to incorporate all molecular pharmacology done before then and, by re-looking at the chain of events, we learned there was a far more complex series of adaptive events that followed the primary action of drugs. Many of those events could be shown in vitro and in cell cultures without invoking more neurotransmitters hitting the receptor. In the period from the mid-1980s to almost the present we have been retrenching and learning more about how these complicated systems really work and redefining the downstream biochemical effects of drugs. The question is whether we would be able to profile those effects in sufficient depth to distinguish different actions across individuals and then to relate that back to treatment response. So we are going back to the strategy of the 1970s, but at a higher level. At that time we simply didn't have the tools to do it well.

TB: What was the impact of your findings that, down the road, serotonin and norepinephrine reuptake inhibitors follow a common path in their mechanism of action?

WP: A great number of people persisted there was a norepinephrine and a serotonin depression and we should be able to separate them. Others went along. One of the biochemical scientists at Lilly told me it was the most important clinical paper he had seen; it has had a large impact in the way people think by supporting a shift in focus from single neurotransmitters to interacting and coupling systems. What I viewed at the time as a very simple and obvious experiment has had a substantial impact.

TB: So, you think it has had an impact on the thinking of people?

WP: It changed people's thinking and strategies at Lilly. I am sure it has been the most impact-full single paper I was ever involved with.

TB: Would it be correct to say that the biochemical measures we used have not contributed so far to the classification of depression?

WP: Right. We have remained as a field of psychiatry, in a descriptive phase. Most of what people put forward as biochemical hypotheses are far too simplistic because we are not adequately describing, in objective terms, the state of individuals. We can do that partly with behavioural and functional measures, but rating scales have their limits. To subdivide people it seems clear we need a combination of genetic, biochemical and other objective functional measures. Brain imaging measures have been evolving continuously but the initial enthusiasm of fitting brain imaging measures to drug development has to be balanced by the reality. Anything beyond receptor occupancy still has not shown predictive, reproducible, dose response relationships. The pharmaceutical industry, the NIH and other authorities, are funding the employment of brain imaging techniques in research for studying drug effects, but the data bases are only just emerging. Many of us hope proteomics might open up development. It is already applied in the cancer field with some early success but it is too early to say what it will deliver.

TB: You believe one would need to integrate findings from various areas of research in order to describe individuals' in sufficiently objective terms for clinical psychopharmacological investigations?

WP: For doing clinical psychopharmacology well one is going to need a matrix, a team with investigative skills that go beyond what any individual scientist can adequately master in terms of fully understanding the methodologies of different disciplines and the limits of each of them. For successful drug development in such a complicated system as the brain, it is extraordinarily important we find ways to get people with the right skills to work together. I am hoping, over the next few years, to find ways to do that.

TB: Are you involved in any project in clinical psychopharmacology in which people with the "right skills" work together?

WP: We are trying to develop such a project with the National Institute of Aging, looking for new drugs in Alzheimer's disease. This will be the biggest joint effort ever put together, at least for the CNS field, whereby industry will put in upwards of 20 to 30 million dollars for a five year prospective study of minimal cognitive impairment preceding to Alzheimer's because, if you diagnose MCI the right way, about 80% go on to get Alzheimer's. Imbedded in that project will be a complex combination of imaging, MRI, PET scans, and cerebral spinal fluid studies of proteomics.

The study should start in early 2005; so we are still in the planning stages. This is very exciting to me because it is the sort of research that needs to be done if we are going to find breakthrough treatments for important CNS diseases.

TB: What about research in schizophrenia and bipolar disorder?

WP: We would have a concerted effort in bipolar disease before we go after schizophrenia. It is interesting that we are back to the recognition that schizophrenia is, in the broad sense, a disorder in thinking including cognitive function. Even if you successfully treat the positive symptoms it is obvious people are left with substantial cognitive impairment. The NIMH, working with FDA and industry in the MATRICS Project is recognizing the need to go after cognition in schizophrenia. I am very excited to be part of that project, trying to sponsor the development of novel scales for assessing cognitive disturbances in schizophrenia.

TB: The projects you are talking about will generate lots of data.

WP: One of the other exciting opportunities I have recognized since coming to industry is that it has the capability of generating enormous data sets from which one could extract information.

TB: Any big project planned in bipolar disorder?

WP: Bipolar disorder would be one area where, if we all invested enough, we might be able to find more compelling patterns of biochemical dysfunctions we could relate to treatment, but right now there is no unified program or approach doing that.

TR: Don't you think that before undertaking such expensive projects it would be important to define the diagnostic populations better than in current consensus-based classifications?

WP: I still believe the classic bipolar phenotype remains one of the clearest defined. Genetic research keeps supporting there is something there. Genes associated with risk for psychosis coupled with other susceptibility genes seem to confer the bipolar phenotype. As genetic research evolves, maybe this will become clearer, and we will identify people at risk, understand the biochemical pathways susceptible to alterations under the genetic circumstances, and do something that is more than palliative. Those are dreams but one can see a path.

TB: It is a long journey we covered from your first research project as a student on hydrazines.

WP: I was a young graduate student who knew nothing about science, and who never thought of himself as a scientist. I was studying philosophy. But then I learned the process of generating questions and found testing them in research very gratifying. It is like a chess game. It has the

advantage over philosophy that you can propose a question and test it. Unfortunately, in philosophy, you could never test your core questions.

TB: What was your primary area of interest in philosophy?

WP: Logic with an underpinning in ontology.

TB: You probably learned from philosophy that you have to start research by formulating a testable hypothesis.

WP: You formulate it, and then you test it. I came from a background where pursuing truth and doing the right thing was very important. I have always felt you had to use knowledge the best you can, like translating new knowledge into new treatments. I have always wanted to be part of those who are translating new biological knowledge to better treatments. All through my professional career I have been interested in applying what I learned in pharmacology to more rational drug development. My role is to bring together and implement things which allow us to develop better treatments, not just “me too drugs”.

TB: You mentioned you did some research with lithium?

WP: We did a series of work to try to understand the mechanism of action of lithium; from a learning experience that was tremendously important although we didn’t find it. People are still working on that.

TB: We talked about briefly about you training in psychiatry.

WP: My psychiatric training gave me the opportunity to have direct relationships with patients. I still see patients, believe it or not. All those years at the NIMH, in addition to the patients on the ward, I also saw patients outside.

TB: Do you still have a practice?

WP: Yes, even now. At the NIH I had a small practice in which I did a few hours a week, but I followed many people with complicated manic depressive illness or severe depression. I became very interested with the limitations of our ability to assess the condition of a patient. It was not until I went to Lilly in 1996 that I had access to databases to look at some of the issues. One of the first things I did was to put together, with the help of David Debroda, meta-data sets. We have now the largest meta-data set of antidepressant trials ever put together. We also have a large data base on olanzapine. We are beginning to put together the meta-data sets and understand the extent to which measures do or do not reveal similar information over time. Being in a position to see how these scales perform I think maybe we should invest in additional refinement of them. Scale development and validation are just as important as molecular studies.

TB: Let me switch to something completely different. When did you become a member of ACNP?

WP: It must have been early 1980s.

TB: Have you been active?

WP: Oh, yes.

TB: Do you remember your first presentation at an annual meeting?

WP: I don't remember but it must have had to do with pharmacokinetics. It probably was the prediction of steady state based on a single dose, because, working with Jim Gillette, I understood that from acute dose pharmacokinetics you should be able to predict a steady state. There were also misunderstandings about protein binding I dealt with. I was able to tell people to stop worrying so much about protein binding because it is only relevant for certain phenomena; people were misinterpreting its meaning and thought protein binding limited access to the brain. It doesn't. It merely says something about how you should interpret total blood levels. I was also involved in presentations that dealt with active metabolites.

TB: What are you doing these days?

WP: My current activities are much broader since I am involved in coordinating early development of drugs. What I am trying to do at Lilly, and more broadly in the field, is convince people to build into studies with CNS drugs documentation about the biochemical target they are hitting in humans. I'm also interested in finding ways to enhance signal detection and outcome measures in early clinical trials. I understand people like Don Klein say, if you had a drug that worked, picked your patients right, and measured them right, you should be able to tell in a small number of people whether the drug is useful or not.

TB: So you think it is important to enhance signal detection.

WP: I have been trying to convey that without enhancing signal detection you waste your efforts in clinical trials. An example of the need for enhancing signal detection is buspirone. Since its introduction at least 10 and probably 15 pharmacologically similar serotonin_{1a} partial agonists and full agonists have been tested without any of them making it to market. We estimate probably a billion dollars has been spent to test these drugs. That is a lot of money but nobody knows the extent to which the doses used produced an effect in the brain. Not only have we spent all this money and not come up with anything, but we haven't learned anything either. This repeats itself several times over.

TB: What would you like to see to happen in the future?

WP: Real knowledge emerging. From an ethical view as a clinical investigator you should hesitate going forward with a study unless you can say you have learned something from the research about the mechanism of action of the drug you are working with. If you're using doses of drugs which, if the technology exists, don't show you are hitting your target,

then you have omitted an essential component to your study. Then, if you have negative data from a study in which you tested a hypothesis, you should be required to share the data. This is not a game where you let another company go down the wrong path if you know it is the wrong path.

TB: You seem to feel strongly about this.

WP: I feel very strongly. We need to do something about that because it can happen.

TB: Anything else you would like to add?

WP: I think I have talked enough.

TB: Then, we should close this interview. Thank you for sharing this information with us.

WP: Thank you for the opportunity. It has been a lot of fun.

ARTHUR J. PRANGE JR.*

**Interviewed by Robert H. Belmaker
San Juan, Puerto Rico, December 12, 1996**

RB: Good morning, Art. It's a great pleasure to interview you this morning about your contributions to psychopharmacology, which have been very great, and I've followed them for many years. I'm wondering how you yourself got into the field?

AP: I graduated from the University of Michigan in 1950 and after I did a general internship I still didn't know what I wanted to do. I was interested in neurology, so I interviewed neurologists in Detroit and they said, "One thing you have to realize about neurology is that you're going to do a lot of psychiatry." So I went into anesthesia, instead. At the end of that year which was 1952, the Korean War was still on, I was drafted and ended up doing anesthesia at Key West Navy Hospital; by that time I was sure I didn't want to go on with anesthesia either. So I asked for shipboard general duty and was posted a ship out of Norfolk on which I was the only doctor for seven hundred men. It was a repair ship so we took care of the needs of the two or three other ships that came alongside, usually at the dock but sometimes at sea. I became fascinated by psychiatry of all things. There were so many complaints with no other explanation. I saw conversion reactions and heard all sorts of psychophysiologic complaints; I even wrote a paper about it. When I got out of the Navy I decided to go into psychiatry. I learned there was a place in Chapel Hill at the medical school in the department of psychiatry headed by George Ham, a hotshot analyst and internist, who came from Chicago. I was interviewed in March 1954 by George and then started as a member of the first regular class at Chapel Hill in that year and finished up in 1957.

RB: Do you think internship with general duty influenced you to become interested in biological psychiatry and psychopharmacology?

AP: Yes.

RB: Did you resist psychoanalysis?

AP: Interesting question. I've had a lot of personal analysis but I didn't want to be an analyst. When George Ham offered me a faculty position and instructorship in 1957, I had to ask if it would be possible to be a first class member of the department without being a psychoanalyst? He laughed and said, sure, we're going to do some research at this place; you just wait and see. If I look back, my interest was probably physiology and pharmacology, because, in anesthesia, the one thing that fascinated

* Arthur J. Prange Jr. was born in Grand Rapids, Michigan in 1926.

me was the pharmacology. When I was in residency for anesthesia I took courses at Wayne's State University and got my only A+ in applied pharmacology. There wasn't any CNS pharmacology in 1957 but towards the end of my residency we began to have drugs and that amusing because people divide into two camps, the reserpine people and the chlorpromazine people. In our shop they barely spoke to each other, at coffee breaks they sat at different tables.

RB: My goodness! People can find anything to divide themselves on. That's a story I have to quote.

AP: It didn't last long and I wrote a paper about that. Early on, there was a fellow named Abse, a British analyst, in the Department. He was broadly trained in psychiatry and wanted to use deodorized tincture of opium (DTO) in treatment so we compared DTO to chlorpromazine and reserpine. Chlorpromazine won. We paid strict attention to the drop out rate in the various groups and one of the telling things was that many more people dropped on placebo and reserpine than chlorpromazine.

RB: I'm fascinated the idea of a controlled clinical trial was already so obvious to you. Was this something that was obvious to most psychiatrists or people in medicine at the time?

AP: By the late fifties it was gaining ground but I don't think it was everywhere appreciated. I've always thought the North American style of doing things is very different from others. We end up with a small number of patients and with a more controlled design, a placebo group, double blind, crossover and the rest of it. The Europeans, especially the Latins, seem to say, we are going to study everybody who comes and even if we know what they're getting we will be able to tell the difference because we are good doctors. They end up with hundreds of patients but arrive at much the same conclusions, even if in a different way.

RB: You mentioned you had a personal analysis and I gather many, if not most, of the early psychopharmacologists had training in psychodynamic theory. This doesn't seem to be the case anymore. Do you think that's a loss to the field?

AP: It is a loss and it's a loss also that the psychology of situations is, in these days, underplayed, although it was overplayed before. These things go in cycles; everything's genetic now, and predetermined. There were, even then, analysts who thought the best way to prescribe a drug was based on psychodynamic considerations. You could get three experts in the same room and get three different interpretations. Introduction of psychotropic drugs has forced us to use diagnosis and classification of psychiatric disorders. Accurate diagnoses made drug trials possible.

- RB: How did you get interested in psychopharmacology and how did you get the foundation in biology that allowed you to make important contributions?
- AP: The key is Morrie Lipton. Morrie and George had been friends in Chicago, trained together. I'm not sure which years and where but at a certain point they were at Michael Reese. So, George planned to get Morrie down, and, indeed, he did arrive in July of 1959. By that time I had been two years out of residency.
- RB: I see.
- AP: With one of my running mates, Martin Keeler, we had been teaching each other research that consisted, in part, of recording everything. Then Morrie came and got us going. He had a strong background of research in the Army and was trained in medicine and psychiatry. He also had a PhD in chemistry from Wisconsin. He lit the fire under several people including me.
- RB: Would you consider him your mentor?
- AP: There were others but Morrie was the one who provided the critical opportunities and opened up a way of thinking.
- RB: I suppose there were other protégés of Morrie as well?
- AP: There was Marty Keeler who remains my dear friend. He and I were contemporaries and competitors. But Marty was more interested in psychophysiology and Morrie didn't know much about that. He saw better opportunities at other places and left very early on. So I was the only young faculty person almost entirely focused on research. As time passed several people came to work with us, like Ed Vann, Bill McKinney and Peter Whybrow. Peter was one of our residents in the early nineteen-sixties.
- RB: How did you get involved in research on depression?
- AP: Morrie always kept his hand in the clinic and my career started with the observation of a case Frank Kane brought to my attention. There was a woman with thyroidectomy taking thyroid who was depressed and probably receiving a bit too much. After Frank started treating her with a new drug, Imipramine, she developed extrasystoles and paroxysmal tachycardia. Morrie said it could be excess thyroid hormone potentiating the imipramine and responsible for the toxic effects. He also said we could make mice hypothyroid and give them various doses of imipramine and thyroid hormone to see whether thyroid potentiated the toxic effect of imipramine. We went to the bench for the first time and, sure enough, we could alter the toxicity of imipramine by altering thyroid state. That was interesting in itself, but then Morrie said, "Maybe, with small doses of thyroid hormone, you could enhance the beneficial effects of imipramine, let's try that". We made an alliance with Ian Wilson at the State

Hospital and those studies led to a research grant for potentiating the effect of imipramine with thyroid hormone. That grant still goes on today, and led to a very rich association with the Dorothea Dix Hospital, thirty miles away in Raleigh. In the first study we were able to show administration of imipramine in the dose of 150 mg a day and T3, or a placebo, in depressed patients those who got the T3 improved twice as fast as the others.

RB: What year was that?

AP: We made the observation in a first patient in 1961 and it was about 1963 before the first paper.

RB: Were there issues about priority in that research?

AP: That pertains to a paper I wrote with the title "*Evidence in Favor of the Role of Norepinephrine in Depression.*" Our formulation of the T3-imipramine interaction pertained exclusively to noradrenergic events. Guy Everett, a late member of this college, had published results to that effect so there was some question about priority. It was kind of a non issue but I might have been a little sore at the time.

RB: We all have feelings like that.

AP: You have to have some kind of ego to do this work.

RB: Absolutely, a healthy ego is a driving force. There's a phrase in the TORAH that says jealousy among scholars promotes wisdom.

AP: I'm glad to learn that. It's so well phrased.

RB: I was aware that you had a unit at Dorothea Dix but wasn't that unusual? Many investigators in the ivory tower at universities stayed far away from the State Hospital. Did you also have some social or humanitarian motivation?

AP: There was nothing that heroic about it. It was a thirty minute drive, today, with the interstate, it's forty minutes. And, when George came from Chicago, he was recruited specifically to improve public mental health care in the State of North Carolina as his mission. He had enormous support from the State Legislature for doing that. One man, John Umstead, who'd lost his son in the war, dedicated himself to improving the abysmal public mental health care in the state. So George went right to the State Hospitals after his arrival and we devised a program whereby their doctors came to Chapel Hill one or two days a week on a part-time residency and, after a period of time, qualified to take the board examination in psychiatry. Then, by the end of the sixties, we sent our residents to the hospital. It was an enormously successful program. After the liquidation of State Hospitals we established about thirty Mental Health Centers as well as Health Education Centers, which were not limited to psychiatry, but in which we played a part. The Medical School obtained three planes to

- fly physicians to some of these centers and three other medical schools, Duke, East Carolina and Bowman Gray participated in the program.
- RB: What would you say was your role in this outreach program?
- AP: I was the university based psychiatrist, who established a research program that's since become a model. It wasn't that hard to do because the training program was in place from 1957.
- RB: Could we get back to the thyroid story? You've given credit to Morrie to setting you on track but when I entered psychopharmacology in 1971 thyroid and affective disorder was synonymous with Art Prange. For the sake of history, I wonder if I could move from the modest position you've taken and whether you can say what happened between 1963 and 1972?
- AP: We did more studies and, with Wilson as first author, we published a second study in the *New England Journal* that confirmed the findings in a slightly different population of depressed patients. Then we published another study in which we gave a single dose by injection in the deltoid muscle, ten units of TSH or saline, before starting patients on Imipramine. Those who got TSH were out of the woods in about half the time as the others. By then, in the same way as there had been a reserpine and a chlorpromazine camp, now there was a serotonin camp and a norepinephrine camp in affective disorders. I'm partly guilty for the norepinephrine story in North America, so I was interested in the serotonin story in the United Kingdom and Europe. To find out more I took a sabbatical year, from 1968 to 1969 in London, with Alec Coppen. We worked with tryptophan and did more T3 studies. Peter Whybrow, after his residency in Chapel Hill, decided to come over to begin his British career. Peter arrived in August of that year and the three of us, Whybrow and Coppen and I, worked together for eleven months.
- RB: Did you work on thyroid with Whybrow in Chapel Hill? Was his interest something that you initiated?
- AP: He had a thyroid interest when he came to Chapel Hill. He'd done work as a medical student with thyroid in London, so his interest was already there and meshed with mine.
- RB: When did your thyroid-focus become a peptide focus? You were one of the first, if not the first, to use peptides in psychiatry.
- AP: It was a complete accident; it was just luck that TRH was the first peptide in the modern era people got interested in, otherwise I would have been the last to know about peptides. When Abbott had their synthetic TRH they were looking to see who would be interested in psychiatry. Anderson, from the endocrine division at Abbott, called to tell me about it and I expressed interest.
- RB: What year was that?

AP: About 1974. He asked if I would like some pure injectable synthetic TRH, the protein that stimulated the thyroid. I thought it over for a millisecond and said, yes. Wilkes and I got involved and, with Nick Plotnikoff, we published a paper that it was extremely active and claimed it had a very substantial, quick and trenchant antidepressant effect. That's become very controversial, not that it's centrally active; it wakes animals up from barbiturates, anesthesia or alcohol. But is it an antidepressant? I do think it has antidepressant effects and also some beneficial effects in schizophrenic patients.

RB: Wasn't that the first clinical study with a peptide in psychiatry?

AP: I think it was, probably.

RB: I don't think you need to be apologetic about being controversial. I find it hard to point to any finding in the last decades, in our field, that isn't controversial. Maybe I should ask how you have been able to maintain both motivation and scepticism at the same time.

AP: Flexibility.

RB: It would be difficult for many others.

AP: What's controversial is whether TRH is an antidepressant. It's not controversial in adults and Charlie Nemeroff and I have written a lot about that. It's one of our contributions to suggest peptides with clear endocrine properties may have behavioural effects. Research with TRH led to the discovery of the behavioural effects of two other peptides: oxytocin and neurotensin. In the discovery of the behavioural properties of oxytocin, Cort Pedersen, at the time a medical student, played an important role. Since oxytocin promotes the contraction of the uterus and the ejection of breast milk, he suggested that the substance may have a role in maternal behaviour. We were able to show this was the case in virgin rats.

RB: What about neurotensin? How did you discover its central effects?

AP: That was mere luck. We had a little money in a grant and we had a peptide catalog, so we ordered all the peptides, about forty five that we didn't already have. We didn't know anything about neurotensins, but we'd devised an animal screen, going way back to our TRH days. TRH would wake animals up from barbiturate anesthesia and we found a few peptides, other than TRH, also woke animals up, but none as potently as TRH. We also found one that makes animals sleep forever. When the guys brought the box in which the rat had been asleep for four hours I asked, "What did you give him?" we found out it was neurotensin. That's what chlorpromazine does. If you go back thirty years or more chlorpromazine was a means of potentiating the effect of anesthetics. This was my old anesthetist speaking! So we were off to the races with neurotensin. Now, Charlie, Mike Owens, and others at Emory are following that avidly.

- RB: You mentioned Charles Nemeroff. How did he get started with you?
- AP: He enrolled in our neurobiology program; he was interested in peptides and heard about TRH and the work we'd done so he wanted to work in my lab. I told him I'm not much of a bench scientist, but some of my best friends next door are. So if you want to do it, okay.
- RB: Was this a combined MD and PhD program?
- AP: No, it wasn't. Charlie got his PhD in neurobiology at our place, and then went to medical school and on into Psychiatry. Charlie got a certificate in psychiatry and a gorgeous wife at UNC.
- RB: Are there any other contributions you would like to mention?
- AP: When I came back from Coppen's shop in 1969 I thought of a way to put norepinephrine and serotonin together into an inclusive hypothesis of affective disorder based on our finding that imipramine, a mainly noradrenergic substance, was enhanced by T3, and that tryptophan, the precursor of serotonin, has both antidepressant and antimanic actions. We published that in 1974.
- RB: A very widely quoted paper.
- AP: In more recent years, I've gone back to clinical thyroidology and become interested in subclinical hypothyroidism. It's enormously prevalent in women, beginning in the third and fourth decade of life, increasing with age and it accounts for significant morbidity. With Haggerty's leadership, we've published the notion it is a risk factor for depression and could be easily treated. I keep trying to scrounge up money for a big study to identify it in a population of vulnerable women, treat them and see if I can ablate it. We've done the retrospective stuff, identifying women blindly who have subclinical hypothyroidism from those who don't. Among women with a past history of depression it is about three times as frequent as in others. It's a true bill and we ought to exploit it so I've begun to work on it with colleagues in Lithuania. What we're interested in is whether T3 and T4 are really equivalent as far as the brain is concerned. Right now we're looking at endocrine effects in Lithuania among patients who had thyroid ablation and are on thyroid supplement for life. These patients, like almost everywhere, are maintained solely on T4. Recently we replaced some of them with T3 and many do much better when some of their supplement is T3; in some patients the combination is notably better. That suggests some people don't make T3 from T4 in brain as efficiently as other people, or as efficiently as they do in the periphery.
- RB: We've covered quite a bit of ground but before we end, I wonder if there are other people you would like to mention who were your mentors or who you mentored. You mentioned Morrie Lipton, Alec Coppen, Charlie Nemeroff and Peter Whybrow.

AP: Peter Kalivas, who got the Elkes award yesterday, was in our lab; Garth Bissette, leading the group in Mississippi also.

RB: Do you want to run down that list?

AP: Oh no, because I might miss somebody. It has been a great pleasure to give people a chance in the same way I was. If we can maintain that sense of fraternity and continuity we're in good shape.

RB: Thank you very much; it's been very interesting for me this morning.

AP: Thanks Bob.

ELLIOTT RICHELSON

**Interviewed by Thomas A. Ban
Waikoloa Village, Hawaii, December 9, 2001**

TB: We are at the annual meeting of the American College of Neuropsychopharmacology in Hawaii. It is December 9, 2001, and I will be interviewing Dr. Elliott Richelson* for the archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Elliott, tell us where and when you were born, about your early interests and education, and how you got involved in neuropsychopharmacology.

ER: I was born in Cambridge, Massachusetts on April 3, 1943 and raised in a town close by called Waltham. My father was a dentist and my mother a secretary. I went to public schools in Waltham. In high school, I had a chemistry teacher who was very influential in getting me interested in science, so I majored in chemistry at Brandeis University in my hometown. But even before then, in high school or earlier, I had interests in becoming a physician with the idealism of youth, to help people. I didn't want to be a dentist because I saw what my father did and that didn't interest me. I also thought in college that the best way to help a lot of people is to do medical research, because a physician can only see so many people in a lifetime, but if you develop a treatment for a disease, you could help millions potentially. Those were the things I was thinking about in college. I did have some interest in psychology, took a course or two and did some reading on Freud in high school and college. I went to the Johns Hopkins University School of Medicine where it was required, as part of the pharmacology course, to write a thesis supervised by one of the faculty members in the department.

TB: Was this in the early 1960s?

ER: I graduated from Brandeis in June of 1965 and started at Hopkins in the same year. Sol Snyder was a new faculty member in the Department of Pharmacology and it was from his influence I am in psychopharmacology; he was my mentor for the thesis I had to do. We worked on a project together; it was armchair chemistry in which we related the structure of some psychedelic drugs to serotonin. From that came a paper we published in PNAS. The paper is probably of no import, the importance was contact with Sol Snyder.

TB: Was it your first paper?

ER: It was not my first paper.

TB: Did you do any research before?

* Elliott Richelson was born in Cambridge, Massachusetts in 1943.

ER: From early on in college, I started to do research. My first research job was the summer after my freshman year when I worked at a Dow Chemical facility close to my hometown doing synthetic organic chemistry.

TB: What was your first paper?

ER: I did a senior honors thesis in chemistry as part of my undergraduate work and that led me into the Biochemistry Department. Nathan Kaplan was Chair and I co-authored a paper with Mary Ellen Jones, my supervisor.

TB: What about in medical school?

ER: I was involved with two research projects, one with Sol Snyder I already mentioned and another one with Dan Nathans who won the Nobel Prize, along with Hamilton Smith and Dr. Werner Arber from Switzerland in 1978. I spent a full 12 months while in medical school in the laboratory of Dan Nathans.

TB: What was your project with Dan Nathans?

ER: I was working on RNA bacteriophages and looking at protein RNA interactions. It was very exciting, although I didn't appreciate it fully at the time.

TB: Even if you did not fully appreciate it, it had to be a very stimulating environment.

ER: In the adjacent laboratory to Dan Nathans, Hamilton Smith was trying to infect an *Haemophilus* bacterium with a bacteriophage and the bacteria were resisting the infection. He just could not succeed but ultimately recognized the bacterium had an enzyme which cleaved the DNA of the injected bacteriophage; that led to the discovery of restriction endonucleases.

TB: This took place in Hamilton Smith's adjacent lab?

ER: Yes, but Dan Nathans used those enzymes to selectively and precisely cut up DNA, working with a virus called SV40, simian virus 40, to figure out what the various genes were doing. The discovery of the first restriction endonucleases led to where we are today in the human genome project and genetic engineering. So, I was associated with that project and very fortunate to have interactions with such incredibly intelligent folks like Dan Nathans and Sol Snyder.

TB: So you were involved in two research projects while in medical school.

ER: Also, somewhere early in medical school, I went back to Boston and did a summer at Mass General working on a thyroid biochemistry project, which, unfortunately, didn't go anywhere.

TB: How did you get involved in psychiatry?

ER: This happened later. When I entered medical school, Joel Elkes was Chair of Psychiatry, and Paul Tallalay was Chair of Pharmacology. But very shortly after arriving at Hopkins, Dr. Elkes and Dr. Tallalay both resigned,

so things were in flux. But I did enjoy my interactions with Dr. Elkes and still value him as a colleague and friend. I was interested in psychiatry, but ambivalent about making that my clinical specialty. It was either neurology or psychiatry, but I postponed the decision for awhile. My association with Dan Nathans led me to apply for a research fellowship at NIH, after my internship year.

TB: Where did you do your internship?

ER: I did my internship in straight medicine at Washington University in St. Louis and then went to NIH to the laboratory of Dr. Marshall Nirenberg. Marshall Nirenberg had won the Nobel Prize two years before I joined his laboratory in 1970 for working out the genetic code. He shared that prize with a few others.

TB: The second Nobel Laureate you worked with.

ER: Right. It's interesting how things evolve because when I interviewed at NIH for a position, my first choice was not Marshall Nirenberg. I hope he doesn't see this tape. It was to work in Dr. Kaufman's laboratory. He was an outstanding scientist, an enzymologist, who purified and isolated phenylalanine hydroxylase; he was involved with tyrosine hydroxylase as well. I didn't get my first choice and went to Marshall Nirenberg's laboratory instead which was great luck. My stay in his laboratory was a marvellous experience, trying to soak up as much knowledge as I could. Because of his stature, he attracted outstanding young scientists to his group who were a lot more sophisticated and knowledgeable than I in biochemistry and molecular biology. One of them was Al Gilman. Marshall Nirenberg liked to have definite ideas about who should be working on what in his laboratory, but Al Gilman managed to work on a project that he was interested in. This project involved β -adrenergic-stimulation of cyclic AMP production. And it was seven years ago, in 1994, that Al Gilman shared the Nobel Prize for the work he started in Marshall Nirenberg's laboratory in about 1970. Those were probably the best two years of my career in terms of setting me up for future research, because of the knowledge I gained in that environment. NIH was a superb place to be; I worked very hard and learned a heck of a lot. About a year and a half, maybe less, into that fellowship, Sol Snyder paid me a visit. He wanted me to come back to Johns Hopkins to join his division of psychopharmacology and to work it out so I could also do my residency in psychiatry. You call this, "Doing the Sol Snyder" because that's what he did. When I was a medical student at Johns Hopkins and Sol was an Assistant Professor of Pharmacology, he was also a resident in psychiatry so that's what I did. I returned to Johns Hopkins as an Assistant Professor of pharmacology and a resident in psychiatry; this was a great way to do psychiatry because I'd be able to

have some sanity in my life by working in the laboratory. So I got my first NIH grant while doing my training in psychiatry. It was towards the end of my residency, when Dr. Tallalay was resigning and Dr. Elkes had already resigned, that I made a presentation in Montreal, at the meeting of the American Society for Pharmacology and Experimental Therapeutics.

TB: When was that?

ER: The summer of 1974. There were a couple of folks at the meeting from Mayo, one of whom was Richard Weinshilboum. An absolutely brilliant man I had met at NIH when he worked with Julie Axelrod on dopamine beta-hydroxylase in the blood. He had gone to Mayo a couple of years before and was on a search committee to find a biologically oriented psychiatrist; so he asked if I would be interested. I was, so I went to Rochester, Minnesota in November 1974. It was a lot colder in Rochester than Baltimore but I was very, very impressed with Mayo. They made an offer I couldn't refuse and 26 years later I'm still there, except, 12 years ago, Mayo again made me an offer I couldn't refuse; to transfer to Florida. After spending 14 winters in Minnesota I was happy to take the job!

TB: When did you start at Mayo?

ER: I joined the Mayo Clinic on July 1, 1975, and held a primary appointment in the Department of Psychiatry with a secondary appointment in pharmacology. My office and laboratory were in the Guggenheim Building, across from the Mayo Clinic building. I spent one afternoon a week seeing patients, which I still do after 26 years. That has given me firsthand experience with the drugs we study in the laboratory. The Mayo Clinic is very different from a university; you can be on staff and not have an academic appointment. In universities, the medical school comes first and the hospital is built around the medical school; Mayo Clinic was a clinic for almost 100 years before they decided to start a medical school. The Mayo Clinic in Rochester has two separate hospitals and in the early 1970s they decided to start a medical school; my recruitment was related to beefing up the staff for that purpose. But, as I said before, one can have an appointment at Mayo Clinic but no academic appointment. We're called Consultants at the Mayo Clinic. I'm a Consultant in Psychiatry and Pharmacology at the Medical Center, but I'm also a Professor of Psychiatry and Pharmacology at the Mayo Medical School and at the Mayo Graduate School for Medical Education. There is a story why we are called consultants at the medical center.

TB: What is the story?

ER: The Mayo brothers, who started the first group practice in medicine at the end of the 19th century that grew into the Clinic, were both surgeons and they brought on staff internists to consult if they thought the patient

had a medical problem. So in this first group practice of medicine they established, they called their staff consultants.

TB: I see.

ER: The Mayo Clinic is one of the world's great medical institutions, but the Mayo Clinic is not doing much in the way of research. So, my Career Development Award from NIH, which I obtained at Hopkins, could not be transferred to Mayo. Nonetheless, I continued my research and flourished, published a lot of papers and accomplished things.

TB: What was your first research project after you arrived in Rochester?

ER: It was a continuation of what I was doing at Johns Hopkins, studying the regulation of tyrosine hydroxylase.

TB: Could you give us the background to that project?

ER: When I was at NIH in Marshall Nirenberg's laboratory, he was interested in developing model systems of neurons that grow in culture so he could study the chemistry of neuronal cells, What he wanted to develop in culture was synaptogenesis, and he did succeed. My project was to isolate a cell line with high levels of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines. He had been working before I got there on an established cell line of a tumor that was a neuroblastoma, from the mouse. The neuroblastoma was a spontaneous tumor serially transferred from mouse to mouse for many years until, in the early or mid-1960s, somebody took the tumor from an animal, dissociated it, and grew it in culture. Those cells were called mouse neuroblastoma C1300, made up of many different cell types. Now we think about neuroblastomas as being adrenergic tumors, but we had difficulty even measuring tyrosine hydroxylase activity in those cells.

TB: What was your task in that project?

ER: My task was twofold. First, I was to develop the enzyme assay for tyrosine hydroxylase and folks had been trying to do this for a while before I came to Marshall Nirenberg's laboratory. It was very difficult to develop that assay because of the presence of inhibitors of this enzyme's activity in the neuroblastoma cells. In addition, the activity of the enzyme was very low. After I got the assay developed and working very well, we set about to clone it, to isolate a single cell from this heterogeneous population of cells. We used the glass shard technique. You place small broken pieces of sterile glass on a culture plate and then plate out cells at very low densities so you find either no cells or just one cell on a shard. Under sterile conditions, with forceps under a microscope, you pick up the shard with one cell and place it onto its own culture plate. If cells grow you're reasonably certain the population came from that single cell. We use the term cloning to mean other things now, but back then it was just cloning

of cells. We had a very large number of cell lines I screened for tyrosine hydroxylase activity and found one cell line, N1E-115 with exceedingly high, higher than the adrenal medulla, level of activity. This cell line is the most widely studied neuroblastoma cell line in the world. There are literally hundreds upon hundreds of papers published using this cell line. If the authors ever cited the original paper I'd have a certain citation classic, but nobody does!

TB: Where and when was it published?

ER: The Amano, Richelson, Nirenberg paper on "*Neurotransmitter Synthesis by Neuroblastoma Clones*," was published in Proceedings of the National Academy of Sciences USA in 1972. So, when I went to Hopkins I continued working with that cell line, studying the regulation of tyrosine hydroxylase because of its relevance to the action of some psychiatric drugs. Catecholamines have been important in theories of the pathophysiology of affective illness and the action of antidepressant drugs. At Mayo, I continued with that same cell line to study tyrosine hydroxylase, but then I became interested in its receptors.

TB: How did that come about?

ER: At Hopkins, from about 1973 to 1975, there was a scientist named Pedro Cuatrecasas, in the Department of Pharmacology. He was a brilliant man and brilliant researcher, who had developed radioligand binding assays and was interested in hormone receptors and particularly the insulin receptor. He taught Sol Snyder how to do binding assays, and Sol Snyder ran with the technology. I, quite frankly, was intimidated by all that receptorology going on at Hopkins and I did not move into the area until I went to Mayo. Then, I discovered that the cell line I studied, had muscarinic receptors, which, when activated, elevate intracellular levels of cyclic GMP (cGMP). With this functional assay measuring cGMP production in living cells, I was able to study muscarinic receptors in various ways, looking at agonist stimulation of the receptor, regulation of sensitivity of the receptor to various agonists and at desensitization and down regulation. I also used the assay as a way of looking at the potency of psychiatric drugs to block the muscarinic receptor. So we did studies determining inhibitor constants for antidepressants, antipsychotics and related compounds by their ability to block receptor-mediated cGMP production. I wrote a paper with Divinetz-Romero on the "*Blockade by Psychotropic Drugs of the Muscarinic Acetylcholine Receptors*" that won an A. E. Bennett Award from the Society of Biological Psychiatry in 1977 and was published in Biological Psychiatry the same year. So we got into receptors in a big way. We also started to see if we could get any response from these cells by adding other neurotransmitters and discovered histamine worked

quite well. We now had another receptor we could study by this functional assay, the histamine- H_1 receptor. Then we looked at the ability of antidepressants and other psychiatric drugs to block histamine-mediated cGMP production in these cells. From this work we discovered drugs like doxepin were incredibly potent antihistamines. Next we were interested to see whether peptides, particularly neuropeptides, had any effects on cGMP production in these cells so we screened bradykinin, angiotensin, and neurotensin with this same cell line, N1E-115. We found, in the early 1980s, stimulation of cGMP by each of these peptides. The medical literature at the time was interested only in one of those peptides, neurotensin. In 1980, Charlie Nemeroff had published his A. E. Bennett Award paper, "*Neurotensin Per Chance Endogenous Neuroleptic?*" in Biological Psychiatry. Having discovered the neurotensin receptor on these cells and knowing this might be important in terms of a psychiatric illness, we decided to focus on neurotensin and its receptors. To this day we continue this research.

TB: So, you became involved in research with neurotensin?

ER: We have a patent issued last April, U.S. Patent No. 6,214,790, on some of the neurotensin analogs we have, and we're moving forward with pre-clinical toxicology studies to get one of these compounds into humans and see if it has any antipsychotic effect. Now, what goes around comes around. There's evidence neurotensin has to be directly injected into the brain to get an effect, but our neurotensin receptor agonists can be injected outside the brain and still get into it. There's also literature to suggest neurotensin can activate and up-regulate tyrosine hydroxylase.

TB: So you are back to tyrosine hydroxylase?

ER: I'm back where I started. It's incredible! I'm doing experiments we did 30 years ago. So, we thawed out the N1E-115 cells, we're growing them and looking at the ability of neurotensin to activate tyrosine hydroxylase. We want to understand the basic mechanisms involved.

TB: You mentioned you have a model for studying receptor binding for acetylcholine, histamine and neurotensin, right?

ER: Yes.

TB: And you have published on receptor binding with different series of psychotropic drugs?

ER: Yes, thank you for reminding me. We had a wonderful neuropathologist at Mayo in Rochester, Dr. Okazaki, and when there was criticism about doing binding studies on rat brain or studies on receptors in mouse cells, it occurred to me maybe we should do human brain binding studies. So I went to Okazaki; he was incredibly cooperative and happy to provide us with normal human brain tissue whenever we needed it. He's co-author

on a series of studies that looked at binding of psychotropic drugs to several different receptors in normal human brain tissue. We included studies on antipsychotic drugs and antidepressant drugs, defining their receptor binding properties at human brain receptors.

ER: You have delineated the receptor profile of numerous psychotropic drugs in humans?

ER: Exactly. We still a few binding studies with human brain tissue, but with our capability for molecular cloning of human receptors, it's unnecessary to get the tissue at autopsy any longer. Nowadays it's almost impossible to get normal human brain tissue at autopsy. We have a brain bank at Mayo in Jacksonville with hundreds of brains from Alzheimer's, Parkinson's and other degenerative diseases, but normal brain tissue is very hard to come by. At the time, we were envied by many, because it was hard for colleagues to get the normal human brain tissue we had been able to obtain. So we were in the forefront with respect to that research. From the data we've obtained we continue to fill in gaps by looking at new drugs when they become available. I've published many review articles on receptor binding of antidepressants and antipsychotics and what that relates to clinically, mainly side effects. I think I'm best known for these review articles rather than the many more basic science papers I've published.

TB: Your review articles are based on your own research?

ER: Correct. On findings we reported in peer reviewed basic science journals, such as *European Journal of Pharmacology*, *Journal of Pharmacology and Experimental Therapeutics*, etc. In my review papers I interpreted the findings in those papers for clinicians.

TB: I have been using the data from your review articles as reference points for many years.

ER: Thank you.

TB: I don't think anyone had studied the receptor profile of antidepressants and antipsychotics as systematically as you.

ER: That's correct but I don't consider this terribly creative research. It is clinically very important for predicting adverse effects and making it possible for clinicians to choose a treatment on the basis of the receptor binding profile of a drug.

TB: You were first to provide information that should be available for any new drug.

ER: I think we're seeing this information now in new compounds.

TB: Drug companies are providing the information now.

ER: Yes, they are selecting compounds for clinical development with weak effects at least on muscarinic acetylcholine, α_1 -adrenergic, and hista-

- mine- H_1 receptors. What I provided was a standard with respect to one laboratory compiling the data and rank ordering the drugs.
- TB: What kind of interaction do you have with drug companies?
- ER: I have had small grants from pharmaceutical companies to look specifically at the receptor binding profile of their compound in human brain receptors compared to standard compounds. But it's been a minor effort in terms of overall production.
- TB: Each company is doing this now in-house? Is each company doing it the same way?
- ER: They're looking mainly at cloned human receptors. They don't have available the human brain tissue we still have.
- TB: You still have?
- ER: Yes. So occasionally a pharmaceutical company will come to me for the human brain receptor binding profile of their compound.
- TB: What do we know about interspecies differences in receptor binding?
- ER: There are clearly species differences but they are working with cloned human receptors. Still, because of potential artefacts introduced when you're looking at a molecularly cloned human receptor, actual human brain studies are worthwhile.
- TG: You mentioned the work you are doing is relevant to adverse effects but does it have any relevance to the therapeutic effects, for example in neuroleptics? Do you think the affinity of neuroleptics to the dopamine- D_2 receptor has any relevance to the therapeutic effect?
- ER: Certainly. In 1976 Snyder's group published with rat brain and Seeman's group with calf brain, some studies with a marvellous correlation between dopamine- D_2 receptor binding and daily dosage. We recently did the human brain and got the same results. For sure, the dopamine- D_2 receptor is important in therapeutic as well as adverse effects.
- TB: Is it relevant to schizophrenia or to psychosis?
- ER: It's a good question. It's amazing Snyder's and Seeman's groups both showed, from a test tube assay, that affinity to the dopamine- D_2 receptor on the Y-axis and daily dose on the X-axis have a high correlation.
- TB: But isn't that a relationship between dose requirement and receptor affinity?
- ER: With PET (positron emission tomography) scanning, using radioligand binding assays, we can look at receptor occupancy for dopamine- D_2 receptors, serotonin receptors and the like in vivo in humans and relate the findings to both therapeutic and adverse effects.
- TB: Are the findings state dependent?
- ER: Not really. That's important, but I'm of the mind we can't be certain about the mechanism of action of these drugs and I decided a long time ago I

can more easily explain the mechanism of an adverse rather than a therapeutic effect.

TB: Do we have enough information at this point to generate a hypothesis regarding therapeutic effects?

ER: I think dopamine-D₂ receptor occupancy relates to therapeutic effects in psychosis and also extrapyramidal side effects, but I don't necessarily think that means an aberration of the dopamine system per se explains what psychosis is.

TB: You are always very careful in your papers, much more careful than other people, in relating your findings to therapeutic effect and disease.

ER: Thanks.

TB: What about serotonin receptors?

ER: There's a lot of controversy about serotonin 5HT_{2A} receptors. We found if you knock-down the gene for the 5HT_{2A} receptor you block haloperidol induced catalepsy.

TB: That is very interesting.

ER: So, the 5HT_{2A} receptor is very important in terms of modulating or ameliorating the adverse effects of neuroleptics.

TB: What about antidepressants?

ER: We've just determined, with Randy Blakely, the binding inhibitor constants in very large series of antidepressants and antipsychotic drugs for potency of binding to transporters; that information has been useful in predicting side effects but not efficacy in treating depression.

TB: By binding to transporters, reuptake is blocked, right?

ER: Correct.

TG: Again you are saying it has something to do with adverse effects but is there a relationship between blockade and therapeutic effects?

ER: There may be but one should not overlook there are major differences in potency binding to norepinephrine and serotonin transporters of equally effective antidepressants. Moreover, we have drugs like trimipramine which are not very potent at norepinephrine, serotonin or dopamine, yet are effective antidepressants.

TB: I remember early behavioural pharmacological findings with trimipramine which indicated it could be administered safely in combination with monoamine oxidase inhibitors.

ER: Of course.

TB: What about venlafaxine? Its effect on reuptake looks like the mirror image if imipramine.

ER: Venlafaxine is much more potent on the rat norepinephrine transporter than the human.

- TB: So the effect of venlafaxine is weak on the norepinephrine transporter in humans?
- ER: In our hands venlafaxine in the rat is about four to five times more potent at the serotonin transporter than at the norepinephrine transporter, whereas in humans there is a 100 fold difference.
- TB: So we have to push the dose high to get any norepinephrine effect, otherwise it's like an SSRI?
- ER: Yes, at low dose it is an SSRI.
- TB: You seem to be splitting your time between basic and clinical research?
- ER: I'm continued to be interested in basic research, but now I'm trying to get drugs we've been working on in the laboratory into the clinic. The ultimate goal of the pharmacologist, and I look at myself as a pharmacologist, is to get a drug into the clinic. To do that in academia is extremely difficult, but we're moving in that direction. We have, as I mentioned, a patent for a neurotensin analog, and I've secured funding to do preclinical toxicology through a foundation, so I can get it into the clinic. If this compound passes preclinical toxicology I should be able to get an IND for testing it in schizophrenic patients. That will test the hypothesis Charlie Nemeroff proposed 20 years ago, that a neurotensin agonist would be an antipsychotic. My goal, before I retire, is to get at least one of the compounds we've been working on for many years into the clinic and be involved personally in the clinical trial.
- TB: The compound is a neurotensin agonist you would be testing in schizophrenia?
- ER: Yes. But what is very interesting about this compound is that it might also be very useful in Parkinson's disease. We have data which suggest that, like some antipsychotic drugs, it blocks the behavioural effects of psycho-stimulants such as cocaine and amphetamines. So we have a unique compound that in animal studies suggests efficacy in both schizophrenia and Parkinson's disease while our current antipsychotics induce parkinsonian symptoms in patients.
- TB: It would be interesting to have a compound that is effective in both schizophrenia and Parkinson's disease. Do you have any other compound in the making?
- ER: I'm co-inventor on a patent issued in May, 1999 for a series of compounds that are analogs of venlafaxine. For some of these compounds I use the acronym SNUB, because they are potent blockers of all three transporters; norepinephrine, serotonin and dopamine. These are compounds of a chemist I collaborated with at another institution.
- TB: Are these the first SNUBs?

ER: Apparently there are pharmaceutical companies around the world that have these types of compounds in development. But these could be phenomenal antidepressants if you remember nomifensine.

TB: I remember nomifensine very well.

ER: We have a number of other patent applications pending on a whole other area of research I haven't mentioned.

TB: Would you like to say something about them?

ER: We have been involved for five years looking at a new generation of compounds, called peptide nucleic acids, PNA for short. That's a misnomer because they are neither peptides nor nucleic acids and they are not broken down by either peptidases or nucleases. We did studies with these types of molecules to answer questions about the neurotensin receptor. Nobody had ever done research with them other than in vitro experiments with cells in culture. What researchers observed was they didn't penetrate well into cells. Nonetheless, we went forward with animal studies and were able to knock-down gene expression in brain by directly injecting these molecules into brain. The next experiment was to inject them into the belly of the rat and we showed an effect in the brain as long as there was no impairment of the blood-brain barrier which was quite revolutionary. This is the great thing about science; you have a hypothesis, do an experiment and get a result which is unexpected. Then, you continue down a road you never thought you'd travel on.

TB: What would you consider your most important contribution?

ER: I'm not sure quite frankly. I alluded to the fact I'm best known for my review articles. I'm proud of that because I've tried to take basic information and make it relevant and readable for the clinician; to bring the basic pharmacology of drugs we use every day to the level of clinicians, so they can understand and use it in clinical practice.

TB: You are still involved in clinical practice?

ER: Once a week, half a day, all through the years.

TB: Do you see any patient or just a selected population?

ER: Good question, I see two patients in consultation weekly. The Mayo Clinic in Jacksonville has about 300 physicians now. It opened in 1986 with less than 40. It's a multi-specialty clinic. The patient comes in for a medical work-up and if a colleague thinks a patient has a psychiatric problem, they receive a psychiatric evaluation. I set aside a couple of slots in my afternoon schedule to see whatever, it can be anything.

TB: They are patients from the Mayo Clinic?

ER: Generally. But then I have a group of patients I've been following for years. They are the most difficult, refractory, depressed patients you'd ever want to treat, which keeps me honest and running back to the laboratory to

- develop better drugs. I do a lot of experimentation with them which they understand and accept.
- TB: When you say experimentation are you following an intensive study design?
- ER: I'm not doing anything as systematic as that. I'm trying many different things, combining drugs, using drugs not necessarily considered first line treatment or not even indicated for the condition.
- TB: Could you say something about your training in psychiatry at Hopkins?
- ER: Psychiatric training at Hopkins at that time was very analytically oriented.
- TB: After Joel Elkes resigned?
- ER: Even when he was there. So I had to do a lot of psychotherapy and didn't particularly like that. I wasn't good at it. You don't have to be a physician or even a college graduate to do psychotherapy. I may offend folks by saying it's a waste of a time in medical schools, training someone to be a psychotherapist. A psychiatrist is first a physician and should not renounce the knowledge gained in medical school, as some have done. That doesn't make sense. The way to remain a physician, while being a psychiatrist, is to practice pharmacology. To practice psychiatry well and treat people with drugs you have to know a lot about your patient's health and need to be knowledgeable about internal medicine.
- TB: When did you become a member of ACNP?
- ER: When I went back to Hopkins to work with Sol Snyder who got me invited to ACNP.
- TB: What year was that?
- ER: Around 1972. and I never missed any of the annual meetings. I became a member in 1976. I was also involved in the Society of Biological Psychiatry. I don't know if I should talk about that.
- TB: Please do.
- ER: I was Secretary/Treasurer for five or six years, then became Vice President and President, and now I continue to be and on the Council. I have been so active with the Society of Biological Psychiatry I may have neglected the ACNP but I'm now the incoming Chair of the Credentials Committee.
- TB: You mentioned you received the Bennett Award of the Society of Biological Psychiatry.
- ER: Yes.
- TB: Any other awards you have received?
- ER: The Daniel Efron Award of the ACNP which I shared with Bob Post. That was quite an honor.
- TB: What is your position now at the Mayo in Jacksonville?
- ER: I'm the first Director of Research. I started research from scratch, which was enormously difficult but I had a lot of help. If you can imagine working

in trailers for four years before we had a building! We started from a site where we didn't even have permission from the state to use radioactive materials; we had to go through the process of filling out applications and applying to the State just to do the first experiment with radioactivity. It was starting from scratch and quite difficult for seven or eight years. The focus of research in Jacksonville was on Alzheimer's and neurodegenerative diseases which made my situation even more difficult because I didn't consider myself an Alzheimer's researcher. But, I had enough interest in the field and liked the idea of going to Jacksonville so much, I jumped at the job. The second Director for Research is a very distinguished scientist in the Alzheimer's field, Steven Younkin. He, in turn, recruited some outstanding researchers and we have made our place a first-class research institute in Alzheimer's and other neurodegenerative diseases. So that's going well.

TB: Is there anything we left out and you would like to add?

ER: I'm impressed with how much you know about what I've done and I appreciate that.

TB: You've done a great job, in addition to your other research, by translating findings from basic science to clinicians. You certainly achieved your objective and should be happy about that.

ER: Thank you.

TB: I would like to wish you good luck in developing the compounds generated through your research.

ER: Thank you very much.

TB: Thank you, Elliott, for sharing this information with us.

ER: My pleasure. It was fun.

DONALD S. ROBINSON

**Interviewed by Joel Braslow
San Juan, Puerto Rico, December 7, 2003**

JB: It is December 7, 2003. I am Joel Braslow and I am interviewing Donald Robinson.* If you will, talk about how you got interested in medicine.

DR: Perhaps, it was a somewhat unique course of events as compared with others because I started out as an engineer, attending Rensselaer Polytechnic Institute in Troy, New York where I graduated in Chemical Engineering. I went to work as an engineer for Eastman Kodak Company in Rochester, New York.

JB: And, when was this?

DR: It so happens that the day I started work for Eastman Kodak in June 1950, the Korean War broke out that very day. It didn't take many months for the selective service agency to catch up with me, and I was drafted into the US Army. Because there was a shortage of engineers with some professional experience, the Army offered me a Commission and I went on to work in the Ordnance Corps guided missile program. I had the unique experience of being assigned to detached duty at Bell Telephone Laboratories in Whippany, New Jersey, which was the primary contractor for the Nike Anti-Aircraft Missile program. In this capacity I interacted extensively with the German missile scientists at White Sands Proving Ground, New Mexico and Redstone Arsenal in Huntsville, Alabama. Also, I got to associate with Bell Telephone Laboratories wizards, who had recently developed the transistor, a key discovery in making space travel possible. This capability to miniaturize components and to have on-board computers eventually helped get us to the moon. That was an interesting experience, and I enjoyed it very much, but it also reevaluated what I really wanted to do with my life. I found some aspects of engineering to be not very gratifying.

JB: What sort of aspects weren't?

DR: Well, engineering can be a highly impersonal profession in many ways. It's very data-driven while I tended to place greater value on interpersonal relationships. I saw medicine as a way to combine science with the ability to help others. I fortunately was able to complete pre-med requirements while in the Army, only requiring a biology course, which I completed at Seton Hall University in New Jersey. When I was discharged from the military, I had already been accepted to the University of Pennsylvania,

* Donald S. Robinson was born in Pittsfield, Massachusetts in 1928.

School of Medicine, where I received an MD in 1959. In brief, that's how I came to pursue a medical career.

JB: That is a different route than most people take.

DR: I want to mention that I had many friends over the years who were involved in health care. Obviously, they had a positive influence on my ultimate career choice.

JB: How about your family background?

DR: There was no one in my family in the health professions. My father was an engineer for General Electric Company. I grew up in western Massachusetts in the city of Pittsfield, Mass, a "GE town", as they say. I had no real contacts with people in medicine until in college years and beyond.

JB: How did your father feel about you switching?

DR: My father died when I was at a young age. Interestingly enough, he died of a hematologic disorder that would be eminently curable today but was not at that time. When I made the decision to go into medicine, I was away from home and didn't have much feedback from my family about my decision. It came mostly from friends and associates in medicine and health care.

JB: So, when you started medical school did you know what you were going to do?

DR: I had no idea. Probably fairly typically, particularly for someone who did not come from a medical family, I had little idea in medical school about what I wanted to do. A lot of us in medical school at that time were enchanted with the idea of general practice; we were going to deliver babies, care for kids, do surgery, maybe, and be the "universal doc." Even then, it was evident, as I was completing a rotating internship and family practice residency, that this was not possible, or desirable. My wife and I, both being from northeast, wanted to look into practice situations in Vermont so I took a position at the Vermont State Hospital to care for medical problems.

JB: Was that after your general practice residency?

DR: That followed my general practice residency year, so I'd had two years of clinical training. While at Vermont State Hospital, I had the opportunity to work with a psychiatrist, Dr. George Brooks, whose name may not be known to you, but he was well known and highly regarded back in the 1960's, for his pioneering work in getting patients out of the mental hospitals and into the community. He had published extensively and was internationally known for his work. In the meantime, when I was there, I realized I was not interested in family practice. Because of the affiliation of the state hospital with the University of Vermont College of Medicine,

consultants came from the Vermont Medical Center. They encouraged me to enrol in the residency program at the Vermont Medical Center, so I ended up there in internal medicine.

JB: Not in psychiatry?

DR: Not in psychiatry. While a resident, my career was influenced by the fact that I had gotten involved in monitoring adverse reactions within the hospital under a federally funded grant. I collected adverse reactions, compiling them in a monthly report.

JB: Adverse reactions from which drugs?

DR: Any drug administered in the hospital associated with an untoward reaction.

JB: Were these drug trials?

DR: No, they were case reports of what we now term Adverse Experiences. It was a form of FDA post-marketing surveillance program.

JB: This was during your residency?

DR: Yes, during the second and third years of residency. That activity got me involved with the Pharmacology Department at the Vermont College of Medicine. I began attending Pharmacology Department functions and interacted with the faculty and guest lecturers. One of the guest speakers was Dr. John Burns, a pioneer in the field of pharmacology and psychopharmacology. He had been very influential during his tenure at NIH in recruiting scientists who made major contributions to the fields of pharmacology and clinical pharmacology. One was Bernard Brodie, who headed a large laboratory group at NIH that included Julius Axelrod, James Gillespie, and others. Anyway, Dr. Burns was a guest lecturer in the Department of Pharmacology at Vermont.

JB: What was Dr. John Burns known for?

DR: I'm not sure about his original research, but he was known for bringing together a team of superb researchers, the fathers of pharmacology at NIH.

JB: Was he critical in bringing Brodie and Axelrod to NIH?

DR: I believe so. Later, he was recruited from NIH by Hoffman LaRoche to head their R& D (Research and Development) program, so he moved to Nutley, New Jersey. While there, he subsequently established, what became the Roche Institute of Molecular Biology, a "mini-NIH" in New Jersey. He recruited many well known scientists, including Sidney Udenfriend, who was noted for the work of his NIH laboratory in delineating serotonin biosynthesis and metabolism, and was joined by Ronald Kuntzman and Sydney Spector from NIH and other prominent investigators.

JB: So, you attended Dr. Burns' lecture. What was the topic?

DR: At that time, the phenomenon of hepatic microsomal enzyme induction had just been described; it really was one of his major contributions. Dr. Burns had sponsored some of the initial *in vitro* studies showing that microsomal enzymes could be induced, i.e., activated, by exposure to a variety of drugs including phenobarbital. Subsequently, it was learned that all barbiturates possess this property of inducing hepatic drug-metabolizing enzymes, and this was the topic of his lecture.

JB: For the lay audience, maybe you can explain what you mean by hepatic induction.

DR: Many substances, both drugs and environmental substances, can stimulate hepatic enzymes that transform and detoxify other drugs. Through this mechanism, a drug may accelerate clearance of a variety of other drugs that are biotransformed via the activated hepatic enzyme pathway. The practical implications are that if someone were to take an enzyme-inducing drug like phenobarbital, while taking a maintenance dose of a second drug, like the anticoagulant warfarin, warfarin would be cleared more rapidly and the anticoagulant effect would be diminished.

JB: Was that phenomenon just recognized at the time?

DR: Yes, in the mid-1960s.

JB: And, the concept of one drug inducing clearance of another?

DR: It was unknown, so this was an important new finding; a discovery that evolved largely from John Burns' group in Brodie's lab at NIH. The impact of the lecture on me was that I became intrigued by the potential clinical effects of barbiturates on other drugs because one of my tasks as a resident was to manage outpatients on anticoagulants at the medical center. Patients would be tested regularly for prothrombin times. My task was to determine what change, if any, in warfarin dose was indicated. Most patients were stabilized on a given dose for long periods with little change from month to month. With ready access to this group of patients, it occurred to me that it would be a relatively easy to test the effect of barbiturate on prothrombin time. I was able to recruit a number of these patients to start taking a small dose of phenobarbital, which in those days, prior to benzodiazepines, was a mild sedative in common use. Enough outpatients were willing to take phenobarbital in modest dosage along with warfarin to do this experiment.

JB: This was before IRB?

DR: Yes, before IRBs. We followed the patients with weekly prothrombin tests to assess the effect, if any.

JB: These were all patients that were on warfarin?

DR: They were all patients taking stable doses of warfarin for coronary heart disease. Predictably, their anticoagulation went out of control rapidly

because the phenobarbital induced the drug-metabolizing enzyme system for warfarin. As a result the warfarin was metabolized much more rapidly than it had been before phenobarbital administration. We wrote up the clinical trial results and submitted the paper.

JB: The phenomenon of decreasing warfarin levels?

DR: Yes, decreasing warfarin levels and resultant shorter prothrombin times. We sent the paper to JAMA but the referees rejected it. Apparently it was the first clinical paper describing this phenomenon and had only been shown prior to these in vitro and animal experiments. The editor stated, "We're not going to accept this paper, even though this probably is one of the very first clinical papers on this topic because the study was not placebo-controlled and could be a chance finding". Well, I accepted that as fair criticism.

JB: What date was this?

DR: This was 1964.

JB: This was still pretty early for placebo-controlled trials in clinical research.

DR: Yes, absolutely.

JB: So, was that a surprising kind of criticism?

DR: It was because the notion of a placebo-controlled clinical trial was novel and a sophisticated concept in that era. I felt there's still got to be a way to satisfy the reviewers. So, I undertook a before and after study utilizing identical-appearing placebo tablets.

JB: This was a single-blind, crossover trial?

DR: A crossover trial design, exactly. Well, very neatly, the degree of warfarin anticoagulation was unaffected during placebo administration. We resubmitted the paper, and JAMA accepted it this time.

JB: Was this your first paper?

DR: I'd written a few case reports, but this was my first published clinical trial.

JB: Had you planned on doing research before this trial?

DR: No, this trial influenced my career direction profoundly and ultimately led to an intense interest in pharmacology and clinical therapeutics. I was offered an extra year under a NIMH training grant to earn a master's degree in pharmacology at the University of Vermont. That seemed like a good idea, so I spent a fellowship year qualifying for a graduate degree in pharmacology and accruing scientific credentials. Then I realized if I wanted to make an academic career in clinical pharmacology it was important to go elsewhere for a post-doctoral experience. I applied to NIH and was accepted in the laboratory of Dr. Al Sjoerdsma, now an emeritus member of ACNP. He headed the Laboratory of Experimental Therapeutics, which was heavily vested in investigating catecholamine and serotonin metabolism. Sjoerdsma's and Udenfriend's labs were adjoining in the NIH Clinical

Center, with extensive collaboration. There was ready access to subjects and patients located in the NIH Clinical Center. Much of my research efforts in those two years involved patient care studies relating to the area of monoamines.

JB: What types of patient care studies?

DR: Carcinoid syndrome, pheochromocytoma and essential hypertension were major research interests of the Experimental Therapeutics Laboratory.

JB: Carcinoid is a tumor isn't it?

DR: Carcinoid is a tumor of cell types that produce serotonin, bradykinin and histamine, among other substances. My research project, and how I ultimately got into psychopharmacology, is perhaps an interesting tale. When I arrived at NIH, Al Sjoerdsma asked, "Well, what would you like to do?" Of course, I didn't have a clue; I wanted him to tell me what I should do! In my clinical training I spent a year in hematology and he was aware of this. He said, "You know hematology. Maybe you'd like to look at a blood enzyme. Plasma benzylamine oxidase has recently been described by McEwen". There had, in fact, been two papers published by him describing a form of monoamine oxidase in plasma, termed benzylamine oxidase. Using rather crude assay methodology, McEwen had shown one could measure plasma oxidation of the artificial monoamine substrate, benzylamine. Aware of this work, Sjoerdsma said, "This might be worth your looking at, because of your haematology training, and it certainly has implications for monoamines," which was a major thrust of his laboratory. I agreed it was a good idea and started to work on it.

JB: Did you have an interest in monoamines when you went to NIH?

DR: No, I didn't know anything other than what I had learned in pharmacology.

JB: It was chance you ended up in his lab?

DR: Yes, in a sense it was chance. The reason I was interested in his lab was because he was well regarded and influential in the field of clinical pharmacology. He was active in the Pharmacology Society of FASEB and in the budding Society of Clinical Pharmacology organized by Lou Lasagna, a distinguished member and past president of our College, who died this year. I chose to go to Al's lab because I wanted an opportunity to conduct bench and clinical research, to marry the two disciplines. I tackled the task of figuring out how best to study plasma benzylamine oxidase. Al suggested I consider adapting the newly described radiometric assay of Wurtman and Axelrod. This utilized radioisotopic-labeled monoamine substrates incubated with a source of the enzyme to measure MAO activity. This advance in methodology to assay enzyme activity was new at

that time and dramatically changed the sensitivity of tests to quantify enzyme activities.

JB: The assays would be to what end?

DR: To look at the enzymatic activity for converting monoamine substrates to end-product in a blood specimen. Previous assay methods like the one employed by McEwen for MAO activity measured end products of oxidation by chromatography or spectography, a laborious and less sensitive methodology. I studied blood specimens of volunteers to see what MAO activity I could detect in plasma. I succeeded but was getting very erratic results, with poor reproducibility, even within the same subject from day to day. This didn't make much sense, particularly since McEwen had not mentioned this problem in his publications. After a few weeks, it finally dawned on me that maybe the problem was some unknown blood source of MAO contaminating the plasma specimens. The obvious thing to investigate was the tube of centrifuged blood, which contained red cells in the bottom layer, an intermediate layer of white cells and plasma supernatant. I knew platelets tend to cluster with white cells so I realized if one wasn't careful in decanting the plasma, platelets from the buffy coat might contaminate the plasma supernatant. This focused me on the platelets, which were an extremely rich source of monoamine oxidase, in fact, one of the richest sources in the body.

JB: Had anyone recognized that before?

DR: No, they had not.

JB: So, this was surely a significant finding?

DR: It was, and I consider myself fortunate because one doesn't make many significant findings in one's research career. It was a milestone event and I was fortunate indeed.

JB: How did you determine that it was platelets?

DR: Methodology existed for differential centrifugation of blood to yield platelets.

JB: How did you realize they were the platelets which were contributing to the MAO activity?

DR: I thought it must have something to do with the buffy coat layer, because I was not fastidious in aspirating the supernatant layer. It wouldn't take a lot of contamination from platelets in the buffy coat layer to yield a marked increase in MAO activity. We isolated the pure platelet layer and found it a rich source of monoamine oxidase. This finding was instrumental in directing my research interests towards psychopharmacology. For the remainder of my two years at NIH I focused on the MAO enzyme, characterizing the platelet enzyme biochemically and pharmacologically, as well as monitoring patients on MAO inhibitors to follow the time course

of MAO inhibition with different MAO inhibitors at different doses. The first paper, which I co-authored with Dr. Sjoerdsma, was published in 1968 in *Biochemical Pharmacology* and created a lot of interest within the field of psychopharmacology as evidenced by numerous queries from investigators interested in employing the method of platelet MAO assay.

JB: What was the significance in that finding? Why would that generate a lot of interest?

DR: One could now conveniently follow the time course of platelet MAO inhibition in patients using the percent of platelet MAO inhibition as a surrogate marker for drug effect, analogous to measuring plasma levels with TCAs. We correlated time course of MAO inhibition at different doses of MAO inhibitors with the onset of clinical effects. The assay was useful in characterizing human MAO enzyme, and also to clinically monitor patients using it like a drug level assay.

JB: Prior to the introduction of this assay how was MAO activity measured?

DR: It was laborious. To assay MAO inhibition, one collected 24-hour urine from the subject and measured the amount of tryptamine, a biogenic amine in urine, then administered the MAO inhibitor and collected a second 24-hour urine to detect change in tryptamine excretion. The only other *in vivo* method was obtaining a jejunal biopsy of the GI mucosa for assay of tissue MAO.

JB: So it became a really useful way of measuring monoamine oxidase inhibition for clinical purposes and for research?

DR: Yes, both scientific and therapeutic use. A number of research centers set up to assay platelet MAO.

JB: It's amazing that monoamine oxidase inhibitors and MAO platelet assays became popular in treatment. And, what happened to that?

DR: It was very popular for a period of time. In the 1970s and even into the 1980s there were "blood level gurus" who began offering tricyclic plasma levels and platelet MAO inhibition as adjuncts to patient care. This practice has fallen by the wayside in recent years. One of the reasons is MAO inhibitors are much less used mostly for treating difficult, treatment resistant patients. Tricyclic blood levels were never terribly helpful because they correlated poorly with therapeutic effect. There was less impetus to set up drug level determinations for SSRIs because toxicity was less of an issue compared with TCAs, which have a narrow therapeutic ratio.

JB: So, after NIH, where did you go?

DR: I returned to the University of Vermont where I joined the departments of pharmacology and medicine. I collaborated extensively with Dr. Alexander Nies, who had studied and trained at McGill University, although he was from New Jersey and graduated from Alford University. After his psychiatry

residency at the Royal Victoria Hospital in Montreal, Al migrated to the Medical Center in Burlington, Vermont. A modern department of psychiatry was created in Vermont by importing faculty mostly from the Royal Victoria Hospital in Montreal. Dr. Tom Boag became Chairman of the department and recruited full time academic psychiatrists. Al and I were peers during our residency and fellowship years and close friends. When I returned to the Vermont College of Medicine, Al was intrigued by the platelet MAO activity work I had done, due to the fact that MAO inhibitors were widely used in Canada. In 1968 in the United States you could hardly find a psychiatrist who prescribed a MAO inhibitor. However, the Vermont Psychiatry Department was accustomed to using them extensively.

JB: What do you think is the reason for that?

DR: I suppose there are two possible explanations. One is that American psychiatry was not biologically oriented in the 1960s; until recently it was analytically oriented. Training programs in the US offered little formal instruction in psychopharmacology.

JB: Was that true for your own personal training?

DR: I'm not trained in psychiatry. As a pharmacologist I knew there was an extensive literature from the UK by West and Dally and by Sargent and others, on the clinical use of MAO inhibitors. They reported that MAO inhibitor drugs were uniquely effective in certain sub-types of reactive or neurotic depression. As a result, MAOIs were widely used in the UK and in Canada where psychiatry was more biologically oriented than in the US.

JB: Especially since the analytical approach never flourished in England.

DR: Right. Al Nies suggested the blood MAO assay offered a unique research opportunity since we had ready access to patients on MAOI treatment in the Vermont Medical Center. So we submitted a NIMH grant proposal as co-investigators and it was funded. That was the start of more than 20 years of NIMH grants support, largely in the area of depressive disorders and their treatment. Al Nies and I published one of the very first double-blind, placebo-controlled trials of a MAO inhibitor.

JB: What about studies in England?

DR: There was one placebo-controlled trial by Eva Johnstone published about the same time as our initial phenelzine paper. To my knowledge, these were the first two well controlled placebo comparison trials of an MAOI in depression. There was also a large sample size study sponsored by the UK Medical Research Council but phenelzine did not differentiate from placebo and raised questions which further dampened enthusiasm for MAOIs.

JB: Was that a controversial study?

DR: It was controversial because of design flaws, although it was published in the British Medical Journal.

JB: And this British study came out before yours?

DR: Yes. The concept was good, in that it was placebo-controlled, which in those days was quite revolutionary. The study was part of a larger effort to comprehensively evaluate different antidepressants including tricyclics.

JB: And in your placebo-controlled trial you were also monitoring MAO inhibition?

DR: Right. Our study also differed by using depressed outpatients, unlike the MRC study, which was conducted in a mental hospital setting. There were issues with the MRC study data, including the fact the patient sample was not well characterized and involved a mixed bag of patients in large mental institutions. The subjects had not undergone rigorous diagnosis by anything resembling valid criteria today, like the DSM. There was a similar type of mental hospital treatment study around the same time in the US, by ECDEU (Early Clinical Drug Evaluation Units) but it used a marginally effective dose of phenelzine. Our phenelzine study involved outpatients who underwent careful screening and diagnosis unlike those two trials.

JB: What was motivating you to do your study?

DR: We were aware there was a faction of US psychiatry that did not believe MAO inhibitors to be effective, perhaps reinforced by the MRC and ECDEU study results. The majority of American psychiatrists had never used MAOIs so they tended to believe they were ineffective. We reasoned a study examining the usefulness of monitoring platelet MAO inhibition would also demonstrate the drug was effective. Our initial phenelzine study accomplished two things; it showed phenelzine was significantly better than placebo in the treatment of depression across a number of depression measures, and that responding patients achieved a minimum threshold of platelet MAO inhibition, above 75%. It appeared platelet MAO levels could serve as a surrogate measure, analogous to plasma TCA levels.

JB: I want to make sure that we have a chance to talk about your transition to industry. Were you in Vermont your entire academic career?

DR: I was a member of the Vermont faculty for about 10 years after returning from NIH. Subsequently, I spent seven years as Chairman, Department of Pharmacology, Marshall University School of Medicine. It was then that The Mead Johnson Co was launching its first CNS drug Desyrel (trazodone) and formed a CNS drug advisory committee. Subsequently, the parent company, Bristol-Myers, hired me as Director, Central Nervous System Clinical Research.

- JB: So, your initial contact was with Mead Johnson involved trazodone clinical trials?
- DR: I had done one Phase Three clinical trial with trazodone. Mead Johnson did a wise thing, somewhat revolutionary at the time, by forming this advisory committee. Mead Johnson also established the first Travel Awards Program of the ACNP on advice of this committee. Other drug companies have followed suit since. The principal role of the committee was to advise Mead Johnson during the transition from the drug development stage, with imminent FDA approval of trazodone, to a successful marketing program. I considered myself fortunate to have been included with this group of distinguished ACNP members on the advisory committee.
- JB: So this committee advised Mead Johnson?
- DR: Initially, regarding Desyrel, then BuSpar (buspirone) which was in early clinical testing when the committee was formed.
- JB: What was the date?
- DR: Approximately 1982.
- JB: Was this while you were at Marshall?
- DR: Yes. It was a fabulous committee and included, Danny Freedman, Lou Lasagna, Jonathan Cole, Dave Janowsky, Dick Shader, Sam Gershon, Tom Detre and John Davis; a cross section of prominent individuals in academic psychiatry and psychopharmacology. Meeting three times yearly, we reviewed basic and clinical data and offered advice about trazodone, which represented a departure from the TCAs and was a novel antidepressant, and buspirone.
- JB: You weren't involved in the discovery of trazodone?
- DR: I had nothing to do with that, nor did anyone else on the committee. Our role was to help interpret the drug profile data, brainstorm how to capitalize on it and how best to convey clinical findings to the psychiatric community.
- JB: And, at the time they convened this committee, the company wanted answers about these issues?
- DR: Yes, Desyrel was within a year of receiving FDA approval as an antidepressant when the committee was formed.
- JB: And after it was approved?
- DR: The committee helped the company transition from R&D to a post-marketing Phase 4 program.
- JB: What was your role on the committee?
- DR: The committee's role was to be available to the senior Mead Johnson people within the therapeutic area, including R&D and business groups. The president of Mead Johnson attended most meetings.
- JB: And, following approval of Desyrel what did the committee do?

DR: Marketing of a drug is a special skill; one can have a novel drug, like Desyrel, and jump through all the FDA hoops with solid data but not necessarily achieve commercial success. Novel drugs, although effective, may not make a significant clinical impact, illogical as that may seem. One might think a drug would sell itself on its merits, but that may not happen. One needs a sophisticated program of educational and training materials, panel sessions and poster-presentations to inform practitioners. In psychiatry, a special dedicated sales team is important. The committee recommended, this may have been new to the business at the time, developing a team of specialists to interact with academic centers and psychiatric training programs to inform doctors in training about the novel features of Desyrel and how best to use it.

JB: Were they training people who worked for the drug company to do that?

DR: Yes, it's common practice today. Most drug companies have hospital specialists in sales who focus on medical centers and training programs. These are individuals who are more sophisticated than the average detail person and more academic in their approach. If a new drug is to have significant impact the discipline of psychiatry needs to endorse it. This process precedes success in primary care and general practice.

JB: Was the panel for Desyrel enlisting luminaries to help with the marketing?

DR: To my knowledge, yes. It was a rather brilliant thing for Mead Johnson to do because it was a mid-size, mid-western pharmaceutical company located in Evansville, Indiana. They realized the company lacked sophistication so they went out and got it. It proved to be highly successful. As a matter of fact, the ACNP Mead Johnson trainee program, a brainchild of the committee, has benefited both the College and Mead Johnson (and ultimately Bristol-Myers, the parent company). The ACNP Trainee program has been going on since the early 1980's and includes some of the officers of the College who began their scientific careers in the program.

JB: Going back to your academic credits, what was your most significant study in your field, the one you're most proud of?

DR: I am particularly proud of the initial phenelzine trial, which conclusively established its antidepressant efficacy. In the early 1970's, the FDA, as a result of the Kefauver Amendments to the Food and Drug law, reviewed all of the "grandfathered" drugs. Drugs approved by the FDA prior to the 1960's, were now required to show evidence of efficacy that would satisfy a group of experts knowledgeable in the field. In psychopharmacology this generally meant providing efficacy data from placebo-controlled trials, otherwise the FDA would withdraw drug marketing approval. The FDA put sponsors of MAO inhibitors on notice that they were going to withdraw

those drugs because their approval predated the Kefauver amendment and existing efficacy data were deficient. In the case of phenelzine (Nardil) the FDA became aware of our study through John Davis who was a member of the FDA Psychopharmacology Advisory Committee. Our group was invited to make a presentation to the FDA Committee on the findings of our NIMH-funded phenelzine trial. The FDA accepted this as proof of efficacy, and Nardil was the first MAOI to receive an effective rating based on our study findings. Warner Lambert, the manufacturer of Nardil, gained an effective rating before Smith-Kline for Parnate (tranylcypromine) or Abbott for Marplan (isocarboxazide.). Our subsequent study is also worth mentioning. We had realized one of the reasons MAO inhibitors had a reputation for lack of efficacy was because their therapeutic dose range had not been delineated, and MAOIs were being prescribed at ineffective doses. The approved labelling for Nardil, for example, gave the recommended dose range as being 15 to 45 mg per day. Our initial study used a fixed 60 milligrams a day dose, above the approved dose for the product labelling. This follow-up study was perhaps another first in psychopharmacology; it was a multiple fixed-dose placebo-controlled trial design to explore dose-response relationships. The study design had three treatment arms; phenelzine 60 mg per day, (above the approved dose range), phenelzine 30 mg per day (an intermediate dose), and placebo. The study showed 30 mg daily to be an ineffective dose, as it did not differentiate from placebo, while the 60 mg dose was superior to placebo, replicating the positive findings of the first study. The labelling for Nardil provided an incorrect therapeutic dose and needed to be revised. These two placebo-controlled phenelzine trials were both gratifying because they informed psychiatrists about an increasingly useful therapeutic agent. Al Nies and I always felt these two studies represented major contributions to the field of psychopharmacology.

We also investigated the utility of drug level assays in our research. We carried out double-blind comparison studies of tricyclics and MAOIs while measuring tricyclic drug levels and, of course, monitoring platelet MAO. In these studies, we assessed the clinical utility of amitriptyline plasma levels and platelet MAO inhibition during phenelzine treatment. This work failed to find meaningful relationships between amitriptyline/nortriptyline plasma levels and clinical outcome. We were among the minority who were sceptical about the real value of tricyclic blood levels in routine clinical management. In retrospect, many would now agree that TCA levels were not all that helpful in managing patients except for the occasional patient who was treatment resistant or experiencing severe side effects.

JB: One wonders about the attractiveness of doing blood levels in the 1970's, compared to now. Using levels inferred you were practicing scientific drug therapy.

DR: You're right. Often the primary reason for ordering the test was that it was available. One has to question the value of some funded research solely because it employs new technology without sound hypothesis testing. PET scan studies abound because of access to the technology, as is also true for MRI studies. These new technologies should be used with scientific rigor, not just because you can measure something.

JB: What led you to do the work on tricyclic blood levels?

DR: One of the original papers by John Biggs at Washington University, St. Louis, touted measuring TCA levels in the routine management of patients. However, the study had significant shortcomings in design and analysis.

JB: What year was Biggs' study done?

DR: In 1970. Dr. Biggs did the study because a GC Mass-Spectrometer was available to the Department of Psychiatry that was considered to be "state of the art technology". In a very small sample size clinical trial, he measured TCA levels during treatment. Because of two or three outlier values, there was a low but positive correlation between improvement and plasma TCA levels. When one looked critically at the data there appeared to be little association between blood level and clinical response except for the outliers, which skewed the distribution. Soon, there was a plethora of studies purporting to show meaningful clinical value in doing drug levels. Many studies showed some, but rather low, correlations of TCA levels with response, so the predictive value of the test was poor. In other words, a TCA level would have limited value in adjusting the dose in most patients, less than by assessing clinical response. I'm not saying such studies should not be done because we learn from them, but for many published reports the conclusions were often overdrawn.

JB: Getting back to your early career, what made you move from Vermont to Marshall University? Was it to become Chair of Pharmacology?

DR: I was attracted to Marshall because of its strong commitment to clinical pharmacology and teaching it.

JB: While you were Professor of Pharmacology, did you see patients?

DR: I provided patient care in both the Departments of Medicine and Psychiatry. Al Nies joined me at Marshall University with his primary appointment in Psychiatry, while my primary appointment was in Pharmacology as chairman. I was also Professor of Medicine and Psychiatry. Al and I established a Mood Disorders Clinic where we perfected clinical methodology,

such as use of a structured interview in clinical trials, which at that time was an innovation. It is worth mentioning that AI created a structured interview for depression in the early days at Vermont by adapting relevant items from the Present State Examination to form the Structured Hamilton Interview for Depression. This was utilized in all of our clinical studies, both at Vermont and at Marshall. The use of this structured interview probably predated by 5 to 10 years the SCID (Structured Clinical Interview in Depression) and other interview schedules for use in clinical trials. This is a reflection of AI's unique expertise; he was both an astute scientist and clinician. We ran a very large outpatient program with the main focus on mood disorders. We conducted a maintenance treatment, placebo- substitution trial for patients with major depressive disorder who were phenelzine responders. Responders were randomized after four months either to remain on phenelzine, or to switch double-blind to placebo for a year. The study showed maintaining treatment with phenelzine for at least a year prevented relapse or recurrence of major depressive disorder. This study was published in *Psychopharmacology Bulletin* in the early 1980s. My work in clinical psychopharmacology led Mead Johnson to invite me to become one of the founding members of their advisory committee for CNS drugs, as we discussed earlier.

JB: What led you to leave Marshall?

DR: The Clinical Director of Central Nervous System Clinical Development at Mead Johnson resigned from the company. I had been a member of the advisory committee for perhaps a year and a half. While I entertained no particular thoughts about going into industry, I agreed to look at the position. It was an unusual move from full-time academia to industry at that time.

JB: Unusual, because?

DR: There was little precedent for leaving academic psychiatry and clinical psychopharmacology to join industry. For whatever reasons, it was rare.

JB: Why?

DR: A career in industry had a negative connotation for many academicians. 25 years ago, the majority of sophisticated research was in academia and NIMH, while industry was considered a cut below in terms of the quality of research. The cutting edge resided in academia. I think we'd agree today that, given the resources industry has, the quality of research is much different than in 1984.

JB: So, the difficulty that most people had going from academia to industry was more a question of science?

DR: Yes.

JB: Was there also a sense that you sometimes shunned leaving an institution where your goal was pursuit of knowledge to join a commercial firm; did that also play into the perception?

DR: Very much so. Another inaccurate perception was the accepted wisdom that if you wanted to “retire”, you should leave clinical medicine and go into industry.

JB: Was that what was motivating you?

DR: Not at all, in fact I was reluctant to leave what I had been doing. Our research programs were productive and well funded by NIMH, and we were also doing industry sponsored studies at the University. I surmised, rightly, there would be excellent potential for exciting research in industry. In industry you have some limitations on what to study, but one has lots of influence on how to conduct research. I saw it as an opportunity to marry sound clinical methodology and superb pharmacology from preclinical research. I liked the people throughout the whole R&D program, including the head of their Institute for Pharmaceutical Research. As I mentioned, even the President of Mead Johnson Company attended most of our advisory committee meetings. I viewed the move to industry as a unique opportunity, one where I would have ample opportunity for state-of-the-art clinical research; and that proved to be the case.

JB: It did prove to be the case?

DR: One doesn't go into industry to “retire” because, as hard as academia was, industry was even more demanding. In academic medicine you hold down three full-time jobs; patient care, teaching, and research! You have to be very dedicated because all three make undue demands on your time, but you're only compensated for one full-time job! But, I have to say, I worked extremely hard in industry. I held worldwide responsibility for the clinical CNS program of Bristol-Myers Squibb so my responsibilities weren't limited to the United States but involved all of the major countries.

JB: It sounds like there were expanding CNS projects during your tenure at Mead Johnson and Bristol Myers?

DR: That is often the trend when a company gets a foot in the door for a new therapeutic area. When I joined the committee, buspirone was already in the works, so I inherited the clinical development of BuSpar.

JB: What was your role in the BuSpar program?

DR: To coordinate and oversee all R&D clinical trials worldwide. We had studies in most major European countries as well as in Japan. During many trips to Japan, I met with their committees of psychiatrists who performed trials “the Japanese way” with little decision-making from the sponsor. That could be very frustrating.

JB: What was the fate of BuSpar in Japan?

DR: It was never approved.

JB: Never got approved? Their use of benzodiazepines is much higher, in comparison to antidepressant drugs. Did Mead Johnson think there would be a big market?

DR: Yes, the Japanese market can be very significant for some therapeutic areas, second only to the United States. In depression it was never as big; Japanese physicians tend not to diagnose depressive disorder. When they do, they don't treat it the way many other countries do.

JB: They have stringent cost controls and consider drugs a large expense.

DR: Getting back to BuSpar, the task I inherited was to satisfy all of the different countries and, their regulatory agencies about the adequacy of the clinical data for BuSpar. BuSpar was not an easy drug to develop because it differs markedly from the benzodiazepines. There was a whole methodology of studying benzodiazepines for the purpose of approval that didn't readily apply to drugs like BuSpar, because of its markedly different pharmacology. We now know, in retrospect, that the azapirones have a different target population among anxiety disorder patients. This wasn't appreciated in the beginning when the BuSpar studies were undertaken. Much of my efforts focused on understanding how BuSpar differed from the benzodiazepines so we could study it in a manner that would convince governments of its clinical usefulness.

JB: What are your personal views on BuSpar? As a clinician, I think there was some scepticism about it.

DR: The best answer I can give is that it works for a fairly select patient population, in fact, a population not well defined by DSM-III or DSM-IV criteria. It's a very effective drug, but only for selected patients.

JB: What kinds of patients?

DR: For patients with what used to be diagnosed as mixed anxiety-depression. Such patients now fall between DSM diagnostic categories; depending on one's mindset, they are either diagnosed as anxiety disorders with associated depression, or primary depressive disorders with prominent anxiety. There also are elderly patients with anxiety and depressive symptoms that do very well on BuSpar. That's the short answer to your question.

JB: There have been recent discussions of company generated negative studies of BuSpar. What is your opinion about that?

DR: As I mentioned earlier, one of the problems with buspirone is its distinct pharmacology as a 5HT_{1a} partial agonist. It can exacerbate benzodiazepine withdrawal symptoms, perhaps because of its 1-PP metabolite. Patients recruited into benzodiazepine vs. buspirone trials, even if they

had been off benzodiazepines for up to one month, still may experience overt or sub-clinical manifestations of benzodiazepine withdrawal, which could be exacerbated by a 5HT_{1a} agonist. This exacerbation of withdrawal symptoms created difficulties in placebo and benzodiazepine controlled trials. Some patients randomized to buspirone showed less early improvement and had more adverse effects at the beginning. They had to suffer through the first couple weeks of the trial with exacerbation of subtle benzodiazepine withdrawal symptoms. This affected anxiety symptom ratings, not only side effect ratings, and was detrimental in the comparison with the active benzodiazepine controls. We did a number of re-analyses that clearly showed 5HT_{1a} drugs can exacerbate withdrawal symptoms unless patients are free of benzodiazepines for several weeks. It was hard to recruit patients with anxiety or depression that had not received benzodiazepines or been free of benzodiazepines for at least six months because of the wide use of benzodiazepines in clinical medicine. That was a major issue we had to contend with during development of this novel anxiolytic drug.

JB: Were there other drugs you shepherded through while you were at Mead Johnson?

DR: We also developed nefazodone (Serzone).

JB: What was your role in the nefazodone program?

DR: As head of CNS clinical development, nefazodone was my responsibility. Nefazodone also proved to be a challenge because its therapeutic dose range wasn't at all clear from Phase I studies. A real challenge during early Phase II trials is to define the therapeutic dose range of a new agent. This is not easy to discern, yet it's a critical decision prior to moving into phase III. With nefazodone, clinical development was already underway when I joined the company. The first Phase II study turned out to have employed an ineffective dose, although this was not appreciated at the time. In some ways, it was somewhat reminiscent of the situation with Nardil which employed suboptimal dosage that ended up in the original labelling but was not defined until the mandated placebo-controlled trials. One of my first challenges was to set up a multiple fixed-dose placebo-controlled trial to ascertain the therapeutic dose range. Nefazodone had other dosing issues because it had to be administered at least twice a day due to its relatively short half-life. It probably would be a better tolerated and more effective agent as an extended release formulation, but that wasn't the plan. Dosing the immediate release formulation presented a challenge. Among many other things I learned in industry is the importance of carefully defining the therapeutic dose range and proper dosing strategy during early development even if it delays the phase III program.

One needs to define the minimally effective dose as well as the maximum therapeutic dose. This may be difficult, particularly for drugs with subtle pharmacologic effects.

JB: When did you retire?

DR: I retired from Bristol-Myers Squibb in 1993.

JB: You continued to consult?

DR: Yes, I enjoy it very much. Over the years I have consulted with many different companies and found it to be most interesting. The different pharmacologic strategies companies are pursuing in the central nervous system area are fascinating.

JB: How long were you in industry?

DR: Ten years.

JB: What sort of changes have you seen over the 10 years? Where do you think things are headed today?

DR: The biggest change I've seen is the vast increase in resources that industry is devoting to central nervous system research. In the 1980's, when I joined Bristol-Myers Squibb, Prozac (fluoxetine) had not yet emerged. Essentially, all antidepressant drugs had been off patent so it was not a big market then so there were not a lot of R&D funds devoted to the area. It took the SSRIs becoming the first so-called "blockbusters" among CNS drugs, a term industry likes to use, for the funding explosion to result. So today there are many ambitious programs not only for depression but also for anxiety disorders, schizophrenia and Alzheimer's.

JB: I've been told that when Prozac came out, profit-margins for psychotropic drugs were fairly modest?

DR: Profits were modest then.

JB: With Prozac and other SSRIs, followed by Effexor (venlafaxine), profitability went up.

DR: Definitely.

JB: When we compare the number of people on benzodiazepines, tricyclics, monoamine oxidase inhibitors, and phenothiazines up until 1980 with after that, has there been an increase in the market?

DR: It was in the antidepressant field until more recently. Before the SSRI era, depression was rarely recognized in clinical practice by non-psychiatrists, while today many primary care physicians are able to discern clinical depression and are comfortable treating it with antidepressant drugs because of the marked safety of the SSRIs.

JB: Historically, how did primary care manage the kind of complaints that would be considered due to depressive disorder today?

DR: Primary care physicians did not recognize these largely somatic complaints as manifestations of depression.

JB: They were still treating it with maybe benzodiazepines.

DR: Yes, with lots of benzodiazepines.

JB: How about tricyclic antidepressants?

DR: Well, tricyclics were not user-friendly for primary care physicians. So it's the introduction of SSRIs in primary care that exploded the prescribing of antidepressants. One of the favourable consequences of having the enormous wealth generated by Prozac (fluoxetine), Zoloft (sertraline) and Paxil (paroxetine) is that public education, as well as physician education, about depression became widespread. Yet, even today, only roughly 50 percent of patients with depression are diagnosed and treated for depressive disorder. That still leaves many depressed patients in the community undiagnosed and untreated. But it's a lot better than it was 15 years ago when probably only 10 percent of depressed patients received treatment.

JB: Are there any downsides to this?

DR: There's no longer the stigma attached to mental illness there was a decade ago. Everyone talks freely of depression, being on Prozac, or seeing a psychiatrist. It's socially acceptable to be on drug treatment with a psychotropic drug, and that's a good thing. One of the negative sequelae of this flood of funding for antidepressants is that it has made conducting sound clinical trials more challenging. What has evolved is a plethora of post-marketing phase IV studies that companies fund to expand their market share and promote their product. This strategy has proven a commercial success. Unlike formerly, there are many competing company-sponsored studies today and competition for proven investigators who provide quality research facilities is greater. What's happened, as a result, is that it has become more of a business than a scientific endeavour.

JB: What do you think of the increase in CRO's?

DR: Having a CRO serve as an intermediary between the personnel of the sponsor and the investigators, poses concerns which can impair the quality of clinical trials. Because clinical trials are highly profitable, there are a lot of people with a profit motive doing clinical research without rigorous training, experience, or appreciation of the scientific method.

JB: You're thinking of "for profit clinical trial institutions"?

DR: Exactly. I don't mean to demean all "for profit institutions", but there are concerns.

JB: You have published your concerns about this?

DR: We have published commentaries about our concerns in conjunction with Karl Rickels and Arif Khan. There is considerable heterogeneity in investigator quality. Many companies, unfortunately, have shown little insight or appreciation of the potential problems, at least until quite recently. At the corporate level companies strive to rush development and shorten

timelines to approval. This places undue pressure on the R& D division to expedite studies by recruiting additional sites, often delegating site selection to a profit motive contract firm. There have been many panel discussions at recent meetings about why there are so many “failed” trials today, probably exceeding 50 percent, in anxiety and mood disorders. A major contributing factor is the uneven quality across investigative sites. It’s important to carefully select skilled investigators and to not pressure them, with inappropriate inducements to accelerate acquisition of patients. This is counterproductive. By adding more sites or putting pressure on existing investigators one may affect screening processes, even subtly, leading to less critical subject selection. The most important thing in good clinical research is what I term “guarding the front door,” paying attention to patient selection and symptom ratings unbiased by inappropriate inducements. Because clinical trials have become big business screening and intake often gets delegated by the psychiatrist, who may have excellent credentials, to those with inadequate clinical training and experience or who lack rigor in diagnostic interviewing and symptom ratings.

JB: Is that a phenomenon that emerged since you’ve left like Mead Johnson?

DR: It’s happened over the past decade or two.

JB: Ten years or so?

DR: Beginning in the 1990’s. It goes back to the point you brought up about whether this explosion in new drugs and psychotropic drug funding has been a good thing or not. I believe it’s the price we’ve paid for success. There has been a blossoming of private research, both profit-oriented investigators and CROs. Profits are important to research, no one would deny that, but one must not deviate from sound scientific principles. If you don’t understand and observe the scientific method, then you can’t conduct quality research. There is much heterogeneity in the quality of clinical research today. Sound clinical methodology is something we’re going to have to improve on, or suffer the consequences. Today meetings often center on what can be done to improve the quality of clinical trial methodology in our field.

JB: We are about out of time. Is there anything you wanted to add that we haven’t covered?

DR: We’ve covered a lot and I’ve enjoyed talking with you, Joel.

JB: I’ve enjoyed talking with you, too.

JOSEPH J. SCHILDKRAUT*

Interviewed by David Healy
Las Croabas, Puerto Rico, December 13, 1998

DH: Joe could you begin with where you were born and how come you ended up going into medicine?

JS: Well I was born in Brooklyn, New York in 1934. A product of the public school system there and then I went on to college at Harvard College at nineteen, graduating in 1955. I was very naive like many coming out of Brooklyn. The first time I saw Boston and the first time I saw Harvard was when I arrived in September for my freshman year. And it was a very different world from what I knew. It was a very exciting, enchanting world and one I came to be very comfortable with and grew to love. I've not strayed far from Harvard ever since. You asked how I came to go into medicine and that happened by evolution rather than design. I was very interested in math and the sciences; there was no question, when I went to college I'd be going into those areas and conceivably philosophy. Through my college experiences majoring in chemistry I began to deal with the question of whether I wanted to be a chemist or perhaps go into medicine. Medicine was a more traditional place for kids from Brooklyn to go into. I was approached by the Chemistry Department to consider becoming a graduate student and parenthetically, William van Ormanline suggested he might like to see me in the philosophy program. It was on the basis of a freshman introductory course I decided on psychiatry. In my junior year at Harvard I took two courses in what was then the Department of Social Relations. They were on personality theory. I took them because friends ahead of me in college talked about how exciting and interesting the courses were. I hoped to have a fabled Professor, Robert White, for abnormal psychology; he had written a textbook on it and was a magnet at Harvard. For whatever reason, that year he decided he was going to be more interested in the development of a normal personality. As a result John Spiegel, who was brought in from the University of Chicago and ultimately became a Harvard Professor, taught us the course on abnormal psychology. John Spiegel was a psychoanalyst and his abnormal personality course awakened my interest in the unconscious, in Freud and in psychodynamics. I went the following term to take the normal personality course with Robert White but that introduction to psychodynamic thinking and psychological development by Spiegel, made me seriously consider becoming a psychiatrist. In the course of making that decision I also

* Joseph J. Schildkraut was born in Brooklyn, New York in 1934. Schildkraut died in 2009.

made the decision to go into medicine. So I went to medical school with plans to become a psychiatrist and go on to be a psychoanalyst. Medical school was also at Harvard and, like most people, I found many subjects fascinating. I was thinking about various areas of internal medicine, like renal physiology, but my experiences as a third and fourth year medical student in psychiatry at the Massachusetts Mental Health Center, persuaded me psychiatry was the place to go.

DH: Could I ask you about those experiences. The Mass Mental Health Center at the time was very, very famous. It was home of an analytic approach.

JS: Some of us think it's still very, very famous. And some of us are trying to keep it that way.

DH: Who was there? Who were the influential teachers? Elvin Simrad was there.

JS: Yes, and Elvin will come into this story during my residency. As a medical student he was less prominent in my decision making than the patients I saw in psychiatry. I found my work with patients was fascinating, intriguing, compelling, and that I enjoyed it; I was also good at it. I finally made the decision to become a psychiatrist while working with a schizophrenic patient. As a fourth year medical student I had the opportunity to treat this patient for the whole time I was on the rotation, to see first hand what psychosis was and what a psychotic patient was experiencing, going through suffering and sometimes coming out of it; that really locked me into psychiatry. After that experience there was no question I wanted to be a psychiatrist. Wanting to be a psychiatrist meant doing dynamic psychotherapy and ultimately training as a psychoanalyst. Then, after medical school, I went to San Francisco for internship in medicine at the University of California hospital in San Francisco. My reason for choosing San Francisco was rather non-traditional at least in Harvard medical school. I went because I was intrigued with Jack Kerouac and the "beat" movement. I also had a mind that I might be spending much of my professional career in Boston as part of the Harvard community so I wanted to spend time somewhere else. This was a very, very unusual decision at that time. The dean's office actually called me in when I gave my rankings for internships and rated the University of California hospital number one, over Harvard. He told me, "I shouldn't let you know this, but you obviously made a mistake in your rankings." I told him, "No, I don't think I have." He said, "I should let you know the Boston City hospital, where you did medicine, really wants you as an intern. Surely, you wouldn't turn down a Harvard teaching hospital for the University of California in San Francisco?" I told him I had done a good job on my rotation at Boston City Hospital and had very fond feelings for them too, as I did for a number of

the other Harvard teaching hospitals, but I wanted to spend my internship in San Francisco, doing something different. He went on trying to persuade me I was jeopardizing my career, didn't know what I was doing and would I please rethink it. I went to San Francisco!

DH: That's nice.

JS: During the internship in San Francisco, I made my application for residency in psychiatry to Harvard, and Jack Ewalt, who was Professor and Chairman of Psychiatry, played strictly by the rules, informing potential residents of their acceptance only on the God given day of the match. One of the programs I was seriously considering, if I didn't go to the Mass Mental Health Center was at Yale. They let me know they were prepared to accept me but wanted to have an answer prior to the official deadline. I told Jack Ewalt of my dilemma and he got back to me, in writing, in a very typical yet old fashioned way; "We cannot give you our decision until the agreed upon date, so that's non negotiable, but anybody with your record and accomplishments who settles for less than his first choice, ought to have his head examined. Jack R Ewalt, Professor of Psychiatry." Well, I turned down Yale and began my first year of residency in psychiatry as part of Jack Ewalts' self picked group of residents. It was an extraordinary class.

DH: You'd have to tell me who was in the class.

JS: It included a cast of characters such as, Eric Kandel, Allen Hopson, George Valiant, Judy Rapaport, Judy Levant, Tony Kriss, Paul Wender, and I'm sure I'm leaving out someone. It was a class that was clearly academically oriented and a group Jack could be proud of selecting. He always had a committee but ignored what they said and made his own choices.

DH: Can you fill me in a bit more on Jack Ewalt?

JS: Jack Ewalt came from a very eclectic background. He came to Massachusetts to be Commissioner of the Department of Mental Health, sometime in the 1950s. At the time Harry Solomon was head of Mass Mental Health Center, and professor and chairman at Harvard. Harvard had a sixty-five year retirement rule in effect back then so he had to retire. As usual in the Harvard and Boston circles those days, there was an inside arrangement; Harry Solomon succeeded Jack Ewalt as Commissioner of Mental Health and Jack Ewalt succeeded Harry Solomon as the head of the Department of Psychiatry at Mass Mental Health Center. Jack was a very interesting guy. Short fused, he was known for his volcanic explosions. He was straight and direct talking; there was no bullshit. If he promised something you got it, and if he said no, you couldn't do anything more but suck it up and walk out or else you'd be thrown out of the

office. I was very fond of him; I just learned of his death a few weeks ago. Jack was really very, very supportive of broad ranging academic issues. I don't think he was a psychoanalyst before he came to Massachusetts, but became one by the time I arrived for my residency. But, as you mentioned, the key and revered figure at Mass Mental Health Center was Elvin Semrad, the compassionate Buddha like figure, one of the most charismatic men I've ever met. The only person who rivalled him in terms of insight and capacity to get to people, the only person who tempted me to leave my wife and become a follower, was the Dalai Lama, who I met and spoke to a number of years ago

DH: Where did Elvin Semrad come from?

JS: From the Midwest; he was a roly-poly guy with a quizzical smile, known for turning questions and issues back to the person he was speaking with. He spoke in enigmatic phrases that made one reflect on what was going on between the two of you. He also had the uncanny capacity to communicate with very psychotic patients. It was typical in rounds where a resident or faculty member would present a patient who was catatonic and mute, or spoke in some psychotic language that communicated nothing, that when Elvin sat down with the patient and they would open up and start responding. And Elvin was able to help the patient to talk and talk in a way that most of these patients hadn't done in months or even years. Very often there was a little bit of carryover from these interviews to treatment with the residents, but most of these folks were very sick chronic patients, who reverted back to their former selves. There was no question in my mind, at the time I started at the Mass Mental Health Center, that I would become a dynamic psychotherapist, hopefully a psychoanalyst, and devote my career to studying schizophrenia. But things don't always happen as one expects and I was fortunate to have entered Mass Mental Health Center at the very time the new antidepressant drugs were entering the Center, which was in 1960. As you said, Mass Mental Health Center in those days was largely psychoanalytic and the drugs were greeted with great, great scepticism by the faculty in general and Elvin Simrad in particular. Elvin used to refer to their use as "taking your patient to a cocktail party". His theme for the first year residency was; you've got to learn to sit with patients, to listen to your patients, to help bear the pain of your patients, and anything that got in the way of that was, in one way or another, a form of resistance. That's what he taught. Because I came to know him over the years, I found there were many Elvin's; there was Elvin as he presented himself to medical students and the Elvin that presented himself to first year residents, who was different again from the person who taught second or third year residents. He

was far more complex, far more intellectual and inquisitive than he ever let us to see as residents. He made us feel, if we resorted to a psychoactive drug with one of our patients, be it an antidepressant or a major tranquilizer such as chlorpromazine or thioridazine, we were giving up on psychotherapy. It happened in the early months of my residency that I was treating a number of depressed patients and found that my therapeutic attempts were not getting very far. These were very sick patients, the kind we don't see anymore. It was a common experience to tube feed hospitalized patients starving themselves to death. These were patients pacing the floor ceaselessly, exhausting themselves saying, "Oh my God, oh my God what have I done, oh my God, oh my God why did I do it, ". At the time I began residency I thought it was a misfortune, but now I see it was a great fortune, that I had been assigned to the ECT rotation. All first year residents did a couple of months on this rotation. As a budding psychoanalyst I felt this was getting in the way of what I really wanted to be doing. But that gave me the opportunity to see these starving, near dead vegetating human beings, given a course of electroconvulsive therapy and turn, before my eyes, into engaging people with charm and dignity. It was far more dramatic than any other procedure I witnessed on surgical or medical wards. And that made an important, important impression.

DH: Who was actually responsible for ECT, it must have been outside the main stream of treatments?

JS: Yes and no. The Mass Mental Health Center was never what it appeared to be. It was a very eclectic institution that entertained people of very different persuasions who managed to communicate in a way so there wasn't an orthodox religion. Simrad preached and taught the way he did and was wonderful. He might chide you for doing certain things but there was no animosity between the psychoanalytic and the more eclectic group, such as somebody like Milt Greenblatt who was assistant superintendent at the State hospital and nominally responsible for teaching biological treatments that included ECT and psychopharmacology. I say nominally because psychopharmacology hadn't permeated the hospital. There was a psychopharmacology service overseen by a psychologist, Al Di Mascio, who tragically died some years ago. Al, at the time, had not yet obtained his PhD and there was the psychopharmacology nurse, a man named Carpenter, called Carp. A group of residents came around on weekly or biweekly rounds, following those few patients who were being given drugs and making recommendations; that was how the psychopharmacology service was run. There were others besides Milton Greenblatt, but his name stood out prominently.

DH: Could you mention any of the others?

- JS: Daniel Funkenstien, who developed the Funkenstien test, was there.
- DH: Who did the testing?
- JS: It was done by a group of junior faculty, one of whom, Lester Havens, would go on to become a leading psychoanalyst.
- DH: You mentioned you were disappointed your depressed patients did not respond to your psychotherapy.
- YS: I was thinking if Elvin Semrad had been treating them the patient would have been better and the fault was mine. Another thing I was struck by in my first year was that I didn't understand some of the diagnostic language.
- DH: Like what?
- DH: My supervisors were talking about psychotic depression and for a long time I didn't get what they meant. I talked to about five supervisors and got five different definitions. And it wasn't that I didn't get it; I got it all too well, but differently from five supervisors. It was clear to me that with babble about the ego and psychotic decompensation, communication was impossible.
- DH: How did you resolve it?
- JS: Eventually I had to resort to antidepressant drugs.
- DH: Which ones?
- JS: The range was pretty narrow; we're talking about imipramine, a tricyclic antidepressant, and phenelzine a monoamine oxidase inhibitor. That was the psychopharmacology armamentarium. The doses were very different in those days; fifty milligrams of imipramine per day was the standard dose and it was used very cautiously. It could not be used in outside hospital, only hospitalized patients could get imipramine, it was considered so scary.
- DH: You used imipramine in the daily dose of 50 mg?
- SS: It was considered heroic to push up to seventy five or a hundred; I don't think anybody went above a hundred. One of the things I learned was patients got better on these lower doses. It might have taken longer, but they did get better, better than I could accomplish with my psychotherapeutic attempts. So these drugs to me were a kind of magic. With my interest and background in chemistry my imagination started to run wild. I got to thinking these pharmacological agents had to be working through some kind of biochemical processes, and if we started learning about their pharmacology we should be able to find out the biochemistry, which might give us clues to the underlying substrate of psychiatric disorders. All of this was going without any loss of interest in the psychodynamics of psychotherapy. These were not competitive in my head and still aren't, but it was just another avenue opening up.

DH: So, you became intrigued with antidepressants?

JS: I also became intrigued with lithium. Lithium was not being used in the US at that time, but I was talking about it with Chuck Renspoon, the chief resident when I was a first year resident. He and I talked about the possibility of using lithium in manic patients and we went ahead and tried it. You couldn't get lithium in a pharmacy so we got it from a chemical supply house. I don't remember what sort of lithium we were using. It was probably lithium chloride, but we had it put up in gelatine capsules by the pharmacist and gave it to manic patients who wanted to try it. We didn't know much about monitoring levels; we did know the history of lithium, the scare that occurred when it was used as a salt substitute in cardiac patients with dire results. We were cautious and careful, but I was able to see the effects of lithium on mania. And what I saw captured my imagination.

DH: All this happened while you were in your first year of residency?

JS: During my first year. Then, one day I was walking back from the coffee shop at Mass Mental Health Center, when Milt Greenblatt put an arm across my shoulder and said to me, "Young man, I have an offer you might find appealing". To make a long story short we set up a depression research unit. It was a very small space, it only had one toilet, and unisex toilets had not yet been invented. So we were restricted in having only one sex of patients on this unit. We opted for females, because depression was more common in women than men. It was an awfully small, five or six bed unit. I was designated chief resident, which was an unusual title for a second year resident. Jerry Klerman, who had trained at Mass Mental Health Center, was the attending psychiatrist and he and I ran the unit. Jerry had a couple of first year residents working with us including Dick Shader and George Henninger, whose names I expect you know. So they were my junior residents.

DH: Could you say something about the research you did?

JS: One of the projects was treating depressed patients with DOPA. It was not L-DOPA, because that was too expensive; we clearly missed the boat. We worked with DL-DOPA, which was much more economical but useless.

DH: Any other project?

JS: Another project that came out of Jerry Klerman's and my head was taking advantage of the VMA assay of Dale Friend, by trying to see if the monoamine oxidase inhibitor, phenelzine, caused a decrease in this metabolite of norepinephrine, as one assumed it would in the course of treatment. We learned later this experiment had partially been done a couple of years earlier. Our study was a double blind randomized trial;

we had a placebo as well as an active control group. We used imipramine as the active control because we knew it was not a monoamine oxidase inhibitor. We weren't sure what it was doing but we knew that it was not inhibiting monoamine oxidase. We tried to tease out whether the decrease in VMA we hypothesized with phenelzine would be due to its being a monoamine oxidase inhibitor or might just be due to clinical improvement. So imipramine in this experiment was an active comparison drug. The patients were carefully selected because I had the chance to see virtually all the depressed patients coming through Mass Mental Health Center, and there were many because depression was treated in hospital. So I selected patients with pure depression, no hints of any personality problems. They were women at home who were raising successful families and living productive lives. They were folks who suddenly became depressed but couldn't explain why; the depression came out of the blue to the point of being unable to function. They were people who got better quite quickly with the antidepressant drugs, using very low doses. It might have taken four weeks, but sometimes not even that long. It was from my experience with these patients that I developed the hypothesis that if you can pick your patients very, very carefully, they get better quite quickly with low doses of imipramine.

DH: What did you find in the study?

DS: The results were surprising because what we found a decrease in VMA in the depressed patients treated with phenelzine, as one would predict from a monoamine oxidase inhibitor. There was no change in VMA in the placebo treated group, which you'd expect, but there was also a significant decrease in VMA in the imipramine treated group which wasn't supposed to happen. So I started to wonder, why did this occur? The magnitude of the change wasn't as great as with the MAO inhibitor but it was substantial and highly significant even though we were dealing with numbers of only six subjects in each cell. In starting to think about these findings and writing it up for publication I found myself starting to dip into the literature to make myself conversant with neuropharmacology. Jerry Klerman had known Seymour Kety from his time at NIH and in the summer we visited Seymour. That was my first introduction to Seymour Kety; he opened my eyes to a new world and I started to avidly pour over the literature. When we published that paper in 1964 I put forth the notion that imipramine by acting on membranes was preventing norepinephrine coming back into the neuron.

DH: And you published your paper.

JS: I submitted the paper to the *Journal of Psychiatric Research*, edited by Seymour Kety, with a long discussion, letting my mind freely play out

what were speculative suggestions. Seymour's comments came back and I remember them to this day, "Good paper, interesting, small amount of new data, worthy of publication, be glad to publish it if you write your discussion like a neuropharmacologist and not like a psychiatrist". So the discussion was cut way back!

DH: So that paper was based on research before you went to NIMH?

JS: I was supposed to go to work at NIMH with Dave Hamburg at the time, but Seymour asked whether I would consider switching from David Hamburg's branch to his. It turned out it was no longer David Hamburg's branch any way, because he went to Stanford to become Chairman and Lyman Wynn succeeded at NIMH. I gave very serious thought to Seymour's offer and decided to do it. With this decision, my career path was set.

DH: So you got to NIMH.

JS: Yes, and the first clinical study I did was a replication of my findings with imipramine. It was a slightly different design with frequent clinical ratings and urine collections in a semi-metabolic ward, looking at VMA and normetephrine with 24 hour urine samples. What we found again was a decrease in VMA during treatment with imipramine. It was a pharmacologic effect of the drug not linked to its clinical effect. But we also found that normetanephrine, the O-methylated metabolite of norepinephrine, started to increase slowly and this was linked to the onset of the anti-depressant effect. And that spiked my excitement. You'll note that the paper from NIMH is titled "*The Catecholamine Hypothesis of Affective Disorders. A review of supporting evidence.*"

DH: Yes.

JS: I had done a very thorough review of the literature and I became convinced if what I was reading between the lines could be put together in a logical and compelling way that could start the biological revolution in psychiatry.

DH: What about the arguments against the hypothesis?

JS: It's hard for me to remember all the arguments against it because it comes from an era of research that has passed. There was much controversy in the animal literature about what these drugs were doing. I was anguishing over this, because I am that kind of guy. It was during my second year at NIMH the paper was done, when Dick Green, a clinical associate, was working on our unit. Dick is a clever guy, a psychiatrist who has made his career in gender sex research, a professor on the West Coast. He looked at me one day and said, "Look, you've got a story there. You think it's real. You think there is a story to tell. But you're going to kill it if you don't qualify what you say. Change the goddamn title; it's not 'a critical review', it's

‘a review of supporting evidence’.” I suddenly saw the light and I did what he suggested. I felt this was the way I was going to be able to bring the world of neuropharmacology and the world of clinical psychiatry together, by giving people a paper both sides might read, understand and appreciate. I felt fairly confident psychiatry was at a watershed at the moment.

DH: It was the critical paper in the development of the field.

JS: It was written with that purpose. I very much knew the potential in this paper. And I had known I was writing about more than catecholamine’s in depression. I was really writing about the place of biochemical studies in psychiatry. That paper put forth the notion I subsequently came to call “The Pharmacological Bridge.” The notion that pharmacology can be a bridge, linking neuroscience, chemistry, and clinical psychiatry. The catecholamine hypothesis was the fourth paper I had written in my career.

DH: Why did you choose to send it to the American Journal of Psychiatry?

JS: It is the journal that is most commonly read in psychiatry, it has the widest distribution, and it communicates to psychiatrists. By the time the paper was published in 1965 there were other issues we can discuss off camera, if you’re interested. When the paper was published in 1965 I had extended my stay at NIMH by doing research in the laboratory of Irwin Kopin. I wanted to get first hand lab bench experience in catecholamine research because by that time I had seen this was going to be an important part of my future. And while working in Irv’s laboratory with rats one day there was a knock on the door, and a towering figure came in and said, “Is there somebody named Schildkraut here?” And I turned from my laboratory bench and said, “I’m Schildkraut.” The person introduced himself saying, “I’m Paul MacLean and I’ve just seen a paper you published in the American Journal of Psychiatry. Young man, you don’t know what you’ve done to yourself.” I figured, oh my God, what had I done? I figured the hypothesis was very controversial and formulated without enough data. I made a private deal with myself that if it was embarrassing scientifically it would be my last paper and I’d go back to Boston to be a psychotherapist or a psychoanalyst. I thought I will do just fine because I loved doing that. But MacLean went on, “I have a prediction to make, just as I found myself having written about the brain and having to spend the rest of my career talking about it, I predict you’re going to spend the rest of your career defending this paper, because it is going to make a mark on the field, and there will be many who’ll want to tear it apart. Good luck to you, young man, you’ve got a rough road ahead.” And he laughed.

DH: That was very dramatic.

JS: It was very dramatic, and, needless to say very, very flattering.

DH: And also very pathetic?

-
- JS: At that point, I saw it as very flattering because I was delighted to be in his company, and to be put there by him. Actually, the catecholamine hypothesis paper was brushed off, amplified, and written as an article in collaboration with Seymour Kety.
- DH: Which went to Science?
- JS: Seymour was invited to do a review of this, was familiar with my work, and asked me if I would collaborate with him, which was a pleasure and delight. The Science paper was read by neuropharmacologists; clinical psychiatrists didn't read Science in those days.
- DH: The paper in the APA journal was widely read.
- JS: As you probably know, the catecholamine hypothesis paper is the most frequently cited paper ever published in the American Journal of Psychiatry. I learned it is not only the most frequently cited paper but the most frequently cited paper by a large enough margin that someone told me, "I don't think you have any danger of ever being surpassed." I learned this couple of years ago, when the Journal of Psychiatry and Clinical Science selected it as one of the so-called citation classics. And I was in the company of such people as Alessandro Guidotti, and Elliot Slater.
- DH: How did the Brodie people take your norepinephrine line?
- JS: There was a kind of culture clash, competitiveness between the Brodie and the Kety labs, and as you know, Julie Axelrod, who was training in the Brodie lab, was essentially liberated by Seymour Kety. Brody was somebody who had a much tighter reign on what was done in his laboratory and how things came out. But that was not a major issue. I ended my paper by saying this is a highly oversimplified, reductionistic hypothesis and the ultimate understanding of depressive disorders will have to take into consideration many other biological substances including acetylcholine, dopamine, serotonin, hormones, ionic changes, etc. I couldn't come up with a hypothesis that could affect one neurotransmitter without affecting the others. Nor did I have the notion that somehow norepinephrine was just there for turning the mood key. I didn't even mean to throw out psychodynamics and all of the other side of psychiatry that was potentially so rich, rewarding and helpful.
- DH: I see.
- JS: I meant to add to it but, as things so often happen, the pendulum swung and suddenly this huge biological and pharmacological revolution occurred. There was a swing towards the biology of psychiatric disorders and the use of drugs. Once I saw I was going to stay at NIMH for four years instead of two, I resumed my analysis in the Washington area. And it was in the course of my analysis I made the decision I was not going

to pursue further psychoanalytic training by recognizing my day only had 24 hours and any time I took for psychoanalytic training was taken away from time I could spend in research. I had the good fortune of riding the crest of a wave, a kind of wave that comes along once in a lifetime, and I couldn't let go of it.

DH: It was a few years later that NIMH set up the collaborative program to look at research in mood disorders. It started with the Williamsburg conference in Virginia. You were at that?

JS: Oh, yes.

DH: Could you tell us about that conference. It was an important meeting in the sense that development of DSM-III started there. People from the St. Louis group and Klerman met and things began to roll.

JS: The facts are a little different. Jerry Klerman was not included at the beginning of that endeavor. He was in fact excluded. Even if I was part of the conference, I was excluded also. It was organized by a group trying to put together research that was going to be a clinical program in psychiatry which included nosology, epidemiology and some epidemiological genetic studies. It was exclusively orchestrated by Eli Robbins and the folks from St. Louis, to Eli's great credit. It was Eli who directed interest to descriptive psychiatry, to Kraepelin and to purging psychiatric nosology from psychoanalytic notions. The DSM-I and DSM-II were nosologies where psychotic depression could be defined in five different ways as I found out as a resident. But the program that was set up to replace that had the same problems all these mega goliath programs have. I can't even remember the date of that conference any longer; it was sometime in the late 1960s.

DH: 1969, I think.

JS: They were setting up a ten or twelve year program and you can't set up a project in a new field to run for such a long time. On the biological side we had to standardize assays and that created problems. On the nosology side the problem was that the DSM-III was pulled together from a consensus of experts looking for was reliability in diagnosis. What they felt important was diagnosis should be reliable from one clinician to another.

DH: True.

JS: They opted for reliability and skirted issues of validity.

DH: Right.

JS: They came up with things they could define reliably but not necessarily things that always made clinical or biological sense. For example, the category of major depressive disorder is such a heterogeneous hodge-podge it almost tells you nothing. In our own research, which extended

from the time I got back to the Mass Mental Health Center in 1967 'till very recently, I was still able, early on, to get drug free patients but, as time passed, it was increasingly difficult to find such patients because by then patients with depression who have had prior mania were on lithium and nobody could justifiably take them off for a study.

DH: True.

JS: Virtually all the studies we did in patients with bipolar manic depressive disorder under drug free conditions were in the late 1960s and early 1970s. And we found those drug-free groups had differences in catecholamine metabolism from all other types of depressive disorder. There were similar findings by other research groups. But it became increasingly hard to replicate those findings because you couldn't get those kinds of patients anymore.

DH: True.

JS: I don't know if you're familiar with our series of papers called "Towards the Biochemical Classification of Depressive Disorders". We were able to show in that series that bipolar I depressions without the character pathology you see in so many patients with bipolar disorders, were characterized by low catecholamine output significantly different from every other group. Whereas patients with bipolar II disorder had catecholamine outputs similar to patients with unipolar endogenous depressions; it was not low like it was in bipolar manic-depressive bipolar I depressions.

DH: I see.

JS: I worked with Jerry Klerman when he had come back to Mass Health Center and he and I used to engage in pitched battles because he was looking for reliability and I kept saying I'd rather be somewhat unreliable but pick cases I feel have biological validity. So we developed our own system for classifying depressive disorders, very different from the DSM system. Our first cut was what I call the schizophrenia related depressions and these were patients with clear cut depression who do not qualify for a diagnosis of schizophrenia but have characteristics of what I call chronic eccentric and bizarre social behaviour. These people have never been psychotic but lead a rather isolated life. The next cut was the bipolar manic depressive depression and these were patients who meet certain criteria for depressive and for manic or hypo-manic symptoms. The hallmark of mania in my book is if a patient kicks me in the belly or breaks up furniture and the hallmarks of hypomania are in speech. For the detection of possible hypomania I often tell patients, "Okay, you're not that way now, but if I was sitting in this room with you and you were that way now, what would I notice would be different"? Invariably the patient says you would notice I am talking a lot more, my friends would tell me I'm talking

a lot more, I have flight of ideas, grandiose ideas, or may even be a little aggressive.

DH: Do you think that by using your system you, a darling of biological psychiatry, are beginning to diverge from the mainstream.

JS: Not really. I always make it very clear there's a difference between what a diagnostic system has to do for clinical, research and educational purposes. In our present state of ignorance a diagnostic system can't serve all purposes.

DH: But once DSM-III was produced you've got a set of criteria that's supposed to do a range of different things.

JS: I've always felt diagnostic systems have to be developed for specific purposes.

DH: But an awful lot of other people doing biological research were happy to run with the DSM system.

JS: Actually DSM-III developed from the RDC and before the RDC, a group I led developed what we called a Clinical Inventory for the Diagnosis and Classification of Affective Disorders, affectionately known as CIDCAD. But this was a system that was developed for very different purposes from the RDC and we were using our system to keep our various diagnostic categories pure. For biological studies like ours you cannot afford to have false positive diagnoses, because then you are going to have biochemical findings that are not going to agree with the main grouping of the patients you are trying to study. So that's how we found out that what was called unipolar endogenous depression was wildly heterogeneous with the respect to catecholamine metabolism. But we also demonstrated there were meaningful biochemical differences among some groups of depressive disorders that could be defined clinically. Some interesting things came out of looking at unclassifiable depressions by not mixing them up with the other diagnostic categories. You mentioned earlier on something about my being the darling of biological psychiatry and I found that comment amusing because I know what you mean, but that was never the case. It was rather as Paul McLean told me it was going to be; from the onset I was the whipping boy of biological psychiatry at least with respect to the catecholamine hypothesis. At a meeting twenty-five years ago I told Eli Robbins that all I ever claimed was that abnormalities of catecholamines were part of the physiology in depression.

DH: Uh huh.

JS: I was willing to bet him a nickel that, when the final words were written, catecholamines would be part of the physiology of depression. That's still not fully resolved and Eli's gone on to a place where I can't pay him a nickel until I follow him to that place and collect from him.

DH: So you still think there's a chance you're going to be collecting?

JS: I sure as hell do.

DH: Right.

JS: I do think that catecholamines are an important part of the physiology of depressive disorders but I also believe they are only a starting point for research. We are on a very long and exciting expedition where we are going to keep learning more and more about the biological and biochemical physiology of depressive disorders. I'm not sure we are ever going to be able to fully understand the functioning of the brain, but it's an exciting adventure and it has been a most gratifying one. When I look back I can sense the excitement I felt thinking that maybe I was contributing to a paradigm shift in psychiatry. And when I published that paper on the catecholamine hypothesis I did not know which way it was going to go, whether I was going to make a damn fool of myself and was ruining my academic career. But my sense was it could end up happily for me either way and its very gratifying, thirty plus years later, to see that it wound up where it did; being interviewed by David Healy for the archives of the ACNP. It was good talking with you!

DH: Great, that's wonderful. Thanks very much.

BARON SHOPSIN

**Interviewed by Andrea Tone
San Juan, Puerto Rico, December 11, 2003**

AT: My name is Andrea Tone, and we are at the 42nd annual meeting of the ACNP in San Juan, Puerto Rico. It is 2003, and I am interviewing Dr. Baron Shopsin.* Tell us something about your upbringing, early education, and how you got drawn into the field of medicine.

BS: I was anticipating this interview would focus on the body of scientific work and contributions in collaborative and translational research that led to my early membership, in 1974, to the ACNP. While my life story may well be interesting the events that led me to medicine and a career as a research academic, teacher and clinician surely exceeds the scope of this interview.

AT: Tell us about these aspects of your life anyway.

BS: After graduating high school at the age seventeen, the Korean War abruptly and painfully ended my career as a professional musician - playing sax, clarinet and flute with the Mitchell Ayres Orchestra on the Perry Como Show - obliged to attend College or be drafted. The anticipated rapid end to the war never happened. I graduated two years later with a Liberal Arts degree but without a recognized major apart from some Japanese & Far Eastern history.

Living in Paris later on, I met an acquaintance on the Champs D'Elysée who was in transit to Belgium where he was entering medical school in Louvain. To make a long story short, after a ski vacation in Austria that December, I left Paris and enrolled in L'Ecole de Medicine, L' Universite Catholique de Louvain, Belgium, without ever having taken a science course in college other than biology. As a condition for eventual graduation, I was required to take courses in all the basic sciences, biophysics and catholic ethics for the first two years in addition to the usual first and second year medical school curriculum. I graduated Cum Laude six years later after five years of medical school and a year of rotating internship at the University Hospitals and Clinics in Louvain. After living in Europe during the formative years during the 1950's I was reluctant to return to the States in 1963. I left Europe but Europe remained in the fiber of my being. I still think to this day alternatively in French and English.

My fluency in French contributed to my eventual recruitment and long term relationship as scientific consultant to a Paris based French Pharmaceutical company during the 1970's and 1980's.

* Baron Shopsin was born in Brooklyn, New York in 1935.

AT: What did you do after returning to the States and graduation from medical school? At what point did you decide you wanted to do psychiatry?

BS: After the rotating internship year in Louvain, I was obliged to complete another rotating internship in the States as a requirement for taking the NY State Board Examinations for Physician Licensure, which I completed at Long Island Jewish Hospital in Queens/Nassau New York, an affiliate of Downstate Medical School. I started my residency in psychiatry at Cornell-NY Hospital, located on the fashionable upper east side of Manhattan on 69th Street, steeped in the academic atmosphere of medical and scientific excellence that embraced the combined campuses of Cornell-NY Hospital, The Rockefeller University & Memorial Sloan Kettering Cancer Institute. Earning \$50 a month, in the midst of residency, in December 1965, I was drafted into the Navy during the Viet Nam War and spent two years on active duty as a commissioned officer. The first year was spent as General Medical Officer and Department Head aboard the US Duluth, part of a new fleet of Marine Attack Ships. I was the only physician with two enlisted corpsmen serving a crew of 600 marines, navy enlisted men and officers. The second year I served as a staff psychiatrist at the Navy Hospital, Camp Pendleton, a Marine Base Staging Area in southern California, for which I was given 1 year residency credit. By now I was married to a Swede I met when she was working at her Embassy in NYC during my residency at Cornell. After discharge from the Navy in Jan 1969 I didn't return to Cornell, choosing instead to complete residency at NYU-Bellevue Hospital Center, NYU School of Medicine. It was there, during the first 6 months of a research elective with Sam Gershon, Head of Neuropsychopharmacology Research, that I got irretrievably hooked on the sheer fun of carrying out cutting edge investigative work, side by side with Sam as one of the early pioneers in biological psychiatry and neuropsychopharmacology. I appreciated Sam's infectious enthusiasm, his encouragement and appreciation of my research initiatives which led to my becoming a committed research psychiatrist throughout the remainder of my residency before graduating seamlessly into an academic career as a full time faculty member at NYU.

AT: Did't you have already several papers by the time you finished residency?

BS: I had about ten publications by the time I finished residency.

AT: Were they on lithium?

BS: About half were related to lithium, the others to schizophrenia and affective disorder. From 1969 throughout the 1970's and into the 1980's during the "Golden Age" of NYU psychiatry I was Associate Professor of Pschiatry and Chief of the Unit for the Study and Treatment of the Affective Disorders and Lithium Clinic at Bellevue. I was also associated

with Nathan Kline in the most visible private practice for psychiatry in NYC during the 1970's where we also carried out clinical drug trials. We remained colleagues and friends until his untimely death in 1983.

AT: Tell me about the Affective Disorders Unit.

BS: The Affective Disorders Unit and Lithium Clinic was the first of its kind in the United States, consisting of inpatient beds at Bellevue Psychiatric Hospital and a metabolic unit in the Endocrine Division of Bellevue General Hospital, which included outpatient clinics and staff offices in the privately endowed Millhauser Laboratories, directed by Arnold Friedhoff.

AT: So, you were involved in research in affective disorder?

BS: The studies relating to lithium ion necessarily involved investigational initiatives relating to the affective disorders. The studies with lithium contributed in the United States to FDA approval, marketing and clinical use of the lithium by psychiatrists as the first drug with therapeutic specificity for the manic phase of bipolar illness and as a prophylactic against acute recurrences of mania and depression. The first textbook related to the use of lithium in research and treatment was edited by Gershon and Shopsin; the book on *Manic Illness* edited by Shopsin contributed to the widespread use of lithium by practicing clinicians. The affective disorder research was focused on biomarkers potentially related to the molecular biology of depression. Many clinical drug trials with investigational compounds contributed data towards this end.

AT: Can you say more about that?

BS: The effects of antidepressant drugs such as the tricyclic compounds and monoamine oxidase inhibitors on brain monoamines suggested an involvement of both catecholamines, i.e., norepinephrine and dopamine, and the indolamine serotonin (5-HT) in the pathophysiology of depression. Theories concerning the pathogenesis of depression were generally united in postulating a role for these different biogenic amines, but the specific amine or amines involved in either depression or the antidepressant effects of the tricyclics and MAO inhibitor drugs remained elusive. Clinical studies exploring amine metabolism had largely concentrated on examining the different monoamines or enzyme systems in biological media such as blood, urine, and spinal fluid. I was spending a good deal of my time and energy doing just that. But attempts to scrutinize the concentrations of monoamines or their metabolites, i.e., NE, MHPG, 5-HT and 5-HIAA, in peripheral biological fluids had come to represent the metaphoric equivalent of looking at sewage. So, I had a brainstorming session one sunny Sunday afternoon with Menek Goldstein, the Chair of Neurochemistry at NYU and by dinner time we had hammered out an innovative study paradigm that served to delineate the future scope of my

work by focusing on synthesis inhibitor challenges rather than the detection of a potential chemical defect. It involved a small number of voluntary patients with each individual serving as his or her own control.

AT: Can you explain this to someone who is not familiar with the subject?

BS: In attempts to define more clearly the specific biogenic amine responsible for the antidepressant effect of the tricyclic and MAOI class drugs like imipramine (Tofranil) and tranylcypromine (Parnate), we treated patients with these drugs until showing clinical improvement. Then, we gave them either a selective norepinephrine synthesis inhibitor or a serotonin synthesis inhibitor. The reversal of depression in patients treated with imipramine and tranylcypromine was annulled when they were concurrently treated with PCPA, but not with α -MPT. Parallel drug studies in animals showed that statistically significant reductions in brain catecholamine and indolamine concentrations occurred with combined imipramine and α -MPT or imipramine and PCPA treatment, respectively. In their entirety the data suggested what appeared to be an irreconcilable role for serotonin in the antidepressant effects of the tricyclic drug, imipramine and the MAOI tranylcypromine. The difficulty in getting the clinical studies done was obtaining the synthesis inhibitor drugs from pharmaceutical manufacturers and the inherent risk in treating patients concomitantly with an antidepressant and a synthesis inhibitor.

AT: What made you think at all that the culprit might be serotonin?

BS: The existing research pointed to norepinephrine and serotonin as the putative monoamines at the heart of both depression and antidepressant drug effects. The findings with serotonin using synthesis inhibition were not anticipated. It was a by product of well designed unbiased research. Our studies and published reports were never able to substantiate involvement of norepinephrine. I authored several reviews on the need for revision of the noradrenergic hypothesis based on the absence of documentation of an evidentiary nature. Some colleagues in Europe, notably Alec Coppen in the UK and Herman Van Praag in the Netherlands, suggested the involvement of serotonin based on the measurement of peripheral biomarkers, but the theory and funding for NE research in the USA was so mindlessly entrenched that a serotonergic theory of depression was never a serious contention before my synthesis inhibitor studies furnished good and sufficient proof of the concept.

AT: So you published your findings, and what was the response?

BS: The paper published in *Archives of General Psychiatry* in 1976, by Shopsin et al. entitled *Parachlorophenylalanine Reversal of Tranylcypromine Effects in Depressed Patients* served as the metaphoric shot heard round the world that triggered widespread recognition of the role of serotonin

as the pivotal monoamine underlying the therapeutic effects of the tricyclic and MAOI class antidepressant drugs and as pathogenic in depression. The Archives paper synthesized the data and recorded the effects of PCPA to induce a robust and rapid depressive relapse in endogenously depressed patients who had shown an incontrovertible antidepressant response to the MAO inhibitor, tranylcypromine. Our findings served as the basis for the discovery, and development of a series of more serotonin selective and potent 4-alkylpiperidine derivatives such as Indalpine, Viqueline and Pipequeline, of which Indalpine, became the first marketed SSRI (Upstène) “Blockbuster” drug worldwide, except the United States. It was marketed in 1982, several years before the commercial availability in the United States of fluvoxamine and then fluoxetine in 1988.

AT: What was the response to the marketing of Indalpine in France and your involvement with Pharmuka the company involved with this drug?

BS: My name was celebrated in Europe and in particular of course in France as a consequence of the media coverage of my involvement with Pharmuka. I was the “American Professor” whose research led to the discovery and marketing of Indalpin.

AT: Did Indalpine get to the United States?

BS: Yes, but it never came to market. I represented Pharmuka in the United States with the FDA in obtaining an IND for the investigational use of Indalpine and Viqueline, and carried out and published the first clinical trials in the United States with Indalpine in depressed outpatients. Having established offices in New York City, Pharmuka was setting up to conduct the necessary clinical trials in the US in anticipation of eventual marketing but the timing was wretched. Zimelidine, another SSRI, marketed in Scandinavia in 1983, was soon withdrawn due to the occurrence of Guillain Barré Syndrome, a serious neurological disease. In a smouldering climate of concerns about potential adverse neurological effects with SSRI's Indalpine ran into trouble around the issue of some patients developing adverse haematological effects. Meanwhile, under the socialist government of Mitterrand during the 1980s, Pharmuka and its scientists were absorbed by the industry giant Rhône-Poulenc, and the fate of Indalpine with it. In or about 1987 Rhône Poulenc abruptly pulled the drug off the market. There are other examples of wrong timing for good drugs: Wellbutrin is one of them.

AT: Wellbutrin?

BS: It's a fantastic antidepressant. We did the original open and dose-ranging studies with it and I used it with excellent results. Burroughs Welcome wrong mindedly decided to conduct clinical trials with it in people with bulimia. On the eve of its commercial availability some of them developed

seizures and the fate of Wellbutrin was sealed. Epilepsy is the death knoll for an investigational drug.

AT: Why is epilepsy more stigmatized than other side effects?

BS: A grand mal seizure while driving in New York City traffic is more ominous than a dry mouth.

AT: I am struck by your comment about Wellbutrin being a very potent antidepressant. Many of the SSRI's are now being marketed for both depression and anxiety, and one of the things about Wellbutrin is that it supposedly exacerbates anxiety.

BS: The aim of psychopharmacology should be to come up with new drugs having diagnostically related pharmacological specificity, like lithium for manic illness. Most antidepressants have anxiolytic effects as well but anxiety and depression are regarded by most people as opposite sides of the same coin. However, anxiety accompanying depression is not the same anxiety as the primary illness. Therapeutic specificity is not incompatible with the ability of an antipsychotic drug to put someone to sleep but it is incompatible with FDA approval to market the drug for use as a sleeping pill.

AT: So why are pharmaceutical companies reluctant to market drugs targeted to a specific diagnosis?

BS: I don't think they're reluctant; they probably don't have a drug that fits the bill. If they did there would be no rational reason why they wouldn't. To date the only drug with diagnostically related pharmacotherapeutic specificity is lithium for the treatment of the acute manic phase of bipolar illness.

AT: So why aren't they developing them?

BS: Because the current entrenched reluctance of industry to carry out research unrelated to serotonin has delayed the search for newer, better antidepressants and will continue to result in more marketing of drugs that are the same. They make billions by the sale of SSRIs and aren't in a rush to change things by spending billions on R&D to find new drug the cost for which has become prohibitive. The older antidepressant drugs that targeted all the brain monoamines will be reintroduced as new antidepressants, better than SSRI's because they affect the availability at central receptor sites of not one but multiple neurotransmitter systems. They will reinvent the wheel to generate more income for different flavours of the same compounds. Since the 1990's I have been calling the attention of ACNP colleagues to the role of excessive exposure and overstimulation of receptors in the brain to the essential excitatory amino acid glutamate with resulting effects in modulating synaptic plasticity, learning and memory. All of the existing antidepressant drugs are antagonists

of some aspect of glutamatergic activity. Investigational scrutiny of glial cells, especially astrocytes, as pivotal players can no longer be neglected in understanding how the brain works in depression. Depression is the phenotypic expression of the disordered, unregulated molecular biology of glutamatergic neuronoglia transmitter events in brain. This is the bottom line answer to your question relating to the failure of industry to come up with drugs that have diagnostically related therapeutic specificity in depression. Development of a drug with an inhibitory action of glutamatergic activity drug will not be easy.

AT: You are quite right we should be looking at things more specifically. Well, back to your career. What are your key contributions to the field of neuropsychopharmacology?

BS: I've already talked about my studies with synthesis inhibitors and Indalpine. I also contributed to knowledge on the antithyroid and goitrogenic effects of lithium; on the immuno- adjuvant effect of lithium; on the effect of lithium on white cell count, etc. I was involved in clinical studies with clozapine, penfluridol, pimozide, loxapine, bromocriptine, Wellbutrine, Wiqueline and many others. I published textbooks on *Lithium*, and on *Manic Illness* as I told you, and also on the *Psychobiology of Childhood*.

AT: Thinking back to when you entered psychiatry and where it is now, what do you think have been the most significant changes in the field?

BS: Psychiatry has been in decline for over a decade, replaced by a system of mental health care presided over by paraprofessionals who include every type and stripe of social workers, certified mental health workers, practical nurses, nurse practitioners, physician assistants, counselors of all sorts, everyone but psychiatrists! Psychiatrists are token participants at best in most hospitals, outpatient clinics and mental health facilities throughout the US, for medico-legal reasons. We in the ACNP, who pioneered the revolution called biological psychiatry hoped to change the theory and practice of psychiatry but got more than we wished for. We created a monster that has done more harm than good. We made scientific advances but failed to translate them into practical therapies or applied to applicable patients, for the well being of the public we serve. The psychiatrists and non-physician mental health care workers being trained are ill equipped. Incidence and prevalence statistics show mental illness has become epidemic; drugs are prescribed or abused by everyone starting in childhood. Children are prescribed drugs as if they were M & M's, whilst more and more adults and children have allegedly become "treatment resistant", and more children commit suicide. The pharmaceutical companies are making untold billions, advertising directly to the

public via newspapers, magazines, TV and computer websites suggesting that patients ask their doctor about a prescription. Alcoholics and abusers of prescribed or illicit stimulants and opiates are misdiagnosed as bipolar or treated as such by labelling them dual diagnostic cases for third party payment reasons. The system is broken. Psychiatrists without an idea about pharmacology bill themselves as psychopharmacologists because they give drugs; they no longer have the time or inclination to speak to patients. We've created a monster. If you listened to the history lecture the other night, it was clear that diagnostic accuracy and specificity are irrelevant to some of us; it doesn't matter what type of depression, unipolar, bipolar, neurotic, induced or associated with the use of illicit drugs. We are told, as long as there are depressive features, the practicing clinician should give an antidepressant.

AT: So you're not sure patients or society have benefited, at least in the United States, or are better off today than they were 30 or 40 years ago?

BS: Thirty or forty years ago, is a long time ago for comparisons. Forty years ago it was too early for the mentally ill to have benefitted from the advances brought about in the "Golden Age" of neuropsychopharmacology in the 1970's-1980', the real "Decade of the Brain". The 1970's and 1980's were the best of times for cutting edge psychiatric care available from physician-scientists who were able to stabilize and maintain more than 85%-90% of the patients who walked into their private practices or clinics. We saw few treatment resistant patients and needed only one drug, given to the appropriate patient in adequate dosages for sufficient time, to do the trick in most cases. Those were the best of times.

AT: We need to wrap up it up now. Thank you.

BS: OK. You're welcome.

DANIEL P. VAN KAMMEN

Interviewed by Thomas A. Ban
Waikoloa Village, Hawaii, December 10, 2001

TB: This will be an interview with Dr. Daniel van Kammen* for the archives of the American College of Neuropsychopharmacology. It's December 10, 2001. We are in Hawaii at the annual meeting of the American College of Neuropsychopharmacology. I am Thomas Ban. So let's start from the very beginning: where and when were you born? If you could tell us something about your early interests, education and how you got involved in neuropsychopharmacology?

DvK: I was born in Dordrecht in The Netherlands in 1943. This meant there was still a year and a half to go before World War II ended. My parents were both physicians and very early on I got involved in research. My parents were very much interested in research; I was one of the first children to get tuberculosis inoculation with BCG after WWII and one of the first to get polio vaccination and those kinds of things. So there was always an interesting new development in medicine as I grew up. Then I went to the "gymnasium," which is a six-year program with science, such as physics, chemistry, biology, extensive math, languages, such as Dutch, English, German French, Latin and Greek, history and geography.

TB: Where did you go to the gymnasium?

DvK: In the town that I was born in, Dordrecht, 15 miles south of Rotterdam. Then I went to the University of Utrecht and like my brother, my parents and my grandfather, I was going to be a physician. During high school, I got interested in psychiatry. I was an avid reader from early adolescence on Dutch history, world literature, poetry and anything I could find in my parents' library. I was very much excited by that.

TB: So, you entered medical school because it was a family tradition and became interested in psychiatry while still in high school.

DvK: Right. Psychiatry was not a family tradition. We used to say, psychiatrists are reluctant physicians, but that seemed to be the obvious choice for me.

TB: During the period you were a medical student, pharmacological treatment was not very much accepted in psychiatry in your country. Is this correct?

DvK: In academia there was still a strong influence of psychodynamics and particularly psychoanalysis but any experienced psychiatrist was very excited about the new developments in psychopharmacology. Rümke,

* Daniel P. van Kammen was born in Dordrecht, The Netherlands in 1943.

who died shortly before I started to attend psychiatry lectures, was a great proponent of the emerging psychopharmacology. He was a psychoanalyst but very interested in psychopharmacology.

TB: So, you did not know him.

DvK: No, but my brother, who is two years older, knew him.

TB: He was a very important figure in psychiatry. Wasn't he the one who first described the "praecox feeling"?

DvK: Indeed. He published a lot of good text books and case histories. He was known for the praecox feeling which we don't rely on any longer for diagnosing schizophrenia.

TB: Did you have any contact with Herman van Praag?

DvK: Not at that time, but his book on *Psychopharmacology* had come out during the years I was a medical student. That was a tremendous help early on, before Donald Klein and John Davis wrote their book. Later I did my PhD thesis with Herman Van Praag and David De Wied, who was professor of Pharmacology in Utrecht. I was Herman's first PhD after he became chairman of psychiatry. The title of my thesis was: *Studies with Amphetamine in Depression and Schizophrenia*.

TB: Who succeeded Rümke?

DvK: Professor Plokker who asked me, following my first year psychiatry exams, to become a junior resident at the Utrecht University hospital. That was very exciting; it was where I prescribed lithium to the first manic patient I treated, a 14 year old girl. I did my psychiatric clerkship at a State hospital near Utrecht and worked with a psychiatrist and a resident responsible for an admission unit of 30 beds and two chronic units of 60 to 70 patients. That gave me the opportunity to see psychopharmacology in action. As the psychiatrist Dr Fuldauer used to say, "These drugs are supposed to work". Many times, of course, we saw good results but for chronic schizophrenia or bipolar patients we needed better and different drugs.

TB: What year are we in?

DvK: Between 1966 and 1968. My clerkship was a two year program with the first year internal medicine, psychiatry, neurology and the second year surgery, gynecology, obstetrics and some minor programs, dermatology, ophthalmology and ENT. In-between those two years, I did an interview tour in the United States. I started out visiting the Nathan Kline Institute which wasn't called that as Nate was still alive. I visited several programs in New York City, including Bellevue, went through Boston to McLean Hospital and Mass General. McLean was the first program to offer me a residency position. I also visited the programs at Rockland State Hospital, Cornell, Rochester in New York State, Toronto, Pittsburgh

and UPENN before I went on to NIMH where Lyman Wynne suggested I should talk to Joe Stephens at Johns Hopkins. I stayed in Bethesda at the house of Don Fredrickson, the Director of the Heart Lung Institute. What excited me in the United States was the emphasis on systematic clinical research. Out of that interview tour, I got about five offers and decided to go to Hopkins, because Johns Hopkins University was a great place for my fiancée to complete her Art History studies and finish her PhD. I also knew about Hopkins. I had spent some time at the American University in Beirut two years earlier, just before the six-day war in 1967, when Johns Hopkins was supporting the AUB Medical School and Hospital. Hopkins also offered a very eclectic program from psychoanalytic training to psychopharmacology. For all kinds of reasons, Baltimore suited me well. So, after I completed my medical training in Holland in 1969, I moved to the United States within two weeks of graduating and started the internship Hopkins had arranged for me. My psychiatric residency started in July 1970. Seymour Perlin was Residency Director and Gerald Frank was head of outpatient and psychotherapy. Joe Brady ran an experimental behaviour therapy program; he was also very interested in psychopharmacology. Joseph Stevens was doing schizophrenia research. Sol Snyder, fresh from Axelrod's laboratory at NIMH, was my clinical supervisor in the second six months of my first psychiatry residency year.

TB: Was Joel Elkes the chairman of the department of psychiatry at Hopkins at the time?

DvK: He was there during my first two years and then left. Joel Elkes and Frank Ayd sponsored me later for the College.

TB: When did you get involved with the American College?

DvK: When I was at NIMH.

TB: How did you get to NIMH?

DvK: When I left Hopkins, I did a fellowship with Dennis Murphy at NIMH. It was at that time I first attended an annual meeting of ACNP, in 1973 or 1974.

TB: Did you already have a career in psychopharmacology in mind?

DvK: When I was preparing a six month elective in my last residency year, I looked at all kinds of possibilities. Group therapy was very exciting in those days, and so was family therapy. I worked with Virginia Satir, the family therapist where I had intensive training in family therapy that was delightful; it gave me insight into all kinds of clinical matters. I had the usual psychotherapy training and I worked with Joe Brady in a study group on behaviour therapy. So I explored all kinds of interesting opportunities.

TB: Did you have any contact with Joel Elkes while you were a resident?

DvK: Joel was a visionary; he developed all kinds of educational programs. He was involved with Israel in developing mental health centers there; he was setting up the community mental health center in Columbia, Maryland, family therapy with Virginia Satir and group therapy with Irving Yalom, who had just left when I came. All those were started by Joel. Plus, of course, we had our psychopharmacology programs; Frank Ayd was there. Curt Richter, the diurnal rhythm scientist, had an office next to me on the third floor of the Phipps Clinic. Joel would talk to us once a month but not someone we had close contact with. If you wanted to talk to Joel, the story was you had to hide in the men's room, waiting for him.

TB: Did you do any research while a resident at Hopkins?

DvK: I did with Lino Covi and Renato Alarcon, a resident from Peru, who was working with Lino, on anti-anxiety and antidepressant drugs. Renato was my resident mentor. Every junior resident had an older resident as mentor. He is a great colleague and friend.

TB: What did you do after your residency?

DvK: I worked in Dennis Murphy's clinical unit and lab at NIMH.

TB: Did you have any interaction with Biff Bunney?

DvK: Not at the time, but later on. Originally I was going to be at NIMH only for six months but Dennis offered me another year to finish our research. And during that year Biff took over from Lyman Wynn and created the Biological Psychiatry Branch that included Bob Post working in affective disorders, Elliot Gershon doing genetics and Chris Gillin doing sleep studies. Judy Rapaport was there in child psychiatry while Candace and Agu Pert with John Tallman were in the biochemistry laboratory. It was a great group of people. Then Biff asked me to set up biological and pharmacological research in schizophrenia.

TB: Could you say something about the research you did with Dennis Murphy?

DvK: I was studying platelet MAO activity, serotonin uptake in platelets in his lab and in the clinic, and I used the amphetamine challenge for predicting treatment response.

TB: So you used an amphetamine challenge to predict response to antidepressants?

DvK: Yes. It was a follow up of Jan Fawcett's first report.

TB: What did you find?

DvK: The higher they scored on the amphetamine response scale, the more they improved with the amphetamine challenge, the more likely they were to respond to antidepressants. It was really Dennis's idea to do that research.

TB: Was it regardless of the antidepressant?

- DvK: The patients were mainly on imipramine or amitriptyline and that didn't seem to make a difference. We were also trying to block amphetamine induced hyperactivity in lithium treated depressed patients and were working on the effect of lithium on depression. Tom Insel later wrote up the effect of lithium in depressed patients. We also looked at urinary MHPG with Helmut Beckmann in Fred Goodwin's lab. Helmut became professor and chair in Würzburg, Germany and President of the CINP. To me, it was very exciting to have another European around because I still felt European.
- TB: So your first clinical research project dealt with prediction of treatment response to antidepressants?
- DvK: Right.
- TB: And you had positive findings?
- DvK: Right, Jan Fawcett had published on it first with Dennis Murphy. Predicting drug response has remained a very important issue.
- TB: In spite of your positive findings nobody is using the amphetamine challenge test. How do you feel about that?
- DvK: It's disappointing; we had replicated Jan Fawcett's findings. But, in academia we are more interested in coming up with scientific data, rather than practical applications.
- TB: Why was it dropped? It was not because it didn't work.
- DvK: Most clinicians are uncomfortable using amphetamines if they don't have experience with it during their residency.
- TB: When did you move from depression to schizophrenia research?
- DvK: In the middle of 1974. That was an incredibly exciting time. We were talking about the role of dopamine in schizophrenia but it was clear to me already that dopamine could not be the whole story. Not everybody got better by blocking their dopamine receptors. This was before it was demonstrated that neuroleptics block dopamine receptors.
- TB: It was still a hypothesis.
- DvK: We started to do lumbar punctures and endocrine studies in schizophrenia. Again I used amphetamine as a challenge test with the rationale that d-amphetamine enhanced dopamine effects. It was intriguing that the action of amphetamine was supposedly related to dopamine in schizophrenia, and to norepinephrine in depression.
- TB: But in depression it was a favourable response that predicted a positive treatment effect.
- DvK: In schizophrenia we got an acute but short lived worsening in some but not all patients.
- TB: In what proportion of the patients?

DvK: About a third; I saw many flat and uncommunicative patients come alive after amphetamine.

TB: Did any of the mute patients start to talk?

DvK: Some mute patients improved briefly, but not all of them. According to the literature some mute patient responded to barbiturates, some to LSD, and some to other substances. I reviewed the whole literature from the beginning of the 20th century on that topic. It starts around 1929 when the first observations with amphetamine in mute schizophrenic patients were published. In reality the patient population with schizophrenia is very heterogeneous insofar as amphetamine response is concerned. You see worsening, no change and in others even improvement.

TB: Would you think those with worsening represent a different form of schizophrenia from those who don't change or improve?

DvK: We thought the nature of the response was state-dependent. If people were very psychotic, they were more likely to improve; if they just came out of the severe episode but were not stable they were very likely to get worse. We had people who were very stable and who didn't change. So when we looked at patients' baseline it predicted their response. We did not think chronic amphetamine treatment was a good idea but some people have used amphetamine to treat negative symptoms of schizophrenia. By the way we tried naloxone and naltrexone in the Clinical Center. We were still looking primarily at dopamine, serotonin and norepinephrine in schizophrenia and I wrote a paper in those years entitled, *The Dopamine Hypothesis Revisited* because I thought dopamine hyperactivity did not fully explain everything in schizophrenia satisfactorily, even if dopamine activity seemed to move psychotic symptoms.

TB: Was that your first publication in that program?

DvK: That was probably the first paper from our schizophrenia program.

TB: Was it based primarily on your findings with amphetamines in schizophrenia?

DvK: It also included a review of the literature. The paper was not restricted to findings with amphetamine, but included findings with L-DOPA.

TB: Did you find L-DOPA made schizophrenics worse?

DvK: I used L-DOPA only in depressed patients. But we used apomorphine, a dopamine agonist and it did not have much of a behavioural effect in our hands. Burt Angrist, Michael Davidson and Carol Tamminga used L-DOPA and found it made schizophrenia worse. I then developed a hypothesis about an interaction between GABA and dopamine in schizophrenia, and published it in 1977. We followed that up with our first paper in 1982 on GABA levels in the CSF. Our most important finding was the relationship of CSF GABA concentrations and negative symptoms. It was the first

paper in which the idea that negative symptoms could be separated biochemically from positive symptoms in schizophrenia. Tim Crow had just started to separate his two syndromes clinically at that time.

TB: Would you like to elaborate on the GABA-dopamine interaction in schizophrenia?

DvK: When Kim from South Korea reported, in 1977, that CSF glutamate was decreased in schizophrenia it was dismissed by people. Now we believe that glutamate affects dopamine and that causes psychosis, negative and cognitive symptoms. We presented data at the annual meeting of ACNP which indicated that glutamate is the link between dopamine and psychosis. We did a “path-analysis” to see which influences what and in what order. Could it be glutamate, dopamine, then psychosis, and then negative symptoms? Or could the order be dopamine, then glutamate, negative symptoms and positive symptoms. The only model supported by the data was: dopamine → glutamate → psychosis → negative symptoms. I think we’re going to see more data which will shift interest from dopamine to glutamate and GABA, with possibilities for glutamatergic antipsychotics. I’ve always believed that even though dopamine is in all likelihood involved, where it is in the chain of events is not known. So when we talk about an endogenous disorder, we don’t talk about a β -endorphin or a norepinephrine or a GABA or a glutamate or a dopamine or a serotonin disorder, we talk about a multi-transmitter disorder. It probably means we need to move beyond the receptor, perhaps into the mitochondria at one end and to brain pathways at the other. We’re either dealing with second messengers or with completely different intercellular cascades that are altered and probably not in one place but in several. It’s a whole different concept. We looked at serotonin, norepinephrine, peptides, the immune system and membrane turnover. I got interested in the calcium channel binding protein in 1980, because D_2 binding involves calcium binding. Calcium channel blockers seem to be more effective in bipolar mania. Or it could be a disconnectivity disorder; something that may involve impaired white matter. We need to rule that out because it’s the most obvious one. Ninety percent of brain cells are white matter. So, if you study a disorder like schizophrenia the world is still wide open.

TB: When did Tim Crow’s Type 1 and Type 2 schizophrenia enter the scene?

DvK: Tim Crow published his first paper on the two types of schizophrenia in 1979. Negative symptoms seem to be present before the major productive positive symptoms appear.

TB: When did Nancy Andreasen publish on her positive and negative symptoms?

DvK: That was in 1981. She came up with a better scale than Crow. That was a very productive period; we started to look at CAT scans. Years earlier, during my residency, I treated an acutely psychotic patient who had a seizure. In those days we used to do skull x-rays and pneumo-encephalograms; CAT scanning was not yet available. When the report on my patient's pneumoencephalography came back we saw the young woman had severe cortical atrophy and wide ventricles. I asked people, including Sol Snyder, what our findings meant, but nobody knew. Then, when the first CAT reports appeared, our findings made a lot of sense. Furthermore, there was an early paper by Professor Winkler in the Netherlands who had noted a similar finding in chronic schizophrenic patients with pneumoencephalograms in the 1930's or 1940's.

TB: Were you able to fit all your findings together?

DvK: We never really were able to because we didn't have the statistical know-how at that time. But we did find a relationship between CSF GABA concentrations and negative symptoms. We also found that larger ventricle size was associated with lower HVA, DBH, and 5HIAA, as well as with more negative symptoms and worse premorbid functioning. We published a paper in the *Journal of Neuropsychopharmacology* where we reported that slow wave sleep, negative symptoms and ventricle size were related. Interestingly, Krieg at the Max Planck Institute, followed that up in Huntington's disease, because there you also have negative symptoms, like apathy, decreased striatal size and decreased slow wave sleep. But if you want to put all these numbers together, you really need to do statistical modeling in a larger sample. That couldn't be done at NIMH at that time. When I got to Pittsburgh, we started to use Bayesian statistics; we did statistical modeling with relapse prediction and random regression.

TB: When did you move to Pittsburgh?

DvK: In December, 1982.

TB: So from the mid-1970s to the early 1980s you were at NIMH in charge of research of the schizophrenia program and in 1982 you moved to Pittsburgh. During those years at NIMH, surely you had fellows.

DvK: People like Sam Siris, John Docherty, Steve Marder, Paul Alexander, David Sternberg, J.C Garbutt, Carol Tamminga, Jack Rosenblatt, Gerry deFraities, Dan Hommer, Ken Malas, Dan Waters, Chuck Schultz, John Boronow, Phil Ninan, and several others were fellows on my unit. Jack Grebb was a fellow with me as a medical student.

TB: I suppose you have many publications from that period?

DvK: Over 150.

TB: Is there anything else you would like to talk about related to your research at NIMH?

DvK: We did a wide range of research. We showed that hemodialysis did not work in schizophrenia. The treatment trial was based on the assumption that endogenous toxins cause psychotic symptoms. Once we found that increased CSF MHPG and norepinephrine predicts an early drug free worsening, we gave amphetamine to patients on pimozide just before we switched them to placebo and those that showed an acute increase in psychosis were the ones that worsened very quickly after the replacement of pimozide with placebo. There were two patients who got better and remained asymptomatic for several weeks following pimozide withdrawal. This was all done with approval by the IRB at NIMH. When I went to Pittsburgh, we set up a research program that allowed us to study patients who were stabilized on haloperidol with cognitive tests, lumbar punctures, blood withdrawal, electrophysiological measures, polysomnography, CAT scans, and later MRI's. Then, haloperidol was replaced with placebo to see whether we could predict relapse. We found again that people who had elevated norepinephrine, even if they were somewhat stabilized, were the ones who relapsed quickly. In other words, you needed dopamine blockade to protect from the consequences of norepinephrine excess.

TB: Did you measure norepinephrine in blood and plasma as well?

DvK: In the CSF and plasma. So having elevated norepinephrine may actually be a destabilizing factor in the absence of D₂ blockade. We also found that patients with low DBH are more likely to respond to the dopamine blockade produced by antipsychotics.

TB: Is there any clinical indicator of low DBH?

DvK: We reported in our paper at NIH, published in *Science*, that good premorbid functioning was associated with low DBH.

TB: Was it followed up?

DvK: Joe Gelernter who had worked with me in Pittsburgh as a resident, and then moved to Yale, followed up the low CSF DBH data.

TB: Was your research in Pittsburgh focused entirely on schizophrenia?

DvK: Yes, but I had become interested in post traumatic stress disorder (PTSD) because I saw schizophrenia also as a potential disorder of stress regulation. In 1982 PTSD was a diagnosis that didn't exist. Particularly in the VA, there was a lot of controversy and people believed that PTSD starts out in the military as malingering. But I remembered from the post World War II years, that people didn't talk about it that way. If you look at the literature, in the first five years following World War II and also following World War

I, there was an enormous amount of clinical descriptions of PTSD in the psychiatric literature.

TB: What about after Vietnam?

DvK: In the early 1980s people started to realize the early negative reports on Vietnam veterans were not true. Then, with the DSM III-R, we got criteria for PTSD.

TB: What was your position in Pittsburgh?

DvK: I started out as full Professor of Psychiatry, and Chief of Psychiatry at the VA. That was the job I was recruited for. Within a few years I became acting Chief of Staff, and then was appointed Chief of Staff at the VA. I also set up a laboratory and a clinical research unit for schizophrenia studies.

TB: Was Tom Detre the Department Chair?

DvK: Tom recruited me.

TB: I understood that you did electrophysiological studies and polysomnography in your research. Where did your experience, in these areas come from?

DvK: Chris Gillin taught me at NIMH. Chris and I did some sleep studies together in schizophrenic patients before and after amphetamine infusions in the pimozide study. Then, in Pittsburgh, I had a fellow from the University who was interested in sleep, Tom Neylan. He is now on the UCSF/Stanford faculty and the VA in San Francisco. Later Eric Nofzinger joined me and followed up on that work. Once we had the expertise, we published some very interesting data on the decreased level of slow wave sleep in drug free schizophrenia, and on the relationship between decreased slow wave sleep, wider ventricles and negative symptoms in schizophrenia. We started to look at the automated recordings and analyzed some of the spectral sleep data.

TB: Where did your support for research come from in Pittsburgh?

DvK: The research unit was fully funded by the VA. My research grants came from NIMH, VA and from private foundations. When I started out in Pittsburgh, I had no experience with grant writing. At NIH you wrote a four page proposal that was reviewed by the Institutional Review Board and then you went ahead. It was very simple and straightforward, different from writing a full-fledged 20 page scientific proposal for NIMH. I submitted two proposals from Pittsburgh to NIMH, one was on relapse prediction with norepinephrine measures and the other was treating psychotic patients with clonidine. I was asked by the NIMH site visit committee which one was more important for me? I was advised by the chair to go for both but when I said they're equally important, I didn't get funded. But in the next submission we went for relapse prediction only and I have been fully funded since, by NIMH, the VA and private foundations.

TB: Could you tell us something about the clonidine studies you did?

DvK: We put patients who got worse after antipsychotic withdrawal on clonidine and placebo in a double blind fashion and we confirmed Bob Freedman's early findings with Dick Wyatt that clonidine has antipsychotic potential.

TB: What does clonidine do?

DvK: Clonidine is an α_2 agonist that acts mainly presynaptically.

TB: So you decreased, presumably, the norepinephrine in the synapse and by doing that you treated the hyper-noradrenergic condition?

DvK: That is correct. We also looked at cognitive changes with clonidine and showed improvement. Obviously, we did not get the most chronic patients because there is an issue with informed consent. We did informed consent in such a way that the patient had to tell us why they wanted to be in the program, what it was we were trying to accomplish, and what were the risks. We would not proceed if they could not answer those questions to our satisfaction. We believed from day one that a better-informed customer is more cooperative. For the same reason we wanted families to be a part of that process. If the family didn't support it, the patient would most likely withdraw at an inopportune time. It is better not to waste anybody's time, including the patients, if it is unlikely they fully understand what you want them to do.

TB: You have collaborated with many people in your research.

DvK: I have collaborated with a lot of people in my career. Modern clinical research is a large collaborative effort, which requires a very diverse expertise, which nobody can bring by themselves to the table.

TB: Is there anything else you did in Pittsburgh we did not cover?

DvK: As I said before I started out as Chief of Psychiatry at the VA and in 1985 became Chief of Staff. At the same time, I was responsible for the clinical running of the hospital, so I became an administrator. Then, in 1994, we had healthcare reform and I became a member of the VA team mandated to re-invent the VA. That was very exciting. It was like having training in management on a level you very seldom get. At that time the Hospital Director who I had worked with for years got another assignment and someone else came who had also been in the VA Healthcare Reform Group. She and I shared a clear vision about what we needed to do to implement the transformation of the delivery of care. That took a lot of time away from my research.

TB: So from the mid-1980s you were moving more and more into administration. Were you able to continue with your research while you were busy with administration?

DvK: I was continuing with the sleep studies. Mary Kelly, who got her PhD in Statistics in Pittsburgh, was my research assistant and I published

with her on what happens to plasma MHPG and HVA when you discontinue haloperidol in schizophrenia. She moved later to Atlanta to become Faculty at Emory. Mark Beuger came to work with me as a Fellow from The Netherlands, and we wrote a paper about our CSF findings after haloperidol discontinuation. He became a psychiatric resident later. Allan Brown was a resident on the unit and later went to Columbia.

TB: What have you been doing since the mid-1990s?

DvK: I started to do studies for the pharmaceutical industry as a way of learning about new compounds.

TB: Could you tell us some of the drugs you worked with?

DvK: I worked with sertindole, olanzapine, quetiapine, risperidone, and ziprasidone.

TB: With mostly atypical agents?

DvK: Yes and a couple of compounds that didn't make it.

TB: Did you do any research with clozapine in Pittsburgh?

DvK: No, I did not. When Sandoz first came and talked to me about doing a study with clozapine in the early 1980's, the unit wasn't ready and I didn't feel I could do a credible job. Later I started to prepare for the Novartis Clozaril study on suicide prevention just before I left for Industry.

TB: What happened to Sertindole?

DvK: Sertindole, because of a QTc problem, didn't make it in the US.

TB: Is there anything you would like to share with us about your experiences with the new atypical neuroleptics?

DvK: We found they produce fewer extrapyramidal side effects (EPS). Since then issues like weight gain and Type 2 diabetes have emerged. The weight gain we see with these drugs in the community at large is a big problem. One thing that was very intriguing was their effect on negative symptoms. So we looked further into negative symptoms because it seemed to me that some of the negative symptoms were secondary to EPS. Since then, that's been shown to be the case. We had a poster presentation in which we showed the gamut of negative symptoms in those who relapsed and those that didn't. In the early years, we saw people who got better for a while after being taken off antipsychotics, which suggested some symptoms were secondary to antipsychotic use.

TB: Any other research you did in Pittsburgh you would like to talk about?

DvK: We have done a lot of work with membrane phospholipids and the immune system. There seems to be a relationship between arachidonic acid turnover and cytokines and I'm sure we're going to see some more developments in those areas.

TB: Why did you leave Pittsburgh?

DvK: During my last year in Pittsburgh, the VA decided to go ahead with a merger of two VA hospitals and I abolished my own position, assuming I would then spend full-time on my research. Then I realized I was a general without an army. I also did not believe that writing 10 papers a year would make a dent in improving treatment options. Clinical development is hard to do in academia and I thought there must be other places I could do research. So I started to look around and the only place I found where research could be done without spending all your time writing grants and building infrastructures was the Pharmaceutical Industry. The Research Institute of Johnson & Johnson hired me to develop topiramate (Topamax), an anticonvulsant for the treatment of bipolar disorder.

TB: Are you still with Johnson & Johnson?

DvK: Yes.

TB: And still in charge of the topiramate project?

DvK: Yes, but we also have positive data in alcoholism and bulimia.

TB: What is your title at the Institute?

DvK: I am the Global Medical Leader which means basically the lead psychiatrist in developing the drug. So I deal with protocol design, overseeing execution of the trials and safety.

TB: Could you say something about some of your ongoing studies with topiramate?

DvK: We are doing studies in mania. We use the Young Mania Rating scale (YMRS) as the primary end point. The basic protocol lasts three weeks, but the European regulatory agency wants 12 week data. It's intriguing because there's no precedent for doing 12 week mania trials and there is no way of statistically analyzing those trials because you lose 50 percent of your subjects even in those three week trials. When you're out at 12 week it's a big problem.

TB: So you're testing the drug in mania?

DvK: Yes. It also seems to work in depression and in prevention of relapse in bipolar disorder. We see effects also in Gilles de la Tourette's.

TB: So it is working in the prevention of bipolar disease.

DvK: There are some intriguing case reports in treatment resistant depression but we don't know how good those are. Topiramate induces weight loss. It may work in eating disorders and a number of other indications as well, for example PTSD, treatment resistant OCD, etc. It is almost too good to be true. It has some cognitive side effects, though.

TB: Are you doing your studies globally around the world?

DvK: Yes. We have clinical sites participating in South America, South Africa, Australia, East and West Europe.

TB: In what phase of development is the drug?

DvK: In Phase III. We hope by the end of next year we'll go to the FDA; we'll keep our fingers crossed.

TB: Is there anything which we didn't talk about and you would like to add?

DvK: When I left Pittsburgh, I thought I had to resign my faculty appointment, but they said, well why don't you become an Emeritus? So, I'm an Emeritus Professor of Psychiatry at Pittsburgh University. I am also an adjunct Professor at the University of Pennsylvania and Columbia University.

TB: Are you involved with teaching?

DvK: Yes and no. What I do is grand rounds and I give talks when people ask me.

TB: Are you also seeing patients?

DvK: Not anymore.

TB: Anything else you would like to add?

DvK: Psychopharmacology has been very good to me and these are very exciting times. I am also involved these days in evaluation of new compounds.

TB: So, you are very interested in developing new drugs. There are tremendous unmet medical needs and our patients definitely need new effective and safe drugs. Have you been active in the ACNP?

DvK: I have been on the Membership Committee, the Committee on Government Industry Relations and on the Protection of Animals Committee. The ACNP has always been my intellectual center. I hope to remain active.

TB: Have you written or edited any books?

DvK: I have not written any book, I've edited a book series on *Research and Clinical Developments in Mental Health*, and a book with Malcolm Weller about *Mental Health*.

TB: You are still very active and you seem to intend to stay active.

DvK: I am very grateful for the opportunities I have had and still have, and particularly for the wonderful people I have worked with.

TB: So on this note we conclude this interview with Dr. van Kammen and I would like to thank you for sharing this information with us.

DvK: Thank you, Thomas.

HERMAN M. VAN PRAAG

Interviewed by David Healy
Las Croabas, Puerto Rico, December 13, 1998

DH: My name is David Healy. Today is Sunday, the 13th of December 1998. On behalf of ACNP, I'm interviewing Herman Van Praag,* from Holland, on his impact on early psychopharmacology in Holland, and his experiences about psychopharmacology when he moved to the USA. So, Herman, where were you born?

HvP: In the Netherlands, Schiedam. That is a smallish city near Rotterdam.

DH: Did you always plan to go into medicine?

HvP: No, not really. I had two other ambitions, Biology and in particular Ethology, but after discussing it with my father I decided against becoming a teacher. Most biologists became teachers at the time. In 1948, when I matriculated from secondary school, it was just a year after that a Faculty for the Scientific Training of Politicians and Journalists was started at the University of Amsterdam and since I had a great interest in politics I considered, maybe that would be an excellent idea. But again, I discussed it with my father and he said that politics is not a science and for a politician to study law or economics would be better. I told him I was not so interested in that so my final decision was to enter medical school. And, I never regretted it.

DH: After you entered medicine, when did you begin to think you might be interested in Psychiatry?

HvP: Very late. I was, as a schoolboy, already interested in brain, behaviour and mind, but discussions related to these issues were purely philosophical until late in my studies. It still is a philosophical problem.

DH: What do you mean?

HvP: I was primarily interested in mind-matter interrelationships, not so much in psychiatric hospitals.

DH: Before you went into medicine?

HvP: Oh yes! Even today, mind-matter relationship is the most intriguing question to be addressed for mankind. When I was a medical student there was nothing to be studied from an empirical scientific point of view about the brain and the psyche. Because of this I decided to go into Neurology, the closest you could come to the brain at that time. I finished my studies in the 1950s. At that time, in Holland, neurologists had to do one and a half years in psychiatry and psychiatrists about one and a half years of neurology in their training. So, as a future neurologist, I happened to start

* Herman M. Van Praag was born in Schiedam, The Netherlands in 1929.

my training with psychiatry. It was just about the time the first neuroleptics appeared and we learned about possible chemical transmission in the brain; the possible ones were sympathin A and B. Lithium was already there and the first antidepressants, imipramine and iproniazid were just introduced. From the very beginning it was known that iproniazid inhibited monoamine oxidase (MAO), the enzyme involved in the degradation of the just discovered monoamines, norepinephrine and serotonin. So there was a revolution in psychiatry in sight and I thought that brain and behaviour, mind and matter would become accessible to study. In my mind I entertained the question whether MAO inhibition was responsible for iproniazid's antidepressant effects? I also asked myself is it possible that there is something wrong with central monoamines in the brain of depressed patients who show a favourable response to iproniazid and could we study that in humans? So I decided to change direction from neurology to psychiatry. I went to my teacher in neurology and said I was going to change direction into psychiatry. And, he said, "Don't do that. It is a fascinating discipline, but it is almost a hundred percent dominated by non-biological, philosophical, psychological approaches. It is full of sometimes brilliant hypotheses, but without any means or intention to substantiate them. You know, it is one hypothesis on top of the other and no ability to prove anything. You should stay in neurology". I disagreed and said: "I want to study complex behaviours, not elementary motoric or sensory phenomena. So I have to turn to psychiatry". What he tried to bring to my attention was that I would be alone because there were no psychiatrists interested in biology. And he was right, because that was the case for many years. It was a very small group of people in the 1950s, '60s and even in the '70s who were active in psychopharmacology or biological psychiatry. Mainstream psychiatry was not only not interested but considered biological psychiatry a threat.

When I turned to psychiatry my teacher was the well known psychiatrist, Prof. Rümke. During my residency I wrote my thesis on monoamines and depression. When I told Rümke I would do my thesis on monoamines and antidepressant activity, he said, "So you're going to study urine and blood? What does that have to do with psychiatry? It's not psychiatry. That's not what you ought to learn." When I replied, "But you always taught us that the biological framework was extremely important," he responded, "Yes, but when I use the term biology, I mean the basic vital force that is instrumental for human life, at an energetic level." Even for him a biological framework in psychiatry was possible only at a philosophical level. I couldn't believe my ears, but that is what he said.

DH: So, your thesis dealt with monoamines and depression.

HvP: Yes.

DH: You defended your dissertation in 1962?

HvP: I completed my thesis in 1962 while I was still a resident and finished my training in psychiatry and neurology in 1963. Then, I was a Chef de Clinique, responsible for the daily activities of the clinic, and, while doing that, I was collaborating with psychologists because I realized if you cannot reliably diagnose and measure abnormal behaviour, a biological study would be without much value. Then a couple of years later I was invited to go to Groningen to establish a Department of Biological Psychiatry, the first in Europe. The university had given me space and money for labs and people. This was real foresight by the University because, in 1965, there was not that much indication psychiatry would become a brain science.

DH: Who did you find there and what were you working on in 1965 and 1966?

HvP: There was nothing there at that time. The Professor of Psychiatry was a psychoanalyst, the Professor of Clinical Psychology was an analyst, the Chef de Clinique was an analyst and the Chef de Polyclinique was an analyst. It was an analytic group and I was a strange figure there. Then, I went to the Chairman of Psychiatry and said, "I'm here now and I have a very tiny office, on the upper floor but that's not the point. I'm happy I can work, but if you ask me to set up a new department or division, there needs to be some correlation between the office and what you think that division will be." So, I was somewhat unhappy; there was absolutely nothing there. So the negotiations started and soon after my arrival, we moved to a new building and with a lot of space so we could attract people. So, I recruited biochemists, an electrophysiologist, a clinical psychologist and a biologist-ethologist and we started.

DH: Started to do what?

HvP: At the time the relationship between monoamines and behaviour was the center of our interest.

DH: What could you actually measure at the time? Was it gross 5-HT or 5-HIAA levels? When did you move from studying blood to studying CSF?

HvP: I started in the late 1950s with studies analyzing blood and urine; first, we were doing challenge tests by giving the precursor of serotonin and measuring the output of 5HIAA, its metabolite in urine. But very early I said to Korf, one of the biochemists on our team, we should move to CSF, the closest we can get to the brain. So he developed excellent methods to measure 5HIAA in the CSF. In the mid- or late-1960s, three groups, simultaneously, but independent from each other developed the probenecid method to study turnover of serotonin in the brain. We also developed methods of challenging serotonin and dopamine by the administration of agonists or antagonists. Doing that, we identified functions apparently

under the influence of the monoaminergic system and determined whether it was working on too high or low a level. Those studies were mirrored and extended in ethological animal studies. In the physiology lab we studied sleep.

DH: Sleep?

HvP: We studied sleep because there was evidence that sleep or certain aspects of sleep are controlled by the serotonergic system. We were also interested in the monoaminergic underpinning of biological rhythms.

DH: You were interested in the role of the serotonin system in the antidepressant effect of drugs. The industry has been focused on the disease side of the story but the pills seem to have an effect on personality and social functioning that is distinct from curing the disease.

HvP: I think Axis II diagnoses are indeed underestimated. There's almost no Axis I disorder without a coexisting Axis II personality disorder, be it psychosis, schizophrenia, depression, addiction, anxiety, panic, you name it. Maybe the Axis II diagnoses are at the heart of the matter, and especially when you speak about difficulties in social relations, adjusting to society and communicating with others. We should probably shift focus from the biology of depression and panic disorder to the biology of personality disorder or certain aspects of personality disorder. The problem is that studying personality disorders is probably more difficult than studying Axis I diagnoses, such as major depression.

DH: This is interesting but perhaps we should get back to chronology. In the 1960's you're one of the few people in Holland doing research in biological psychiatry which involved not just taking blood, collecting urine but also doing spinal taps, and you began to run into trouble.

HvP: First there was indifference, later trouble. When I started to do my research people said what I was doing was not psychiatry, because biological measures were not considered to be related to psychiatry. Another argument came from the psychoanalysts who considered each individual unique in pathological behaviour but features that could be generalized, like depressed mood, psychosis were irrelevant to treatment decisions. They used to say what we did was second or third rate psychiatry because drugs are just "mother's little helpers," they combat symptoms, and only psychotherapists focus on the essence of mental disorders. Then the anti-psychiatric movement arose with the Cultural Revolution in the 1960s against all authority and political views were often expressed in violent behaviour. Abnormal behaviour, or behaviour earmarked as such was a product of an abnormal society. Society should be treated, not the so called patient. It was not a quiet discussion, but a clash of belief

systems expressed in a very emotional way. And violence was not far away, not only in my case, but in general.

DH: It couldn't have been easy for your wife.

HvP: My wife said, for you it's easy; you are in the frontline but I and the children, we are sitting behind; it is better to be in the frontline than sitting at home and hearing all kinds of things about Van Praag, the terrible things he is doing, giving ECTs and drugs, he is like the Nazi's. Our boys and our girl didn't like to hear that.

DH: Then you spent some time in Jerusalem.

HvP: I was asked to become Chairman of the Department of Psychiatry at Hadassah University in Jerusalem. I said I would like to spend a trial year during which I can decide whether I can do it. I enjoyed my time in Israel tremendously, working with excellent residents but then I had to decide. That was a difficult time for all kinds of emotional reasons. I would have liked to stay but I struggled so much with the language that at the very end I decided not to accept. Anyhow, I came back and was offered the General Chair of Psychiatry in Utrecht. I said, wow, that may be important for psychiatry and accepted the offer. In Groningen I was Professor of Biological Psychiatry.

DH: Now after Utrecht, you moved to the USA?

HvP: Right.

DH: Was there a link between the troubles in Utrecht and moving to the USA?

HvP: Absolutely not. Within the academic context I worked in, I was free and people liked what I did. But, all of a sudden I got a call from New York and was asked to go to Albert Einstein, a well known medical school with great opportunities for further research. And I liked management very much, beside research and teaching. My charge in New York was to boost research and unify two completely independent departments, Einstein and Montefiori along with their affiliated hospitals.

DH: Who where you called by?

HvP: By the Dean, Dr Purpura, Dr. Freedman, Chair of the search committee, and Dr. Kline. After several visits I decided to do it. Then, very soon after my arrival, the first confrontation with the highly politicized New York scene occurred and all of a sudden it became clear that the Dean of Einstein was very eager to get me to Einstein, but the faculty was not. Einstein, when I came, was still the Mecca of psychoanalysis and I was initially considered a biological barbarian. Soon I realized maybe I accepted the job too easily and there was a chance I will be asked to leave.

DH: What happened?

HvP: Montefiore was a large teaching hospital in Albert Einstein College of Medicine; they had their own Chairs of Psychiatry and both had to leave because they asked me to merge two departments, and I managed pretty soon to do that.

DH: How did you go about doing it?

HvP: Essentially by making the decision that the unified Department should be run by a large Executive Committee consisting of 22 people; the heads of the 12 divisions, enlarged with some researchers, clinicians and teachers from these Departments. We would meet every week for an hour. They said at first, "Every week! No, that is much too much. What are we going to do?" And I said, "First of all listen to what I have to say, and I have to hear what you have to say." We did just that for eleven years, and it went very well. In addition, if you meet frequently, it's much more difficult to put a knife in your neighbours back. If you see someone every three or four months it's easy, but if you see them each week, it's very difficult to do something very nasty. It was very, very important to induce a certain amount of trust and solidarity. I like constructive meetings and I like to make fun and jokes, so it was very relaxed, and very open. Also, by having regular meetings, people started to believe I was talking the truth, and not just demonstrating some elegant window dressing.

DH: How did things go research wise during the eighties? Did you keep on with the work you were doing at home?

HvP: I did quite well, collaborating with many others. At the time I arrived there was not very much research, let alone biological research at Einstein, so I developed a program. That was fascinating. In America, if you are active and more or less creative there's a great opportunity to do that, because the rules are not so strict and creativity and initiative are admired. I raised a lot of money from grants and benefactors which the school matched. When I came to Einstein there was one laboratory and when I left there were six, all raised primarily from monies received from benefactors and matched by the school.

DH: One of the important things you did during the 1980s was to challenge the orthodoxy of the new DSM. You felt there was something wrong.

HvP: Yes.

DH: You said, it's important to have some classificatory system but here we have a system that is wrong and ultimately unfriendly to the biological approach. Even here, at ACNP, which is supposed to be a brain storming meeting, there's not a hint that DSM IV has got things wrong. Were there any meetings in which you actually talked to these issues?

HvP: I did several times at the APA.

DH: Was this in the early 1980s?

HvP: Early and late '80s or early '90s, I said the DSM is less a classification than a belief system.

DH: It's a philosophy, isn't it?

HvP: A kind of philosophy. What I said in the early eighties was, don't throw nosology away, but try to study it and if there is reason to have doubts about the validity, act on it and compare different disease models. Do the ground-work. Study the diagnostic concepts and their validity, otherwise, you run into the same problems as the psychoanalysis, adding one hypothesis on top of another, without having proven if the first one is right. And that is what happened. The DSM is a new "holy cow". Psychoanalysis has been a "holy cow", anti-psychiatry a "holy cow", now diagnosis is a "holy cow." If you don't have a system of diagnosis that is precise, valid and reliable, then biological psychiatry is worthless. I would be the most surprised person in the world if there would be a gene or a biological factor specific for major depression or generalized anxiety disorder (GAD) or schizophrenia. To pretend there is something like an entity schizophrenia, an entity dysphoria, an entity panic disorder, an entity major depression, is a fiction, an illusion. I could be wrong, but let us discuss it, and let's study it.

DH: When you said these things I assume you got no response. Could I ask you how you perceive psychiatry in the US, over the last twenty years or so? In the '60s it was Freudian but also very dimensional, looking at personality and things like that.

HvP: Right.

DH: Now it has become almost anti-bacterial. They want to hit the bug that causes panic disorder; hit the bug that causes GAD, and we've almost lost the constitutional element of the picture completely. Do you have something to say about this?

HvP: I've always had interest in psychoanalysis, or better in developmental psychology. I think Freud's ideas, as a philosophy, are fascinating. Freud was a great philosopher. I have less interest or confidence in the practical applications of psychoanalysis.

DH: What are your thoughts about classification today?

HvP: I'm moving away from nosology towards functional approaches, looking for the biological underpinning of psychic dysfunctions, in cognitive functioning, affective functioning, and so on. In 1964, I had a paper on the conceptualization of what was then called functional psychopathology. It seems it has been forgotten. People don't go back and they forget about people who said the same things years before and over and over again. But, I'm optimistic that the concept, the point of view, will be accepted in the course of time. I repeat, functionalization of diagnosis, and treatment

for that matter, is the way to go. We have worked along those lines for years.

DH: Let me pick out a very concrete issue which seems to cut across the diagnostic classes, 5HT and suicide. Do you want to pick up on that and how you began to get into this area?

HvP: We started out with studying serotonin, 5HT, and its metabolite, 5-hydroxy-indole acetic acid, 5HIAA in depression and in particular, in vital depression, endogenous depression, major depression. Because of my functional inclination, I thought we should look at depression not just as a nosological concept but also with consideration of its functional aspects, like disturbances in mood and anxiety regulation, disruptive aggression regulation, outward directed aggression, irritability, hostility, suicide and so on. This is how I got to studying 5HT and 5HIAA in suicide. It was in the 1970s, and it made anti-psychiatrists extremely angry, because suicide was considered to be absolutely non-biological. To go beyond studying the biology of endogenous depression and schizophrenia, was considered to be confrontational, to the utmost.

DH: When you began doing all this research your work was, more or less, considered as the work of the devil, implying that the soul is made of things like 5HT. At that time with your functional approach you tried to refine diagnosis, but now, we've got broad diagnostic concepts, like major depression, in the DSM-III-R and DSM-IV. They have become the mainstream and led to the introduction of drugs like Prozac (fluoxetine.)

HvP: I am an optimist. Time is with me. The nosologic approach has proven to be a dead end. Fifty years of biological research with no hint of "the" cause of schizophrenia or of major depression. Soon the nosological blinds will be removed. With regards to antidepressants, I still think antidepressants are not universal treatments for all depression, but that is not what industry likes to hear. But since there is no syndromal acuity anymore, we just prescribe antidepressants for any kind of mood lowering. That is a very unscientific way, it is very unfortunate. And, there was no attempt to critically analyze the enormous impact the introduction of DSM had on psychiatric practice and research. Of course, this is more profitable for the industry but it is very unfortunate. I have coined the term "nosologomania". Our entire field is geared towards imaginary "entities". If I were to wake up in 2050, and I would find that there's a gene for schizophrenia and a gene for mental depression I would be the most surprised man in the world. If anything is transmitted, I think it's the vulnerability factor. To look for a gene for schizophrenia, is useless. But, when I say that there is no gene for schizophrenia, there is a lot of opposition because people look for a schizophrenia gene, and get grants for it.

So they say I'm an outsider, not a geneticist that I don't know what I am talking about.

DH: Outsider?

HvP: Yes, but I have not been convinced by any argument that what I believe in is totally wrong. To go one step further; I think I am right.

DH: I wonder whether with antidepressants, when we get to the stage of being able to radiolabel things, we would get more predictability of how the responses will go. My hunch is that one personality type would respond to a particular antidepressant, .and another personality type would respond to another and that would bring the personality issue back in.

HvP: I totally agree. Dysfunctioning personalities, personality vulnerability, vulnerability to stresses that disrupt brain function are extremely important.

DH: What about in Holland? How do you see things there? Do they have still a big ideological divide?

HvP: Much less so. Biological psychiatry is accepted, is nowadays mainstream psychiatry. There is some resistance against evidence based medicine. It is wrong. If I go to a doctor, I hope that his decisions are based on more than his private convictions. So, the attitude is unfortunate.

DH: Is ECT still so unacceptable?

HvP: Not so much any more. But people are still very sensitive about it and ECT is given only in some places as for example at our place in Maastricht. You should have it at all places where there is a qualified person. There should be a certification that allows people to do ECT. But that didn't happen yet and so ECT is still underutilized.

DH: Holland and USA are the two countries where ECT has provoked such violent reactions that has led to its being banned or not used.

HvP: They had problems with it in other countries as well, but I don't know what the situation is now.

DH: Is there any hope for the future even if things are not moving quite the way you want.

HvP: I am an optimist. The process of psychiatry becoming a science is moving irresistibly ahead. Too slow, but it moves. What genetics can offer to psychiatry is overestimated, and I have doubts about what knowledge of the human genome will contribute to understanding the biology of mental illness.

DH: What about the understanding of personality?

HvP: There are too many genes involved to have great expectations. I am much more optimistic about gene-environment interaction studies. That's basic for psychiatry to learn how environmental factors and genes interact so the gene becomes expressed or not. There are many hopeful trends and I'm optimistic psychiatry will develop more and more into a real scientific

multidisciplinary science. But development of a valid, refined diagnostic system is the root-issue. I'm very happy I've lived in this time; in spite of all the shortcomings; psychiatry is a totally different discipline than it was fifty years ago.

DH: Do you think the next thirty years are going to be as interesting as the past fifty?

HvP: I think so. I would have liked to live until 2050, but I know that won't happen. The changes will be very dramatic and, hopefully, we'll understand much better how genes come to expression and how environmental factors work in disturbing behaviour.

DH: Have you been involved in the development of any particular drug?

HvP: No, but I think our work on serotonin and depression has been instrumental in the development of the SSRI's. Furthermore we have studied drugs of interest scientifically, but avoided a big drug screening operation. I want to be independent of industrial money. It has been an interesting life and I hope I didn't bore you. One more point. I am more than a biological psychiatrist. I have a great interest in the other side of the coin: human behaviour and spirituality. My neurobiological friends consider this odd, primitive and unscientific. Right now, we are trying to organize an international meeting on psychiatry in the Bible. So, you see, whatever I do, there is some degree of controversy.

DH: Well, that has to be another issue.

HvP: Right.

DH: We should take a break. You've only been here for two hours, but I've been here for eight.

HvP: How do you like listening to all of these personal statements?

PETER C. WHYBROW

Interviewed by Andrea Tone
San Juan, Puerto Rico, December 15, 2004

AT: My name is Dr. Andrea Tone and we are here at the 2004 ACNP Annual Meeting and, today, I have the pleasure of interviewing Dr. Peter Whybrow.* Thank you for agreeing to be interviewed. Let's start with your upbringing. Tell us a little bit about it and why you chose to go into medicine.

PW: I grew up in England in the country. And, why did I want to be a doctor? Well, I was going to be an architect.

AT: We just had someone, who said the exact same thing.

PW: I think the influence was that my father had been ill. He was a veteran of the Second World War and he had been ill for some years after that so we got to be very close to a local family doctor. He used to visit our house all the time and he was a wonderful fellow. I think it was probably his influence that eventually made me turn to medicine. He was a sort of doctor you don't see any more, who visits houses. He was a very kindly thoughtful fellow. He sat down with all of us and told us about my father's various illnesses and so on. So that was one of the influences. As a high school student, probably for the same reasons, I worked in a local hospital as a surgical dresser in the operating theatre, getting the instruments ready and things like that. Then I also worked in a mental hospital for a summer, which was fun, very interesting and confusing for a young fellow.

AT: Could you tell us about that?

PW: I was an attendant on a male unit for chronic patients with a mixture of diagnoses. At the time it was totally confusing. The inmates must have been suffering from schizophrenia or manic-depressive illness, plus people with dementias, all mixed up together. Essentially I used to help the nurses. I would take a little basket down every afternoon to the pharmacy. It was filled with bottles for paraldehyde, which they would refill, and I would take them back to the unit. The patients were all men and we'd give them paraldehyde so they would slowly go to sleep as a terrible stench rose throughout the unit. You know what paraldehyde is like; it's a thick alcohol like substance which has a terrible smell. The whole place would reek, but the patients went quietly to sleep until the next morning when they'd wake up and start beating each other again. It was a tragic situation, as I described it in my book, *A Mood Apart*. There was one fellow, who probably had manic-depressive disease who was a farmer, and since I lived in a farming community we became friends. He had periods

* Peter Whybrow was born in Hatfield, Hertfordshire, England in 1939.

when he was quite well, and then he would go into maniacal rages or sit in a corner depressed. That was one man who impressed me. There was another fellow who obviously had some sort of obsessive-compulsive disease. He was the patient who would butter the bread for the unit. The nurses would give him a loaf and a pat of butter and he would proceed to butter bread until one or the other of the items was finished. He would stop, they'd give him more and he'd do it all again. He was an amazing fellow, in terms of buttering bread. He'd have it perfectly, smoothly, spread. All the patients were sitting there on the unit, were confined by their illness. They had no way out; those were the days when hospitals were truly asylums. It was quite impressive to me and probably influenced my going into psychiatry, although I didn't do that immediately. I went to University College in London and later to University College Hospital Medical School, graduated and went into endocrinology.

I studied thyroid disease, thyroid carcinoma actually, with a very famous doctor named Eric Pochin, who was head of the Medical Research Council Unit at University College in London. We took care of people from all over England and Europe who had thyroid carcinoma. We treated them much the same as we do now. We'd take the thyroid out and give them radioactive iodine to obliterate the cancer cells, because most thyroid cancer cells take up iodine as thyroid gland cells do. And then we'd sit and wait. Six or seven months would go by and any remaining bits of carcinomatous tissue would begin to multiply again. Since they were still thyroid cells; they would take up iodine, so when we gave them another pulse of radioactive iodine it would kill them. In the meantime, you had to deprive the body of thyroxine but, in those days, we didn't have T3 (triiodothyronine), which is used now to substitute for it. So, the patients would become profoundly hypothyroid during their six to seven months of treatment. By the time treatment was completed they were different people.

I remember the Ambassador to Norway, who became a friend of mine who had this illness, the same disease that Rehnquist, the Supreme Court Judge, has now. The Ambassador told me that during the phase after surgery, when he was deprived of thyroxine, he couldn't calculate anything. If it hadn't been for his staff, he felt he wouldn't have been able to do his job. Just going to the store, he couldn't figure out how much money to give people and how much he got back. Other patients used to talk about forgetting recipes they'd known since they were kids and things like that. He suggested if I was interested in the brain, which I was, then I should study these things because doctors knew they happened but nobody knew why. So, that was why I started studying the thyroid axis.

AT: Do people also complain of some of the other things we associate with hypothyroidism? Was the language there that allowed them to discuss symptoms in the same way psychiatrists might today?

PW: The patients definitely complained of lassitude, not being able to think and would be melancholic. That was one of the things I became interested in; whether hypothyroidism could masquerade as a mood disorder.

At that time in England, we were encouraged to get a varied post-graduate experience. I had been a surgeon and endocrinologist, so, out of curiosity, for a short period I went into psychiatry as a Senior House Officer at the University College. I then decided I needed some new adventures. So I thought of going to go to Africa to work with Professor Lambo, in Nigeria. He was a psychiatrist who had been trained in London. But, my professor said, "Oh no, that's crazy, you don't want to do that". That would be interesting for about six months, but you wouldn't learn anything. What you should do is go to America." The professor was Desmond Pond who had been to America himself when he was younger. During the Second World War a lot of medical students had been shipped to America because England was being bombed heavily and most of the hospitals were in the center of London. Some went to America, Canada and places like that. Pond went to North Carolina where he was at Duke. Pond said to me, "In Chapel Hill there's an interesting fellow who has this wild idea about psychoanalysis and thyroid diseases. His name is George Ham. You should go and work with him." Well, indeed, George Ham was sort of wild. He had this theory that thyrotoxicosis was all due to the stress of being deprived and the hyperactivity occurred as compensation. The theory didn't hold up with time, but the idea that stress is important did. Anyway, I went to North Carolina as a research Fellow and a resident and met Arthur Prange who was also interested in thyroid matters. So Prange and I began doing studies together. He was an assistant professor in the department when I got there and we worked together looking into the question that you asked, namely how does an individual who has hypothyroidism experience the abnormalities and are the abnormalities overlapping with depression. We did a study of people with thyrotoxicosis and people with hypothyroidism before and after they were treated for the illness. We found that the hypothyroid people were profoundly depressed and most of them had cognitive deficits. We began to realize from these studies that hypothyroidism mimics psychiatric illnesses, particularly cognitive dysfunction and mood disturbance and, in some instances people can become quasi psychotic, developing so called "myxedema madness." In those days there weren't good chemi-

cal tests for thyroid disease so people became quite ill before they were diagnosed, especially in rural North Carolina.

AT: Synthroid was developed in the late 1950's, is that right?

PW: Synthroid was synthesized in the 1950's. But there was no T3 because that wasn't synthesized until the 1960's. So the major test for thyroid function was protein bound iodine, which was presumed to be bound to the thyroxine molecule, because that's how most iodine is transported around the body, and not by measuring the hormone itself. Hence protein bound iodine was the major serum measure of thyroid function. We also used ankle reflex time and metabolic measures, which were helpful because they measured the body's metabolism in relation to thyroid. The science was evolving along with the technology. We couldn't measure many of the parameters we measure now, such as TSH.

Arthur Prange had just started working on a related idea; that there might be an enhancement of the action of antidepressants by triiodothyronine, which had just come on the market. This idea developed from the case history of a woman seen in the emergency room in North Carolina. The patient, who had depression and had been given a tricyclic antidepressant also had hypothyroidism. She'd mistaken the dose of her thyroxine so that she was taking double the amount she should have been taking. Taking a double dose of thyroxine, she had developed atrial fibrillation, a rapid beating of the heart as a result of the toxic synergism between the thyroid hormone and the adrenergic increase produced by the tricyclic agent. We now know that one of the physiological actions of thyroid hormone is enhancement of adrenergic function. We also know serotonergic function is increased. It was the synergism he saw in this patient that led Prange to the idea that if you gave thyroid hormone this might be an advantage in the treatment of depression. That turned out to be the case and he published his seminal paper on in 1969. Our paper on *Myxedema Madness* and other papers including *The Thyroid and Mental Changes Occurring with Thyroid Dysfunction* were also published in the late 1960s. This initiated collaboration that has lasted for many years. After I went back to London to work at the Medical Research Council Depression Unit at Greenbank Art Prange joined us on sabbatical and we did some studies together with Alec Coppen. That was the year we demonstrated that thyroid hormone supplementation of antidepressant treatment seemed to be a particularly advantage to women. It was also in that year that we found a correlation between the level of circulating thyroid hormone and speed of recovery from depression. This was an interesting finding, which has held up till this day. Some people, when they are depressed, have elevated levels of thyroid hormone in their blood stream

and these individuals are the ones who do well when you give them anti-depressant drugs. This natural finding was the physiological equivalent, to giving thyroid hormone to a depressed individual to enhance the anti-depressant response. Furthermore, it turned out that women, who have poor thyroid function compared to men throughout their lives, which gets worse with age, do better with adjunctive thyroid hormones than men. Or, more precisely, men do not gain advantage from thyroid hormone because there isn't an advantage to be taken. They already have good thyroid function.

AT: If someone with hypothyroidism and thyroid levels within an acceptable range experiences depression, could they just increase their Synthroid?

PW: That is often a good idea although it is one of the things that has been in contention between general endocrinologists and psychoendocrinologists. The truth is the general endocrinologist doesn't pay too much attention to the brain or to behavioural symptoms. They don't rank such patient complaints very high in their list. So you get this ongoing struggle, which many patients report that the internist or general endocrinologist doesn't want to increase thyroid replacement because the patient has what they consider to be adequate thyroid function. But, there's a lot of evidence that if you happen to become depressed it is an advantage to have the circulating level of thyroxine in the higher quartile. In other words, it's not a good thing to have it lower, even though that level might be in the normal range. It's much better to have it in the upper range of normal. The evidence is that people who have thyroid disease who also happen to have a depression and especially retarded depression are better off taking enough thyroxine to maintain a circulating level of thyroxine within the upper quartile of the normal range.

AT: But this isn't well known among internists.

PW: It's not well known but it's getting better now. I do get invited now to general endocrine meetings to give talks in plenary sessions and so on. And, some internists are taking an interest in behaviour and recognize the importance of this in patient care, but in general they're sceptical about the brain. Yet it is clear thyroid hormones have a powerful influence on the brain. Some thirty years after I started this line of research we've just finished studies that show using PET that thyroid hormones can profoundly change blood flow in the brain.

AT: That's very interesting.

PW: We can change the behaviour of depressed person to normal if you give a high enough dose. Predominantly these are people who have treatment resistant bipolar depression. What happened after working at the Medical Research Council Unit in the early 1970s in England was that I decided

to come back to America. I was working with Alec Coppen in London, who was the director of the Medical Research Council depression unit at West Park Hospital. At the time I was also teaching at my old medical school for nothing, and steadily going broke. I had two children by this time and I was spending a lot more money than I was earning. In those days, the pound and the dollar were different and coming to America one earned more money than one earned in England. That's not true so much now. Also I was offered all sorts of jobs, one in North Carolina, one in Dartmouth, one in Pennsylvania, and after awhile I broke down and decided I should take one.

So one snowy winter I came here and looked around. Because I like to ski, I ended up going to Dartmouth. I was a junior professor for about a year, started my research and ran the residency program. Then Bob Weiss, the Chairman, who had gone on sabbatical shortly after I arrived, decided he was not going to come back to Dartmouth. An interim Chair was not working out very well so the Dean asked me to step in. So, at the tender age of thirty-one, I became Chairman of the Psychiatry Department, which was amusing. I learned rapidly that I was quite good at it for reasons I can't figure out, even now. And one thing led to another. I continued to do my thyroid work and was amazed to find that, in America, people weren't using lithium, which was a very common treatment in England for bipolar manic-depressive disease. I had participated at the Medical Research Council (MRC) in some of the original studies of lithium that showed it was not only an antimanic agent, but also prophylactic and capable of reducing the frequency of cycling. It was quite interesting to go to Dartmouth and to find nobody was using lithium, so I started to do so. We followed thyroid function in our patients because it had been reported lithium was an antithyroid agent. And so my thyroid interest began to merge with an interest in bipolar disorder. We discovered what Schou and others also reported that lithium was a powerful antithyroid agent and, in some people, could induce thyroid disease.

After a few years, in the late 1970s, I had built the department up to being quite good and I decided when I became President of the Chairman's Association at about age thirty-six, that was a sign I needed a new job. I got a Macy Fellowship to go to the National Institutes of Health (NIH) for a year. I should say, parenthetically, that living in New England, you get to be appreciative of the cold, because it's pretty chilly in winter. We lived on a farm and doing the chores with the cattle every morning I had become interested in how animals adapt to cold weather. Of course, thyroid hormones are an important part of this adaptation.

There's evidence, thyroid metabolism changes in the winter months with a higher ratio of T3 to T4 (thyroxine). I began to wonder whether, if people did not have an efficient T4 to T3 conversion, that it might have something to do with winter depression. I wrote some articles about that, one of which appeared in *Yankee Magazine* so I became famous briefly for the study of seasonal behaviour and its associated physiology. So, when I went to NIH it was with the idea I was going to study thyroid hormones and seasonal variation. I knew Fred Goodwin because he had been in North Carolina as a resident when I was a fellow there. By now he was in the intramural program and running one of the research units for the psychobiology of depression. So I spent the year in Fred's unit and studied some of these ideas with the notion I might be able to change the clinical course of bipolar illness by giving high doses of thyroxine at certain points in the cycle. It didn't work.

But then Al Lewy, who also was working at the NIH on his assay of melatonin, became interested in seasonal affective disorder. Al had gone to Australia while measuring his own melatonin circadian rhythm and found that melatonin was very responsive to sunlight. This had not been clear in humans before. It was recognized melatonin drove some seasonal behaviours, such as reproductive behaviours in animals, but it wasn't clear in human beings because we lived in a dramatically different light environment from animals. Thus it was thought seasonal variation was not likely to be light driven. But Lewy showed it was. So, I took another sidetrack and became interested in light and thyroid.

When I went back to Dartmouth I became the Dean of Dartmouth Medical School for a short period. The Dean wasn't doing too well, so they wanted me to take over, which I said I would do for a short period. I did it for three years, but didn't really like being a Dean because it took me away from all the things that really interested me. I've really been a Chairman or a Dean since my early 30s, but because I don't find it that stressful, it's easy for me to do that. So that's how I put bread on the table. But in addition, I've always had these interesting intellectual sidebars in research. The outcome of that particular episode when I was the Dean was I didn't do much thyroid work, but I did start a study looking at seasonal variations of behaviour in northern New England and found some interesting things. Among them was that depression is more common in Northern climates and human babies get born in a seasonal cycle as do other animals. With large animals living on a farm, for example, the calves are born in the spring. It is similar with sheep. The rams get very excited in the fall of the year. It's a cycle orchestrated by melatonin and the sex hormones that enables lambs to be born in the spring

when they have a better chance of survival. It turns out, when you look at human beings, there is still a residual cycle. In northern New England most babies are conceived in the late summer, a disproportionate number of them, anyway.

AT: Do you think that's correlated to vacation time?

PW: It could be, but another vacation is Christmas and that's not quite so potent. So there seems to be a residual seasonal cycle tied to mating in human beings just as in other mammals. So I began to pursue the idea I could use thyroxine to mitigate the illness of people who suffered malignant rapid cycling bipolar illness. I had been referred by colleagues to a small sub-group of people who were severely ill. I remember one man who was cycling every three weeks or so from mania to depression. Quite a few of these people had thyroid dysfunction. At first I thought this was because they were receiving lithium, which blocked thyroid function. So I reasoned, if we gave them thyroxine perhaps that would improve their illness. That, in fact, turned out to be the case, although it wasn't quite as simple as we thought.

By this time I'd been at Dartmouth for about twelve years. I had been doing some basic science work, looking at the activity of de-iodinase enzymes with Don St. Germain, who was in the Department of Medicine and Valerie Galton, in Physiology. We were pretty certain that lithium was interfering with de-iodinase function in the brain and pituitary, which is why you see a rise in TSH when you give lithium to somebody that corrects in people with normal thyroid metabolism. In people who don't have a normal thyroid axis, however, it tends to stay high. I was trying to put all of this together when somebody came up from Pennsylvania and wanted me to run the Institute of Pennsylvania Hospital. I didn't want to do that, but the Chairmanship of the Pennsylvania Department became open and I thought I'd rather be a Chairman than a Dean. So I went to Penn to run their Department of Psychiatry, which was a mess. I spent the next twelve years at Penn building up the department.

AT: What time period were you there?

PW: I went to Penn in 1984 and I left in 1996. It was during those twelve years I did most of my work on rapid cycling. We started a very large clinic for people who had thyroid and behaviour disorders and that mushroomed into what I called the Malignant Bipolar Illness Clinic, where people came from all over the east coast with intractable bipolar illness. I started that clinic with a research fellow, named Mark Bauer. I've worked with two Bauers in my life, Mark Bauer and Michael Bauer, and they each get credit for each other's work, which is nice!

AT: Their last names are spelled identically?

PW: They're identical, yes. It's an interesting resonance because Bauer in German means "farmer." So, we have all these farmers working together. Anyway, Mark and I started this clinic and we rapidly discovered you couldn't give thyroid hormone alone because it causes the patient to become very irritable and manic. We had several notable characters; I remember a physician who became wildly manic when we took him off lithium. What we also discovered was that, in some people, who had very severe illness thyroxine was a miracle. Literally, some people who had been cycling in and out of severe episodes of mania and depression and were unresponsive to lithium or Tegretol (carbamazepine), when you gave them high dose thyroxine the illness completely remitted. We found as you pushed the thyroxine dose up to a level where you completely suppressed TSH, to about one and a half times the usual serum levels in the normal population then sometimes you got a miraculous cessation of cycling. This effect was so impressive that families of the patients couldn't believe it. The physician I just mentioned, who got manic when taken off lithium was an example. He was a thirty-six year old man who had a cold thyroid nodule removed. A cold thyroid nodule means a lump in your thyroid that doesn't produce hormone. Sometimes they are removed because of concern they're pre-cancerous. This man had his removed ten years before we met him. Then, perhaps two years before we met, he'd started this odd behaviour where he'd be extremely erratic. He was married with a couple of kids, but he would go out at night and not come home. Afterwards he'd go to bed for a week and not get up. And so he'd lost his job; he was an ophthalmologist who everybody thought was a drug addict so his superiors were going to assign him to the scrap heap. He saw a psychiatrist who thought he probably was manic-depressive and put him on lithium, but the cycle didn't get any better. So, when we first saw him, he was headed for the local asylum. We did some thyroid studies and we found when we gave him a TSH stimulation test he had an incredibly high TRH response, which suggested he had marginal thyroid disease. So we put him on thyroxine and pushed up the dose. Then we briefly took him off his lithium, which was a mistake because he became maniacal. We managed, with Tegretol and lithium, to get his illness back under control. But the remarkable thing about this patient was he completely remitted, he came out of these cycles and became normal. So, for six to nine months he was completely well, which was staggering to his family. And then he had an episode of illness when he decided, because he was a physician, he wasn't going to take lithium anymore. Finally we stabilized his illness on Tegretol, lithium and thyroxine and, fifteen years later, he's doing fine. So, there are these extraordinary cases. We wrote

him up in the *American Journal of Psychiatry*. What we also found was that if you look at people with rapid cycling they tend to have far more thyroid disease than patients treated with lithium that do not have rapid cycling disease. So there seems to be a correlation between the amount of circulating thyroxine, vulnerability to lithium and vulnerability to the rapid cycling phenotype of bipolar illness.

Then, we discovered those who suffer rapid cycling are predominantly pre-menopausal women. Hence another variable entered the picture, which is an estrogen-thyroid hormone interaction in the brain. Thyroid hormone and estrogen share genetically a set of receptors that compete with each other. So if you have bipolar disease, too little thyroxine circulating and you're pre-menopausal, the estrous cycle fosters rapid cycling. Hence some young women when they are still menstruating are particularly vulnerable when given lithium and their thyroid axis collapses. So we designed a series of studies where we looked at these individuals and we gave them high doses of thyroxine just like we had given the man, and we found that about seventy-five percent of them were responsive. That was an open trial. Then we did crossover studies where we gave thyroxine at high levels and reduced it blind to the patient and the observer and found the person would start cycling again. When the thyroxine was raised up again, they'd stop cycling. These studies were conducted through the late 1980s and we published some of the results in the early 1990s. Then various people around the world started to pick this up, particularly Andreas Baumgartner in Berlin, who did some of the original studies on the basic pharmacology of Tegretol and lithium and what these drugs do to the de-iodinase enzymes in the brain. Andreas became a great fan of the technique and moved it forward by suggesting you could treat people chronically ill with bipolar depression using high dose thyroxine.

Sometimes people treated for bipolar depression do well in regard to mania, but you can't get them out of their depression. They stick there forever. So the Berlin group employed, in these patients, high doses, 0.4 to 0.6 milligrams of thyroxine, which is about four times the normal replacement dose, and found the depression would get better. Andreas Baumgartner had an associate named Michael Bauer and Michael at one depression conference said that he wanted to come and work with me in America. I was about to leave Pennsylvania to go to UCLA. I have this internal clock where I don't like to do anything for too long and the Penn department was flourishing. It was considered number two in the country, next to Pittsburgh. We had a lot of research grants and so on and so forth. So I decided I was going to California and see what I could accomplish at UCLA. They had offered me the job in 1990 but I didn't want it then

because they didn't organize it the way I felt was optimum. Then they got a new Dean. UCLA's Neuropsychiatric Institute (NPI) is a huge institute, probably the largest institute of human neuroscience in the country with psychiatry, neurology, and neurosurgery all wrapped up together. So it was an attractive idea. It has its' own hospital and it's a very interesting place. And so, when I was offered the job again, I decided to take it. So, instead of coming to Penn to work with me, Michael Bauer came to Los Angeles and was there for about three years. He was first on a German scholarship and then I helped to support him with an endowment I had. We extended the studies of acute treatment of severely depressed people and started looking at brain imaging at the same time. I had pushed forward the basic science work in Penn looking at the genetics of how lithium interfered with the thyroid receptor function. And Mary Dratman and I had done some work together.

So Michael and I started looking at severely depressed bipolar patients and recently, in the last two or three years, we've been able to show that people who have this chronic phenotype have a different brain physiology, as measured by blood flow using PET. In fact you find a physiology very similar to other depressed patients, but they're not getting better from the treatments. Despite heroic doses of drugs they remain depressed and their cerebral blood flow remains similar to ordinary depressives. We found, using cerebral blood flow measures, high activity in the limbic areas of the brain and low activity in the frontal lobes. It's as if the frontal lobes, which are the structures that give us executive function, disappear and behaviour becomes driven largely by limbic activity. In teaching the medical students I describe this pattern as analogous to a horse without a rider. High doses of thyroxine in about seventy-percent of cases change the brain blood-flow physiology. The limbic system becomes quiet and the frontal lobes wake up. Exactly why the shifts happen and what thyroxine does, we're not sure, but other findings are intriguing. For example, we discovered most of those who respond to thyroxine have no peripheral thyroid dysfunction. So it looks now as if thyroxine is acting in these cases as a pharmacologic agent rather than a hormonal replacement. I use the analogy that it's rather akin to using high doses of steroids to disrupt chronic asthma or chronic arthritis.

AT: Let me ask you about the kinds of challenges one faces as the Chair of a Psychiatry Department and how dwindling support from the public sector for neuroscience research has increased pressure on Chairs to get support from private companies.

PW: I've been in this academic business too long. I try to cover it up now, because people start calculating how long it is and how old I am! They

think, “Oh, my goodness, that guy’s in his dotage”, which I certainly don’t feel. So, yes, there’s a lot of “the sky is falling” in the Chairman’s Group. I don’t go to those meetings anymore, but I used to when I was younger. I was the President, as I mentioned. I call it the Chicken Little Group. They’re always wringing their hands and saying, “The sky is falling; the sky is falling” and they’ve been doing that for thirty years. The fact is there are about 10 or 15, maybe 20, big departments of psychiatry in this country, many of which are highly research intensive and they do very well. Then there’s another group of departments of psychiatry that are primarily clinical and teaching departments and they have very few grants. So if you’re talking about the high-end group, yes, the public dollar does go up and down. But it’s so highly competitive that most of the big ones remain pretty well okay. They go through their own cycles, so Penn was in a nadir when I arrived and it went up again. Yale was doing great and it’s been going down. UCLA was down when I went there and it’s gone back up again. As with all things, academic departments have their cycles. Pittsburgh has been unusual; it’s been pretty steady, because it’s had good steady leadership for a long time. So the trick to being a good Chairman is not so much worrying about the national scene as in getting the infrastructure of the department working properly. First the support systems that enable the faculty to figure out how much money they have in their grants, the way in which the grants are written, how smoothly they get managed by administration, helping them work through the IRBs, etc. You remove every barrier you possibly can that is preventing the faculty from doing well. At the same time you have to run a fair ship with no favourites. When I first went to Dartmouth, the man before me had told everybody, he or she, was the favourite son. “You know, you’re my best person, my best faculty member. I’m going to make sure you’ll do well,” etc., etc. When he left everybody realized they were only one of many favourite sons and all hell broke loose. They all thought they were tricked rather than getting some kind of special privilege. That never works in my experience. The most important thing is to be honest with everybody and if you’re having bad financial times you should discuss that with the faculty. Most people are very smart in these universities and they’ll work hard to achieve what they need to achieve if they know what the goals are and the impediments are. So, it’s a matter of openness and having a sense of vision about what we are doing and where we are trying to go. If it’s a really big department like UCLA, with four hundred full-time faculty, you must break it down into groups that are cohesive. Human beings like to work in groups of maybe 12 to 20 significant people. You can have a large staff, but the working groups need to be about the same size as a football team because once it gets any bigger the

cohesion is lost; the members of the group don't have a common cause. So, big departments need to be divided into small departments of about that size. There's no magic to running an academic department. It's just a matter of being honest and answering the mail.

I don't know whether the issue with industry is a real one. Yes, many departments have had a lot of drug company money, but I've always stayed away from that. Nobody gives money to endocrinologists anyway because the drugs used don't make a lot of money. I think there's a useful collaboration between the pharmaceutical industry and neuroscience. It's like all things where you've got the demand of the market place, which is highly competitive and highly centralized. The goal of industry toward profit and maximizing financial outcome gets to be dangerous because that's not what academia does. So you have this disconnect between a company that wants to find a new therapeutic agent and an academic institution that wants to find out what's going on. And then you've got the boundary people, some of whom have got caught up in the money sink. That has become a problem, a scandal in some cases, as we've seen. There have been a few exposes' in various parts of our profession. In moderation, it's important to have a union between industry and academia. But industry can't take over the role of the public dollar. Otherwise, the research will be driven by the need for commercial gain.

AT: You don't see that threshold as having been crossed already?

PW: Not in America. It's dangerously close in Europe where there is much less federal money for research and so people are frequently pushed into the jaws of the pharmaceutical companies.

AT: From where you sit is ghostwriting as much of a problem in psychiatry departments as someone like David Healy alleges?

PW: All members of our faculty write their own papers. And we have some significant researchers, even in the pharmaceutical area, like Steve Marder and Lori Altshuler and they've never had a ghost-writer. Rather than "ghost-writing" in the true sense, a company writes the paper and then asks somebody to put his or her name on it. There may be some people who are desperate to do that, but I don't think you'll find many of the truly significant academic players in the country among them. Maybe I'm naive, but I have no knowledge of that going on in any faculty I've been associated with. Now, David Healy is an interesting man. We've had him come out to UCLA several times to give talks. I think he has a very important point to make and, like many people who are change agents, he's zealous about it. So he's ruffled some feathers. I think it was important to say some of the things he has said, but I don't think the practice of ghost-writing is necessarily as pervasive as he thinks.

AT: This is a question I ask everybody. Where do you think we are in terms of the life cycle of great triumphs in neuroscience? Are we just learning what needs to be learned about the brain? Are we celebrating decades and decades of magnificent progress?

PW: Both probably, you have to take a long view. Think of the story I told about when I was a high school student. We've come a long, long way from that now. That was thirty-five years ago and there are lots of people now living outside mental hospitals and pursuing very productive lives, coping with illnesses that would have confined them for life thirty years ago. That's particularly true of the affective disorders, but also some of the other disorders, like obsessive-compulsive disease. We've got excellent treatments for that, for anxiety and so on and so forth. There have been very significant clinical advances over the last few years but some of the other things that have happened, however, are not so good. It's something akin to what Healy has been talking about. As we've become more affluent, we've become richer in the agents at our disposal, especially the psychotropic agents. Many of them are slightly different, but they're all out there, tens of them now, indeed hundreds of them. Because of this clinicians have become less interested in the interpersonal aspects of how the brain works and have focused on pharmacology. I was fascinated this morning when going to a study section on obesity where the first talk was mainly about Leptin. Well, Leptin accounts for maybe two percent, if you stretch it perhaps five percent, of people with severe obesity. Ninety-five percent of people who have obesity are victims of a dramatically changed environmental input. It's a behavioural disorder.

AT: That was diplomatically worded.

PW: We have to figure out a way in which behaviour and pharmacology come together. What we've tended to do is to hide behind biological and neuroscience achievements and say we're going to find a pill for each new problem. Well, the human brain is a transducer; it transduces the environment to the benefit of the organism, to the body, and the survival of the individual. So, we have to come to grips with the idea you can think and change your brain. It's not all biology, but it is also environment, and it is how you interpret that environment that changes your brain. One of the big advances we're going to see in the next few years is that neurobiology will increasingly demonstrate that the brain is extremely plastic and moulded by what happens to us. Behaviour is not deterministic. We used to think the brain is like this table, that once it had formed, once it's been built, it stays that way. The neurons are finite and you lose them slowly over your life. They weren't replaceable, etc., etc. All that has gone out of the window in the last ten years and we realize the brain is an extremely

plastic organ. If you want to learn to play tennis and then do so, you end up with a different set of networks afterwards than before you learned to play. What neurobiology has taught us is that we have to go back to thinking much more creatively about the way in which the environment and brain interact. On the flip side, we need to recognize that neurobiology and an understanding of brain can teach us about ourselves and how to stay healthy, an important thing the public at the moment is not recognizing. I can give an example. As a side interest I write popular books. I've written several: one on seasonal affective disorders, which was called *The Hibernation Response*, one on mood called, *A Mood Apart: The Thinker's Guide to Emotion and its Disorder*, and, then, my most recent book, which comes out in January, is called, *American Mania, Why More Is Not Enough*.

AT: That's a great title.

PW: The thesis there is that the world has changed dramatically. We have built for ourselves a demand driven, reward driven environment, which is extremely rich in information and everything including choice. But probably it's increasing the number of people who are vulnerable to behavioural disability. In other words, as the environment has changed, the genome is now expressed in a different way because the phenotype is changing under the stress of those changes. Obesity is a perfect example. If you look at the statistics, until about 1985 the obesity level in America was the same as in most other countries, somewhere between ten to fourteen percent. Now, it's around thirty-five percent and the number of people that are overweight is about sixty-five percent. That sudden increase cannot be because of a change in the genome; it's because we have changed the environment. Similarly we have rising anxiety in this country. And it's the same in regard to what I consider to be a behavioural disorder with an old friend called greed. In our affluence we have spawned an extraordinary outbreak of people becoming invested largely in themselves and not in the community. The book explores all this within the construct of the neurobiology of capitalism.

AT: That sounds wonderful.

PW: To answer your question succinctly, we have learned a lot about how the brain works. It's just we haven't yet come to a holistic understanding of what that means for society. And we're tending to be still in love with this idea that if you can see it under a microscope, or you can play with it genetically, then it's more important than figuring out the psychosocial aspect. I don't think that's true; the sociobehavioural and biological elements of knowledge complement each other. In the next few years, as we play around with genomics, which is a fancy name for physiology, we'll

go back to the idea that the only way we can understand these illnesses is to understand the environmental-gene interaction. Most of the severe psychiatric illnesses have a tail in them, which is normal behaviour. Take anxiety for example. There are some people who are extremely anxious and they've always been extremely anxious. But there are a lot more people now who are anxious but who weren't anxious before in a less driven environment. If you look at the epidemiological studies, thirty-five percent of the American population says now they're anxious. Well that's a huge number of people. Again we have an environmental change t playing on a neurobiology sensitive to that change. Another analogy is smoking. For many years people smoked cigarettes, addicted to nicotine. It was nice. It helped if you were anxious. It lifted you up if you were a little depressed. It's good stuff, nicotine. But it came with a vehicle that tended to give you lung cancer. Slowly, people began to realize that. That was a toxic environment, so then they said, "No, we don't want any more of that." I think you're going to find there will be the same backlash in the next few years because we'll realize we are vulnerable, neurobiologically, to too much demand, too much reward. I don't think we know what to do with affluence. We're great when we haven't got much and must make do. But you put out six chocolate cakes and, God knows, people eat them. They don't think about it, but it's not good for them. America is the first truly affluent society. Just about everybody has access to an extraordinary number of material goods and we're endangering ourselves physiologically, I think.

AT: That's really interesting. I know you have to go to dinner.

PW: I have to go to the poster session and then to the dinner.

AT: Is there anything you'd like to add?

PW: I don't think so. What is the purpose of this? So that people in a hundred years time will look back and ask, "There were funny people back then, what did they do?"

AT: I'll probably use this interview for my own purpose because there's a lot you said that I think is directly relevant. I can't guarantee that many other people will use it, but I hope it will be. We now have a travel grant in place. This is something you should know about in your capacity as Chair, to underwrite the cost for graduate students who might be interested in the history of psychopharmacology. So they can go to ACNP and look at this material among the other treasures there. I guess a final question, a question I ask everybody as well. What advice would you give to someone who's new in the field in psychiatry? What are the great opportunities and possibilities and a small agenda that you would share with them?

PW: I still tell the students that it's the best discipline to go into because human behaviour is so vast and it is what we are, after all. Psychiatry is the most fascinating part of human behaviour. It's the core, the pith of the person. If you strip it down to its fundamentals, it's emotion and memory and attention and concentration and all those things that, when put together, make the person. That's the domain of a psychiatrist. When you have dysfunctions of these generic systems within brain you get peculiar syndromes we call manic depressive illness, schizophrenia, etc., but they are composites and dysfunctions of familiar normal elements. So the student of psychiatry can be interested in fundamental cognitive neuroscience, for example, and help apply it to a disease entity. Also they can be interested in the genomic drive of the system, or they can be interested in the way it interacts with the environment. And, as a practitioner, we still have the wonderful opportunity to sit down and talk to real people about real things. One of the problems faced by general physicians is they have become technicians. When I was trained in medical school my teachers were the most amazing physicians who, with just their own art and their own skills, could tap out the cavity of a tuberculosis lung, or interpret heart sounds, or feel livers. People still do that, but we're much more technically driven now. Even in our discipline we're getting to the point of sticking the patient's head in a machine to see whether it is malfunctioning. It doesn't tell you very much very often, but that's the trend. Fortunately we're still not able to rely on that in psychiatry, probably never will. So you have to pay attention to the person. You have to. And physicians, many of us anyway, come into the business not to be technicians. We came into the business because at some level we have compassion and concern for other people. That's especially true for people who go into pediatrics, general medicine, psychiatry and that sort of thing. So I think psychiatry is for somebody who's really interested in people, interested in ideas, interested in everything about being human; philosophy, art, it's all there and so it's an incredible specialty. I'm interested to see students are beginning to come back to it now. During the biological nadir we turned a whole lot of people off because they thought psychiatry was just about prescribing drugs, which I don't think it is at all.

AT: The biological nadir instead of the biological apex, an interesting characterization. Thank you very much. It was so interesting.

PW: My pleasure.

INDEX

Note: The page numbers for each interviewee's entry appear in boldface type

- 17-hydroxycorticosteroids, xvii, xx, xxi, 61, 132
- 5HT. *See* Serotonin (5HT)
- 5-hydroxyindoleacetic acid (5HIAA), xvii, xxii, 348, 357, 362
- Abuzzahab, Frank, 166
- Acetylcholine, xvi, xxii, lii, 117, 121, 192, 193
hypothesis of stress regulation, 193
- Add-on studies, xxiv, 42, 255
- Ader, Robert, 72
- Affective disorders, xii, xxiv, lv, lviii, 16, 28, 32, 93, 94, 95, 107, 114, 117, 120, 140, 167, 214, 242, 246, 249, 277, 335, 378
catecholamine hypothesis, xx, 115, 325
cholinergic-adrenergic hypothesis, xxi, 192, 195, 198
endocrine approaches, li, lvi, 277
- Agam, Galila, 37
- Aghajanian, George K., xxii, lii, 127, 179
- Agranoff, Bernard, 91
- Ahearn, Eileen, 98
- Akathisia, 4, 22, 105
- Akbarian, Schahram, 65
- Akerfeldt test, 148–49
- Akil, Huda, 65, 168, 170, 171
- Akiskal, Hagop, 253
- Alarcon, Renato, 344
- Albert, Murray, 149
- Alcohol, Drug Abuse and Mental Health Administration (ADAMHA), 159, 160
- Alexander, Paul, 348
- Alprazolam, 108
- ALS (amyotrophic lateral sclerosis), 54
- Alzheimer's disease, liv, 67, 86, 95, 237, 268, 288, 294, 313
- American College of Neuropsychopharmacology (ACNP), 6, 33, 34, 53, 68, 82, 162, 235, 257, 293, 299, 305, 306, 343, 354, 360
- Archives, 100
basic vs. clinical neuroscience, 35, 121–22
meetings, 48, 170, 239, 264, 265, 270
members, 54, 117, 125
- American Psychiatric Association (APA), 16, 19, 22, 111, 360
- Amitriptyline, xvi, 87, 109, 135, 172, 345
- Amphetamine(s), xviii, xxi, 49, 118, 345
and antidepressant response, xxi, 135, 136, 233, 344, 345
psychosis, xi, xix, xlix, 4–9
- Anderson, David, 72
- Andreasen, Nancy C., 78, 204, 347
- Angrist, Burton, xix, xlix, **3–11**, 346
- Angst, Jules, 251, 253
- Anhedonia, 79, 141
- Anticholinergic agents, xvi, xvii, 86, 172, 195
- Anticonvulsants, xxv, 33, 106, 107, 111, 243, 255
in bipolar disorder, 244, 245, 248
- Antidepressant agents, xv, xvi, xvii, xx, xxi, xxii, lvi, lvii, 50, 52, 55, 89, 106, 108, 109, 114, 124, 128–29, 157, 179, 183, 232–36, 238–39, 290, 292, 305, 313, 322, 337–38, 344, 362
dosage issues, 264, 306
introduction, 16, 320, 356
mode of action, lii, lv, 87, 114, 179, 235, 267, 286, 288, 335, 336
potentiation, xxii, 129, 233, 266, 368
thyroid hormones, xxiii, 278

- Antidepressant amphetamine combinations, 136
- Antimanic agents, 107, 157, 232, 244, 279, 370
- Antipsychotic agents, xxii, 19, 22, 32, 34, 55, 78, 81, 106, 107, 208, 221–22, 291
and negative symptoms, 79, 81
anticonvulsant augmentation, 111
atypical, 110, 124, 237, 254, 352
dopamine blockers, xlix, 118, 349
dosing, 23–24, 26, 264
mode of action, liv, lv, 21, 205, 288
non-dopaminergic, 221, 224, 225
- Anxiety disorders, xv, xvii, 16, 31, 108, 311, 313
mixed anxiety-depression, 311, 338
- Anxiolytics, 16, 232, 312, 338
- Apomorphine, 22–23, 49, 346
- Arato, Mihaly, 50, 51
- Axelrod, Julius, xiii, xvi, xx, 14, 19, 114, 115, 116, 126, 131, 157, 264, 284, 297, 300
Nobel Lecture, 211
- Ayd, Frank, 21, 100, 343, 344
- Bailey, Percival, 133
- Baldessarini, Ross J., xix, **12–35**
- Ball, Ira, 167
- Ballanger, James, xxiv, 243
- Ban, Thomas A., 104, 105, 281–94
as interviewer, 57–69, 70–83, 84–101, 164–75, 228–39, 240–59, 260–72, 341–54
- Barchas, Jack D., 68, 179
- Bartko, John, 73, 76
- Bass, Allan, 117
- Bauer, Mark, 372
- Bauer, Michael, xxiv, 372, 374, 375
- Baumgartner, Andreas, 374
- Beck, Lyle, 262
- Beckmann, Helmut, 345
- Bekhterev, Vladimir M., 231–32
- Belmaker, Robert H., xxiv, I, **37–45**
as interviewer, 273–80
- Benjamin, Jonathan, 43, 44
- Benzodiazepines, 104, 108, 125, 142, 237, 311–12, 314
- Benzylamine oxidase, 300
- Beringer, Kurt, x
- Bernard, Claude, x
- Besser, Gerald, 88
- Beuger, Mark, 352
- Biederman, Joseph, 41
- Biggs, John, 308
- Biogenic amines, 114, 119, 178, 335, 336
in depression, li, 114, 117, 177
- Bipolar depression, xx, xxi, 219, 244, 251, 369, 374, 375
- Bipolar disorders, xxiv–xxv, liv, lv, 26–29, 41, 42, 98, 107, 142, 162, 198, 242, 250, 253, 256, 257, 269, 329, 353, 370, 372–75
broadly diagnosed, 33
funding issues, 258–59
heterogeneity, 251
rapid cycling, 195, 372
treatment-refractory, 245, 247
- Bissette, Garth, 280
- Blakely, Randy, 290
- Bleuler, Eugen, 77
- Bleuler, Manfred, xvii
- Blier, Pierre, xxii, 121
- Bloom, Floyd, 225
- Boag, Thomas, 303
- Bonhoeffer, Karl, xi
- Boronow, John, 348
- Bowers, Malcolm, 245
- Brady, Joseph, 343
- Brady, Linda, 8
- Brain imaging, 55, 65, 118, 204, 205, 226, 255, 256, 266, 268, 375
functional, 135

- Brain stimulation. *See* repetitive transcranial stimulation (rTMS); vagus nerve stimulation (VNS)
- Braslow, Joel
as interviewer, 295–315
- Brill, Norman, 189
- Bristol-Myers Squibb, lvi, 304, 306, 310, 313
- Brodie, Bernard B. (Steve), ix, 119, 126, 235, 262–63, 265, 297, 298, 327
- Brodie, Keith, 62, 90, 191
- Bromley, Elizabeth
as interviewer, 201–9
- Bromocriptine, 7, 152
- Brooks, George, 296
- Brown, Allan, 352
- Brown, Burton, 62, 63
- Brown, Walter A., xxiii, I, **46–55**
- Buchanan, Robert, 80, 82
- Buchsbaum, Monte, 64
- Bullard, Dexter, 132
- Bunney, Benjamin S. (Steve)
as interviewer, 146–54
- Bunney, Blynn, 65
- Bunney, William E., Jr. (Biff), xviii, xx–xxi, xxi, I, li, **57–69**, 71, 73, 77, 114–16, 119, 131–34, 138, 140, 143, 156–58, 177, 190–91, 235, 242, 245, 256, 344
- Bupropion, xxii, xxiii, 109, 179–80, 183, 337–38
- Burns, John, 297–98
- Burroughs Wellcome, 179, 337
- BuSpar. *See* Buspirone
- Buspirone, lvi, 271, 305, 310–12
- Byerley, William, 65
- Cade, John, xii, 87, 98–101
- Calabrese, Joseph R., 255
as interviewer, 37–45
- Cameron, D. Ewen, 129
- Carbamazepine, xxiv, 42, 111, 243–45, 248, 373
- Carlsson, Arvid, xv, 223, 233, 235, 265
- Carman, John, 245–46, 246, 253
- Carpenter, William T., Jr., xviii, I–li, 63, **70–83**, 143, 157, 190
- Carroll, Bernard J., xxiii, li, 50, 53, 73, **84–101**, 166–67, 169, 172, 235
- Casper, Regina, 125
- Cassidy, Frederick, 98
- Castelnuovo-Tedesco, Pietro, 190
- Catatonia, 251, 320
drug-induced, 103
periodic, xii, 252
- Catecholamine(s), xii, xv, lii, 42, 135, 151, 181, 242, 247, 264, 285, 286, 335
hypothesis of depression, xvi, xx, lvi, 61–62, 115, 116, 131, 158, 325–27
metabolism, xii, xxi, 245, 264, 299, 329
- Centorrino, Franca, 26
- Cerebrospinal fluid (CSF), xix, xxii, 8, 125, 180, 346, 349, 357
GABA concentrations, xix, 346, 348
- Charney, Dennis, 170
- Chlorimipramine, 199
- Chlorpromazine, xv, xxi, 21, 23, 25, 87, 111, 119, 131
metabolism, 119
vs. reserpine, 274
- Cholinergic system, xxiv, liv, 86, 147, 172, 193
- Cholinesterase inhibitors, xxi, 85, 194, 195
- Chouinard, Guy, xix, li, **102–12**
- Circadian rhythm, xxiv, liv, 73, 211, 213–14, 215, 218, 219, 371
abnormalities, 212, 216
- Clark, David, 143
- Clinical trials, xiv, I, 33, 35, 41, 44, 50, 52, 55, 75, 82, 83, 104, 105, 109, 112, 123, 132, 137, 179, 238, 239, 271, 274, 305, 310, 337
and clinical research organizations (CRO), 314
- Clonazepam, 106, 107–8, 111

- Clonidine, xviii, xix, 182, 350–51
- Cloninger, C. Robert, 43, 196, 197, 199
- Clozapine, xx, xxii, 10, 81, 110, 123, 124, 222, 225, 226, 352
- Clozaril. *See* Clozapine
- Cobb, Stanley, 17
- Cocaine, 6, 11, 63, 121, 233, 242, 291
sensitization, xxiv, 8, 9, 243, 251, 256
- Cohen, Bruce, 195
- Cohen, Mandel, 18
- Cohen, Robert A., 60, 63
- Colburn, Robert C., 191
- Cole, Jonathan O., xvi, 305
- Coleman, Jules, 59
- Collegium Internationale Neuro-
Psychopharmacologicum (CINP), 22,
129, 130, 345
- Computed tomography (CT), 348, 349
- Cooper, John, 77
- Cooper, Theodore, 155
- Coppen, Alec, 66, 277, 279, 336, 368, 370
- Corticotrophin releasing hormone (CRH), 142,
173
- Cortisol, xvii–xviii, xxiii, 47, 49, 50, 73, 88–89,
93, 122, 167, 193, 195
- Coryell, William, 51, 93
- Costa, Erminio, 123, 125, 265
- Covi, Lino, 344
- Cox, David, 65
- Coyle, Joseph, 170
- Crow, Timothy J., 7, 78, 347
- Cuatrecasas, Pedro, 286
- Curry, Stephen, xxi, 119
- Curtis, David, 86, 97
- Curzon, Gerald, 245
- Cyclic adenosine monophosphate (cyclic
AMP), xxiv, 42–43, 191, 283
- Davies, Brian, xxiii, 87, 89, 97
- Davis, John M., xx, xxi, li–lii, liv, 62, 63, 72, 90,
113–26, 131, 132, 143, 157, 158, 190,
191, 245, 305, 307, 342
as interviewer, 210–20
- Davis, Kenneth, 170
- De Montigny, Claude, xviii, xxii, lii, 121,
127–30
- De Wied, David, 342
- Debroda, David, 270
- DeFraities, Gerry, 348
- Dementia, 72, 95
- DeMet, Edward, 180
- Depression, xv–xvii, xxii, xx–xxiii, xxiv, li, lii, liv,
16, 61, 80, 116, 121, 128–29, 135, 158,
169, 171–73, 174, 192, 275–77, 309,
313, 314, 323–24, 371
atypical, xv, 97
bipolar. *See* Bipolar depression
catecholamine hypothesis, lvi, 191, 327
classification, 95, 329
collaborative studies, 137, 139–40, 144
dopamine in, 180, 245
endocrine aspects, 50, 73–74, 88, 279,
367–74
endogenous, xviii, xxii, xxiii, 329, 330, 362
geriatric, 93, 95, 97
heterogeneity, 142, 174, 330, 362
longitudinal course, liii, 166
major. *See* Major depression
melancholic. *See* Melancholia
neuroendocrine aspects, xvii–xviii, xxiii, li,
lvi, lviii
personality aspects, 196–98
psychotic. *See* Psychotic depression
rating scales, 96–97
treatment-resistant, xxii, 129, 172, 353
winter. *See* Winter depression; Seasonal
affective disorder (SAD)
- Desipramine, xvi, xxi, xxii, xxiii, 135, 183,
199
- Desyrel. *See* Trazodone
- Detre, Thomas, 59, 96, 223, 305, 350
as interviewer, 155–63
- Dewey, Stephen L., 8
- Dexamethasone, xviii, 88

- Dexamethasone suppression test (DST), xxiii–xxiv, 50–51, 53, 73, 88, 93–94, 166–67, 174, 237
and psychotic depression, 122
- Dextroamphetamine, 135, 136
- Di Mascio, Albert, 321
- Diagnosis, psychiatric, 31, 136–37, 144, 198, 274, 340, 361, 362
American vs. European, 74
diagnostic criteria, 18, 76, 98, 122
heterogeneity, 43, 268
- Diagnostic and Statistical Manual, American Psychiatric Association (DSM series), 198, 252, 329, 360–61, 362
criteria/diagnoses, 42, 136, 251, 311
DSM-I, 328
DSM-II, 108, 136, 328
DSM-III, 18, 19, 31, 41, 75, 76, 122, 136–37, 183, 311, 328, 330
DSM-III-R, 350
DSM-III-R, 362
DSM-IV, 32, 97, 183, 311, 360, 362
DSM-IV-R, 76
DSM-V, lv
- Dilman, Vladimir M., 230, 239
- Dimethyltryptamine (DMT), x, xiii, xv, xix
- Discontinuation syndromes, 26–30, 32
- Diskin, Maurice, 125
- Docherty, John, 348
- Dongier, Maurice, 110
- Dopamine (DA), xxii, xxiv, xlix, 6–8, 63, 121, 142, 151, 152, 204, 345–47
agonists, xix, xxi, 7, 8, 49, 118
antagonists, xv, xvii
hypothesis of schizophrenia, xv, 25, 78, 105, 118, 192, 223
in depression, 179, 246
receptors, xx, xxii, 28, 43, 204, 289–90
- Dopaminergic system, 21, 152–53, 180, 183, 224
supersensitivity, 23
- Dratman, Mary, 375
- Drug development, 32, 35, 81, 206, 266, 271, 305, 354
- Drug discovery, 80, 81, 159
- Drug metabolism, lv, 41, 119, 264, 266
- DSM. See Diagnostic and Statistical Manual, American Psychiatric Association DSM series)
- Dunner, David, 249, 253
- Durell, Jack, 60, 62, 157, 190, 223–24, 225
- Eberhart, John C., 60
- Ebstein, Richard, 42, 43
- Eccles, John, 86
- Eiduson, Samuel, 180
- Eisenberg, Leon, 17, 18
- Electroconvulsive therapy (ECT), 3, 89, 97, 136, 248, 321
opposition to, 359, 363
regressive, 60
- Eli Lilly. See Lilly
- Elkes, Joel, 15, 35, 60, 282, 284, 293, 343, 344
- Elmer, Gregory, 82
- Emens, Jon, 215
- Endicott, Jean, 140, 144
- Endocrine psychiatry, xvii–xviii, lvi, 87, 345, 369
- Engel, George, 72, 73
- Epinephrine, xiii, xiv, xvi, xxiv, 42, 193
- Epstein, Richard, 191
- Essman, Walter B., 239
- Estrogen, xxi, 191, 374
- Everett, Guy, 276
- Ewalt, Jack R., 319–20
- Extrapyramidal Symptom Rating Scale (ESRS), 105, 106
- Extrapyramidal symptoms (EPS), xv, 22, 26, 34, 105, 110, 225, 290, 352
- Faedda, Gianni, 28
- Fann, Edward, 125
- Farberow, Norman, 141

- Fawcett, Jan A., xxi, lii, 73, 88, 114, **131–45**, 157, 158, 344, 345
- Feather, Benjamin, 39
- Feinberg, Michael, 96, 166
- Fieve, Ronald, 62
- First rank symptoms, xiii, 74, 75–76, 76
- Fischer, Josef, 20–21
- Fishman, Murray, 121
- Fluoxetine, 30, 108–9, 128, 129, 183, 195, 225, 314, 337, 362
indications, 199
- Fluphenazine, 10, 23, 110–11
- Fluvoxamine, 51, 337
- Flynn, Heather, 170
- Fodor, Stephen P.A., 65
- Food and Drug Administration (FDA), 79, 123, 142, 162, 222, 269, 297, 306, 354
and black box warnings, 52
and lithium, 16, 335
approvals, 32, 109, 255, 305, 338
efficacy review, 306–7
Psychopharmacology Advisory
Committee, 307
- Frank, Gerald, 343
- Frazer, Alan, 28
- Fredrickson, Donald, 343
- Freedman, Daniel X., 59, 63, 163, 178–79, 178–79, 184, 185, 186, 223, 224, 305
- Freedman, Robert, 351
- Freyhan, Fritz, 60
- Friedhoff, Arnold J., xviii, xix, lii–liii, **146–54**, 335
- Frye, Mark, 249
- Functional magnetic resonance imaging (fMRI), 142, 168, 206, 208
- Funkenstein, Daniel, 322
- GABA (γ -aminobutyric acid), xix, 63, 86, 225
and dopamine in schizophrenia, 346–47
- Gabapentin, xxiv, 111–12, 245, 247
- Gaddum, John Henry, x
- Galambos, Robert, 241
- Gallagher, Dorothy, 63
- Galton, Valerie, 372
- Garbutt, James C., 348
- Garmacy, Norman, 74
- Garman, Nicholas, 223
- Garrod, Alfred Baring, xii
- Garver, David, 125
- Geller, Edward, 180
- George, Mark, 246, 249
- Gerard, Ralph, 91
- Gerner, Robert, 246
- Gershon, Elliott, 41, 63, 249, 344
- Gershon, Samuel, xv, xix, lii, 3, 4–6, 62, 85, 86–87, 97, 100, 101, 115, 117, 124, 235, 236, 239, 305, 334, 335
- Gibbons, Robert, 144
- Gillespie, James, 297
- Gillette, James, 263, 271
- Gillin, J. Christian, 62, 63, 193, 344, 350
- Gilman, Alfred G., 283
- Gjessing, Leiv, xii
- Gjessing, Rolv, xii, 252
- Glassman, Alexander, 122
- Glowinski, Jacques, 14
- Goddard, Graham, xxiv, 243
- Gold, Philip W., 159, 211
- Goldstein, Menek, 151, 335
- Goodwin, Frederick K., xxiv, liii, lv, 62, 63, 72, 115, **155–63**, 190, 211, 212, 242, 243, 253, 257, 263, 264, 345, 371
as interviewer, 131–45
- Gorney, Rodney, 189, 190
- Grebb, Jack, 348
- Greden, John F., xxiii, xlvi–lv, 96, **164–75**
as interviewer, 46–55
- Green, Jack Peter, 224
- Green, Richard, 325
- Greenblatt, Milton, 321, 323
- Griffith, John, 5, 6, 7
- Grof, Paul, 252, 253

- Grossman, Moses, 188
Growth hormone (GH), xviii, 47, 49, 193
Guidotti, Alessandro, 327
- Haase, Hans-Joachim, xv
Hadley, Suzanne, 162
Haggerty, J.J., 279
Halaris, Angelos E., xxii–xxiii, liv, **176–86**
Haldol. *See* Haloperidol
Hallett, Mark, 43, 246
Hallucinogens, x, 19, 20, 86, 149
Haloperidol, xv, xix, xx, xxiv, 7, 8, 10, 16, 41, 79, 107, 111, 222
Ham, George, 273, 275, 276, 367
Hamburg, David, 60, 61, 85, 88, 115, 116, 158, 325
Hamer, Dean, 43
Hamilton, Max, 96
Hammond, William, xii
Harley-Mason, J., xii, xiii, xix
Haskett, Reoger, 96
Haskett, Roger, 167
Hastings, Donald, 166
Havens, Lester, 322
Healy, David, 377
 as interviewer, 12–35, 113–26, 316–31, 355–64
Heninger, George, 48, 245, 323
Hiblan, Joseph, 125
Hippius, Hanns, 66, 178, 224
Hirschfeld, Robert, 145
Hoch, Paul, 74
Hoffer, Abram, xiii, xiv
Hofmann, Albert, x
Holcomb, Henry, 80
Hollister, Leo E.
 as interviewer, 84–101, 176–86, 199
Holtzman, Philip S., 224
Hommer, Daniel, 348
Homovanillic acid (HVA), xix, 7, 8, 121, 152, 153, 180, 182, 348, 352
- Hopson, Allen, 319
Horowitz, Martin, 188
Huey, Leighton, 193
Huntington's disease, lvii, 195, 348
Hypothyroidism, xxiv, 203, 275, 366, 367, 369
 subclinical, 279
- Imidazoline, xxiii, 182
Imipramine, xvi–xvii, xx, xxii, xxiii, 59, 87, 131, 134, 135, 163, 172, 232, 275–76, 322, 324, 336, 345
Indalpine, 337, 339
Informed consent, 33, 61, 351
Institutional Review Boards (IRB), 6, 61, 142, 298, 349, 350, 376
Insulin coma therapy, 60
Iproniazid, ix, xi, xv, 356
Iversen, Leslie L., 14
- Jamison, Kay, liii, 162
Janisak, Philip, 126
Janowsky, David S., xxi, lii, liv, 7, 62, 72, 117, 118, 157, **187–99**, 305
 as interviewer, 3–11
Janssen, Paul, 110, 123, 225
Javitt, Daniel, 82
Jimerson, David, 246
Jones, Edward G., 64–65
Jones, Mary Ellen, 282
Judd, Louis, 193
- Kales, Helen, 170
Kalivas, Peter, 280
Kandel, Eric, 319
Kane, Frank, 275
Kane, John, 23, 123
Kaplan, Nathan, 282
Kapur, Shitij, xx, liv, **201–9**
Katz, Martin, 77
Keeler, Martin H., 275
Keller, Martin, 145

- Kelly, Mary, 351
Kendler, Kenneth, 251
Kern, Herbert, 212, 213, 216
Kessing, Lars V., 251
Kety, Seymour, xiii, 14, 15, 17, 18, 60, 76, 147, 224, 324–27
Khan, Arif, 314
Khaunina, Rebecca, 231, 232
Khvelevetskiy (Professor), 229, 230, 232, 239
Kindling, xxiv, 111, 243–44, 250, 256, 257
Kirkpatrick, Brian, 79, 80
Kiseleva, Irina, 231
Klawans, Harold, 23
Klein, Donald F., lii, 3, 98, 108, 116, 159, 271, 342
Klein, Ehud, 42
Klerman, Gerald L., xvi, 16, 159, 235, 323, 324, 328, 329
Kline, Nathan S., 335
Klüver, Heinrich, x
Knauer, Alwyn, x
Knoll, Joseph, 235
Koenig, James, 82
Kopin, Irwin J., xx, 14, 15, 20, 115, 116, 235, 245, 264, 326
Koslow, Stephen H.
 as interviewer, 221–27
Kotin, Joel, 243, 257
Kraepelin, Emil, x, 51, 77, 81, 250–51
Kraepelinian tradition, 18, 76, 99, 158, 166
 and neo-Kraepelinian movement, 18–19, 31
Kramer, Morton, 77
Kramlinger, Keith, 249
Krieger, Dorothy, 48
Kripke, Daniel, 216
Krishnan, Ranga, 92, 95, 96
Kriss, Anthony, 319
Kuntzman, Ronald, 297
Kupfer, David, 62, 96, 190, 245
Kurland, Albert A., 82
Lahti, Adrienne, 80
Lal, Harbans, 49
Lamotrigine, xxiv, 244–45, 247, 248
Lange, Carl, xii
Lange, Fritz, xii
Langer, Salomon Z., 66
Langfeldt, Gabriel, 75
Lapin, Izyaslav (Slava), xxi, lv, 230–35, 239
Lasagna, Louis, 104, 300
L-DOPA (levo-dihydroxyphenylalanine), liii, 21, 89, 158, 191, 233, 346
Lebedev, Boris, 231
Leber, Paul, 123
Lehmann, François, 103
Lehmann, Heinz E., 21, 103, 104, 105, 129–30
Lerer, Bernard, 42, 43, 130
Leshner, Allen, 160
Lewis, David, 64
Lewy, Alfred J., xxiv, liv, **210–20**, 371
Liberzon, Istaël, 170
Lidz, Theodore, 47
Lieberman, Jeffrey, 237
Lilly, Ivi, 124, 137, 265, 266, 267, 268, 270, 271
 and fluoxetine, 128, 129
Lin, T.-Y., 77
Linnoila, Mark, 160
Lipton, Morris, 155, 156, 163, 275, 277, 279
Lithium, xi, xii, xxi, xxii, xxiv, lii, lvii, 16, 62, 67, 73, 87, 99–101, 107, 115, 124, 135, 334–35, 253, 323, 334–35, 338, 345, 356, 370, 372
 antidepressant potentiation, xxii, 129
 clinics, 91
 discontinuation issues, 27–29
 in add-on studies, xxiv, 41–42
 mechanism of action, 270
London, Edythe, 8
Lithium, 265
Lysergic acid diethylamide (LSD-25), x, 346

- Maas, James, lii, 60, 72, 133, 134, 143, 156
- MacLean, Paul, 326, 330
- Magnetic resonance imaging (MRI), 95, 106, 268, 308, 349
- Maintenance treatment, 29, 120, 248
discontinuation issues, 27
efficacy, 124–25
- Major depression, xx, liii, 25, 31, 109, 128, 137, 309, 358
as artefact, 361–62
heterogeneity, 183, 328
- Malas, Kenneth, 348
- Mandell, Arnold, 189
- Mania, xxi, xxiv, 16, 99, 107, 158, 191, 194, 244, 250, 253, 323, 329, 347, 353, 374
adrenergic-cholinergic hypothesis, 192
psychotic, 27, 247
- Manic-depressive illness, xii, xvi, xvii, xxi, xxiv, liii, 132, 139, 162, 191, 211, 250–51, 264
natural course, 250
rapid cycling, 249
severe depression as, 135
vs. schizophrenia, 16
- Marder, Stephen, 82, 180, 348, 377
- Markey, S.P., 211, 212
- Marsden, David, 22, 27
- Martin, F. Ian R. (Skip), 87, 98
- Mason, John, 48
- Matussek, Norbert, 177–78, 179, 186
- May, Philip, 180
- McEwen, Charles M., 300, 301
- McIntyre, Iain M., 236
- McKinney, William, 275
- McLeod, William, xxiii
- Mead Johnson, 304–6, 309, 310, 311, 312
- Melancholia, 93, 95, 97, 183, 367
- Melatonin, xxii, xxiv, lv, 211–14, 215–19, 235–36, 238
- Meltzer, Herbert Y., xviii, xx, liv–lv, 190, **221–27**
- Mescaline, x, xix, 149
- Meta-analysis, xxi, 120, 122, 123
- Methylphenidate, xxi, 7, 8, 49, 118, 192, 193, 199
- Meyer, Adolf, 14, 16
- Meyer, John, 38
- Meyersburg, Arnold, 243
- Mezzich, Juan, 203
- MHPG (3-methoxy-4-hydroxy phenylglycol), xx, xxi, xxii, 121, 133, 134–35, 143, 180–82, 345, 349, 352
- Michael, Roger, 263
- Miller, James, 91
- Miller, Neil, 39, 40
- Mitchell, Jerry, 263
- Model psychosis, ix–xi, xlix, 178
- Monoamine oxidase (MAO), 39–40, 300, 301, 303, 356
- Monoamine oxidase A (MAO-A) inhibitors, xxii, 236
- Monoamine oxidase inhibitors (MAOI), ix, xv, xvii, xxi, lvi, lvii, 16, 30, 108, 135, 136, 290, 301, 302, 303–4, 313, 322, 323–24, 335, 337
efficacy, xx, 306–7
- Monoamine precursors, 85, 89
- Montgomery, Stuart, 251
- Mood disorders, 98, *See* Affective disorders
- Mood stabilizers, 37, 112, 244, 248, 254
- Moreau de Tours, Jacques-Joseph, x
- Motto, Jerome, 188
- Mountcastle, Vernon, 14
- Mowbray, Robert, 89, 98
- Murphy, Dennis, 41, 62, 63, 72, 73, 116, 156, 157, 191, 236, 344, 345
- Muscarinic receptors, xvi, xxii, 286, 288
- Myers, Richard, 65
- Nardil. *See* Phenelzine

- Nathans, Daniel, 282–83
- National Alliance for Research on Schizophrenia and Depression (NARSAD), 67, 207
- National Institute of Mental Health (NIMH), I, li, 39, 41, 57, 59, 60, 88, 124, 148, 157, 245, 328, 348, 350
- ambivalence toward antipsychotics, 125
- Biological Psychiatry Branch, Iv, 62, 245, 256, 344
- collaborative projects, 269
- funding, 64, 82, 83, 168, 237, 255, 262, 310
- International Pilot Study of Schizophrenia, 77
- Intramural Research Program, liii, Iv, 63, 71, 72, 77, 133, 159, 263, 371
- model, 41
- Pharmacology Research Associate Trainee (PRAT) program, 262, 263
- research training, 4, 131–33, 165, 190, 211, 223, 242, 299, 131–33, 343
- National Institute on Drug Abuse (NIDA), 39, 62–63, 159
- National Institutes of Health (NIH), 14–15, 58, 59, 115, 119, 120, 156, 169, 208, 213, 266, 283–85
- Brodie laboratory, 297–98
- Clinical Center, 131, 220, 300, 346
- funding, 285, 370
- research environment, 157
- Negative symptoms, xix, xlix, 7, 75, 76, 77, 78–81, 83, 110, 346, 347, 348, 352
- primary vs. secondary, 78–81
- Nemeroff, Charles, 170, 173, 278, 279, 287, 291
- Neuroendocrine research, xviii, xxiii, 47, 48, 50, 87, 88–90, 93, 96, 166, 193, 197
- Neuroimaging, 34, 77, 82
- Neuroleptic malignant syndrome (NMS), 22, 26
- Neuroleptics, xiv, xvi, xix–xx, xxi, li, 6, 7, 8, 10, 16, 27, 31, 67, 152, 247, 289, 345, 356
- atypical, xix, xx, 103
- dosage issues, xv, xix, 23, 25, 26
- Neuroscience, I, li, 14–15, 35, 64, 65, 68, 82, 127, 142, 166, 182, 204, 241, 375, 377
- and de-stigmatization of mental illness, 208
- basic, liii, 35
- Neurotensin, xxii, xxiii, 287, 291, 292
- Neurotransmitter(s), ix, 19, 20, 49, 60, 67, 86, 87, 106, 128, 142, 172, 286, 327
- endogenous, 21
- interaction, 267, 338
- receptors, 35, 267
- Newsome, David, 212
- Neylan, Thomas, 350
- Nicotinic acid, xi, xiii, xiv, 107
- Nies, Alexander, 302, 308, 309
- Nimodipine, xxiv, 248, 253–54, 253–54
- Ninan, Philip, 348
- Nirenberg, Marshall, 283, 285
- NMDA (N-methyl-D-aspartic acid) receptor, 64, 82, 142, 224
- Nobel Prize, 42, 86, 211, 282, 283
- Nofzinger, Eric, 350
- Noradrenergic, 158, 235, 276, 279
- hypothesis of depression, 177, 264, 336
- properties, xvi, 234
- Norepinephrine (NE), xv, xvi–xvii, xxii, 47, 50, 116, 119, 135, 142, 179, 233, 327, 336, 356
- and depression, xxi, 25, 67, 135, 245
- metabolism, lvii, 265
- Normetanephrine, xii, xv, xx, 325
- Nosology, li, 18, 140, 198, 328, 361
- Nuller, Yuri, 231
- Oates, John, 192
- Okazaki, Haruo, 287
- Okuma, Teruo, xxiv, 244

- Olanzapine, xx, 124, 221, 225, 237, 270
Olson, Stephen C., 78
Ormankline, William, 317
Osmond, Humphrey Fortescue, xiii, xiv
Ostrow, David, 125
Overstreet, David, 194
Owens, Michael, 278
Oxenkrug, Gregory F., xxi–xxii, lv, 52, **228–39**
- Panic disorder, 108, 112, 116, 125, 141
Pardes, Herbert, 159
Parkinson's disease, 7, 79, 105, 288, 291
Parkinsonism, liii, 105
 drug associated, 22, 291
Parnate. *See* Tranylcypromine
Pathophysiology, ix, 19, 20, 21, 25, 55, 66, 87
 of depression, xxv, 286, 335
 of schizophrenia, xv, li, 75, 78
 of tardive dyskinesia, 21, 22, 23
Paul, Michael, 191
Paul, Steven M., 159, 265
Pavlov, Ivan Petrovich, 231, 232
Pazzaglia, Peggy, 184, 253
Pedersen, Cort, 278
Perlin, Seymour, 343
Personality disorders, 33, 197, 198, 358
Pert, Agu, 344
Pert, Candace, 63, 344
Pfann, Edward, 275
Pharmaceutical industry, lvii, 30, 32, 207, 268, 289, 292, 313, 352, 353
 collaborations, 207, 265, 269, 377
 development issues, 32
 quality of research, 309
Phencyclidine (PCP), 224
Phenelzine, xx, 303, 304, 306–7, 309, 312, 322, 323, 324
Physostigmine, xxi, lii, 125, 173, 195, 197, 198
 mood effects, 117, 192–93
Piletz, John, 182
Pimozide, 104, 349, 350
Pink spot, xii–xiii, xix, liii, 149, 150
Placebo, xvi, 34, 41, 44, 53–54, 117, 276, 349
 non-responders, xxiii, 50–51
Placebo-controlled trials, 27, 62, 104, 105, 109, 245, 299, 306, 307, 312
Pletscher, Alfred, ix, 235
Plokker, Johannes H., 342
Plotnikoff, Nicholas, 278
Pochin, Eric, 366
Pollin, William, 39, 157
Pond, Desmond, 367
Pope, Harrison, 111
Positive and Negative Syndrome Scale (PANSS), 106, 124
Positive symptoms, xix, 7, 55, 78, 110, 269, 347
Positron emission tomography (PET), xx, liv, 8, 10, 34, 64, 80, 106, 118, 142, 204, 205, 206, 255, 266, 268, 289, 308, 369, 375
Post traumatic stress disorder (PTSD), 10, 349, 350, 353
Post, Felix, 95
Post, Robert M., xxiv, lv, 41, 63, 145, 156, 184, **240–59**, 293, 344
Potkin, Stephen, 64
Potter, William Z., xxii, lv–lvi, 137, **260–72**
Prakhie, Irina, 231, 232
Prange, Arthur J., xviii, xxiii, lvi, 155, **273–80**, 367–68
Premenstrual tension, xxi, 189, 190, 191, 199
 aldosterone-angiotension hypothesis, 195
Prien, Robert, 255
Progesterone, xxi, 191
Prozac. *See* Fluoxetine
Psychoendocrinology. *See* Endocrine psychiatry
Psychoses, xi, 7, 16, 79, 80, 89, 119, 152, 203, 205, 225, 318
 dopaminergic, 7, 118

- drug-induced, 4, 5, 72
 endogenous, xii
 excited, xxiv, 41, 42
 experimental. *See* Model psychosis
 in schizophrenia, 221–22
 measurement, 75, 106
 supersensitivity. *See* Supersensitivity psychosis
 vs. “schizophrenia”, 32, 106
 Psychotic depression, 74, 122, 132, 183, 248, 322, 328
 Psychotoxins, xi–xiv, xix
 Psychotropic drugs, ix, xi, l, 24, 26, 30, 43, 49, 105, 114, 116, 148, 274, 287, 288, 313, 314, 315, 378
 development, xix, lvii
 indications, 31, 112
 mode of action, lviii, 265, 288
 Public Health Service. *See* US Public Health Service
 Purpura, Dominick, 359

 Quarton, Gardner, 91
 Quastel, Juda Hirsch, x

 Radin, Norman, 91
 Rapid cycling, xxiv, 100, 248, 249, 252, 254, 372, 374
 and treatment resistance, 249
 Rapid eye movement (REM) sleep, xxi, 59, 73, 241
 Rapoport, Anatol, 91
 Rapoport, Judith Livant, 63, 159, 319, 344
 Rating scales, xliv, 60, 61, 66, 79, 86, 88, 96, 104, 106, 124
 vs. behavior, 205
 Ray, Oakley, 40, 185
 Redlich, Fritz, 47, 134
 Reichlin, Seymour, 48
 Reiser, Morton, 47
 Reiss, Max, xvii

 Renspoon, Charles, 323
 Repetitive transcranial magnetic stimulation (rTMS), 173, 246, 255, 256
 Research Diagnostic Criteria (RDC), 136, 137, 139, 330
 Reserpine, xi, xii, xvi, 22, 59, 178, 233–34, 235
 depressive effects, ix, 115
 vs. chlorpromazine, 274, 277
 Rezvani, Amir, 194
 Richelson, Elliott, xxii, lvi, **281–94**
 Rickels, Karl, 314
 Risch, Craig, 193
 Risperidone, xix, 109, 110, 123–24, 221, 225, 237
 Ritalin. *See* Methylphenidate
 Robins, Eli, 18, 328, 330
 Robinson, Donald S., xx, lvi, **295–315**
 Robinson, Terry, 8
 Romano, John, 71, 131
 Rose, Robert, 48
 Rosenau, Werner, 189
 Rosenbaum, Jerrold F., 108
 Rosenblatt, Jack, 348
 Ross, Andrée, 105
 Roth, Robert H., 224
 Rubin, Robert T., 189, 195
 Rümke, Henricus C., 341, 356
 Rush, Benjamin, 51
 Rush, Craig, 184

 Sachar, Edward J., 73, 88, 89
 Sack, David, 158
 Sack, Robert L., 212, 213, 220
 Salbutamol, xxiv
 SAME (S-adenosylmethionine), 19–20
 Samsonova, Maya, 231, 232, 234
 Sandler, Merton, 235
 Sartorius, Norman, 77
 Satel, Sally, 8
 Satir, Virginia, 343, 344

- Schanberg, Saul, 235
- Schatzberg, Alan, 169, 173
- Schelkunov, Eugene, 231, 232
- Schiele, Bert, 166
- Schildkraut, Joseph J., xx, li, lvi–lvii, 61, 114, 117, 119, 191, 245, **316–31**
- Schizoaffective disorder, xxiv, 31, 41, 42, 125, 140
- Schizophrenia, xiv–xv, xvii, xviii–xx, xxi, xlix, l, li, liv, lv, lviii, 7–10, 39–40, 59, 63, 64, 67, 82, 99, 106, 111, 148–53, 156, 203, 221–22, 223–26, 269, 313, 334, 350, 345–50, 361
- deficit vs. non-deficit, xviii–xix, 77, 79–80, 83
- dopamine hypothesis, 105, 118, 152
- heterogeneity, xix, 77, 82, 125, 142
- neurodevelopmental hypothesis, 123
- nuclear vs. broad-based, 74–76
- overdiagnosis in US, 16, 74, 77, 114
- treatment refractory, xx, 10, 110
- Type I/Type II distinction, 7, 78, 347
- vs. drug-induced psychoses, 4–5
- Schneider, Kurt, xiii, 75, 76
- Schooler, Nina, 82
- Schou, Mogens, 62, 99, 101, 124, 253, 370
- Schultz, Charles, 348
- Schuster, Robert, 121, 123, 184
- Seasonal affective disorder (SAD), xxiv, 212, 213, 219, 371, 379
- Sedvall, Göran, 14
- Seeman, Philip, xx, 289
- Seiber, Larry, 198
- Seiden, Lewis, 211
- Selbach, Helmut, xvi
- Selective norepinephrine reuptake inhibitors, 265, 267
- Selective serotonin reuptake inhibitors (SSRI), xvii, xxii, xxiii, 128, 136, 171, 265, 267, 291, 314, 364
- as anxiolytics, 31, 338
- as blockbuster drugs, 313, 337
- in PMDD, 125
- Semrad, Elvin, 17, 318, 320–21, 322
- Serotonergic system, xvi, xvii, xxii, 107, 108, 368
- hypothesis of depression, 129, 193, 264, 336
- Serotonin (5HT), ix, xvi, xvii, xxii, lii, lv, 25, 50, 107, 116, 119, 121, 128, 135, 142, 179, 234, 233–35, 235, 238, 245, 265, 336–37, 356, 364
- and schizophrenia, 224–25
- and suicide, 362
- inhibition, x, xv, xxii
- metabolism, xxii, 265, 297, 299
- receptors, xvii, xx, 225, 271, 290, 311, 312
- vs. norepinephrine (NE) advocates, 277
- Serotonin-norepinephrine
- balance, 236
- metabolism, 265
- reuptake inhibitors (SNRI), 124, 171, 173
- Sertindole, xix, 221
- Shader, Richard, 323
- Shannon, James, 58
- Shneidman, Edwin S., 141
- Shopsin, Baron, xxii, lvii, **332–40**
- Shore, Parkhurst A., ix
- Shrivastava, Ram, 51
- Siever, Larry, 181
- Sigg, Ernest, xvi
- Silverman, Albert J., 90, 91, 92, 167, 168
- Siris, Samuel, 348
- Sjoerdsma, Albert, 299, 300, 302
- Slater, Eliot, 327
- Sleep studies, 350, 351, 358
- Smith, Hamilton O., 282
- Smith, James, 23
- Smith, Jerry, 242
- Smythies, John, xiii
- Snyder, Solomon H., 14, 63, 118, 126, 179, 281–82, 283, 286, 289, 293, 343, 348

- Solomon, Harry S., 319
Sourkes, Theodore, 107
Spector, Sydney, 297
Speer, Andrew, 255
Spiegel, John, 317
Spitzer, Robert L., 140
St. Germain, Donald, 372
Stahl, Stephen, 223
Steiner, Meir, 96
Stephens, Joseph, 74, 343
Sterlin, Helm, 76
Stern, Warren, 179
Sternberg, David, 348
Stevens, Joseph, 343
Stoddard, Frederick, 245
Stokes, Peter E., 88
Stoll, Albert, x
Stramentinoli, Giorgio, xix, 19
Strauss, John, 73, 74, 76
Suicide/suicidality, xx, xxi, lii, 29, 52, 51–52, 55, 61, 69, 97, 132, 136, 137, 139, 140–42, 171, 362
 and hyperadrenal function, 132–33, 134–35
Sullivan, Louis, 160, 161
Sulser, Fridolin, xvi, 42, 192, 267
Summer, Francis, 126
Supersensitivity psychosis, xix, 23, 106, 111–12
Suppes, Trisha, 26, 27
Sutherland, Earl, 42
Szára, Stephen, x
- T3. See Triiodothyronine (T3)
Tacrine, 85, 86
Tallalay, Paul, 282, 284
Tallman, John, 63, 344
Tamminga, Carol, 80, 346, 348
Tardive dyskinesia (TD), 19, 21–23, 26, 106, 195, 248
Tarsy, Daniel, 22, 23
Tétréault, Léon, 104, 105
Thorazine. See Chlorpromazine
Thyroid hormones, xxiii–xxiv, lvi, 275–76, 368–69, 370, 371, 373
Thyroid stimulating hormone (TSH), xviii, 277, 368, 372, 373
Thyrotropin releasing hormone (TRH), xviii, xxiii, 246, 277, 278–79, 373
Thyroxine (T4), xii, xxiv, 279, 366, 368, 369, 371, 372, 373–75
Tinden, Bridget, 170
Tohen, Mauricio, 32
Tondo, Leonardo, 28, 29
Tone, Andrea, 332–40
 as interviewer, 102–12, 127–30, 365–81
Torbery, Lucas, 148
Tranlycypromine, xxii, 336–37
Trazodone, lvi, 172, 304–6
Tricyclic antidepressants (TCA), xxi, xxii, xxv, 16, 122, 129, 171, 172, 171–73, 233, 335, 368
 augmentation trials, 136
 blood levels, 307–8
 mode of action, xxii, 265, 337
 vs SSRI, 314
Tridimensional personality scale/questionnaire (TPQ), 43, 196, 199
Triiodothyronine (T3), 276, 277, 279, 366, 368, 371
Trimipramine, xvii, 290
Tryptamine, xiii, xx, 19, 302
Tryptophan, xiii, xv, xvii, 89, 106–7, 108, 128, 234, 236, 277, 279
- Udenfriend, Sidney, 297, 299
Uhlenhuth, Eberhard H. (Uhli), 16, 184
Umstead, John, 276
US Public Health Service, 15, 190, 242, 263
 Career Development program, 132
Usdin, Earl, 64, 68

- Vagus nerve stimulation (VNS), 173
- Vaillant, George, 74, 319
- Valproate, 44, 111, 244, 248
- Van Kammen, Daniel P., xix, lvii, **341–54**
- Van Praag, Herman M., xxii, lviii, 245, 336, 342, **355–64**
- Van Putten, Theodore, 180
- Vanylmandelic acid (VMA), xii, xx, 324, 323–25
- Venlafaxine, 173, 290, 291, 313
- Verapamil, 194, 253–54, 254
- Vestergaard, Per, 253
- Veterans Administration (VA), 141, 226, 349, 350, 351
hospitals, 10, 50, 52, 180, 236, 353
- Viguera, Adele, 29
- Vogel, Michael, 82
- Wasserman, Eric, 246
- Waters, Daniel, 348
- Watkins, Jeff, 86
- Watson, Stanley J., 65, 168, 170, 171
- Wehr, Thomas, 159, 211, 212, 216
- Weinberger, Daniel, 159
- Weinshilboum, Richard, 284
- Weiss, Robert, 370
- Weiss, Susan, 256
- Weissman, Myrna, 249
- Wellbutrin. See Bupropion
- Wender, Paul, 319
- Wexler, David, 148
- White, Robert, 317
- Whitehorn, John, 14
- Whybrow, Peter C., xxiii–xxiv, lviii, 275, 277, 279, **365–81**
- Wig, Narendra N., 202, 203
- Wilson, Ian, 275, 277
- Wing, John, 74, 77
- Winkelman, William, 21
- Winokur, George, 97, 144
- Winter depression, xxiv, 213–14, 216, 219, 237, 371
- Wolkin, Adam, 8
- Woodruff, James Edward, 170
- Woolverton, William L., 184
- World Health Organization (WHO), xvi, 73, 174, 202, 231
collaborative research programs, 66
International Pilot Study of Schizophrenia (IPSS), 71, 74, 77
- Wortis, Samuel Bernard, 148
- Wurtman, Richard J., xx, 14, 21, 126, 300
- Wyatt, Richard, 39–40, 190, 351
- Wynne, Lyman, 60, 63, 73, 74, 77, 115, 156, 157, 325, 343, 344
- Yalom, Irving, 344
- Young, Elizabeth, 96, 168, 170
- Young, Simon, 107
- Younkin, Steven, 294
- Yuwilier, Arthur, 180
- Zajacks, John, 143
- Zimelidine, xvii, xxii, 234, 265, 337
- Ziprasidone, xix, 221, 225
- Zis, Thanasis, 96
- Zohar, Joseph, 42
- Zung, William, 96

The College

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.

The Series

The 10 volumes in this series record a fifty year history of neuropsychopharmacology related by 213 pioneer clinical, academic, industrial and basic scientists in videotaped interviews, conducted by 66 colleagues between 1994 and 2008. These volumes include a preface by the series editor placing its contents in an historical context and linking each volume to the next. Each volume is dedicated to a former President of the ACNP and edited by a distinguished historian or Fellow of the College who provides an introduction to its themes and a biography of each scientist's career. The series provides insights into a half century of discovery and innovation with its rewards and disappointments, progress and setbacks, including future expectations and hopes for the field as a whole and the ACNP as an organization.

In This Volume

In the first four volumes in this series interviewees reflect on their contributions to the detection of the effects of psychotropic drugs on behavioral measures (Volume One: Starting Up), on cerebral electrical activity (Volume Two: Neurophysiology), on molecular and sub-molecular brain structures (Volume Three: Neuropharmacology), and on mental pathology (Volume Four: Psychopharmacology). In this volume (Volume Five: Neuropsychopharmacology) the emphasis shifts and interviewees talk about their contributions to studying the pathophysiology of mental disorders with the aid of psychotropic drugs. The transcripts of Volume Five show how the introduction of effective psychotropic drugs in treatment together with suitable instrumentation to study their mode of action in the brain, lead to the birth of neuropsychopharmacology, and the transformation of thinking in psychiatry from psychological to biological. Dedicated to the memory of Leo E. Hollister, President ACNP, 1974, Volume Five is edited by Samuel Gershon, one of the pioneers of neuropsychopharmacology. Gershon's research was instrumental in the introduction of lithium in psychiatry and in opening the path for the development of cognitive enhancers.