

# An Oral History Of Neuropsychopharmacology

# The First Fifty Years Peer Interviews

SERIES EDITED BY: Thomas A. Ban



EDITED BY: Barry Blackwell

American College of Neuropsychopharmacology

# AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY

## THE FIRST FIFTY YEARS

**Peer Interviews** 

**Volume Seven: Special Areas** 

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

#### Barry Blackwell (volume editor) VOLUME 7: Special Areas

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## AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY THE FIRST FIFTY YEARS

**Peer Interviews** 

Edited by Thomas A. Ban

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#### VOLUME 7

#### SPECIAL AREAS

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VOLUME 7

**Barry Blackwell** 

SPECIAL AREAS "Desiderata"

Preface Thomas A. Ban

Dedicated to the Memory of Louis Lasagna, President ACNP, 1980

### PREFACE Thomas A. Ban

Volume Seven, Special Areas, is dedicated to contributions to child psychiatry, gerontopsychiatry, psychiatric diagnosis and pharmacokinetics. The volume also accommodates transcripts which could not be included in the other volumes. Hence it received the subtitle Desidarata from the volume editor. (See, Introduction.)

In Volume Seven, as in all other volumes in this series, interviewees reflect on their contributions to research in their respective field of inquiry.\* But unlike the first six volumes, some of the contributions presented in this volume are only indirectly related to neuropsychopharmacological research.

#### **Child Psychiatry**

In the early years of the 20<sup>th</sup> century a wide variety of disciplines from pediatrics to psychiatry, including education, criminology, psychology, psychoanalysis, and child guidance, were concerned with the health, and welfare of children.<sup>1</sup> It was only the mid-1920s that August Homburger<sup>2</sup> set the foundation of a subspecialty of psychiatry that was to become known as Child Psychiatry.

The term Child Psychiatry ("Kinder Psychiatrie") was first used in the early 1930s by Moritz Tramer in the name of his journal, Zeitschrift für Kinderpsychiatrie. The term was widely diffused in the English speaking world through the title of Leo Kanner's Child Psychiatry, published in 1935.<sup>3</sup> It was about the same time that the first psychiatric units for children, founded by Eugen Bleuler in Zurich, August Homburger in Heidelberg and Adolf Meyer in Baltimore, were opened.<sup>4</sup>

Developments which lead to Child Psychiatry began in the 1860s and '70s with the separation of three genetically-distinct diagnostic populations within mental deficiency: (1) the Laurence-Moon-Biedl syndrome;<sup>5</sup> (2) the Langdon- Down syndrome or mongolism;<sup>6,7,8</sup> and (3) Tay-Sachs disease, or familial amaurotic idiocy.<sup>9,10</sup> Then, in 1934, the same year as the term "child psychiatry" was introduced, Fölling discovered, "phenylketonuria," an inborn error of metabolism,<sup>11</sup> by detecting phenylpyruvic acid in the urine in a group of children with severe mental deficiency.<sup>12</sup> Three years later, in 1937, Penrose

<sup>\*</sup> The -different fields of inquiry in the first six volumes are: (1) Behavioral pharmacology, (2) Neurophysiology & Brain imaging, (3) Neuropharmacology, (4) Psychopharmacology, (5) Neuropsychophramacology) and (6) Addiction.

and Quastel demonstrated the absence of enzymes splitting phenylalanine, in phenylketonuric children.<sup>13</sup> By the end of the 1930s Jervis had shown that phenylketonuria runs in families; he implicated an autosomal recessive gene in the pathogenesis of the disease.<sup>14</sup> The first report on successful treatment of phenylketonuria with a diet low in phenylalanine was published over 15 years later, in 1955, by Woolf, Griffiths and Moncrieff.<sup>15</sup>

A major impetus for the development of child psychiatry was the encephalitis lethargica epidemic between 1917 and the late 1920s<sup>16</sup> with the subsequent identification of three mental syndromes (diseases) of childhood. The first, "hyperkinetic disease" ("hyperkinetische Erkrankung") was described by Kramer and Polnow in 1932<sup>17</sup>; the second, "elective mutism" was discovered in 1934 by Tramer<sup>18</sup>; and the third, "infantile autism" was introduced by Kanner in 1943.<sup>19,20</sup>

Interest in pharmacotherapy in child psychiatry was triggered by the publication of Charles Bradley's paper in 1938 on the behavior of children receiving Benzedrine (amphetamins slfate)<sup>21</sup> and his subsequent report with Bowen on improvement in school performance of children receiving amphetamine sulfate in 1940.<sup>22</sup> In the same year Cutler, Little and Strauss<sup>23</sup> published the findings of their controlled study with Benzedrine in mentally deficient children. By the early 1950s the amphetamines found their place in the treatment of hyperkinetic children. <sup>24,25</sup> There were also other drugs, e.g., diphenylhydantoin, an anticonvulsant,<sup>26,27,28</sup> diphenhydramine, an antihistamine,<sup>29</sup> used in child psychiatry in the 1940s.

The first reports on chlorpromazine in child psychiatry in the United States were published in 1955 by Bein and Herold,<sup>30</sup> and Gatski.<sup>31</sup> It was also in 1955 that the first papers appeared on the use of myanesin<sup>32</sup> and glutamic acid<sup>33</sup> in children. By the end of the 1950s there were also reports on findings with reserpine<sup>34</sup> and meprobamate.<sup>35</sup>. The first book on research in pediatric psychopharmacology was published in 1959.<sup>36</sup>

#### **Geriatric Psychiatry**

While individual life span has remained unchanged, average life expectancy has increased at least four-fold over the course of recorded history.<sup>37</sup> There was an unprecedented rapid increase in life-expectancy during the first half of the 20<sup>th</sup> century; from 1900 to 1960 the percentage of old people tripled, reaching 13% of the total population of Europe and 10% of North America.<sup>38</sup> The increase in individuals aged 65 years or older has directed attention to gerontology, a term introduced in 1907 by the Russian medical scientist Eli Metschnikoff, the scientific study of the aging process,<sup>39</sup> and to geriatrics, a term introduced in 1914 by the American pediatrician, Ignatz Nascher, the medical specialty concerned with the study, prevention and treatment of pathologic conditions in the aged.<sup>40</sup> Gerontology deals with primary aging or senescence, which is a biologic process rooted in heredity; geriatrics deals with secondary aging or senility, i.e., defects and disabilities resulting from trauma, including disease.<sup>41</sup>

Psychiatric morbidity is high in the aged. The three-fold increase in the number of people 65 or over in the United States was associated with a nine-fold increase in admissions to mental hospitals from this age group.<sup>42</sup> A study in Baltimore from the 1960s showed that 12% of the non-institutionalized geriatric population suffered from mental illness.<sup>43</sup> In San Franciso, the figure was 15%.<sup>44</sup> It was the high prevalence of psychiatric morbidity in old people that created the need for the geropsychiatry, or psychogeriatrics.<sup>45</sup>

Developments which lead to psychogeriatrics began in the 1870s with Krafft-Ebing's introduction of the term "dementia senilis" and with his separation of senile dementia from the other organic dementias.<sup>46</sup> It continued in the 1880s with the description of what was to become known as the Wernicke – Korsakoff amnestic syndrome<sup>47,48</sup> and the separation of the dysmnesias from the dementias. In 1892 the disease that was to bear his name was described by Pick<sup>49</sup> and separated from senile dementia. In 1899 Binswanger coined the term, "pre-senile dementia"<sup>50</sup> that was to include Pick's disease, Alzheimer's disease, described in 1907,<sup>51</sup> Jacob – Creutzfeld's disease,<sup>52,53</sup> described in 1920 and '21, and several other conditions.

In the mid-1930s, a possible relationship between Alzheimer's disease and senile conditions was raised by Rothschild and Kasanin<sup>54</sup>; and in the mid-1940s Jervis suggested that atrophy of nerve cells and fibers with some glial reaction is the common basic process of the senile and presenile dementias.<sup>55</sup> Yet, it was also in the mid 1940s that Rothschild described the differential clinical features of senile and arteriosclerotic (referred to as multiinfarct today<sup>56</sup>) "psychoses".<sup>57</sup>

By the 1950s it was recognized that psychiatric diseases in the aged are not restricted to the dementias and dysmnesias A survey in the UK indicated that the in 30 to and 50 percent of patients admitted to mental hospitals over 60 years of age, the clinical picture was dominated by depressive clinical features.<sup>58</sup> Martin Roth and his associates found little overlap in symptomatology between these patients and patients with organic degenerative diseases. They also demonstrated that only about three percent of them developed dementia in two to three years.<sup>59</sup>

In Kraepelin's estimation about 6 to 7 percent of the first episode of manic-depressive psychosis occurs at age 60 or later.<sup>60</sup> A similar figure was reported in 1952 by Stenstedt.<sup>61</sup>. "Late paraphrenia", another distinct diagnostic population in the aged, was identified in 1957 by Roth.<sup>62</sup> It differs from "late schizophrenia" by firmly systematized delusions.

Late schizophrenia was first recognized in 1911 by Eugen Bleuler.<sup>63</sup> In 1943, Manfred Bleuler found that in 15 to 17 percent of patients, schizophrenia, starts at age 40 or later. He referred to this population as "late on-set schizophrenia". In Bleuler's estimation in 4 percent of patients with late schizophrenia the onset of the disease starts at age 60 or later.<sup>64</sup> Frank Fish, in the early 1960, found that in 1 percent of patients with schizophrenia the disease starts at age 69 or later.<sup>65</sup>

In the late 1940s deWardener and Lennox found that Vitamin B1 insufficiency induced loss of memory for recent events, disorientation, and confabulations, a clinical picture similar to that seen in the Wernicke-Korsakoff syndrome. They also demonstrated that thiamine administration reversed the memory disturbance.<sup>66</sup>

In the 1950s, V. A. Kral separated "benign senescent forgetfulness" from "malignant senescent forgetfulness".<sup>67,68,69,70</sup> He also reported on favorable effects with fluoxymesterone, in "benign senescent forgetfulness".<sup>71,72</sup>

Stimulated by Holger Hyden's discovery of the role of ribonucleic acid (RNA) in learning<sup>73</sup> Ewen Cameron, administered yeast RNA to patients with senile and arteriosclerotic dementia in the late 1950s.<sup>74</sup> In spite of his initial favorable impression<sup>75</sup> and of the supportive findings of Leonard Cook in animal pharmacological research,<sup>76</sup> later studies by Cameron and his assiociates with labeled RNA revealed that RNA molecules don't enter the cerebral neurons. (See, Cook Volume 1.) They could only be found in the cells of the ependyma and plexus choroideus.<sup>77</sup>

During the 1950s a wide variety of drugs - including gonadal hormones, i.e., estrogen and testosterone alone and in various combinations,<sup>78,79,80,81</sup> psychostimulants, such as pentylenetetrazol,<sup>82,83</sup> pipradrol,<sup>84,85,86,87</sup> and methylphenidate,<sup>88,89,90,91</sup> vasodilators, e.g., isoxsuprine,<sup>92;93</sup> and drugs with an effect on cerebral metabolism, e.g., Hydergine, a hydrogenetaed alkaloid of ergot<sup>94,95,96</sup> - were employed in the treatment of psychiatric diseases in the aged. Prescription practices in elderly patients began to shift in the middle of the decade with the introduction of psychotropic drugs. The first reports on the effects of chlorpromazine in geropsychiatric patients were published in 1955 by Kurland,<sup>97</sup> Seager<sup>98</sup> and Terman;<sup>99</sup> on reserpine alone and in combination with psychostimulants and/or vitamins in 1956<sup>100</sup> and '58;<sup>101</sup> on prochlorperazine in 1957;<sup>102</sup> on meprobamate in 1957<sup>103</sup> and '58;<sup>104</sup> on imipramine in 1958<sup>105,106</sup> and '59;<sup>107,108</sup> and on perphenazine,<sup>109</sup> thioridazine,<sup>110</sup> and trifluoperazine in 1959.<sup>111</sup>

#### **Psychiatric Diagnosis**

The origin of most current diagnostic end-points in neuropsychopharmacological research is in the clinically distinct sub-populations separated from "unitary psychosis" ("Einheitpsychose")<sup>112,113,114</sup> during the second part of the 19th century. In order of chronology they are as follows: Lasègue's "délire de persecution" (1852);<sup>115</sup> Falret's "folie circulaire" (1854);<sup>116</sup> Briquet's "hysteria" (1859);<sup>117</sup> Morel's "démence precoce" (1860)<sup>118</sup> & "délire emotiff" (1867);<sup>119</sup> Beard's "neurasthenia" (1869);<sup>120</sup> Benedict's "Platztschwindel" (agoraphobia) (1870);<sup>121</sup> Hecker's "Hebephrenie" (1871);<sup>122</sup> Westphal's "Agoraphobie" (1871<sup>123</sup> & 1872<sup>124</sup>); Lasèque's "l'anorexie hystérique" (1873)<sup>125</sup> & Gall's "anorexia nervosa" (1873);<sup>126</sup> Kahlbaum's "Katatonie" (1874);<sup>127</sup> and Westphal's "Zwangsvorstellungen" (obsessive-compulsive disorder) (1978).<sup>128,129</sup> At present, hysteria (referred to as "somatization disorder" in some of the current classifications<sup>130</sup>), neurasthenia, agoraphobia, anorexia nervosa, and obsessive-compulsive states have remained valid diagnostic concepts; délire de persecution developed in the early 1890s into Magnan and Sérieux's diagnostic concept of "chronic delusional state of systematic evolution";<sup>131</sup> folie circulaire provided the core for Kraepelin's diagnostic concept of manicdepressive insanity; and démence precoce served as the starting point for Kraepelin to develop his diagnostic concept of dementia praecox.

The origin of some of the other current diagnostic end-points are in Karl Kahlbaum's classification which distinguishes five classes of disease, i.e., neophrenias, paraphrenias, vecordias, vesanias and dysphrenias,<sup>132</sup> and in Emil Kraepelin's different classifications presented in nine editions of his textbook (the first published in 1883 and the last in 1927).<sup>133,134,135,136,137,138</sup> Diagnostic concepts, like presbyophrenia, dysthymia and cyclothymia, were first introduced in Kahlbaum's classification, and the unifying diagnostic concepts of dementia praecox and manic depressive insanity first appeared in the sixth edition of Kreapelin's text,<sup>140,141</sup> Eugen Bleuler replaced the name dementia praecox with schizophrenia (1908).<sup>142,143,144,145</sup>

Adoption of Kraepelin's classification in the 1950s by the St.Louis School of Psychiatry in the United States was instrumental to the development of the third edition of the diagnostic and statistical manual of mental disorders of the American Psychiatric Association, published in 1980. The DSM-III and its

 <sup>\*</sup> In the seventh edition, published in 1903 and 1904, Kraepelin recognized 15 categories of mental illness:
(1) infectious mental conditions, (2) exhaustion states, (3) intoxications, (4) thyrogenic conditions, (5) dementia praecox, (6) dementia paralytica, (7) mental disorders in brain diseases, (8) involutional diseases, (9) manic–depressive insanity, (10) paranoia (Verrűctheit), (11) epilepsy, (12) psychogenic neuroses, (13) diseases of constitutional origin, (14) psychopathic personalities, and (16) developmental inhibitions.

successors were to provide to-date the diagnostic end-points of neuropsychopharmacological research. (See, Preface to Volume 4.)

#### **Pharmacokinetics**

Pharmacodynamics deals with action of a substance on the body, whereas pharmacokinetics deals with the action of the body on the substance. Pharmacodynamic properties are responsible for the differential effect of a psychotropic drug in different psychiatric diagnoses, whereas pharmacokinetic properties for the differential effect of the same drug within a particular diagnosis.

The term pharmacokinetics was introduced by F.H. Dott in 1953.<sup>146,147</sup> Couple of years later Bernard Brodie and his associates revealed that the main pathways used by the organism for metabolizing drugs are: (1) oxidation by microsomal enzymes in the liver, (2) other oxidative reactions, such as dehydrogenation, oxidative deamination, (3) reduction reactions, (4) O-methylation, (5) hydrolysis (of esters and amides), and (6) conjugation.<sup>148,149</sup> By the end of the 1950s it was shown that oxidation by microsomal enzymes<sup>150,151</sup> was the main pathway in the metabolism of LSD, and N-demethylation, partial oxidation of the sulfur atom, and glucuronide formation in the metabolism of chlorpromazine. It was also recognized that the metabolic degradation of imipramine is similar to that of chlorpromazine.<sup>152,153,154</sup>

Introduction of flame photometry by Victor Wynn rendered the measurement of plasma lithium levels feasible.<sup>155,156</sup> The first clinical studies with lithium plasma level monitoring were conducted in the 1950s by Treutner and his associates,<sup>157,158</sup> and by Schou and his associates.<sup>159,160</sup> It was in those early studies that the "therapeutic window" of lithium was detected by Treutner and his group. (See, Gershon Volume 1.)

The first plasma level determination of chlorpromazine was reported by Curry and Brodie in 1967,<sup>161</sup> and of imipramine by Moody and his associates in the same year.<sup>162</sup>

#### Interviewees & Interviewers

The preceding information provides orientation points in the development of the four major areas of research interviewees contributed to.

From the 29 interviewees included in Volume Seven, 3 (Costa, Eichelman, George) are MD/PhDs; 17 (Akiskal, Alexopoulos, Blazer, Chase, Clayton, Dunner, Fish, Glassman, Halbreich, Halmi, Jeste, Kupfer, Lisanby, McKinney, Reisberg, Rapoport and Wender) are MDs; 8 (Arango, Conners, Dahl, Endicott, Kaufman, Klein, Shooter and Weissman) are PhDs and 1 (Cooper) is an MA.

From the 17 MDs, 16 are psychiatrists - 1 of the psychiatrists (Halmi) is also a qualified pediatrician - and 1 (Chase) is a neurologist. From the 8 PhDs, 3 (Conners, Endicott and Klein) are psychologists, and from the other 5 each is qualified in a different discipline: Arango in neuroanatomy, Dahl in pharmacology, Kaufman in biochemistry, Shooter in chemistry and Weissman in epidemiology.

All interviewees are affiliated with ACNP; two, Kupfer and Rapoport, are past presidents of the organization.

The interviews were conducted from 1996 to 2008 and with the exception of one, Lisanby, who was interviewed at the CINP Congress in Paris, all were interviewed at ACNP's annual meetings.

The 29 interviewees were interviewed by 12 interviewers; 1 interviewee (Fish) was interviewed by 2 interviewers (Meldrum and Bromley). Nine of the interviewers are peers of the interviewees, knowledgeable in the same field and 3 (Bromley, Meldrum and Tone) are medical historians. Eight of the interviewers (Angrist, Clayton, Koslow, Meldrum, Post, Regier, Schatzberg and Van Kammen) conducted one interview, 2 (Bromley and Healy,) conducted two, and from the remaining two, one (Tone) conducted five, and the other (Ban) conducted 13.

By the time the editing of Volume Seven was completed, one of the interviewees (Schuster) passed away.

#### **Contributions of Interviewees**

The 29 interviewees contributed to eleven areas of research. Six of the interviewees (Conners, Fish, Kaufman, Klein, Rapoport and Wender) were engaged in research related to **child psychiatry**. In the 1960s *Seymour Kaufman* described the structure of the phenylalanine cofactor,<sup>163</sup> the physical properties of 3,4 dihydroxyphenylalanine- $\beta$ -hydroxylase. He also defined the role of copper in the catalytic activity of the enzyme.<sup>164</sup> In the 1970s, Kaufman identfied two new forms of phenylketonuria: one (1975) due to deficiency of dihydropteridine release,<sup>165</sup> and the other (1978), due to biopterin deficiency.<sup>166</sup>

In the 1960s and 70s *Barbara Fish*, contributed to the introduction of several psychotropic drugs, including e.g., trifluoperazine,<sup>167</sup> thothixene,<sup>168</sup> chlordiazepoxide,<sup>169</sup> in child psychiatry. She also contributed to the development of a methodology for the detection of drug-induced changes in "an organism that is in the process of changing".<sup>170</sup>

*C.Keith Conners* contributed to the characterization of minimal brain dysfunction,<sup>171</sup> and to the development of rating scales for use in drug studies with children.<sup>172</sup> In a series of clinical investigations carried out in the 1960s he also contributed supportive information on the effectiveness of methylphenidate in disturbed children,<sup>173</sup> and of dextroamphetamnine on the school behaviour of children with learning disabilities.<sup>174</sup> In 1980 Conners was among the first to discuss a possible relationship between food additives and hyperactivity in children.<sup>175</sup>

*Paul H. Wender* extended the diagnostic concept of "minimal brain dysfunction" from children to adults. He was first to explore systematically the pharmacology of minimal brain dysfunction (attention deficit hyperactivity disorder) in both, children and adults He presented his findings in his monographs on *Minimal Brain Dysfunction in Children*, published in 1971<sup>176</sup> and on *Minimal Brain Dysfunction in Adults*, published in 1995.<sup>177, 178</sup> In the 1960s, Wender, in collaboration with Seymour Kety and David Rosenthal, introduced a new methodology in epidemiologic genetic research by studying mental illness in the biological and adoptive families of adopted children with schizophrenia.<sup>179</sup> They also introduced the concept of "schizophrenia spectrum disorders".<sup>180,181</sup>

In the 1970s *Judith Rapoport* contributed to knowledge on the use of methylphenidate in attention deficit hyperactivity disorder.<sup>182,183</sup> She was first to demonstrate that dextroamphetamine produced a marked decrease in reaction time and motor activity in normal pre-pubertal boys.<sup>184</sup> In the 1980s Rapoport's research shifted to the study of the pharmacology of obsessive-compulsive disorder (OCD) in children.<sup>185,186</sup> In the early 1990s she was a member of the team which showed the differential effect of desipramine and clomipramine in children and adolescents with OCD.<sup>187</sup>

*Rachel Gittelman Klein* was first in the 1990s to show the effectiveness of imipramine in the treatment of separation anxiety disorder.<sup>188</sup> She was also among the first to extend the use of methylphenidate to conduct disorders.<sup>189</sup> Klein was member of the team which explored the use of pemoline in conduct disorders.<sup>190</sup> In 1997 in collaboration with Abikoff, Klein had shown that behaviour therapy gives no added benefit to treatment with methylphenidate in attention deficit hyperactivity disorder.<sup>191</sup>

Five of the interviewees (Alexopoulos, Blazer, Chase, Jeste and Reisberg) were engaged in research related to **geriatric psychiatry.** *Dan G. Blazer* was involved in studying the epidemiology and genetics of melancholia in the aged. He was among the first to report on a decrease of depressive illness in old people.<sup>192,193,194,195</sup>

In the early 1980s *Barry Reisberg* developed assessment instruments which were to be used extensively in clinical studies with psychotropic drugs in the aged,e.g., Global Deterioration Scale, Brief Cognitive Rating Scale.<sup>196,197,198,199</sup> Reisberg was among the first to study memantine, a substance synthesized in 1963 that blocks glutametergic NMDA receptors, in

elderly patients. He led the team which reported in 2003 on favourable effects of memantine in moderate to severe AD.<sup>200</sup>

In the 1980s, *Thomas N. Chase* studied cortical abnormalities in Alzheimer's disease (AD) with the employment of glucose utilization.<sup>201,202</sup> He was among the first to explore GABA agonist therapy for AD.<sup>203</sup> Shifting the focus of his research from AD to Parkinson's disease (PD) in the 1990s, Chase with his associates demonstrated the significance of continuous dopaminergic stimulation treatment of PD.<sup>204,205,206</sup> In 2003 Chase waas first to report on the use of an A<sub>24</sub> receptor agonist in the treatment of PD.<sup>207</sup>

In the 1990s *Dilip V. Jeste* contributed to knowledge on late onset schizophrenia.<sup>208,209</sup> In a prospective study he also demonstrated the difference in the risk factor for tardive dyskinesia in old and young patients with schizophrenia.<sup>210</sup> Jeste was a member of the team which reported in 2000 on the incidence and risk factors for hallucinations and delusions in probable Alzheimer's disease.<sup>211</sup>

*George S. Alexopoulos* contributed to knowledge on late onset depression.<sup>212,213</sup> He studied the relationship between: (1) brain changes and depression in geriatric patients;<sup>214</sup> (2) late-life depression and neurological disease;<sup>215</sup> and (3) depressive symptoms, vascular disease and cognitive impairment.<sup>216</sup> In the early years of the 21<sup>st</sup> century, Alexopoulos extended his research to the study of the difference in placebo response between old and young patients.<sup>217</sup> In 2008 he reported on a negative correlation between micro-structural white matter abnormalities and remission in geriatric depression.<sup>218</sup>

Seven of the interviewees (Akiskal, Clayton, Dunner, Eichelman, Endicott, Halbreich and Halmi) were engaged research related to **diagnostic endpoints** in psychopharmacologic research. In the late 1960 *Paula J Clayton* was instrumental in introducing Karl Leonhard's diagnostic concept of "bipolar disorder" in the United States,<sup>219</sup> and in the early 1980, in perpetuating Kasanin's diagnostic concept of "schizoaffective disorder".<sup>220,221</sup> One of the recurring themes in Clayton's research was the separation of symptoms of bereavement from symptoms of depression.<sup>222, 223;224</sup> In the 1970s Clayton was a member of a team which studied the relationship between nortripty-line plasma levels and therapeutic response.<sup>225</sup> In the 1990s she co-authored paper with Jules Angst and his associates in Zurich on mortality of patients with mood disorders.<sup>226</sup>

In the mid 1970s *Jean Endicott*, in collaboration with Robert Spitzer and Eli Robins developed Research Diagnostic Criteria (RDC) for a Selected Group of Functional Psychoses.<sup>227,228</sup> In collaboration with Spitzer she also developed the Schedule of Affective Disorder and Schizophrenia (SADS).<sup>229</sup> The RDC and SADS together with Feighner's Research Diagnostic Crteria <sup>230</sup> provided the bridge between the DSM-II,<sup>231</sup> and the DSM-III.<sup>232</sup> During the

1980s and '90s, Endicott contributed with his research to the recognition of "premenstrual dysphoric disorder" as a distinct diagnostic entity.<sup>233</sup>

Searching for a unifying hypothesis of affective disorders,<sup>234</sup> *Hagop Akiskal*, studied sub-affective disorders, such as dysthymia, cyclothymia, bipolar II disorder, in the "borderline realm".<sup>235</sup> In 1983, he critically reviewed te relationship between personality and affective disorder,<sup>236</sup> and presented his findings on the psychopathology of chronic depressive subtypes.<sup>237</sup> In the 1990s, pursuing the same line of research further, he introduced the concept of "bipolar spectrum disorders";<sup>238</sup> provided evidence for switching from unipolar to bipolar II disorder<sup>239</sup> and described prototypes of bipolar I, II, III and IV disorders.<sup>240</sup>

Studying the genetics of manic-depressive illness in collaboration with Elliot Gershon, *David Dunner*, in the late 1960s identified what was to become known as "bipolar II disorder."<sup>241</sup> Subsequently, studying factors which might be related to failure in responding to lithium, in collaboration with Ronald Fieve,<sup>242,243,244,245,246</sup> Dunner was among the first to describe "rapid cycling" patients.<sup>247</sup> They also proposed a classification of bipolar affective disorder.<sup>248</sup> During the 1980s and '90s Dunner was involved in the clinical evaluation of several psychotropic drugs, including adinazolam,<sup>249</sup> alprazol-am,<sup>250</sup> fluoxetine,<sup>251</sup> citalopram,<sup>252</sup> paroxetine,<sup>253</sup> etc.

Using a specially devised assessment form for the detection of premenstrual symptoms in the mid-1980s, *Uriel Halbreich*, in collaboration with Jean Endicott, found a diversity of premenstrual changes<sup>254</sup> and linked these changes to gonadal hormone secretion.<sup>255</sup> They also revealed a relationship between premenstrual dysphoric changes and depression.<sup>256</sup> In the 1990s Halbreich suggested that "menstrually related disorders" are valid diagnostic end points<sup>257</sup> and embarked on studies on the relationship between gonadal hormones and these disorders.<sup>258</sup> He also explored the use of progesterone antagonists,<sup>259</sup> and sertraline<sup>260</sup> in the treatment of the premenstrual dysphoric syndrome. In his early research Halbreich found a difference in growth hormone response to dextroamphetmine between depressed patients and normal subjects,<sup>261</sup> and between postmenopausal women and normal young men.<sup>262</sup> In 1990 he reported on the effects of oestrogen replacement in the treatment of postmenopausal disorders.<sup>263</sup>

Focusing on eating disorders in her research, *Katherine A Halmi*, in the late 1970s reported on the effectiveness of cyproheptadine, a serotonin antagonist, in the treatment of "anorexia nervosa".<sup>264</sup> She followed up her findings with a comparative study of cyproheptadine and amitriptyline,<sup>265</sup> and by comparing the effectiveness of cyproheptadine in bulimic and non-bulimic anorexia nervosa patients.<sup>266</sup> With the employment of biological measures during the 1980s Halmi found similarities between anorexia nervosa and

depression. <sup>267, 268</sup> Halmi was a member of the team which identified in 2002 a susceptibility gene for anorexia nervosa on chromosome 1.<sup>269</sup>

In a series of experiments conducted in the rat in the early 1970s, *Burt Eichelman* found that social setting influenced physiological response to electric shock.<sup>270</sup> Focusing on the pharmacology of aggression in his research he revealed the effect of sub-cortical lesions on shock-induced aggression.<sup>271</sup> Then, he demonstrated that 6-hydroxydopamine administration facilitated aggressive behaviour.<sup>272</sup> In the mid-1980s, Eichelman reported that combined treatment with tryptophan and trazodone has a favourable effect on aggressive behaviour.<sup>273</sup> In 1990, in recognition of the pharmacological heterogeneity of the population displaying aggressive and violent behaviour.<sup>274</sup> Eichelman developed The Carolina Nosology of Destructive Behaviour.<sup>275</sup>

Three of the interviewees (Cooper, Dahl and Glassman) were engaged in **pharmacokinetic research.** *Thomas B. Cooper* contributed to the determination of plasma and tissue levels of various antipsychotics (including butaperazine<sup>276</sup>, loxapine<sup>277</sup> clozapine,<sup>278</sup> fluphenazine<sup>279</sup>), antidepressants (including mianserin<sup>280</sup> and nortriptyline<sup>281</sup>), and benzodiazepines.<sup>282</sup> In 1973, in collaboration with Bergner and Simpson, Cooper demonstrated that 24hour serum lithium level is a good "prognosticator" of dose requirement in patients.<sup>283</sup> Cooper was member of the team which reported in 1980 on the effect of antiparkinson medication on plasma levels of chlorpromazine.<sup>284</sup> He was also a member of the team which compared (in 2004) the pharmacodynamc and pharmacokinetic effects of d and dl threo-methylphenidate hydrochloride in children with attention deficit disorder.<sup>285</sup>

While studying the relationship between plasma levels and therapeutic effect of imipramine, in the 1970s, *Alexander H. Glassman* and his associates, found that patients with delusions (psychotic depression) did not respond to the drug.<sup>286,287,288,289</sup> They also revealed cardiac conductance changes, similar to those seen with quinidine.<sup>290,291</sup> During the 1980s the focus of Glassman's research shifted to smoking. He was among the first to demonstrate that clonidine, an  $\alpha_2$  adrenergic agonist, reduced the severity of symptoms after "smoking cessation."<sup>292,293</sup> He had also shown the effects of smoking cessation on major depression. <sup>294,295</sup>

*Svejn G. Dahl* was among the first in the mid-1970s to study the pharmacokinetics of chlorpromazine<sup>296</sup> and methotrimeprazine<sup>297</sup> after the administration of single and multiple doses. Ten years later, in the mid-1980s he was again among the first to introduce plasma level monitoring of antipsychotic drugs.<sup>298</sup> During the 1990s the focus of Dahl's research shifted to the study of structure-activity relationships,<sup>299</sup> and to the modeling of neurotransmitter receptors.<sup>300</sup> Two of the interviewees (George and Lisanby) were involved in research with **biophysical approaches to treatment**, Mark S. George was first in the 1990s to employ transcranial magnetic stimulation in the treatment of depression.<sup>301,302,303</sup> He was also first to explore the utility of vagus nerve stimulation in the treatment of psychiatric disorders.<sup>304</sup>

In the early years of the 21<sup>st</sup> century *Sarah Hollingsworth Lisanby* was instrumental in developing magnetic seizure therapy,<sup>305,306</sup> and repetitive transcranial magnetic stimulation<sup>307,308</sup> in the treatment of depression. She also explored the possible augmentation of sertraline treatment with transcranial magnetic stimulation.<sup>309</sup>

Each of the remaining six interviewees (Arango, Costa, Kupfer, McKinney, Shooter and Weissman) was involved in a different are of research. *Victoria Arango* with her associates demonstrated an increase in serotonin 5HT<sub>2</sub> and  $\beta$ -adrenergic receptor binding sites in the brains of suicide victims<sup>310</sup> in the 1990s. They localized the increase of serotonin receptor binding sites to the ventrolateral prefrontal cortex.<sup>311</sup> In 2002 Arrango was member of the team which reported on altered editing of serotonin 5HT<sub>2c</sub> receptor pre-mRNA in the prefrontal cortex in suicide,<sup>312</sup> and in 2006, she was member of the team which demonstrated lower serotonin transporter binding during major depressive episode.<sup>313</sup>

*Erminio Costa* was first to demonstrate the differential expression of serotonin in various areas of the human brain in the late 1950s.<sup>314</sup> His findings indicated multiple serotonin receptors with different sensitivity to inhibition by LSD.<sup>315,316</sup> In the 1970s Costa and his associates demonstrated that potentiation of gabaminergic activity plays an important role in the mode of action of benzodiazepines.<sup>317,318</sup> They also contributed to the characterization of benzodiazepine receptors.<sup>319</sup> In the mid-1980s Costa was member of the team that discovered metabotropic glutamate receptors.<sup>320</sup> In the early years of the 21<sup>st</sup> century Costa and his associates found that reelin protein and mRNA was reduced in several brain areas in schizophrenia and manic-depressive disease and suggested that dendritic spine hypoplasticity with downregulation of reelin and gabaergic tone is a vulnerability factor for schizophrenia.<sup>321</sup> (See also John Davis Volume 5.) In 2002 they postulated that schizophrenia is a disease at the interface of the genome and the Epidenome.<sup>322</sup>

In the 1970s *David J Kupfer* reported on changed interval between the onset of sleep and rapid eye-movement sleep in depressed patients and suggested that shortened REM latency was an indicator ("biological marker") of primary depressive disease.<sup>323,324</sup> Kupfer found a statistically significant relationship between the changes in the tonic component of rapid eye movement (REM) sleep and therapeutic response to antidepressants. He also demonstrated that an increase in REM latency and REM suppression after

a loading dose of 50 mg of amitriptyline was a predictor of favourable treatment outcome with the drug.<sup>325,326</sup> In other areas of research Kupfer contributed to knowledge on maintenance treatment in recurrent depression,<sup>327</sup> and on the management of insomnia.<sup>328</sup>

Working with rhesus monkeys, *William T, McKinney* was first in the 1970s to report on the effect of reserpine on social behaviour<sup>329</sup> and on the effect of chlorpromazine on disturbed behaviour.<sup>330</sup> In the 1980s he studied the effects of several drugs on the response to social isolation,<sup>331</sup> and published his monograph on Animal Models of Mental Disorders.<sup>332</sup>

In 1976, *Eric M. Shooter*, in collaboration with Mobley and Schenker, succeeded with the isolation and characterization of "proteolytically modified nerve growth factor".<sup>333</sup> Twenty-six years later, in 2002, Shooter, in collaboration with Cosgaya and Chan reported that the neurotrophin receptor p75NTR is a positive modulator of myelinization.<sup>334</sup>

*Myrna M Weissman* was among the first to use psychiatric research diagnostic criteria in epidemiological studies.<sup>335</sup> In the late 1970s she published her findings on affective disorder in an urban community of the United States,<sup>336</sup> and in 1980, she presented epidemiological findings on depression in New Haven.<sup>337</sup> During the 1970s and '80s, Weissman in collaboration with Gerald Klerman studied the interaction between drugs and psychotherapy in the treatment of depression,<sup>338</sup> and developed short-term interpersonal psychotherapy (IPT).<sup>339</sup> Subsequently, she became involved in molecular genetic research in psychiatry.<sup>340,341,342,343</sup>

The background of interviewees in Volume Seven varies widely. Their only common feature is that all 29 interviewees are members of ACNP.

Interviewees entered the field at different stages in the development of neiropsychopharmacology. Hence the volume covers fifty years of history.

Barry Blackwell, the editor of Volume Seven is a distinguished researcher in the field. He also contributed the Dramatis Personae to Volume 4, and the editing of Volume 9 to this series. In his Introduction, Blackwell describes the characteristic features of the group of interviewees included in Volume 7, and focus attention on some of the issues they raised. In his Dramatis Personae he integrates interviewees personal story and contributions.

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## ABBREVIATIONS

ACISR	Advanced Center for Interventions and Services Research
ACLU	American Civil Liberties Union
ACT	Association for Convulsive Therapy
ADHD	attention deficit hyperactivity disorder
AECOM	Albert Einstein College of Medicine
AIDS	acquired immune deficiency syndrome
ALS	amyotrophic lateral sclerosis
AMPA	$\alpha$ -amino-3 hydroxy-5 methyl- 4 isoxazoleproprionate
APA	American Psychiatric Association
APO-E4	apoliproprotein E
APPA	American Psychopathological Association
ASENT	American Society of Experimental Neurotherapeutics
BDNF	brain derived neurotrophic factor
BEHAVE-AD	behavioral pathology and Alzheimer's
	disease assessment
CAPPS	current and past psychopathology scales
CBASP	cognitive behavioral analysis system of psychotherapy
CBT	cognitive behavior therapy
CEO	chief executive officer
CME	continuing medical education
CMI	clomipramine
CNS	central nervous system
CNTF	ciliary neurotrophic factor
COMT	catechol-O-methyl transferase
CPT	continuous performance test
CSF	cerebrospinal fluid
CSI	crime scene investigation
CT	computerized tomography
CV	curriculum vitae
DBS	deep brain stimulation
DIS	diagnostic interview schedule
DMI	desmethylimipramine
DNA	deoxyribonucleic acid
DSM	diagnostic and statistical manual
D2	dopamine 2 receptor
ECA	epidemiologic catchment area
ECDEU	early clinical drug evaluation unit

ECFMG ECT	Educational Commission for Foreign Medical Graduates electroconvulsive therapy
EEG	electroencephalogram
ENRICHD	encouraging recovery in coronary heart disease
FDA	Food and Drug Administration
5 HIAA	5-hydroxy-indole- acetic acid
5 HTP	5-hydroxy tryptophan
FSH	follicle stimulating hormone
GABA	γ-amino-butyric acid
GAF	global assessment of functioning
GAS	global assessment scale
GHQ	general health questionnaire
GI	gastro-intestinal
GSK	Glaxo Smith Kline
HIV	human immunodeficiency virus
HPA	hypothalamic pituitary axis
HVA	homovanillic acid
ICD 9	International classification of disease 9th edition
ICGP	International College of Geriatric
	Neuropsychopharmacology
IPA	International Psychogeriatric Association
IPSC-E	inventory for psychic and somatic complaints
	of the elderly
IPT	interpersonal psychotherapy
IRB	international review board
IVR	interactive voice response
JAMA	Journal of the American Medical Association
KEM	King Edward Memorial Hospital
L-DOPA	I-dihydroxy-phenyl-alanine
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
L2PD2	late luteal phase of dysphoric disorder
MAOI	monoamine oxidase inhibitor
MBA	masters in business administration
MBL	marine biological laboratory
MCPP	m-chlorophenylpiperazine
MDD	major depressive disorder
Mellaril	thioridazine
MIT	Massachusetts Institute of Technology
MPTP	1-methyl-4-phenyl-1 2 3 6-tetrahydroxypyridine
MRI	magnetic resonance imaging
	magnetio resoliance imaging

MUSC	Medical University of South Carolina
NARSAD	National Alliance for Research in Schizophrenia
	and Depression
NCS	National Co-morbidity Service
NFT	neurofibrillary tangles
NGF	nerve growth factor
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NIMH	National Institute of Mental Health
NMDA	N-methyl-D-aspartate
NYU	New York University
OCD	obsessive compulsive disorder
PCP	phencyclidine
PET	positive emission tomography
PMDD	premenstrual dysphoric disorder
PMS	premenstrual syndrome
PNS	peripheral nervous system
PROSPECT	prevention of suicide in primary care elderly trial
Q-LES-Q	quality of life enjoyment and satisfaction questionnaire
RBANS	repeatable battery for the assessment of
	neuropsychological status
RDC	research diagnostic criteria
RNA	ribonucleic acid
rTMS	repetitive transcranial magnetic stimulation
SADS	schedule for affective disorders and schizophrenia
SCIDS	structured clinical interview for DSM diagnoses
SNRI	serotonin norepinephrine receptor inhibitor
SPAD	symptoms of psychosis and Alzheimer's disease
SPECT	single photon emission computed tomography
STAR*D	sequence treatment alternatives to relieve depression
SSRI	selective serotonin reuptake inhibitor
TADS	treatment of adolescent depression
TB	tuberculosis
TCI	temperament and character inventory
TMS	transcranial magnetic stimulation
TRK	tyrosine kinase rceptor
UCLA	University of California at Los Angeles
UCSD	University of California at San Diego
UNC	University of North Carolina
VA	Veterans Administration
VNS	vagal nerve stimulation

WHOWorld Health OrganizationYAZdrospirenone and ethyl estradiol

## INTRODUCTION & DRAMATIS PERSONAE Barry Blackwell

The formal title for this Volume is "Special Areas". But special, in what way? As a subtitle I have chosen "Desiderata", defined in the *Oxford English Dictionary* as "something that is needed or wanted". Our field of enquiry did not come into existence complete or without the support of allied disciplines and scientists. The twenty nine interviews in this volume fall into five categories, a few into more than one.

First, this volume includes contributions to clinical conditions often considered the "orphans" of adult psychopharmacology, neglected either because they had scant commercial interest to the pharmaceutical industry or the rigid criteria and safety considerations for controlled double blind studies excluded children, the elderly and women of child bearing age.

Second, these overlooked or other newly identified clinical conditions needed better definition of their nosology and natural history to lay the foundation for informative drug studies. This includes aggression, eating disorders, female hormonal conditions, late onset schizophrenia and spectrum disorders.

Third, are related disciplines essential to understanding the mechanism of action, impact or need for new drug developments including neuropathology, neurochemistry, drug metabolism, epidemiology, familial genetics, structural chemistry, crystallography and bioinformatics.

Fourth, are the techniques to discover new drugs and measure their impact including animal models and age or disease appropriate measuring instruments.

Fifth is the place for novel, non drug, therapeutic techniques such as brain stimulation.

This Volume is dedicated to Lou Lasagna, President of ACNP in 1980. No one person contributed more to the development of our field at its inception and subsequently. Often considered "the father of clinical pharmacology" he established the first department of this new discipline in America at Johns Hopkins University in 1954, the year in which the first modern psychotropic drug, chlorpromazine, began to be systematically studied in patients. His expert testimony to Congress in 1962, during the Kefauver hearings, resulted in the requirement for controlled clinical trials to prove drug efficacy, established the first prescription drug laws in the world and set the evidentiary standards for the FDA and pharmaceutical industry. Dr. Lasagna was active in the ACNP when I became a member in 1970 and his Wikepedia entry (*en.wikipedia.org*) notes his eloquence, humor and humanity, qualities I observed and benefited from.

The honor of editing this volume provided an opportunity to continue a task begun forty years ago. In April 1970 Frank Ayd and I organized the Second Annual Taylor Manor Hospital Scientific Symposium. Both of us were involved in teaching our new discipline to medical students, residents, physicians and the public. We wanted to record the discovery of each of the new drugs, told by those who made them. The speakers included Pierre Deniker from France, (phenothiazines), Nathan Kline, (MAO Inhibitors), Frank Berger, (meprobamate), Ronald Kuhn from Switzerland, (tricyclic antidepressants), Paul Janssen from Belgium, (butyrophenones), Jorgen Ravn from Denmark,(thioxanthenes), Irv Cohen, (benzodiazepines), and John Cade from Australia (lithium).

Frank Ayd provided an overview of the impact of these discoveries on psychiatry. My task was to review a substantial world literature on the process of scientific discovery.

In this volume Tom Ban's preface places the discoveries of the next half century in their scientific context while this introduction dwells on the characteristics of the people and circumstances that enabled their contributions. In 1970 each person came with a presentation prepared for publication on which we had imposed no structure. As is customary, the contents were more scientific than personal. The information in this volume is from semistructured interviews that include dialog with the interviewer. This process expands the opportunity for personal reflection with increased attention to the process of discovery as well as to its outcome.

In 1970 five of the eight original discoveries were made by scientists from other nations. In thisvolume eight of the twenty nine scientists came from overseas and did so in search of opportunity, resources and role models, not available in their own countries, which enabled their later discoveries. They came from Britain, Greece, Italy, Lebanon, Israel and Norway. In the early days of psychopharmacology America was indeed a "land of opportunity" with NIH grants and fellowships available to support talented young researchers. The National Institutes played an important role in the careers of every scientist in this volume with one exception. Over a third (twelve) held fellowships or leadership positions at the NIMH, a few for many years and the remainder (sixteen) had significant grant support. Cultural exchange was not entirely a one way street. Three scientists in our volume took early sabbaticals in Britain to gain experiences not readily available in America and one spent his career in Norway with sabbaticals in France and America.

One striking demographic which reflects a different cultural ethos between the 22 pioneers of Volume 1 (Starting Up) and of this Volume is that all of the interviwees in that volume were men. In this volume almost a third of the scientists are women (9 of 29). All of the earlier sample were MDs while in this volume seventeen are MDs, eight are PhDs (three psychology, two neurobiology, one epidemiology, one neurochemistry and one structural chemistry), three are MD/PhDs (basic animal research, epidemiology and pharmacology) and one is a laboratory scientist. This obviously reflects the widening scope of a developing field and underscores the fact that scientific innovation is increasingly facilitated by interdisciplinary collaboration and dialogue.

Personal attributes reflect and confirm what was already known about the process of making scientific discoveries. The individuals were all young at the time of their peak creativity (under forty) and exceptionally bright, many with scholarships, graduate honors and fellowships. They were strongly motivated as evidenced by early publications (often as students or residents), accelerated academic promotion and purpose driven lives. Many were exposed to research on either a voluntary basis, or as a curriculum requirement, as undergraduates, medical students, residents or graduates. As a group they showed an early propensity for critical, creative and flexible thinking often derived from philosophical, parental or early mentoring experiences. This was an important component in the willingness to challenge the prevailing Zeitgeist in America which was strongly psychoanalytic. To do this also required self assurance, an element of risk taking and curiosity.

The family backgrounds are very variable although all appeared to be stable and supportive. Only a few (three) had family members who were physicians while several came from blue collar backgrounds with no academic traditions. The importance of mentors and role models was ubiquitous. Sometimes these were parents but more often, teachers or faculty members in places like George Washington University and the NIMH where data based, critical thinking was beginning to challenge psychoanalytic hegemony.

Research output, measured by scientific publications, books and book chapters varied from productive to prodigious. It was nurtured by a climate of innovation where new findings were frequent and, as one scientist remarked, almost everything they touched was statistically significant. This natural feedback was highly reinforcing and the result was often reflected in membership of advisory, research or editorial boards and national or international recognition awards.

Not everything in everybody's career was plain sailing. Concerns were expressed by several investigators about the shortcomings of DSM nosology and the FDA's rigidity in applying it to clinical trials. Criteria were sometimes derived from consensus between competing ideologies and on an archaic principle of symptoms that conveyed clinical homogeneity but might conceal biological diversity, (as with pain, fever or high blood pressure). This impasse occurred with perimenstrual mood changes in women, some pediatric and geriatric conditions and with aggression. In the latter case the difficulty prevented the translation of animal to clinical research and significantly disrupted a scientist's career.

A second area of concern has been the discouraging influence of the press, public opinion and the Church of Scientology on research and treatment in eating disorders, attention deficit disorder, ECT and aggression. There is an intriguing cultural divide between Britain, where stimulants for ADHD are shunned, and America where use is more permissive.

Financial issues are an increasing concern. Earlier on there was ample support from the NIH which greatly exceeded that from Foundations or pharmaceutical companies. The latter was almost always restricted to projects involving specific drugs for limited time periods. Federal grants are now more competitive and less readily obtained. Like everything in health care, the cost of research has increased faster than inflation. The vogue for multicenter studies to obtain large sample sizes has become prohibitive, for example, in demonstrating the effect of antidepressants on the morbidity and mortality of cardiovascular disorders.

The fiduciary influence of the pharmaceutical industry has recently come under scrutiny. While there is no direct evidence of a cause for concern in this volume several scientists are worried about the corrupting potential of drug company money on education and research. Indirectly this may be diverting the best scientific and ethical minds away from clinical psychopharmacology research. A repetitive theme among the scientists in this volume is their dedication to clinical work with patients and families as the seed bed for generating research hypotheses. Another is their dedication to becoming mentors to the next generation of neuroscientists.

Finally, there is a strong consensus in this volume about the ACNP's positive influence on research productivity and interdisciplinary dialog. If there is any wish it is that the organization might play a more prominent national role in addressing the areas of concern noted in this volume. One of the interviews provides an in-depth analysis of the ubiquitous influence of the organization on the field and its members as well as a thoughtful dissection of its virtues and shortcomings.

## Dramatis Personae

Hagop Akiskal is an Armenian refugee from genocide, educated in Lebanon at the American University in Beirut where he won first prize in a poetry competition. After graduating Alpha Omega Alpha from medical school he immigrated to the United States to begin his psychiatric training at the University of Tennessee. His interest in psychiatry was triggered in 1969 as a fourth year medical student when he cared for a patient with schizophrenia who recovered while taking perphenazine. In Memphis he was influenced by a faculty member who had graduated from the first class in neuroscience taught at Harvard.

To complete his residency he moved to the University of Wisconsin where his rotations in substance abuse and student health stimulated a career long interest in mood disorders. This led to two early publications, an article on depression with his mentor Bill McKinney, published in *Science*, and a provocative article on *Suicidal Psychiatry* which integrated biology with psychology and was published in the *Archives of General Psychiatry*.

Dr. Akiskal began his career as an educator while still a resident, teaching psychopharmacology to his peers in psychiatry and neurology. After completing residency he returned to the psychiatry department at the University of Tennessee where he moved rapidly up the academic ladder to become Professor of Psychiatry and Pharmacology within eight years, at the age of 33. His research focused on the nosology and treatment of patients in the Mood Disorders Clinic where thousands of patients were seen without a single suicide, perhaps because of close attention to family and social issues. Out of these observations Hagop began "defining the territory in a vigorous way", developing the bipolar spectrum concept of affective disorders, identifying different phenotypes and subtypes of temperament and distinguishing them from personality disorders. He also worked in the sleep laboratory studying the neurophysiology of dysthymia and its response to antidepressants.

As both educator and researcher Dr. Akiskal attributes his influence by close attention he pays to family and patient concerns reflected both in an interest in public education (initially at NIMH) and numerous awards including several as "teacher of the year" and the Gold medal from the Society of Biological Psychiatry for pioneer work with affective disorders (1995).

Following several years at NIMH, (1990 - 1994) he became Director of the International Mood Center at the University of California at San Diego. The title reflects a career long involvement in international research and education. Fluent in five languages he has held consultant or editorial posts and distinguished lectureships in Switzerland, Canada, Greece, Hungary, Russia, Germany, South America, Italy, Spain, Sweden, Lebanon and England.

Activities in the United States are equally prolific across diverse areas of interest, including primary care, psychoanalytic research, sleep research, new drug evaluation, public education, practice guidelines, affective disorders, ethnic minorities and international medical graduates.

As Editor of the Journal of Affective Disorders Hagop takes particular pride in helping young investigators achieve publication and in sustaining

a broad perspective that includes biology, genetics, neurophysiology, and long term outcome studies. But what Hagop Akiskal considers his greatest achievement is "to bring smiles to the faces of people...I never saw a smiling face when I was growing up. People were all talking about genocide, how much pain they had that they could never give up".

George Alexopoulos was born in the middle of a civil war in Greece, shortly after World War II. He and his sister were encouraged by their parents to become doctors. George volunteered in a mental hospital, attended medical school in Athens, trained in both internal medicine and neurology, served in the Greek Navy and then worked as a country doctor before immigrating to the United States.

Attracted to our profession by an interest in the philosophy of science, psychiatry in Greece was poorly developed and fragmented, as elsewhere, between entrenched psychoanalysis and evolving biological psychiatry.

On arrival in America George began a frenetic and unsatisfactory residency in psychiatry at New Jersey Medical School before transferring to Cornell where there was a "luxury of time and resources" to reflect on clinical experiences. His background in philosophy and logical positivism led quickly to discarding the unscientific and untestable hypotheses of psychoanalysis for a research fellowship under the mentorship of a prominent psychoendocrinologist. He had already published his first paper as a resident on tardive dyskinesia which he recognized as a type of agnosia or "body neglect".

Dr. Alexopoulos has spent his entire career at Weill Medical College of Cornell University, achieving the rank of full Professor in just 14 years. Among other responsibilities he now serves as Vice Chair of Geriatric Psychiatry, Director of the NIMH funded Clinical Research Center for Geriatric Mood Disorders and Director of the Weill Cornell Institute of Geriatric Psychiatry.

The focus of his research has been the etiology, pathophysiology, nosology, and treatment responsiveness of depression in the elderly, leading to many original and significant findings at the clinical and basic science level. More recently he has been involved in the transfer of this knowledge to the community in effectiveness research, including the training of primary care practitioners in the detection and treatment of depression in the elderly population. These efforts are epitomized by his citation of Kant's belief that clinical biology without community based practice is empty and services research not rooted in clinical biology is blind.

Over 28 years this research has been supported by 32 research grants, the majority from NIMH and a few from Foundations and Pharmaceutical Companies.

In addition to research Dr. Alexopoulos teaches psychiatric residents in all four years, offers a lecture series to graduates in the Clinical Epidemiology and Health Services Research Program, directs geriatric fellows (supported by NIMH clinical and research training grants) and has mentored six NIMH Career Development Award recipients.

These accomplishments have been recognized at the local and national level by teaching and research awards including the Senior Investigator's Award of the American Association of Geriatric Psychiatry (1977) and the American College of Psychiatrist's Award for Research in Geriatric Psychiatry (2006).

Finally Dr. Alexopoulos holds memberships and is a reviewer on numerous Editorial Boards and serves on National Organizations and Associations, both lay and professional.

*Victoria Arango* is a pre-eminent member of a handful of neuroanatomists in America who study the human brain in a search for correlations between structure, function and behavior.

She grew up with plans to become a physician but was enchanted with basic science in her senior year after she won a first prize for undergraduate research and graduated Cum Laude from the College of New Rochelle.

Her subsequent career path knits together basic science research and clinical psychiatry. After obtaining her PhD in Neuroanatomy she became a research associate in the Division of Neurobiology at Cornell University and a year later was appointed an Instructor in the Cornell Department of Psychiatry. After only ten years she became Co-Director of Neurobiology and seven years after that was appointed Full Professor in the Department of Psychiatry.

The theme of Dr. Arango's research was set when she began a post doctoral fellowship with Dr. John Mann (a psychiatrist) and Dr. Don Reis (a clinical and basic scientist). Later they were joined by her husband Mark Underwood (a neurophysiologist). Her colleagues had discovered that people who committed suicide possessed an elevated number of serotonin receptors and they needed a neuroanatomist to examine the brains to detect any associated anatomical and cellular changes.

This interview relates the innovative basic science and clinical strategies Dr. Arango and her collaborators developed and the intriguing outcomes that unfolded over the next two decades. She also explains how studying death has made her reverential of life and hopeful that one day the research will accomplish the dual benefit of predicting risk and diminishing cultural stigma that so often discourages people from seeking help. Untreated major mental illness remains far too frequently fatal.

While this research has a singular focus its progeny has been prodigious and diverse. In twenty years (1988-2007) the team has published almost a hundred articles in leading peer reviewed journals of which Dr. Arango has been senior or first author in a third. The research has been funded by NIMH grants totaling in excess of \$ 5 million, awarded over periods from ten to twenty years. Victoria has also been a tireless and lifelong mentor to dozens of graduate students, research fellows and young investigators. She has been a guest lecturer and organizer for numerous national and international conferences and an active member of editorial boards and a referee to nearly twenty clinical and basic science journals. Finally she is a member and often chair person to many study sections and review committees that influence and fund the future direction of brain research.

Dan Blazer describes himself as a "Southern boy who grew up in a blue collar family" which was "not involved in medicine at all". His interest evolved in a Christian household from books he read as a teenager about medical missionaries. He entered medical school after working towards a Master's degree in Religion intending to become a primary care physician dedicated to mission work.

By the time he graduated an interest in psychiatry had begun to develop and he was accepted for deferred admission to Duke before beginning a two year stint in Africa, taking with him his wife, infant child and one hundred books about psychiatry. He read them all as he worked in a mobile clinic visiting remote rural villages in a Land Rover, accompanied by a nurse and pharmacist, treating up to four hundred patients a day. This experience spawned new dimensions to his interests and ambitions when it occurred to him that preventing malaria by draining mosquito infested swamps might be more productive than treating it. He medicated a few psychotic patients with chlorpromazine but most of psychiatric illness was cared for by villagers and native healers. An indigenous elderly population seemed relatively content and healthy. Thus began a lifelong commitment to epidemiology, social and environmental influences on individual disease outcomes and a particular interest in the mental health of the aged.

Dr. Blazer returned to his psychiatric residency at Duke feeling "like a bush doctor coming into this high tech center". Reading had reinforced his life experience and tilted his interests toward social and biological psychiatry, away from the dominant paradigm of psychoanalysis. While his fellow residents were being analyzed an eclectic program allowed him to make weekly visits to Chapel Hill to cultivate and learn from Dorothea and Alexander Leighton, world renowned epidemiologists.

After graduation Dan took a fellowship in Consultation-Liaison Psychiatry at Montefiore Medical center in the Bronx where his psychotherapy supervisor Herb Weiner, Chairman of the Department, turned him on to research and encouraged him to apply for a career development award. This supported his training as an epidemiologist at the University of North Carolina where he obtained both a Masters and PhD degree in two short years. His dissertation topic, *Social Support and Mortality in an Elderly Population* remains the most cited paper in a resume of almost 300 publications in refereed journals.

Dan Blazer's modesty during this interview conceals the remarkable depth and breadth of his lifetime contributions to our understanding of mental health and illness in late life. He is the J.P. Gibbons Professor of Psychiatry and Behavioral Sciences as well as Professor of Community and Family Medicine at Duke University and Adjunct Professor of Epidemiology at the University of North Carolina. He has authored or edited 27 text books including repeat editions of *Depression in Late Life*, in print for over a quarter of a century.

Dr. Blazer has been the principle investigator on several multi-year projects funded by the NIMH and National Institutes of Ageing totaling over twelve million dollars to investigate the epidemiology and psychopathology of mental illness in the elderly.

He is a distinguished educator and served as Dean of Medical Education at Duke University for seven years and now as Vice Chair for Education in Psychiatry. He has been a consultant to numerous local, regional and national organizations and on the editorial boards of over twenty medical journals.

Finally, Dan is the recipient of numerous honors, distinguished appointments and named awards as a teacher, scientist and physician. One wonders why he waited to become a member of the ACNP until 2004, thirty five years after he graduated as a physician!

Thomas Chase is a scientist's scientist and an individual whose career has belied his heritage. He was born into a family of lawyers and business men, none of whom were academics or scientists. Yet from childhood he was fascinated by "how things work", taking apart and assembling mechanical gadgets, radio transmitters and televisions. He chose to train as an electrical engineer at MIT and quickly became interested in applying electrical principles to understanding central nervous function, leading to his undergraduate thesis on how cybernetic theory related to cognitive processing.

After graduating, a brief stint as an engineer for a sewing machine company led to the disillusioning discovery that commercial creativity was restricted to deciding which color to paint its product. Two years in Korea as a second lieutenant in the Signal Corps broadened his horizons and honed his organizational skills. Watching medical training films, reading medical books and working in a leper colony shaped a resolve to study medicine.

Tom chose Yale for an emphasis on student responsibility, individual study and research involvement. Once exposed to the "thrill of laboratory research" he was "forever hooked" and determined to pursue "wholesale" rather than "retail" medicine in a search for better treatments. He graduated President of his class and won the Ramsey prize for Clinical Medicine. The chair of that department, Paul Beeson, recommended him highly for the neurology residency at Harvard and Massachusetts General Hospital. Once again he swam against the tide. At a time when neurologists were characterized as "diagnose and adios" he decided to pursue the barren field of neurotherapeutics. This led to the NIMH and the NIH where he worked under Seymour Kety in Irv Kopin's lab and began to develop his own interests in neurotransmitters, the basal ganglia and Parkinson's disease.

Within four years he was Section Chief of Experimental Therapeutics at NIMH (1970) and four years later (1974) was chosen to be Chief of the Laboratory of Neuropharmacology at the National Institute of Neurological and Communicative Disorders and Stroke (NINDS). So, eight years out of residency, he was head of the biggest neuroscience program in America with 600 scientists and support people some of whom were members of the National Academy of Science or Nobel Laureates. Here his organizational skills and research creativity both bore fruit. During the decade he was the Scientific Director the NINDS intramural program doubled in size and scientific output. He began an experimental therapeutics program and established the principal of translational research extending from the cellular to the clinical level. He recruited and trained well over a hundred promising young researchers who have become leaders in academic, government and industrial agencies.

This interview describes in detail the specific programs and research areas that Dr. Chase's vision spawned. They are reflected in a panorama of society memberships, editorial and advisory boards on which he has served during his career. The latter include, the Foundation for Research in Hereditary Disease, Tourette Syndrome Association, Huntington's Chorea Foundation, National Parkinson Foundation, Amyotrophic Lateral Sclerosis Society, National Ataxia Foundation, Movement Disorders Society and Society for Progressive Supranuclear Palsy. This diversity demonstrates the extent to which Thomas Chase has accomplished his lifetime goal of exerting a "wholesale" influence across the entire field of neurotherapeutics.

To read about *Paula Clayton* s early years as a medical student, psychiatric resident and young faculty member is to understand the Zeitgeist which gave birth to neuropsychopharmacology, those who helped create the new discipline and the pioneer role of women during its inception.

Dr. Clayton was born and raised in St. Louis of college educated parents who steered her towards medicine even though she was one of only two female medical students when she entered Washington University in 1956. Eli Robins, Chair of Psychiatry, had graduated from Harvard, imported scientific method to the department and recruited a like minded faculty that included Sam Guze, George Winokur and Eli's wife, Lee Robins. Almost unique in

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America, the department shunned psychoanalysis to embrace the European brand of descriptive psychiatry epitomized by Kraepelin, Bleuler, Fish and Strömgren. From day one residents were required to become involved in research, encouraged in critical thinking and trained in diagnostic interview techniques that later became refined as the Feighner Criteria and incorporated into the DSM III. Imipramine was used as early as 1958 and lithium in 1962 before it was marketed or approved by the FDA. The department included a basic science laboratory with a mass spectroscope and she became involved in the first studies linking drug levels and clinical response.

As a "token" female Paula was on the "lunch brigade" that welcomed many of Europe's outstanding young researchers and Grand Rounds speakers including Jules Angst, Bob Kendall, John Wing and David Goldberg. Mentored by George Winokur she was quickly immersed in research and developed her first funded study comparing the stages of bereavement with depression.

Dr. Clayton moved from chief resident to Full Professor in ten short years, during seven of which she worked half time and raised three children. She co-authored her first book on *Manic Depressive Illness* in 1969 having previously described the clinical and hereditary features of major depression, bipolar and schizoaffective disorder.

In 1980 Dr. Clayton left St. Louis to become the Head of Psychiatry at the University Of Minnesota School Of Medicine attracted by its potential for growth in research. As her administrative roles expanded she became less involved in first hand research but encouraged and mentored young faculty to undertake clinical trials in collaboration with pharmaceutical companies. She established separate academic and clinical faculty tracks to support research and education in the department and expanded the research budget from three hundred thousand to eleven million dollars.

During the 19 years Paula was a department head she became involved in extensive committee work for the ACNP and the AMA and served as president of three organizations, the American Psychopathological Association, the Psychiatric Research Society and the Society of Biological Psychiatry. She also served on the boards of eight psychiatric journals and as a member of national and governmental research advisory committees, private foundations, pharmaceutical companies and advocacy organizations that included psychiatry, medicine, behavioral science and veteran's affairs.

Dr. Clayton's research output has been prolific including over 150 scientific articles on which she is first author of a third. Not surprisingly, in 1991, she received a lifetime research award from the National Depressive and Manic depressive Association. After she stepped down as Head of Psychiatry in Minnesota Paula enjoyed a brief retirement before returning to half time work at the University of New Mexico where she is again involved in research and mentoring women residents. As she says, "I started with research and I'm going to end with research".

*Keith Conners* was interested in philosophy as an undergraduate and in 1955 he was awarded a Rhodes Scholarship to Oxford University. There he took a course in psychology and physiology which exposed him to classic experiments and distinguished mentors that determined the course of his career. On returning to the United States he obtained his PhD in psychology at Harvard University, graduating with highest honors.

From there he entered the field of pediatric psychopharmacology on the ground floor when he joined Leon Eisenberg at Johns Hopkins University to help analyze data from the first trials of psychotropic drugs in children. These included a placebo controlled evaluation of dextroamphetamine in children with conduct disorders. Compared to his previous experience with psychotherapy in this population the drug effects were dramatic with improvements in school interest, bed wetting and aggressive behavior. These effects were replicated with methylphenidate leading to a report on the benefits of stimulants on learning in "disturbed" children, published in the *American Journal of Psychiatry* in 1963.

As a psychologist, trained and interested in outcome measures, Keith Conners found himself in an environment that valued careful observation and detailed description. Eisenberg's predecessor, Leo Kanner's pediatric textbook had chapter headings which described childrens' behavior that Conners modified to develop the first pediatric rating scales which would later evolve into the parent and teacher scales known and used worldwide The teacher scale was described in the *American Journal of Psychiatry* in 1969.

This interview explores how Keith Connors' conceptualizations and strategies evolved and broadened as his career progressed from Harvard (1976-1974), to Pittsburgh (1974-1979), George Washington University (1979-1989) and Duke University Medical Center (1989-). His rating scales became among the most cited papers in world literature and heavily influenced the DSM III, replacing the vague psychodynamic speculations of DSM II. This became a mixed blessing; throughout his career he has resisted the notion that attention deficit disorder is a unitary condition, viewing it instead as a clinical manifestation of a variety of still unidentified brain disorders, a symptom akin to fever. He regrets the virtual absence of brain imaging, neurophysiologic and neuropsychological measures in contemporary studies that rely primarily on categorical clinical criteria. To focus only on this field is a disservice to Dr. Connors' distinguished contributions in other areas. At the time of this interview (1997) he had published six books and almost ninety articles in peer reviewed journals of which he was the first author in two thirds. The topics include a career long interest in visual evoked potentials in a variety of clinical conditions and important contributions on dietary influences on children's behavior, a topic of great contemporary concern.

Dr. Connors' research has been supported by four grants from NIMH totaling almost \$ 4 million over a twenty year period with additional support from the food and pharmaceutical industry. He has also served as a consultant to the FDA and NIMH.

At a time when psychiatry and psychology are sometimes viewed as contentious rivals Keith Conners contributions speak volumes to the value of interdisciplinary collaboration of the highest and most productive order.

Thomas Cooper was born and completed his undergraduate training in Britain, studying medical laboratory technology, biochemistry and biochemical pharmacology. In 1960 he was recruited by Nathan Kline to work at Rockland Research Institute in New York where he has remained throughout a distinguished career. He arrived when biological psychiatry was in its infancy to work under one of its first champions. As he notes, "we were either on the cutting edge or out in left field". Funding was abundant with few competitors. Cooper and his wife lived on the 680 acre campus among the 9000 patients (most with chronic schizophrenia) that have now dwindled to 380. They carried out Nathan Kline's philosophy that young researchers should live alongside their patients to understand their life and illness.

Tom began as an assistant research worker studying the thyroid function of patients, the results of which turned out later to be largely an artifact of a diet supplemented by iodized salt. As he gained Kline's respect and friendship he took on additional responsibilities. In 1975 he became director of the Clinical Psychopharmacology and Clinical Chemistry Laboratory at a time when interest in drug metabolism and its relationship to clinical efficacy was evolving along with the necessary new methodology, including chromatography and mass spectrography. Shortly before Kline's death (in 1981) he became Chief of the Analytical Psychopharmacology Laboratory, dividing his time between the Nathan Kline Institute, New York State Psychiatric Institute and Columbia University.

A central theme of Tom Cooper's career has been his fulfillment of Nathan Kline's philosophy and the ACNP's primary goal of close collaboration between basic scientists and clinicians. His bibliography of 360 publications in 1994 includes a roll call of eminent clinical psychopharmacologists from many academic centers covering a diverse range of topics and methodologies, including hormones, drugs, metabolites and neurotransmitters in blood, spinal fluid, peripheral tissues, hair and brain. This research has been supported by NIMH grants from 1966 and continuing for 20 years. It is reflected in his work as a reviewer for NIMH Center grants and many leading journals in his areas of expert knowledge.

*Ermino (Mimo) Costa* may well be the most distinguished and productive scientist in this volume. That his interview is also the briefest requires explanation. When it reached the editor's desk only months after Dr. Costa's death (November, 2009), the transcript was seriously deficient and undecipherable in places. This biography serves to remedy gaps in the interview.

Mimo was born in Cagliari, Italy, in 1924, obtained his M.D. degree (cum laude) in 1947, became a research fellow in pharmacology, completed his PhD and was a full Professor of Pharmacology in the Medical School at the age of thirty, seven years after graduation (1954).

Resources in post World War II Italy were devoted more to reconstruction than scientific research and in 1954 Dr. Costa obtained a Fulbright Fellowship to join Harold Himwich at the Thudichum Psychiatric Research Laboratory in Illinois which later became the Psychiatric institute of Chicago, where Dr. Costa would be Scientific Director over forty years later.

In between these two milestones (1954-1996) Dr. Costa filled a series of increasingly prestigious appointments. In 1960 he joined Bernard Brodie at the NIH Laboratory of Chemical Pharmacology, became Deputy Chief a year later (1961) and then Head of the Clinical Pharmacology Section (1963-1965). He considered his mentorship in scientific methodology by Dr. Brodie to be a defining experience in his career.

In 1965, ready to spread his wings, he moved to Columbia University to create a new Research Center with an endowment of fifteen million dollars devoted to the neurochemistry of Parkinson's disease.

After three years he returned to the NIH to become Chief of Pre-clinical Pharmacology in the Intramural Program where he remained for seventeen years (1968-1985) before becoming Director of Fidia-Georgetown Institute of Neurosciences for nine years (1985- 1994).

In 1996 he returned to Illinois to become Scientific Director of the Psychiatric Institute of Chicago, Professor of Biochemistry and Psychiatry, where he remained until his death from multiple myeloma thirteen years later, at the age of 85.

During these sixty two years of his professional career Ermino Costa made numerous original and creative scientific contributions documented in over one thousand, frequently cited, publications involving six patents in five major research areas. In temporal sequence these are: 1. Serotonin receptor subtypes relating to the action of antidepressant and antipsychotic medications (1958); 2. The role of cyclic AMP in transsynaptic induction, in the pathophysiology of depression, and in the mechanism of dependence on drugs of abuse (1970s); 3. The mechanism of action of benzodiazepines and the GABA receptor (1974); 4. The existence of metabotropic glutamate receptors (1985); and 5. The relationship of reelin and GAD67 enzyme (which makes GABA) to schizophrenia (1998).

As the interview reveals, despite this impressive catalog of scientific contributions, Dr. Costa valued more highly his role as a mentor of over three hundred young scientists from around the world including China, Afghanistan, Japan, India and Australia. He accomplished this in his own labs and through the International School of Neuroscience he co-founded and directed for seven years in Padua (1988-1995).

Dr. Costa's accomplishments were recognized by many honors, prizes and awards including three gold medals, three honorary doctoral degrees and a knighthood of the Italian Republic. He was an honorary member of Pharmacological Societies in Hungary, Italy, Britain, and Czechoslovakia. He was Chief Editor of Neuropsychopharmacology for twenty seven years (1965-1992) and a Member of the National Academy of Sciences from 1982. Finally, he was a founding member of the ACNP, a Life fellow Emeritus and Vice President of the organization in 1977.

His recent obituary, by his colleague Dr. Dennis Grayson, sums up Ermino Costa's career in the following words, "He was an incredibly passionate leader and an outstanding scientist. He was a creative, dynamic, indefatigable scientist, teacher, editor, organizer and catalyst of people and ideas. He has clearly been a major force in the field of neuroscience over the last half century".

Our brief interview captures the essence of the man and his humanity but falls short of reflecting the scope of his scientific accomplishments and stature.

*Svein G. Dahl* arrived on the American psychopharmacology scene in 1989 at the age of 47 to give an invited plenary lecture at the ACNP annual meeting in Hawaii. He brought with him creative three dimensional video images and novel metaphors to illustrate how drug molecules might interact with receptors. These derived from his unique skill set in structural chemistry, crystallography, bioinformatics and pharmacology. The following year he was elected to the ACNP and has since been a regular participant at annual meetings.

Svein was born in Tromso, Norway, north of the Arctic Circle. He obtained his PhD in Oslo on the pharmacokinetics, plasma levels and clinical effects of the early phenothiazines and their metabolites, returning after six years to the new university in his home town as a full professor at the age of 34. Although Norway is parsimonious with research support the government was generous in allowing Svein to escape the arctic cold with an annual sabbatical every five years. He used these opportunities to broaden his knowledge, interests and reputation in Europe (especially France) and in 1985-1986 he spent a year as visiting professor in America at the University of California San Francisco working on molecular modeling.

Svein Dahl's career and contributions are sufficiently unique and diverse to create a difficult decision about in which of our ten volumes to place his interview. Volume 7 (Special areas or "Desiderata") is an ideal choice at a time when psychopharmacology needs new ideas and stimulation to break from its Procrustean bed of "me-too" molecules and tired metaphors.

Particularly appealing is that Svein has returned to the beginnings of psychopharmacology to construct three dimensional models of the chlorpromazine molecule, identifying the amino acid templates and electrostatic charges with which it embraces the receptor. This is reminiscent of the role the double helix played in the function of DNA. He tells his interviewer, "It is beautiful ... it sort of flows in space". He made a gift of the image to Pierre Deniker. This is so much more appealing and potentially productive than the worn out "Lock and Key" metaphor it replaces.

The interview provides a fuller account of how these creative concepts and techniques evolved; we must wait to see if they help translate today's molecules into new and better drugs.

David Dunner is a clinician and researcher whose career has been shaped by his family origin and research opportunities. As he notes, "I was always in the right place at the right time". His father was a general practitioner who became director of research for the entire Veteran's Administration in Washington DC. David went to medical school at George Washington University and was attracted to psychiatry when Eli Robbins was chair. The department was dedicated to a descriptive, medical and non-psychoanalytic approach where residents were required to do research and faculty included such pioneers and mentors as George Winokur, Paula Clayton, Ted Reich and Sam Guze. Patients treated with ECT, lithium and behavior therapy recovered and the Research Diagnostic Criteria were in use, later influencing the development of the DSM III.

David published his first research paper as a medical student, published more as a resident and after completing training became a clinical associate at NIMH for two years, working with Jules Axelrod, who had just won the Nobel Prize. Together they worked on catechol-O-methyl transferase in different diagnoses (published in *Science*) and then David collaborated with Elliot Gershon on bipolar disorder and clinical genetics where they were the first to define and describe Bipolar Disorder Type II.

Following this Dr. Dunner began an eight year stint at the New York Psychiatric Institute and Columbia University working with Ron Fieve in the Lithium Clinic and running the inpatient research unit. During this period he joined the ACNP (1974) when there were only 200 members and published fifty original scientific papers, including the first description of rapid cycling bipolar disorder and the influence of natural history on treatment outcomes.

In 1979, at age 39, Dr. Dunner became Chief of Psychiatry at Harborview Hospital in Seattle and Professor of Psychiatry and Behavioral Sciences at the University of Washington. Over the next ten years he built an extensive clinical trial program, at one time involving 26 studies in a wide range of diagnoses and treatments, mainly funded by industry and including the early trials of fluoxetine and alprazolam. This decade marked the "crest of the wave" in contemporary new drug development and provided the opportunity and satisfaction to mentor "people who have gone on to do great things" in this arena.

In 1989 Dr. Dunner became Director of the Center for Anxiety and Depression where he continued to do clinical trials and descriptive studies of patients and family members as well as consultation to local physicians in management of difficult cases.

Dr. Dunner has edited several text books and served on the editorial boards of a dozen journals, including Editor in Chief of *Comprehensive Psychiatry*. He has also served on the Scientific Advisory Board of the National Depressive and Manic Depressive Association, the DSM IV Work Group on Mood Disorders, and the Psychopharmacologic Drug Advisory Committee of the FDA. He has been President of the American Psychopathological Association, The Psychiatric Research Society and the Society of Biological Psychiatry and is the recipient of both the Samuel Hamilton and the Morton Prince awards of the American Psychopathological Association.

During a quarter of a century from 1970 to 1995 David Dunner made original and significant contributions to developments in the nosology and psychopharmacology of affective disorders.

*Burr Eichelman* s career in the animal and human study of aggression illustrates Louis Pasteur's aphorism that "chance favors the prepared mind". His parents wanted him to become a doctor and gave him piano lessons to improve his manual dexterity, an asset he later put to use in lesioning rat brains but not as a surgeon (as they had hoped). A bachelor's degree in Biopsychology (with Honors) from the University of Chicago shaped his interest in the "synthesis of morality, biology and behavior" at a time (1964) when stimulant drugs or brain lesions were found to influence behavior. Accepted for a combined PhD,MD program he did a summer internship under Robert McCleary, a mentor (also PhD,MD), who encouraged him to work on pain induced aggression in animals, using amygdala lesions in rats and leading to his first publication while still a student.

Burr completed his MD in 1968 and his PhD in 1970 and then took the advice of Danny Freedman, Chair of Psychiatry in Chicago, to do a pediatric internship before obtaining a two year fellowship at NIMH in Clinical Psychobiology where he continued his rat research in collaboration with a pharmacologist, neurologist and internist, exploring the role of chemistry, genetics and stress in aggression. He notes that "everything we touched was statistically significant", a powerful reinforcement for a young researcher in a new field.

In 1973 Burr moved to Stanford to become a resident fellow under Chairman David Hamburg where he was able to continue his research with Jack Barchas on biogenic amines and rodent aggression. During his fellowship he received three named awards, the A.E. Bennett Award from the Society of Biological Psychiatry, a W.C. Menninger Award (honorable mention) and a Falk Fellowship from the APA. On completing the resident fellowship in 1975 he was awarded a Kennedy Fellowship in Medicine, Law and Ethics which allowed him to take courses in law and ethics which rounded out his credentials for his planned research in aggressive and violent patients.

In 1976 he began a decade of work as Chief of Psychiatry at the VA hospital in Madison where he established a Laboratory of Behavioral Neurochemistry funded by grants from the VA and the NIMH totaling half a million dollars. Here he continued work on the role of biogenic amines and enzyme systems in rodent aggression, concentrating primarily on serotonin and noradrenalin. Within eight years of completing his residency he was appointed a Full Professor in the Department of Psychiatry.

It was at this productive mid-point in Dr. Eichelman's career, as he became interested in the clinical relevance of his animal studies, that he began to experience frustrations inherent in his area of research. Aggression is an episodic behavior in a variety of conditions some of which (dementia, developmental handicap) complicate informed consent. The absence of a definitive nosology, a single etiology or a discrete diagnostic category created barriers to obtaining NIH grant support or FDA approval for investigational drug studies. More pervasive was an ethical climate that labeled aggression as a moral shortcoming, unsuited for drug treatment that might be construed as an excuse from personal accountability. IRBs were reluctant to approve drug studies for what they considered "bad behavior".

Despite a lifetime of careful study and preparation Dr. Eichelman was forced to recognize that clinical aggression was a neglected stepchild of medicine that had become "a durable unmovable problem". In 1987 he closed his laboratory and the next year took a position as Professor of Psychiatry at the University of North Carolina in Chapel Hill and Clinical Director of the Dorothea Dix State Hospital. For two years he worked to develop the Carolina Nosology for Destructive Behavior, attempting to define its components in a multi-axial system that would broaden aggression beyond the single category of Intermittent Explosive Disorder and help identify different etiological factors with distinct clinical features.

At this point in his career Burr Eichelman felt that "the writing was on the wall". Recognizing that his interests were moving away from research toward administration and teaching he accepted the Chair of Psychiatry at Temple University in Philadelphia in 1990. Here he used his biological training to completely revise the first year medical student curriculum into a neuroscience course and his research background to encourage residents to undertake literature reviews and consider publishing their clinical findings. Consulting at a residential facility for developmental disabilities he was able to do some single case studies of  $\beta$ -blockers and SSRIs to reduce aggressive behaviors.

After seven productive years in Philadelphia, Burr and his wife returned "home" to Wisconsin where he runs the consultation-liaison and emergency services at the University hospital in Madison.

He retains strong convictions from his pioneer lifetime interests in animal and human aggression, believing that that the APA, NIMH and American psychiatry have ignored and disenfranchised a group of people whose problems with aggression create major economic and personal costs and are frequently overlooked or undertreated as moral aberrations.

At a time when America is sorely troubled by violence, aggression, military suicides and post traumatic stress disorder one solution might be to create a government endowed chair in aggression research. Perhaps this is something the ACNP might advocate. Nobody could fill such a position with more distinction than Burr Eichelman.

Jean Endicott is Professor of Clinical Psychology at Columbia University, an honorary Fellow of the APA and a member of the ACNP for over a quarter of a century. This interview, by the Director of Research for the APA, details her unique and unequalled contributions to the scientific measurement of psychiatric disorders essential to their classification and the assessment of treatment outcome.

Jean was born with a sense of curiosity and urge, to perform experiments that began as a young child cultivating beans and melons from worm beds in her father's garden. Her initial inclination to become an organic chemist was nipped in the bud when a summer student stint in a hospital emergency room persuaded her that people were more interesting than molecules. She chose an eclectic undergraduate honors program that kept her options open until a course in abnormal psychology "hooked" her and she enrolled in the clinical psychology graduate program at Columbia University Teachers College, known for its strong curriculum in measurement, assessment and statistics. Married to a future psychiatrist at the age of eighteen Jean's first publication, co-authored with her husband, was on *Objective Measures of Somatic Preoccupation*, published in 1963 while she was still a graduate student.

Following graduation Dr. Endicott met Eliot Spitzer at a cocktail party when he had a new grant and was looking for a research assistant to interview patients using the Mental Status Schedule he had developed. Thus began over a decade of close collaboration at the time when NIMH was gearing up to perform large scale collaborative studies of the new psychotropic medications under the aegis of the Early Clinical Drug Evaluation Unit (ECDEU) program. A major task was to expand the Feighner Criteria developed by Eli Robbins and the faculty at St. Louis, leading to the Research Diagnostic Criteria (RDC), which in turn created the framework for DSM III. The scales developed in this period were employed in the five centers Collaborative Depression Study - begun in 1978 - which continues to provide follow up data. Much of the work accomplished in just over a decade was summarized in the Chapter on Psychiatric Rating Scales published in the Global Assessment of Functioning (GAF) scale that replaced Axis V in DSM III R.

Overall Dr. Endicott's contributions to psychometrics have been prodigious. Prior to 1993 she had been a co-author on almost 300 studies or book chapters, many published in the world's leading clinical and pharmacology journals. She has been principal, co-principal or co-investigator on 24 research grants, mostly funded by the branches of NIH and a co-author or consultant in the development of an equal number of evaluation instruments. These include seminal studies of premenstrual mood disorders that led to the inclusion of Premenstrual Dysphoric Disorder (PMDD) as a supplementary diagnosis in DSM IV. This, in turn, resulted in the FDA Psychopharmacology Advisory Committee (of which Jean was a member) approving several drug studies for this indication.

More recently she has been involved in developing quality of life, enjoyment and satisfaction measures (Q-LES-Q) that are independent of diagnosis or specific symptoms, the adult form of which has been translated into 72 languages or dialects for use in both medical and psychiatric settings. Many of these instruments may have an even more important role as computers and electronic records begin to play a larger role in contemporary medicine.

Jean Endicott serves on the editorial board of *Psychosomatic Medicine* and *Neuropsychopharmacology*, has been President of the American

Psychosomatic Society and a consultant or committee member of many national organizations, including NASA as an advisor on astronaut selection!

Somehow or other Jean and her husband also find time to collect tribal and early American art.

*Barbara Fish* is an Emeritus Life Fellow of the ACNP (1961) which, in its earliest days, comprised a membership of one hundred men and five women. She is a pioneer, the first female psychopharmacologist, whose scientific career is described as a model for professional women in Ruth Halcomb's book, *Women Making It*, published in 1979, in New York.

Barbara was the only child of a mechanical engineer devoted to science. As a five year old she remembers her father explaining the 1925 total eclipse of the sun with a light bulb, a grapefruit and an orange. Encouraged to study nature and science she earned scholarships throughout high school and college, graduating summa cum laude from Barnard College of Columbia University before completing medical school at the end of World War II and winning the Alpha Omega Alpha prize for the highest scholastic rating.

She completed internships in medicine and pediatrics before a residency in psychiatry that concluded with two years on the *Child Psychiatry* service at Bellevue Hospital where she was mentored by Loretta Bender as a senior resident, looking after one hundred and fifty psychotic children a year, admitted from the Bronx and Manhattan.

Dr. Fish began her academic career in 1955 as an Instructor in Psychiatry at Cornell Medical Center and Child Psychiatrist in Pediatrics at New York Hospital. She completed psychoanalytic training the following year at a time when the only medical treatments for children with psychotic disorders were electric shock, phenytoin and diphenhydramine. Even before chlorpromazine became available her astute clinical observations in very young children convinced Barbara that "there was definitely something wrong in the brain in schizophrenia". Studying and comparing two birth cohorts from a Well Baby Clinic and a State Hospital sample of children of schizophrenic mothers she detected alterations and fluctuations in neurological and psychological development as early as two and a half months that were clearly genetic. Her observations included home visits, immediate availability to mothers and long term follow up that has lasted fifty years in some cases.

Dr. Fish raised funds and quickly developed a large fellowship and residency training program at Bellevue including inpatient and outpatient care with parent and patient groups as well as weekly parties for the children. When chlorpromazine became available and proved effective in adult schizophrenia she collaborated with Ted Shapiro in a series of placebo controlled ABA designs that were the first successful psychopharmacology studies in children with the drug. In 1961 they set up a psychopharmacology research unit at Bellevue, funded by NIMH for a decade. She became the first child psychiatrist and only woman to interact with the small group of adult investigators that formed the NIMH funded Early Clinical Drug Evaluation Units (ECDEU).

In 1970, fifteen years after the start of her academic career Dr. Fish became Full Professor of Child Psychiatry at NYU and in 1972 she and her husband moved to California where she became Professor of Psychiatry at UCLA. This marked a significant transition in her interests away from psychopharmacology. A number of factors contributed, scientific and socioeconomic to her decision to move. In 1963 or 1964 she had listened and disapproved as the head of NIMH spoke to the ACNP, predicting a biologic cure for schizophrenia and approving of the closure of State Hospitals and inpatient units. This led to shorter durations of inpatient treatment and an attitude where "we start to talk about whether a drug works as opposed to really getting to know a child well". Fragmentation of care made longitudinal studies difficult to conduct.

Dr. Fish also disapproved of the rigidity and diagnostic parsimony of DSM III compared to the typology of child development she had so painstakingly developed. And finally, she felt that pharmaceutical companies used financial incentives to divert academic interests away from long term outcome studies. "It's not where you make money, if you really want to take care of sick people".

These beliefs clearly influenced how Barbara Fish chose to spend the remainder of her career. She returned to her earlier interest in the phenomenology, natural history and outcome of childhood onset schizophrenia seeking funding exclusively from NIMH and private sources including the MacArthur Foundation, the W. T. Grant Foundation, the Scottish Rite Schizophrenia Research Program and the Della Martin Foundation which also endowed a named Chair of Psychiatry in her honor. The topics she pursued included risk and protective factors in prognosis, information processing as a risk factor, adult outcome of infants at risk and the effect of early development on personality.

In 1987 Dr. Fish's lifetime accomplishments led to receiving the Agnes Purcell Mc Gavin award from the APA "for outstanding contributions to the prevention of mental disorders in children, including ground breaking research on the long term outcome of infants born of schizophrenic mothers".

As people read this interview they may well conclude that, for Barbara Fish, psychopharmacology was a rite of passage. When she left Bellevue and relinquished her interest she noted, "I'd learned what I wanted".

Mark George is both a neurologist and a psychiatrist at the forefront of some of the most innovative and occasionally controversial areas of neuroscience. He is Distinguished Professor of Psychiatry, Neurology and Radiology at the Medical University of South Carolina, (MUSC), and Director of both its Brain Stimulation Laboratory and the Functional Neuroimaging Division. Mark is an active and enthusiastic member of the ACNP who began attending meetings as a resident, won a Mead Johnson Travel award in 1992 and was elected a member in 2000. His interview is conducted by Bob Post, his former mentor at the NIMH Biological Psychiatry Research Branch from 1991 to 1995.

Mark was an Eagle Scout, President of his High School Honor Society and a National Honor Society Scholar with an undergraduate degree in philosophy who graduated cum laude from the Honor College at the University of South Carolina before obtaining his MD degree in 1985 at the Medical University of South Carolina. In medical school he was talent spotted by Jim Ballinger who had established a unique interdisciplinary residency program in neurology and psychiatry. This matched Mark's view that neurology knew the brain while psychiatry was brainless but embraced all the interesting ideas that were taboo in neurology, including hopes, emotions and beliefs. He became "hooked on research", won back to back annual awards for the best resident papers and became fascinated with brain imaging after MUSC obtained its first CT scanner, which he recognized would provide access to the organ both his disciplines shared.

Two of the few places in the world doing brain imaging in 1990 were NIH and Queen's Square in London. Mark George wanted to sample both, spending time in England (1990-1991) with Mike Trimble before returning to NIMH.

The interview details his early involvement with Transcranial Magnetic Stimulation (TMS), identifying regions of the brain involved in depression ("the lesion") and non convulsive techniques to stimulate them. This attracted media attention, professional skepticism, the disapproval of some administrators at NIMH and got him "kicked out" of the Association for Convulsive Therapy (ACT) who believed seizures were essential for cure. Mark's ambition to combine stimulation and scanning was frustrated when colleagues in charge of magnetic resonance imaging (MRI) denied him access to the machine. This contributed to a decision to return to MUSC where his creativity was better appreciated (1995).

His interests there expanded to include vagal nerve stimulation (VNS) when its use in epilepsy induced improvements in mood and he collaborated with others to do the first pilot studies and then controlled trials for mood disorders, leading to FDA approval. Mark expresses frustration that those responsible for commercial exploitation of the technique have neglected to explore its neuroscience and underlying neurobiology.

The interview includes many interesting insights and speculations about the future possibilities for focal brain stimulation and discusses the helpful role of the ACNP and his new journal on the topic by encouraging communication between neurologists, psychiatrists and cognitive neuroscientists.

Dr. George is a member of numerous professional organizations, and is on the editorial boards of five journals and a reviewer for many more. In one decade (from 1989 to 1999) he co-authored almost a hundred articles in refereed journals, thirty book chapters and has written and edited two books. His research is funded by multiple grants from diverse sources including Foundations, the VA, NIH Center grants, and commercial or pharmaceutical companies. He has received several research awards during his career including the prestigious NARSAD Falcone Award.

In an exchange with his interviewer Mark George pays homage to his mentor and the ACNP for "key lessons of using critical science to answer questions, to be open minded but skeptical, to be a colleague, to share and work with other people".

*Alexander (Sandy) Glassman* is Professor of Clinical Psychiatry and Chief of Clinical Psychopharmacology at Columbia University, College of Physicians and Surgeons. He has been a Fellow of the ACNP since 1981.

Sandy came to psychopharmacology by a circuitous route. His original plan was to join an uncle in orthopedic practice who was team doctor to the Chicago Bears. During a distinguished undergraduate career at the University of Illinois he was awarded a four year scholarship, won the outstanding student award in physics, and graduated first in his class. During medical school, also at the University of Illinois, he decided he wanted to become a psychoanalyst and began residency training when Milt Rosenbaum was Chair of Psychiatry at Albert Einstein, an analytically oriented department like so many others at that time.

Because he was awarded a Public Health Teaching Fellowship (1963-1964) he was chosen to attend an NIMH conference on the new discipline of psychopharmacology where he met Fred Goodwin, John Davis and Biff Bunney. Due to the Fellowship he had also felt encouraged to obtain a research grant to study tryptophan supplementation in patients treated with an MAO Inhibitor. These two events provided the credentials to teach psychopharmacology to his fellow residents so when he was drafted during the Korean War the army made him Director of Psychiatric Residency Training at Letterman Hospital in San Francisco and invited him to write a monograph on psychopharmacology.

In 1969 Dr. Glassman returned to New York to join Ron Fieve doing lithium research but was soon appointed Acting Director of Biological Psychiatry and then Director (1973). This marked the beginning of a highly productive sequence of original clinical observations and research findings. Together with Jim Perel, a talented physical chemist, they developed the methodology and research support to do the first metabolic studies of imipramine, correlating therapeutic outcome to blood levels. This led to corresponding research on slow metabolizers, high blood levels and cardiac toxicity as well as to the discovery that patients with delusions did poorly despite adequate blood levels.

After studying tricyclic compounds Sandy became interested in the therapeutic effects of stimulants, quickly realizing that nicotine was the stimulant most used by depressed individuals. This led to a series of important discoveries including the modest efficacy of clonidine on nicotine withdrawal (published in *Science*), the adverse effect of depression on smoking cessation and the possibility that antidepressants might be helpful in quitting (leading to Linda Perry's discovery of buproprion for this purpose).

Dr. Glassman's next and probably most thought provoking research, beginning in the late 1980s, was on the relationship between depression, its effect on the morbidity and mortality of cardiovascular disease, and the preventative value of antidepressants. This interview details the still unresolved and ongoing saga of attempts to study this possibility for which there is suggestive but not definitive support. The dilemma this poses illustrates the fact that not every worthwhile hypothesis is amenable to scientific study. To do so would require a sample size of around four thousand and an estimated cost of about thirty million dollars. Meanwhile the death rate of cardiovascular disease is declining, the ethics of placebo controls in a population with a significant prevalence of depression is guestionable and the patents on older antidepressants are expiring while the cardiac safety of newer compounds is not established. For example, duloxetine is extensively (and expensively) advertised for depression in physical conditions but it can alter blood pressure as well as interact with anticoagulants and some antiarrhythmics. It has not been studied in patients with a recent history of myocardial infarction or coronary artery disease as such patients were excluded from early clinical studies.

In 1989 Sandy Glassman received APA's Foundation Fund Prize for Research. He is a consultant or committee member to a large number of organizations and a member of the editorial board of the *Journal of Clinical Psychopharmacology*. He has been an invited lecturer or visiting professor in Japan, China and Germany.

*Uriel Halbreich* s productive and creative career can be divided into two distinct parts, before and after the midpoint of a biblical lifespan. The foundations of his interdisciplinary, multidimensional and innovative conceptualizations of mental illness and its treatment were laid down in the first thirty five

years of professional development in his native Israel. The role models and resources to bring them to full fruition were added when he immigrated to the United States at that age in 1978.

Dr. Halbreich completed his MD degree and dissertation in 1968 at Hadassah University in Jerusalem when he was already interested in neurology, psychiatry and women's hormones. Drafted into the armed services he became Vice Chief Medical Officer of the Israeli Navy at the age of 27, responsible for administration, research and training. In the next eight years he completed a psychiatric residency and additional training in neurology, liaison psychiatry, community psychiatry and psychotherapy. Despite an absence of mentors, and in a psychoanalytic environment, he became involved in research, including dysphoric disorders in women, psychoendocrine rhythms and premenstrual syndromes (PMS) some of which he published in *Archives of General Psychiatry* and *Lancet*. But it was an uphill struggle for recognition and advancement, so he began to seek wider horizons.

In 1978, at age 35, he accepted an invitation from Ed Sachar to take a two year Fellowship in Biological Psychiatry at Columbia University in New York, supported by winning a National Research Service Award. Here he began to meet the "big names" in psychopharmacology, including Don Klein, Sid Malitz, and Sandy Glassman.

From this point on it would not be hyperbolic to describe his career trajectory as meteoric. From Columbia, in 1980, he moved to Albert Einstein College of Medicine (AECOM) to become Director of the Division of Behavioral Endocrinology and Founding Director of both the Affective Disorder Clinic and the Division of Biological Psychiatry (including units of Clinical Psychopharmacology and Behavioral Endocrinology). After five years he moved again to become Director of Biobehavioral Research in Psychiatry at the State University of New York at Buffalo (SUNY/AB) where he later founded the Life Cycle Center to include the Psychosomatic OB/GYN program.

Dr. Halbreich rose from Assistant to Full Professor of Psychiatry in only seven years (1985) and is also Research Professor in OB/GYN (1988). He joined the ACNP in 1982 and became a fellow in 1985. From 1981 to the time of this interview in 1997 his research was continuously supported by eight NIMH grants, an equal number of private Foundations and by over 20 grants from a dozen leading pharmaceutical companies.

As described in the interview, this academic success and economic support is a reflection of Uriel Halbreich's innovative approach to mental illness. This differs markedly from the etiologic and descriptive parsimony of contemporary (DSM) nosology which is "still based on syndromal typing and may not have anything to do with biology". Psychiatry, unlike medicine has not progressed beyond symptomatic phenomenology (pain, fever, hypertension, depression) to differential diagnosis based on genetics, environment or hormonal instability and their interactions.

Dr. Halbreich credits the pharmaceutical industry with helping to shift the focus of depression research from men to women, with their variable hormone fluctuations, but he is critical of its reluctance to take innovative risks for fear of commercially unfavorable results. This is one reason he supports his own research with a balance of federal, foundation and commercial grants.

Consistent with his interdisciplinary beliefs is Dr. Ulbreich's commitment to translational education, to "spreading the word beyond the ivory towers" and to "developing countries". To this end he is Chairman and CEO of the International Institute for Education in Mental Health and Psychopharmacology and also President of the International Society of Psychoneuroendocrinology.

Viewed in the context and continuum of psychopharmacology research Uriel Halbreich may well be a founding member of a new generation of creative thinkers.

*Katherine Halmi* is the self styled "grandmother of the eating disorder field", a title she has earned by devoting over thirty years of her career to research on a topic she was among the first to study.

Katherine earned her undergraduate and medical degrees from the University of Iowa on a General Motor's Scholarship and began her research career doing chromosome counts as a medical student and publishing her first paper on the identification of Trisomy 18 while a pediatric resident in 1968. Her other major interest was endocrinology, fostered by her husband, who was Editor of Endocrinology, and who mentored her in critical thinking.

After board certification in pediatrics she studied cortisol metabolism, completed a fellowship in child development as a faculty member at the University of Iowa and then decided to take a second residency in psychiatry. George Winokur was Chair of the Department, mentored her in research principles and methodology and suggested she explore the topic of anorexia, then a field with few publications on the border with endocrinology. As a first year resident she spent her lunch hours combing through the medical records of the Iowa Psychopathic Hospital to find a cohort of 96 women and 4 men who met the Feighner criteria for anorexia, published in 1972. From these she located a group of 76 subjects, admitted them for endocrine studies and a standardized interview, followed them up and published her findings.

With Winokur's endorsement and encouragement Dr. Halmi soon became identified as a regional and national expert in the new field of eating disorders, in charge of a thirty bed inpatient unit. In 1979 she moved to Cornell Medical Center (Westchester Division) also to run an inpatient unit and eventually become Director of the Anorexia and Bulimia Clinical Research Program and a Full Professor of Psychiatry (1986). This interview provides an account of over twenty years research supported by over three million dollars in grants mainly from federal and foundation sources, including seven NIMH projects, awarded between 1975 and 1996.

Dr. Halmi's studies were among the first to distinguish anorexia from bulimia nervosa and to demonstrate differences between them in response to serotoninergic challenge tests. There were significant difficulties to be overcome, including the problem of adequate sample sizes in anorexia patients reluctant to accept treatment, co-operate with research protocols and whose severe physical condition made randomization to a control group unethical. Bulimia patients on the other hand were motivated to recover and studies soon demonstrated the efficacy of antidepressants, irrespective of mechanism, although only 20 to 30% recovered completely compared to double that number treated with sophisticated cognitive behavioral methods.

Although antipsychotics have been used with modest success to induce weight gain and diminish hyperactivity in anorexia there have been no controlled studies perhaps because the condition is too rare for commercial consideration, prognosis is poor, chlorpromazine is generic and weight gain due to olanzapine might draw attention to an undesirable side effect for its accepted indications.

This interview includes interesting commentary on the role of the press in capitalizing on the dramatic aspects of eating disorders, the popularity of esoteric unproven treatment programs and the influence of culture and cosmetic concerns on the incidence and prevalence of the disorders.

Dr. Halmi is the Chairman of the APA Task Force on Treatment of Eating Disorders and is critical of undue influence exerted by psychoanalysts and family therapists on the development of guidelines based on anecdotal outcomes. This "unempathic" attitude resulted in her being "disinvited" from the deliberations and leads her to the interesting suggestion that, because the APA process is so heavily political, the ACNP might consider producing its own guidelines!

Turning from politics to science Dr. Halmi reveals some fascinating early data in a multinational study, funded by the Price Foundation, of one hundred sibling pairs with either similar or discordant eating disorders which reveals DNA evidence of an abnormality on Chromosome 1 for anorexia nervosa (restricting type). This chromosome involves both a serotonin and an opioid receptor site. She concludes the interview with her opinion that the future development in eating disorders lies in the genetic aspect – an interesting opinion by someone whose career began in that field over forty years ago.

In conclusion, Katherine Halmi has served as President of three national organizations in her areas of research: the American Psychopathological Association, the Society of Biological Psychiatry and the Eating Disorder Research Society. As a metaphorical "grandmother" she has spawned a heritage of fertile research projects and ideas in the field of eating disorders.

*Dilip Jeste's* distinguished and creative career has been driven by a fierce and determined sense of purpose. Born in India, son of a judge and a housewife, fourth of five siblings, he read and was fascinated by Freud as a teenager. He entered medical school certain he wanted to be a psychiatrist and never deviated from his desire to become an academic committed to biological research. His six week student rotation offered mainly ECT administered to psychotic rural villagers too poor to pay for medication. In residency he was fortunate to find a mentor (Dr. Vahia) who had studied in America with strong interests in psychosomatic research. Dilip published his first paper (on Hysteria) as a resident and later won an award in 1973 for best original psychiatric paper in India, on psychotherapy in psychophysiological disorders, published in the *American Journal of Psychotherapy*).

When India could not provide the economic and academic resources to support his research ambitions, Dr. Jeste immigrated to the USA in 1974. He spent his first year as a resident in America at New Jersey Medical School and although it had little to offer in research he completed a very early study on the suppression of tardive dyskinesia by frequent dosing with chlorpromazine (published in *Diseases of the Nervous System*) and began an historical review of serendipity in psychiatric discovery, later published in the *Archives of General Psychiatry*.

Still looking for a good place to do research he transferred to Cornell University (Westchester Division) when Bob Michaels was Chair and the department, though academic, was very oriented to psychoanalysis and psychotherapy. Characteristically he took advantage of what was available in order to do what he wanted. Cornell had an outstanding Department of the History of Behavioral Science where he pored over ancient tomes to write a paper on schizophrenia as a biological disorder present throughout human history and not a product of modern civilization (published in *Comprehensive Psychiatry*). In his final year as a resident he worked in an animal research lab doing stereotactic infusions into the cerebral ventricles of the rat.

By now Dr. Jeste had accomplished enough to obtain a research fellowship at NIMH in 1977 where he remained for nine years with Richard Wyatt in neuropsychiatry, alongside Floyd Bloom, Ermino Costa and Chris Gillin. This was a highly productive period in which he completed a neurology residency, conducted clinical and animal research and worked in neurochemistry labs. In the National Library of Medicine at NIH (the largest in the world) he felt like "a kid in Toys 'R' Us". During his time at the NIMH he published close to one hundred papers, one of which (on biological heterogeneity in schizophrenia) won the A.E. Bennett Award. In 1982 he co-authored his first book with Richard Wyatt on *Understanding and Treating Tardive Dyskinesia*.

Having firmly trained and established himself in neurobiological research Dr.Jeste left the NIMH in 1986 to become Professor of Psychiatry and Neuroscience and Director of Geriatric Neuropsychiatry at the University of California at San Diego.

This interview tells how he spent the next fifteen years of his remarkably productive career (1986-2001). His major focus has been on late onset schizophrenia, the influence of age on early onset patients and the occurrence in rare instances of complete remission. As with everything else, his contributions have been original and thought provoking. "The excitement of something new; that's what turns me on". Like some others in this volume he questions the validity of the DSM classification in schizophrenia, based on clinical symptoms. He views chronic psychosis (his preferred diagnosis) as a multi-dimensional syndrome differentiated by ventricle size, tardive dyskinesia, and neurochemical, cognitive and genetic variables. He believes that understanding the causes for late onset and occasional remission may provide the key to better treatment and possible prevention.

Within this clinical and research framework Dr. Jeste's output has been prolific. His research has been supported by the National Institutes of Health, the VA, Foundations and pharmaceutical companies. In the most recent seven year period (1994- 2001) his research received continuous support from NIMH as a principal investigator with seven awards totaling in excess of nine million dollars and as a co-investigator from three other awards totaling fifteen million dollars. His publications now total over three hundred articles and book chapters and he has co-authored six more books. He is sought after as a member of committees and editorial boards and as a local, regional, national and international speaker. Most importantly, he is a sponsor or mentor to pre and post doctoral students from a variety of disciplines who have won career development or young investigator awards from the National Institutes of Health and Research Foundations.

It is hard to imagine anyone who has so completely fulfilled their early ambitions, but towards the end of this interview Dilip states, "I think my best paper has yet to be written".

Seymour Kaufman began life with an ambition to become an artist, won competitive entrance to the prestigious New York High School of Music and Art, but soon realized he lacked the talent to make a living in a competitive but unremunerative career. Fortunately, he was also interested in chemistry and obtained excellent undergraduate and graduate training under Hans Neurath at the University of Illinois at Champagne Urbana. After obtaining his Master's degree he moved to New York University to work on his PhD in Biochemistry under Severo Ochoa, a future Nobel Laureate. By the time he graduated (1949) he already had eleven publications in enzymology, his career long area of expertise.

Dr. Kaufman spent the next five years in the Pharmacology Department at New York University Medical School (1949-1954) working primarily on phosphorylating enzymes.

In 1954 a fellow post doc moved to NIH to start a new laboratory and invited Seymour to join him. Here he began his life long interest in the metabolism of phenylalanine, a topic he chose because it had an enzyme reaction for which there was no easy equation that resembled a *New York Times* "double acrostic" puzzle.

The interview covers the remainder of Dr. Kaufman's productive career at NIH spanning forty six years (1954-2000), during which he became the Chief of his own Laboratory of Neurochemistry (1971). During this period he elucidated the biochemical mechanism and defects underlying the various forms of phenylketonuria, involving collaboration with pediatricians to identify new forms and obtain a fuller understanding of the dietary treatment and its limitations.

During his career Dr. Kaufman published over 300 articles on his research findings, wrote or edited several books and was the editor of two major journals, *Biological Chemistry* (1964-1976) and *Archives of Biochemistry and Biophysics* (1963-1972). He was elected to the National Academy of Sciences (1986) and the American Academy of Arts and Sciences (1987) and is the recipient of the Meritorious Presidential Rank Award (1989) and the Hillebrand Prize (1991). Dr. Kaufman was a Life fellow Emeritus of the ACNP (1982).

At the time of this interview (2002) Dr. Kaufman had retired from NIH with Emeritus status and returned to his earlier avocation as an artist, encouraged by his daughter, who is a talented sculptress.

*Rachel Klein s* precedent setting career in pediatric psychopharmacology did not evolve exactly as she anticipated.

Born of Russian parents and raised in France, she immigrated to the United States at the age of 15, after World War II ended. During her undergraduate degree in literature at New York City College she worked with ghetto children in a community center, fell in love with the kids and decided to do graduate studies in a prestigious clinical psychology program at Teacher's College, Columbia University. She took a summer job at Hillside Hospital, evaluating patient outcomes in the earliest adult psychopharmacology studies, conducted by Don Klein, Max Fink and Max Pollock. Despite the prejudice of her discipline against drug use she was struck by the contrast between the ideologically based dicta of graduate school and the serious,
empirical and data based approach she encountered in her psychiatric mentors. This viewpoint was strongly reinforced by witnessing the rapid recovery of severely depressed patients treated in one of the first pre-marketing studies of imipramine. "It seemed miraculous".

Rachel's first publication, while still a graduate student was on the *Effects of Psychotropic Drugs on Long Term Adjustment*, published in *Psychopharmacologia* in 1964. Her PhD. dissertation topic on "The Prognosis in Schizophrenia" was influenced by the views of Max Pollock and Don Klein on developmental psychopathology and her reading of Kraepelin's descriptions of the influence of childhood on the natural history of the disorder. She graduated with her PhD in 1966 but only after a hostile and critical review of the dissertation for its relative lack of psychological input and failure to emphasize the role of families in the etiology of schizophrenia, the prevailing psychoanalytic theory at the time.

Following graduation Dr. Rachel Klein joined Dave Engelhardt in the new psychopharmacology branch at Downstate Medical School where he was conducting one of the first studies on the outpatient treatment of schizophrenia. She was hired to prepare and administer a grant for the comparison of chlorpromazine and diphenhydramine in young children with autism and developmental disorders which confirmed the superior benefit of the antipsychotic in reducing uncontrollable behavior.

This outcome reinforced her commitment to child psychiatry and she returned to Hillside Hospital to work with Don Klein (later her husband) on the treatment of separation anxiety in children (aged 6-15) with imipramine. Subsequently they moved on to study the use of stimulants in attention deficit hyperactivity disorder.

This interview documents her subsequent career and move to Columbia University (1978) where she has been Director of Clinical Psychology at Presbyterian Medial Center and Professor of Clinical Psychology (since 1980). The topics discussed cover a wide range of issues in which Dr. Rachel Klein has played a pivotal role. These include the influence of adult psychopharmacology on pediatric research and clinical practice, the controversies surrounding the development of the DSM criteria for separation anxiety and attention deficit disorder, the social and cultural issues in antagonism toward drug use in children, the etiological theories of attention deficit disorder and the ineffective role of adjunctive cognitive, behavioral and social interventions in its treatment outcome.

Prevailing throughout the dialog in this interview is a tone of creative and benevolent skepticism. As Rachel herself comments, "I'm not an easy believer and don't join bandwagons easily; that's probably why I went into research". It has been a productive career which includes over 150 articles and book chapters published in just over thirty years (1964-1995), editorship of four books and author of two, including *Anxiety Disorders in Children* (1989). Dr. Rachel Klein is an Honorary Fellow of the APA and a Fellow of the ACNP (1973), a consultant to the FDA and the APA Task Force on Nomenclature and Statistics (DSM III), Associate editor of the *Journal of Child and Adolescent Psychiatry*, member of six other editorial boards and a reviewer for fifteen journals.

David Kupfer has many claims to fame but his interview focuses on the topic most relevant to this volume. That is his involvement in the American College of Neuropsychopharmacology (ACNP). The founding of the College, its leadership, its goals, its accomplishments and its challenges are the single most important and relevant influence on the development of neuropsychopharmacology over the last half century or more. Its ubiquitous importance to all the contributors in this volume is obvious. The ACNP has been an essential ingredient of the "things needed or wanted", the Desiderata, that have shaped the evolution of our field.

David attended his first meeting of the College in 1970 when he was a post-doctoral fellow and nine years after it was founded. He became a Member in 1975, a Fellow in 1981 and has been Chair of the Credentials and the Nominating Committees, a Council member and President in 1995, the year before this interview.

The interview highlights significant elements of the ACNP's influence on the field and its members. These include the founders' intention to foster and stimulate dialogue and collaboration between clinical and basic scientists. This primary goal has been supported by weeklong annual meetings in sunny locations that showcase the leading experts and developments in the field and which encourage the interaction of young scientists with senior mentors and their peers in related fields.

The interview elaborates on the ACNP's role in advocacy, education and recruitment as well as being a fertile seed bed for the creation and exchange of innovative ideas. It also touches on some inevitable tensions and their potential resolutions. These include the fluctuating balance between clinical trials and basic science, the size of the membership (elitist or inclusive), and the influence of the pharmaceutical industry on the organization's fiscal viability and scientific credibility.

What this interview does not do is portray the scope of Dr. Kupfer's own scientific, educational and administrative achievements in the entire fields of psychiatry and neuropsychopharmacology.

David Kupfer graduated magna cum laude from Yale in history and economics (1961) and also obtained his MD from the university (1965). He was a clinical associate under Fred Snyder at NIMH in the intramural research Clinical Psychobiology Laboratory (1967-1969) before he returned to Yale as Assistant Professor and NIMH Research Career Investigator (1970-1973).

In 1973 Dr. Kupfer moved to the Pittsburgh School of Medicine as Director of Research and Training at Western Psychiatric Institute and Clinic (WPIC) where he was also Director of the Sleep Evaluation Center (1973-1984) and later Director of the Clinical Research Center for Affective Disorders (1977). He was appointed full Professor of Psychiatry in 1975, only ten years after his MD and became Chairman of the Department of Psychiatry (now the Thomas Detre Chair) in 1983, the position he held at the time of this interview, in addition to being a Fellow in Behavioral Science at Stanford University (1995-1996).

Dr. Kupfer's Biographical Sketch on file with the ACNP summarizes his career in the following manner, "He has promoted widespread collaborations between clinical investigators in psychiatry and those in more basic neurosciences. These studies are not limited to depression and other mood disorders but encompass virtually every psychiatric disorder and every age group, from infants to the 'oldest old'. Under Dr. Kupfer's direction WIPC has become one of the nation's preeminent university-based psychiatric centers as evidenced by the quality and number of publications as well as the amount of peerreviewed federal funding for mental health research. For more than twenty years, Dr. Kupfer's research has focused primarily on the conceptualization, diagnosis, and treatment of mood disorders. He has written more than 750 articles, books and book chapters that examine the use of medication in recurrent depression, the causes of depression, and the relationship between biomarkers and depression".

In recognition of these accomplishments Dr. Kupfer has received many named national awards over the course of his career and was elected to the Institute of Medicine of the National Academy of Sciences in 1990. These awards include the A.E. Bennet Research Award (1975), the Daniel H. Efron Award (1979), the Isaac Ray Decade of Excellence Award (1994) and the Gerald Klerman Lifetime Research Award (1996).

As his interview and biography demonstrate, David Kupfer's scientific accomplishments are in obvious synchrony with his leadership role in the ACNP.

Sarah Lisanby is the youngest researcher interviewed for this volume and a member of the newest generation of creative brain scientists in biological research. The milestones of her early career match those pioneered by her predecessors.

At high school, in Washington DC, she showed an early interest in psychological development and spent her vacations working in labs at the NIH and military research facilities including studying the anatomy of the human brain. She volunteered as a nurse in a State mental hospital where she cared for geriatric patients with chronic schizophrenia.

She graduated from Duke University (1987), Magna cum Laude, with a dual bachelor's degree in Psychology and Mathematics, after spending a semester at Oxford University, studying literature.

Sarah attended Medical School, also at Duke, and was already determined to become a psychiatrist although also tempted by surgery. As was the custom there, she spent her entire third year doing research and published her first scientific abstract while still a student (on biochemical changes in rat brain).

Sarah also completed her psychiatric residency at Duke (1991-1995), published her first paper in her second year on MRI changes in Parkinson's diseas, and spent her final year as Executive Chief Resident.

After graduating she became a Post-doctoral Clinical Fellow in Psychiatry at Columbia University (1995-1998) where she was mentored by Harold Sackheim and trained in brain imagery and interventional techniques (ECT and TMS). She was supported by an NIMH training grant and obtained her first independent research award during this time (on the safety of TMS in volunteers).

On completion of her fellowship (1998) she was appointed a faculty member at Columbia University and Director of the Magnetic Brain Stimulation Laboratory at NY State Psychiatric Institution. In the six years leading up to this interview (1998-2004) her research output has been prolific, supported by over ten million dollars in research awards from the National Institutes of Health, the Department of Defense, Stanley Foundation, NARSAD and American Federation for Ageing Research.

Major research topics have included the techniques, mechanism and effects of TMS, animal models (rhesus monkeys), human research (volunteers and patients), the neurobiology of emotional states, reversing the cognitive deficits of sleep deprivation, brain imaging in Lyme's Disease and strategies to reduce cognitive effects of ECT in geriatric patients.

In nine years since graduation (1995-2004) Dr. Lisanby has contributed to forty five scientific publications, (first author on almost half), eleven book chapters, and is the volume editor of *Brain Stimulation in Psychiatric Treatment*, Volume 23 in the *Review of Psychiatry* Series. She was appointed Associate Professor of Psychiatry only seven years after graduation (2002) and in the same year became head of the TMS Unit in the MRI Research Center at Columbia University.

Dr. Lisanby is a member of numerous program committees, editorial boards or organizations in her areas of interest and a member of the ACNP since 2004. She was the winner of the APA Young Faculty Research Award

(2000) and the recipient of the Max Hamilton Award at the CINP Annual Meeting (2004), where this interview was conducted.

This interview focuses on some of Dr. Lisanby's personal career challenges, her role in the decreasingly male dominated areas of her interests and her philosophy and beliefs about psychiatry in general and her chosen field in particular. She is an advocate for a biopsychosocial framework but is also an optimist and pragmatist who supports whatever works and is in the best interest of her patients.

If it is true, as the interviewer suggests, that Sarah Lisanby likes to swim, "against the tide" she will undoubtedly be among the first to reach whatever shore she selects.

*William ( Bill ) McKinney* was raised in a small town in Georgia, the son of the fire chief who financed his son's education by investing in real estate. The family's unspoken expectation was that Bill might become minister in a local church. Instead he became a leading pioneer in the development of animal models for human depression and its treatment.

The first part of this interview reveals the influences that brought this change about. Bill began his undergraduate education at Baylor University in 1955, interested in a possible writing career. During a course in abnormal psychology a visiting lecturer and local psychiatrist talked about his patients and the evolving developments in understanding biological factors, the brain and behavior. Bill changed his major, completed the requirements for medical school, and graduated cum laude in Psychology and Chemistry.

During medical school at Vanderbilt (1959-1963), when the tricyclic antidepressants and MAO inhibitors were discovered, he wrote his first paper with Charles Wells, head of neurology, on neurasthenia in the Civil War. He also did an elective with Art Prange and, between his sophomore and junior year, an apprenticeship to a biostatistician in Preventative Medicine, learning about research design and methodology. At graduation Bill received the Beauchamp award for the medical student showing the greatest promise in psychiatry and neurology.

After a year as an intern in medicine he spent two years as a psychiatric resident at the University of North Carolina and his final year at Stanford University. During his training he was exposed to a number of influential role models including Frank Luton who had trained under Adolf Meyer and taught his students the significance of life events, temperament and genetics in molding adult psychopathology. Many of Bill's resident contemporaries, who are named in the interview and were exposed to the same mentors, went on to become leaders in the field of neuropsychopharmacology.

After completing residency Dr. McKinney spent two years at the NIMH dividing his time between the Psychosomatic Section, under "Biff" Bunney,

the Psychiatry Training Branch and a sabbatical at Cambridge University in England. Under Bunney he learned about clinical trial methodology and rating scales, became interested in animal models of depression, and co-authored a paper with him on the topic. He then corresponded with and was encouraged by Harry Harlow (President of the American Psychological Association) to consider primate research and began to work with primates in the NIH intramural program

These experiences shaped his decision to join the faculty at the University of Wisconsin in Madison (1969) when Milt Miller was Chair and he could collaborate and share an office with Harry Harlow. Within a year he obtained an NIMH Research Career Investigator Award that enabled him to establish his own primate laboratory. In five short years he achieved the rank of full professor in psychiatry, affiliate professor in psychology, and senior staff psychiatrist at the VA hospital. The interview provides an account of his primate research into the isolation and separation research paradigms with their influence on the development of neuropathology, aberrant behaviors and effects of psychotropic drugs in ameliorating or intensifying them.

Dr. McKinney served as Chair of the Department from 1975 to 1980 but continued his research and clinical work in addition to administration and teaching. In 1983 he took a sabbatical and was awarded a Fellowship at the Center for Advanced Study in Behavioral Sciences at Stanford University. During his 32 years of research at Wisconsin he was mainly supported by NIMH grants between 1970 and 1988 totaling over three million dollars and by the MacArthur Foundation from 1998 to 1992 with grants totaling almost two million dollars.

In 1993 Dr. McKinney was offered and accepted an endowed chair as the Asher Professor of Psychiatry at Northwestern University in Chicago and Director of the Asher Center for the Study and Treatment of Depressive Disorders. This is a multidisciplinary basic science and clinical program involved in both molecular neuroscience and extensive multi-center clinical trials in affective disorders, schizophrenia and Alzheimer's disease. He continues to divide his time between teaching, clinical work and research. For ten years (1991-2001) he served as the Director of the American Board of Psychiatry and Neurology.

Dr. McKinney has served on numerous local, national and international boards and committees as well as an editor and reviewer for many leading scientific journals. He is a life fellow emeritus of the ACNP and has been active on its committees.

In addition to this busy professional life Bill is careful to preserve time for family and the energy to pursue his hobby of running marathons. *Judith Rapoport's* lifetime leadership role in child psychiatry began with an NIMH postdoctoral fellowship forty seven years ago (1962) and continues today as Chief of Child Psychiatry at NIMH (since 1984). She is also a full Professor of Psychiatry at George Washington University School of Medicine (since 1979).

Although she claims that her choice of child psychiatry might have been "the best way to get a job" her early career was shaped by a variety of mentors, role models and experiences. Included were a grandfather who produced theatricals, (an asset in making scientific presentations), a friend's mother who was also a psychiatrist and pioneer in the use of Antabuse (disulfiram) and a magna cum laude undergraduate degree from Swarthmore College where she was exposed to an experimental psychology department that did "reliable research in complex behaviors". Because Harvard Medical School psychiatry at that time (1955) was dominated by psychoanalysts, she spent a student elective at Queen's Square in London, working in neurology under MacDonald Critchley, where she learned "strange and wonderful ways" to view phenomenology. Judith completed her psychiatric residency at St. Elizabeths' Hospital in Washington DC looking after three hundred chronic patients, found "Kraepelin more useful than Freud" and learned to make "my own observations and come to my own conclusions".

This was followed by a two year post doctoral fellowship in Sweden (1962-1964) where she was exposed to a strong biological approach including work on amphetamines in humans, physiological arousal in psychopaths and memory deficits following ECT. She also studied women coming from the USA to Sweden for abortions (later published in *Archives of General Psychiatry*).

On returning to America Dr. Rapoport took child fellowships for three years (1964-1967) including work with a pediatric neurologist at Children's Hospital in Washington DC. After this she worked for a year at an inner city clinic where she provided medication for mothers and their children; a kind of "domestic Peace Corps experience". This was where she first saw normal children sharing their siblings' stimulant medication for ADHD and experiencing identical calming effects. This controversial observation (at the time) was later confirmed with carefully controlled experiments at the NIMH on her own and staff members' normal children.

This interview details the next forty years of Dr. Rapoport's distinguished career at NIMH with increasing levels of administrative responsibility and growing international recognition, (1967-2008). Early on she pioneered the introduction of structured interviews, inter-rater reliability and double blind studies. She was involved in the development of pediatric criteria for DSM III and its later editions and describes the competing ideologies among the

public, psychotherapists, psychologists, social workers and managed care companies. She considers most of the criteria "probably premature" and introduced to satisfy the need to document care for reimbursement.

During this time her research included seminal studies demonstrating the specific response of OCD in children to clomipramine at a time when psychoanalytic theory still dominated the field. This work culminated in the publication of her book, *The Boy Who Couldn t Stop Washing* which was translated into twenty two languages, sold over a million copies and transformed public opinion about the condition.

In 1991 she began work on childhood onset schizophrenia and was among the first to show the superior response to clozapine, including an occasional virtual cure.

Later in the interview there is an interesting discussion of the differences between the USA and UK in the use of psychotropic medication in children and of Dr. Rapoport's active involvement in the ACNP and its committees. She is concerned about a tendency of the organization and its members to shy away from clinical trials with a resulting loss of skilled observation in favor of pharmaceutical company sponsored studies designed to satisfy FDA requirements for boiler plate documentation. This is occurring at a time when genetic studies are suggesting discrete new disorders concealed within the clinically homogenous criteria of the DSM system.

Dr. Rapoport has been the recipient of numerous awards including the Ittleson Research Prize (APA), Taylor Manor Research Award, NIMH Director's Award, Sacher Award, Winkleman Award, Presidential Meritorious Executive Award, APA Research Award, and the Institute of Medicine Distinguished Service Award.

She is active on numerous Editorial boards and College councils and has served as President of the American Psychopathological Association and the Society for Research on Child and Adolescent Psychopathology.

*Barry Reisberg* s career epitomizes what has come to be called the purpose driven life, all the more remarkable because it evolved from internal motivations more than external role models.

Born in Brooklyn, to a family without any academic traditions, he knew from an early age that, "the meaningful thing to do in life was to discover new things and, for whatever reason, I though I could do that". Encouraged by his mother, he devoured children's science books at the local library and, at fifteen, won a National Science Foundation Fellowship for a summer study course in comparative histology. Graduating from high school, he won a New York State Regent's scholarship to attend Brooklyn College where he majored in Biochemistry. Between college and medical school he attended a Jesuit school in Hiroshima, Japan, studying anthropology. His first two years of medical education at New York Medical College were dull, dispiriting and devoid of human interest, an environment he reacted to by spending the summer break backpacking from Istanbul to Bombay via Turkey, Iran, Afghanistan, Pakistan, India and Nepal.

Reunited with people and patients in his third year Barry decided on a career in psychiatry where "one could be a doctor and still have a human element". He spent his last summer in medical school in the bush in Nigeria working in a single physician hospital, befriending the local missionaries who worked in the villages and visiting a psychiatric hospital.

Graduating in 1972, Barry did his residency in East Harlem at New York Medical College when it was still strongly psychoanalytic. Deciding that clinical work alone "lacked substance" he decided to include research in his career, worked under a faculty member studying the phenomenology of schizophrenia and mania and concluded his training with a three month fellowship in Behavior Therapy at the Middlesex Hospital in London.

Dr. Reisberg's research career began at the VA hospital in Westchester where he ran a teaching unit and worked with Turan Itil, publishing several papers including on lithium and the worldwide use of psychotropic medications. After obtaining his Boards in 1978 he joined a cadre of junior faculty and research workers on the psychopharmacology unit at Bellevue under Sam Gershon. Here he was exposed to geriatrics which he recognized as a neglected field lacking a meaningful nosology or treatment.

The interview describes the way in which Dr. Reisberg has spent the rest of his career addressing these needs in a creative and highly productive manner. He obtained his first research grants from the National Institute on Ageing (NIA) and the NIMH in 1979 and 1980 and published his book on the clinical stages of dementia in 1981. Within nine years he became a Full Professor of Psychiatry at New York University (NYU) and in 1989 and 1990 obtained over three million dollars in grants from the NIMH and NIA to fund the NYU Medical Center's Aging and Research Center of which he is Clinical Director.

Over the last thirty years Dr. Reisberg has continued to define the clinical stages of Alzheimer's disease, including behavioral, cognitive, EEG and neuroimaging criteria, based on patients some of whom he has followed for this entire period of time. He has developed rating scales to measure these changes and has described the way in which they mirror normal development in reverse ("retrogenesis"). The projects for this research have been continuously funded by NIH grants totaling over three million dollars and to a lesser extent by pharmaceutical companies for particular drugs (including memantine). During this period Dr. Reisberg published a second (edited) textbook and over one hundred and fifty articles describing the findings, including data on seven hundred patients which won an editorial prize from the *Journal of Geriatric Psychiatry*. He has served on numerous International and National Committees, Work Groups and Editorial Boards including the World Health Organization, the International Psychogeriatric Association, the National Institutes of Health, the Veterans Administration and the Alzheimer's Association.

The interview concludes with interesting speculation on the molecular biology of dementia which may help explain its evolution and may have treatment implications.

Two underlying principles stand out in this account. Throughout his career Dr. Reisberg has continued to pay close and devoted attention to patients and their families. "Psychiatry is observation ... I look the illness in the eye". This approach has yielded a continuous and consistent flow of new information. "I'm constantly pursuing that story. It's not accidental. There is a kind of beauty to the story, symmetry to the disease that's beginning to unfold".

*Eric Shooter* was born in a small village on the edge of Sherwood Forest, with a family name that suggests his ancestors may have been archers, like the legendary Robin Hood. His father was a mining engineer and Eric won a scholarship to the local grammar school, (founded in 1521), where he enjoyed the logic of science and the "reasonably straight forward answers" it provided. His headmaster groomed Eric for entry to Cambridge University, tutoring him in Experimental Physics and Chemistry so that he won an exhibition and scholarship to Gonville and Caius College.

Eric's undergraduate degree was in mathematics, physics, chemistry and mineralogy. Because of Government priorities during the Second World War his graduate work was in chemistry and his PhD in the study of large polymers and proteins where he learned the new techniques of high speed ultracentrifuge and electrophoresis. Part of his research was at the Royal Institute in London where he worked in labs originally occupied by Newton and Faraday, adjacent to a giant X-Ray machine used by Madame Curie. His first paper was published in *Science* as a graduate student in 1948.

Following PhD, Dr. Shooter took a post doctoral fellowship in the chemistry department at the University of Wisconsin in Madison and worked on the chemistry of serum proteins. After returning to Britain, this interest evolved into a study of the molecular biology of hemoglobin at University College in London where he shared in the discovery of Hemoglobin G.

In 1961 Dr. Shooter took a sabbatical year at Stanford University School of Medicine supported by a Fellowship funded jointly by NIH and the British Medical Research Council to work in the newly evolving field of DNA structure when David Hamburg was Chair of Psychiatry (among the first biological psychiatrists). Working with Professor Buzz Baldwin, Dr. Shooter participated in demonstrating how the two strands of DNA were connected and how they could be separated to accomplish genetic transfer.

After returning to Britain to complete his work at University College, Dr. Shooter fulfilled a promise to return to Stanford in 1963 where he joined Nobel Laureate Joshua Letterburg in establishing the new field of neurobiology. In 1968 Dr. Shooter was appointed Professor of Genetics and Biochemistry and in 1977 became the Founding Chair of a new Department of Neurobiology.

The remainder of the interview records the outcomes of forty years of research in the study of neuroproteins, their role in degenerative diseases of the central and peripheral nervous system, and the search for new methods to treat them. This has involved the isolation and identification of nerve growth factors and their receptors and led to the formation of a company (Regeneron Pharmaceuticals) to raise venture capital and pursue commercial development of potential treatments for Alzheimer's, Lou Gehrig's disease and ALS.

During his long and distinguished career Dr. Shooter has received numerous awards and is a Fellow of the Royal Society of London (1988), the American Academy of Arts and Sciences (1993) and Emeritus Fellow of the ACNP (1991). He is the author and co-author of almost two hundred scientific articles and has held lectureships throughout the United States and in Canada, Switzerland, France, Israel, Japan and Germany. He is particularly proud of the accomplishments of the almost one hundred post docs, graduate and undergraduate students he has mentored. Finally, he considers the NIH funding mechanism "the best system in the world" because it provides independent direct funding to individuals based on their own work, unlike other countries, which channel research funds to the heads of departments.

*Myrna Weissman* is an icon in our field; a social scientist in a neurobiological arena, a pioneer woman in a male dominated research world, and a person who has balanced and excelled in professional and personal life. In this interview some of these accomplishments are hidden behind her sense of humor and humility. Asked if there are awards she would like to mention her reply is, "awards are only important if you don't get them". Listed on her resume, but hardly mentioned in the interview, are eighteen prestigious awards from national and international organizations recognizing her lifetime scientific contributions.

Also listed are many named lectureships, Fellowships in the New York Academy of Science, the New York Academy of Medicine, the ACNP (1975), the Institute of Medicine of the National Academy of Science and Honorary Fellowships in the American College of Psychiatrists and the Royal College of Psychiatrists of Britain. Several publications Dr. Weissman has co-authored are citation classics and in 2000 the New York Academy of Science named her, "one of the areas outstanding women of science".

The interview reveals a surprisingly mundane start to her outstanding career, the manner in which it blossomed and the influences involved. Myrna was the only child of a Boston small business owner and graduated with honors from Brandeis (1956) before obtaining her MSW from the University of Pennsylvania (1958) at a time when "women were shunted into nursing, social work or teaching". Twelve years later (1970) she was thirty years old, had four children under age six, and didn't like social work, although she had published three articles on social work topics. It was the beginning of the women's movement and when her husband (an NIH scientist) accepted a faculty position at Yale she took a part time job, working two days a week, for Gerry Klerman and Gene Paykel on a study of relapse prevention in depression. She was asked to develop a cognitive treatment package and outcome measures to accomplish this.

Four years later (1974) the research team had failed to find a better qualified full time social worker and Dr. Weissman had proved her worth. She had obtained her PhD in Chronic Disease Epidemiology from Yale, written her first book (with Gene Paykel) on social relationships in depressed women and had published twenty two articles in scientific journals of which she was the first or only author on fifteen. She had obtained several of her own grants; "it wasn't difficult to get funded if you had ideas", continued to work and write at home, care for her children and "had no bosses".

Fifteen years later (1987) she was a Full Professor of Psychiatry and Epidemiology and the first woman to obtain tenure in the Department of Psychiatry at Yale. By now she and Gerry Klerman were married and in that year they moved to New York where Dr. Weissman became Professor of Epidemiology in Psychiatry at Columbia University and Chief of the Division of Clinical and Genetic Epidemiology at New York State Psychiatric Institute.

By this time she and her colleagues had published the Manual of Interpersonal Psychotherapy (IPT) and had initiated the multi-site Epidemiologic Catchment Area study (ECA). Both the Social Adjustment Scale and the IPT Manual had been translated into numerous languages and were in widespread international use.

Recently Dr. Weissman has become involved in the genetic epidemiology of panic disorder and depression, including the identification of children at high risk and the possibility of therapeutic interventions in the depressed mothers.

The interview provides more details of Dr. Weissman's research and the findings. She states that her future plans are focused on areas that are interesting, likely to lead to answers, and require "serious collaboration with

people in biology". If the past is prelude there is little doubt this will be productive. To date she has published seventeen books, over four hundred and fifty articles and more than one hundred and seventy book chapters. She is active on numerous scientific advisory and editorial boards and is the past president of the American Psychopathological Association (1998).

Three young girls who watched their mother working at home are now grown up. One is a psychiatrist and epidemiologist, a second is a physician and epidemiologist running AIDS programs at Yale and the third has an MBA and manages a large medical practice. There are also seven grandchildren whose genes and role models are still helping to mould their future.

Paul Wender's career path and parental influence on it provides a small echo of his subsequent ground breaking research on the roles of genetics and environment in the natural history of schizophrenia. His father was a psychiatrist and his mother a social worker so he "became interested in psychiatry from an early age". But his father was also a psychoanalyst trained by one of Freud's disciples. As an undergraduate at Harvard Paul majored in biochemistry and became interested in "the relatively hard psychological science" of learning theory and behaviorism. When his father provided him with Freud's *Introduction to Psychoanalysis* Paul's innate skepticism led him to question its "provocative but unsubstantiated statements".

When Paul began his resident training in psychiatry at Mass Mental Health Center (1960) he reacted strongly to the "totally psychoanalytic" environment by turning to the descriptive German literature and decided that schizophrenia must be a genetic disorder. With fellow residents, (including Eric Kandel), he organized a seminar focused on research in schizophrenia. Drafted into the Army during the Korean War he was posted as a Special Fellow in the Public Health Service at the NIMH where he became involved in research that included the relationship between early social behavior in children and later cognitive functioning. In 1963 he published his first paper in the *American Journal of Psychiatry* which included, at the editor's request, Kraepelin's prescient quote, "We are always standing at the beginning".

Continuing his reading in schizophrenia Dr. Wender hit on the idea that studying adopted children might help clarify the relative role of nature and nurture in its etiology. As often happens in a new area of enquiry, this idea had occurred simultaneously to two other senior research workers at NIMH; David Rosenthal, Chief of Laboratory Psychology, and Seymour Kety, Chief of the Laboratory of Clinical Sciences. Together they formed a collaborative research triumvirate that expanded to include Danish colleagues who had access to national adoption registers that recorded demographic and diagnostic details. The interview outlines the productive outcomes of this research which not only confirmed the strong genetic component in etiology but made important contributions to the natural history and nosology of schizophrenia that were incorporated into DSM III and also coined the term, "spectrum disorder". During his early years at NIMH the adoption research strategy expanded into other diagnostic areas to demonstrate the genetic contribution in affective disorders, criminality, alcoholism and psychopathy.

In 1964 Dr. Wender decided that to better understand the evolution of psychopathology he needed to turn from adults to children. This led to a Fellowship in Child Psychiatry at Johns Hopkins Hospital followed by an academic appointment in Psychiatry and Pediatrics when Leon Eisenberg was Chair of Child Psychiatry. Throughout this period (1967-1973) Dr. Wender remained a research psychiatrist at NIMH and his interest shifted to the second major area in which he has made original contributions. Early on in his pediatric training he noted the dramatic improvement of children who had minimal brain dysfunction (later ADHD), during treatment with amphetamine which he considers "the most rapid and striking response I have seen to this day".

This second area of research evolved after Dr. Wender became Professor and Director of Psychiatric Research at the University of Utah in 1973, only five years after he became an Assistant Professor. He has remained in this position for over a quarter of a century and in 1990 became a Distinguished Professor. The interview describes his subsequent studies defining the ADHD syndrome in adults including dopamine function and involving precursors, metabolites, MAO Inhibitors and stimulants. The research also demonstrated significant improvements in adult social, marital and occupational adjustment concurrent with effective treatment of the underlying disorder. This research in adults has been supported by fifteen years of NIMH funding with grants totaling one and a half million dollars and much smaller amounts from pharmaceutical companies.

Dr. Wender has been a Fellow Emeritus of ACNP since 1975. He is active in numerous societies and is a reviewer or board member on several journals. He has always "abjured sitting on Committees and avoided Department Chairmanships" preferring to devote himself to research, teaching and especially clinical practice which he describes as, "both a basis for my research and a gratifying and rewarding setting". He is proud of the experts he has trained and his two ground breaking monographs on minimal brain dysfunction in children (1971) and ADHD in adults (1995).

## **INTERVIEWEES & INTERVIEWERS**

## HAGOP S. AKISKAL

## Interviewed by Paula J. Clayton Scottsdale, Arizona, December 9, 2008

- PC: My name is Dr. Paula Clayton and I will be interviewing Dr. Hagop Akiskal,\* who is a distinguished member of the ACNP. The date is December 9, 2008, and we're at the ACNP meeting in Arizona. So, Hagop, tell us about your background, your family and how you got to where you are today.
- HA: As far as background, I am of Armenian origin, born in Beirut, Lebanon, just when the French mandate was ending and Lebanon had become an independent country. I grew up in a multicultural, multi-religious atmosphere. My father and his family were all in engineering fields, and my mother's side in journalism, literature, teaching, and medicine.
- PC: How did that influence you?
- HA: I have been asked this question before, I therefore have had the opportunity to think about it at some length. I believe I "inherited" literary talent and a penchant for medicine from my mother's side and the precision that characterizes physics and math from my father's lineage. This dual heritage may explain the clarity of thinking and persuasive prose that made me a highly cited clinical scientist, and eventually a good editor.
- PC: How about schooling?
- HA: In those days Beirut was considered "the Paris of the Middle East", a comparison that meant to capture the sophisticated culture that characterized that vibrant city. I attended a private Armenian school, whose principal, educated at the Sorbonne and Oxford, was renowned for his "tough-minded" approach, combining a liberal humanistic education, including 4 languages, with a rigorous exposure to the sciences. I then did a year of mathematics my father had been killed in a car accident, and some in my family wanted me to consider electrical engineering all of this preceding my enrollment at the American University of Beirut; if it weren't for that I wouldn't be in the United States.
- PC: Why do you say that?
- HA: Because if you go to a university and medical school of the high ranking of the American University of Beirut, it's natural to come to the United States.
- PC: From your history it followed without interruption. You graduated with honors didn't you?

<sup>\*</sup> Hagop S. Akiskal was born in Beirut, Lebanon in 1944.

- HA: I did, Alpha Omega Alpha.
- PC: Then you came to Memphis?
- HA: That's correct.
- PC: Tell me how you made that decision, because there were many others from that university who went to other places?
- HA: I applied to the University of Washington in Seattle, Tulane and to New York Medical College. On paper, however, the University of Tennessee, Memphis seemed the most solid for a clinical residency, which was flexible for research experience.
- PC: Did you interview with others, or just do this all by paper?
- HA: I didn't interview with anybody, I was accepted, via correspondence, almost as soon as I applied for residency positions at Memphis and at Tulane; Seattle, too, was very much interested in having me; New York had invited me for an Interview. After wavering between Seattle and Memphis for a week - I had had professors in Beirut who had trained or had spent sabbaticals in these two medical centers - I made up my mind for Memphis, and after the ECFMG exam, and the requisite visa formalities for foreign medical graduates, when the time came, I boarded the plane and started the long journey to Memphis. I had never lived - or traveled away - from my family before.
- PC: Oh, my goodness! And, you spoke English when you came?
- HA: Of course.
- PC: You speak many languages?
- HA: Five.
- PC: So, you came to Memphis and started your residency.
- HA: That's correct.
- PC: Did you finish it there?
- HA: No, I went to Wisconsin for my third year.
- PC: Tell us about that transition.
- HA: I had the good fortune of being tutored by Rafic Waziri in Memphis, who was originally from Afghanistan. He was in the first class that was exposed to a neuroscience course in Boston under Eric Kandell, and the private weekly seminar with him was a very important introduction to the brain. In 1970, not too many places were teaching neuroscience. Dr Waziri, a perfect gentleman, was a tough-minded psychiatrist, vintage George Winokur.
- PC: At Washington University?
- HA: No. He took a faculty position in George Winokur's department at the University of Iowa. When we met he was in Memphis for two years in transit to Iowa.
- PC: Is he the one who first got you interested in mood disorders?

- HA: Not entirely, he largely exposed me to the elegance of scientific methodology in psychiatry along biological lines. Parenthetically, the monograph on manic depressive illness by Winokur, you and Reich, which I read in 1969, was a major source of inspiration for me.
- PC: But then you declared an interest in mood disorders very early.
- HA: Actually, it's much more complicated than that.
- PC: Okay, tell us.
- HA: At the American University of Beirut, I had the good fortune of being exposed to Dr Vahe Puzantian, a superb clinician, an Edinboroughtrained Lebanese-Armenian psychiatrist, who had been a disciple of Frank Fish: Fish had published great monographs on phenomenology and schizophrenia, which I read as an intern, underlining in red every other line! Thus, I did arrive at the United States with an interest in Kurt Schneider, Karl Jaspers, and their approach to schizophrenia. Emil Kraeplin had been another major influence. While in Lebanon, as a fourth year medical student, my first psychiatric patient presented with catatonia, and he made a miraculous recovery with perphenazine. That was a remarkable situation for a fourth year medical student to observe first-hand, a patient, in a state of stupor, with all the dramatic signs of catatonia, recover on a high potency neuroleptic within few days.
- PC: So that stirred your interest?
- HA: It re-inforced my interest in psychopharmacology, which was a subspecialty I was considering concurrent with training in psychiatry. However, my interest in schizophrenia was soon to erode. When I came to the States in 1969, most patients with psychotic disorders were diagnosed "schizophrenic", which was at odds with what I had been exposed to in Lebanon, where psychiatric thinking, along the then British model, was oriented towards manic-depression. So, for a while I shifted to psychedelic substance abuse, there was an epidemic of it in those days, and from there to student mental health. I went to Madison, Wisconsin to have exposure to that.
- PC: To student mental health?
- HA: Yes, but I was interested in many other things Madison offered, such as social psychiatry, Seymour Halleck, consultation-liaison, David Graham, as well as primatology and experimental psychopathology, Harry Harlow, William Mckinney, Lorna Benjamin. When I rotated in the student mental health clinic, it appeared to me that a lot of it represented affective disorders. So when I returned to Memphis, it was natural that I would start a mood clinic.
- PC: When was that?

- HA: Although there existed, several lithium clinics in the US, the clinic I was interested in was broader than that. It was one of the first mood clinics, if not the first, in 1973. We started where Washington U left off, and where, eventually, I had to meet you and your colleagues. Wash U studied the major syndromes, with a few exceptions. You guys had pioneered in the systematic study of the major syndromes that were already reasonably well characterized in your department, so I decided to study those patients with fewer symptoms, who fell short of either the full syndromal criteria, or the duration criteria, the "undiagnosed" in the St Louis framework. Very few people were studying these conditions systematically, so I ended up making a whole career of doing so. The outpatient departments in community mental health centers were full of them.
- PC: When did you publish the article on depression with McKinney?
- HA: That was in *Science*, 1973. I must mention what a great mentor Bill Mckinney was, who had been himself tutored by Morrie Lipton and Art Prange at Chapel Hill.
- PC: Were you back at Memphis when you wrote the Science paper?
- HA: I had done that work in Madison.
- PC: So that was your major publication during that period?
- HA: Actually, I also wrote a provocative paper entitled *Psychiatry and Pseudo-psychiatry*, which was published in the *Archives of General Psychiatry*. I had seriously considered leaving psychiatry, but these two papers were, key in outlining what I would pursue in psychiatry.
- PC: When was that critique published?
- HA: Six months earlier than the Science paper.
- PC: Okay.
- HA: The *Science* paper was one of the rare publications written by a psychiatric trainee, attempting to bridge the gulf between psychology and biology and documenting the then sparse data on their interaction, and made a major impact. It's highly cited, and was required reading in psychology and psychiatry for many years – it still is in many universities.
- PC: Right.
- HA: The United States is a remarkable country.
- PC: Why do you say that?
- HA: Because if you publish in the United States, the whole world knows about it. I remember a week after the *Science* paper appeared, I received a reprint request from then Leningrad, now St Petersburg, because we had cited several Russian pharmacologists, like Lapin and Oxenkrug, who had written about serotonin. You would recall, the US was catecholamine-focused then.

- PC: That reprint request was even before e-mail or the Internet.
- HA: Absolutely, 1973. The visibility is much more today, but for a psychiatrist to publish in *Science* was equally unusual.
- PC: It was wonderful. I remember that paper. The other thing I remember is the paper from the outpatient clinic on cyclothymia and its outcome. When was that published?
- HA: 1977.
- PC: Tell us about between 1973 and 1977.
- HA: Publishing was slow; we were collecting data in the clinic. These were long-term prospective studies and took a few years to collect all the data. I also did biological work, especially along psychopharmacotherpeutic lines; psychopharmacology was not formally taught in those days.
- PC: We were just discussing that at an ACNP seminar.
- HA: I learned it by doing it and, even as early as a second year psychiatry resident, I was teaching psychopharmacology to my peers in psychiatry.
- PC: I wonder who replaced you when you went to Wisconsin.
- HA: Waziri was still in Memphis, but soon he left for Iowa. Eventually, when completing my psychiatric training in Madison and returned back to Memphis, I was given joint faculty appointment in psychiatry and pharmacology. When I taught psychiatry in the clinical years, medical students had already been exposed to my lectures in psychopharmacology during the basic science course of pharmacology, as a result many signed up to do research electives with me in the mood clinic in their senior year.
- PC: I didn't realize that.
- HA: I eventually taught psychopharmacology to pharmacy and nursing students, as well as neurology and internal medicine residents. This had the net effect of re-enforcing the view that psychiatry had come of age, and had to be respected as one of the major branches of medicine and basic science, without losing its broad psychosocial, cultural and humanistic roots.
- PC: That's a good message to send.
- HA: The students heard the same guy who taught pharmacology, later teaching psychiatry. That had a great impact.
- PC: You were more credible.
- HA: Absolutely. I was the only psychiatrist who was appointed to various medical school committees.
- PC: You also had another physician psychiatrist who was a mentor in Tennessee, didn't you?

- HA: That was my first Chairman and Professor, the late Garabed Aivazian, who had been trained in Lebanon, Paris, and Cornell. His successor, William Webb, was also a great supporter of my endeavors in research and University-wide activities
- PC: Right, and who both supported you start the mood clinic?
- HA: Yes, I started it with a social worker, Alice Scott-Strauss, because there were so many patients being sent to me in private practice who had affective disorders, and who needed not only pharmacotherapy, but practical interpersonal, social interventions, rather than the more doctrinaire therapies of the day.
- PC: How was it set up? Were you teaching residents in the mood clinic? Where did the patients come from?
- HA: All residents rotated in the mood clinic, but many chose it for their entire fourth year elective. This was a very invigorating experience. As far as patients, some were sent to me, others were screened and recruited from the larger outpatient clinic: eventually many were sending their children. But I want to emphasize that one must see VIPs, including university faculty, and their offspring, in private practice because that's how you develop strong relationships which enlightens family members, who are the ones to spread the good word about psychiatry. These were exciting times for psychiatry, which had the full support of the medical school dean and Chancellor at the University of Tennessee Health Sciences. We did conferences, including a major conference on diagnosis; the Vice-Chancellor, Jim Gay, formerly a neurosurgeon from Baltimore - who had been exposed to Adolph Meyer - gave us twentytwo thousand dollars, a lot of money in those days, to stimulate interest in psychiatry. I decided to devote it to an international congress to examine the question whether laboratory tests could be used in the diagnosis of mental disorders.
- PC: This was at Memphis?
- HA: Yes, 1975, there were 20 national, including Sam Guze, and international speakers, such as Sir Martin Roth, Arvid Carlsson, and 300 attendees. I remember Danny X Freedman saying in his opening remarks that the "biological mafia" had landed in Memphis, an unlikely place for such a conference! Incidentally, we still don't have much in the way of laboratory tests to aid in the diagnosis of the so-called functional mental disorders. This is so, because genes don't recognize the DSM system. The Proceedings of that conference was published in a monograph, *Psychiatric Diagnosis: Exploration of Biological Predictors*, by Spectrum Publications, in New York, in 1978.

- PC: So, a lot was going for you in Memphis, and you stayed there and began to publish the results of your follow up studies. You used a structured interview, didn't you?
- HA: Actually, a semi-structured interview, a modification of the Washington University Diagnostic Interview that Sam Guze was kind enough to provide me during my first "pilgrimage" to St Louis, but we edited and expanded the parts that had to do with the less than syndromal conditions.
- PC: How many patients did you finally end up collecting and publishing on?
- HA: The total number that I personally examined and followed up systematically would be about one thousand.
- PC: It was all on nosology or diagnostics in follow up?
- HA: Treatment, as well. There's something that would interest you. In our mood clinic, there were no suicides. That is a remarkable phenomenon, on which I haven't fully published yet, but was interviewed about on the first page of the *Wall Street Journal* in 1983.
- PC: Is it because you were treating them well and following them closely?
- HA: I think that was the case, looking at what is essential, the correct diagnosis, rigorous treatment, systematic follow-up, and paying attention to the social-interpersonal aspects, rather than the unpractical things from theory-driven schools of psychotherapy. You know what I mean by that?
- PC: I do.
- HA: One other thing. I was hooked to lithium as a resident from as soon as it was approved for clinical use in 1970. My first manic patient, who received lithium with sodium chloride, as was the custom in those days, was a prostitute, and she made a remarkable turn around. We helped her get off the streets, so I fell in love with lithium. That's one of the reasons I started the mood clinic. She helped other prostitutes get off the street. It was social psychiatry via pharmacotherapy and practical psychotherapy. Someone once asked me to define, what is practical psychotherapy? And I said "that which is not unpractical".
- PC: I had the same experience. We had a manic minister, a kind of Elmer Gantry, in the hospital who had twelve or twenty-four ECT's. Nothing made a difference until George Winokur had the pharmacy make up lithium before it was marketed. The patient got completely well. It was the most remarkable change in behavior I've ever seen and I, too, have been hooked ever since.
- HA: One other thing about lithium, we learned that you could use it at doses and blood levels less than what was being officially proposed.
- PC: For patients with mania or depression?

- HA: Once "stabilized" acutely, during prophylaxis as outpatients, whenever feasible we endeavored to lower the dosage compatible with reasonable "euthymia" without obliterating all moods to make sure that they would stay on it. Concurrently you could use something like thioridazine, which was a great agent in those days, to deal with the more "minor" mood swings in either direction, plus psychotic symptoms and mixed states for which thioridazine was crucial.
- PC: Those were my two favorites.
- HA: It took great clinical skill to persuade the patients to ingest these agents that had so many side effects, which we told them were signs that they were beginning to act on their CNS! Curiously, lithium patients got so much attention, that those who were not deemed to be good candidates for it, felt left out.
- PC: Both factors could contribute to their not being a suicide.
- HA: Absolutely. They stayed on their dual prescribed agents, we did not label them as "drugs", while receiving the personal attention regarding their life problems.
- PC: Right. Mellaril (thioridazine) was first tested as an antidepressant and did well in comparison to the older antipsychotics. So it was a good agent to use. You published a set of papers from that clinic and, of those manuscripts, what important points do you want to leave us with?
- HA: I would say the chapter you invited me to write in the APA Reviews volume 2 in 1983, is a good synthetic summary of much of my research papers in the first decade of my academic career. You wanted a review of my ideas on diagnosis and I presented the bipolar spectrum concept, so prevalent in outpatients and the relatives of full-blown manic-depressive patients.
- PC: That is the first step in preventive psychiatry.
- HA: I completely concur. The spectrum concept has become very important in terms of many things like early diagnosis and treatment and in terms of the genetics and phenotypes. In San Diego, I collaborated with John Kelsoe, and we found the linkage on chromosome 18p for cyclothymia. Once you have a temperament identified, we are closer to the origins of the disease, before it becomes clinically declared. I think it's important that we study processes which are closer to the normal in our biological investigations.
- PC: How did you feel then when they made cyclothymia a diagnosis rather than a temperament?
- HA: There was no way of stopping Spitzer and other nosologists in what they were doing. Not to belittle the enormous historic importance of the first DSM-III, but he was borrowing from other people's work, and

transmuting data-based criteria as his logic dictated or "votes" of experts suggested. Things have changed very little since then and I don't attach great hopes to DSM-V either, indeed I have declined to contribute to it.

- PC: Do you think that cyclothymia and hyperthymia should be temperament traits?
- HA: Absolutely, including dysthymia. They should not be considered diseases. That's the beauty of the concept of Temperament. You can diagnose early, not everyone progresses to a disorder, dysfunction level.
- PC: Tell us about that.
- HA: Although I had lived in Memphis for a long time, it wasn't until I met Kareen, my future wife in Paris that I was sensitized to the blues. In those days, many of these singers were more appreciated in Europe, Paris or London. One day, I heard Dr David Evans, a Memphis ethnomusicologist on the radio say something about having the "blues" in the morning. When I realized that the expert on the "blues" was in Memphis, Kareen Akiskal and I did a formal study with him.
- PC: What did you find?
- HA: Much of the data remains unpublished. We published a paper in French in Nervura in 1994. What we found is that the "blues" temperament is split between cyclothymia and hyperthymia; interestingly most did not have any mental disorder, unless you counted excessive use of alcohol before performance. There were a lot of suicide attempts in their families associated with cyclothymic probands blues musicians. That's one of the reasons I was asked to deliver the Eli Robbins lecture.
- PC: We were all fascinated with it and I'd forgotten the part about suicide. You're saying that people need to have the down part to be suicidal?
- HA: Not necessarily. My hypothesis is that it's the sudden change from a relative high to a down mood. That happens in cyclothymia. Hyperthymics may also experience brief, sudden low moods, especially in the later years of their life. Both situations can prove to be dangerous from a suicidality perspective.
- PC: Or the opposite? Going from depression to mania as they get more energy?
- HA: The sudden downshift, in my experience, is more important. Antidepressants don't do very much for the depressive side, if anything they make it worse. Of related interest, one of the challenges for American psychiatry is to teach not to confuse bipolar with borderline personality.
- PC: That's another one of your major contributions, isn't it?

- HA: Avoiding the diagnosis of borderline personality in bipolar disorder, which is tautological, I published on that in the *Journal of Clinical Psychiatry* in 1985.
- PC: If they're not "borderline", what would you call them?
- HA: Cyclothymic. Cyclothymics can be irritable, angry and, obviously, labile, very variable in mood. That's similar to what borderline personality can look like, except that borderline patients by DSM definition also cut and may mutilate themselves.
- PC: I had a patient that burned herself.
- HA: That's perhaps beyond cyclothymia and even borderline personality. We have developed a temperament scale that helps in evaluating cyclothymia, and other temperaments.
- PC: Tell us the name of the scale.
- HA: TEMPS, Temperament Evaluation of Memphis, Pisa, Paris and San Diego, published in *Journal of Affective Disorders* in 2005. It's being used clinically as well as for research in at least 25 countries worldwide. This is a joint research effort, which started with Kareen Akiskal in the evaluation of affective temperaments in creative artists in Paris and, more recently, worldwide. During the last few years we are also using it in collaboration with John Kelsoe to search for the genes underlying the bipolar spectrum, which, as I am proof-reading this typescript just prior to publication, has led to the tentative identification for several genes corresponding to mania subdivided on the basis of longitudinal patterns of hyperthymic vs irritable temperaments. This is of great relevance to pharmacotherapy as it relates to differential response of mania to lithium vs divalproex.
- PC: I want to go back to your history. You were in Memphis for how many years as a resident and faculty member?
- HA: Almost twenty years, I was there until I went to NIMH in 1990.
- PC: And you were Full Professor?
- HA: William Webb, then my Chairman, had proposed me for that rank when I was thirty three. You were one of the external reviewers of my record of publications, and you wrote a letter of reference on my behalf, saying that people who did innovative clinical research are good teachers, and the Dean had agreed.
- PC: So he promoted you.
- HA: The Dean was very impressed by your letter, among those of others like Art Prange. You don't become a professor in a clinical department at the age of 33 in most medical schools.
- PC: Then you went to NIMH?
- HA: Many years later, for four years, 1990-94.

- PC: You had a special title didn't you?
- HA: Senior Science Advisor to the Director, and subsequently you, too, joined in that position.
- PC: Right. I only stayed a short time.
- HA: The four years I stayed at NIMH marked a partial shift in the Institute from schizophrenia to affective disorders, including education of the public and non-psychiatric physicians about mood and anxiety disorders. I was involved in all that and much more, while being in charge of the Collaborative Depression Study (CDS).
- PC: With Dr. Maser?
- HA: Yes, Jack provided fantastic logistic support and methodological rigor. Dr Klerman, the chair of the collaborative study, was very ill during that period, preceding his premature death and asked me to take over the CDS, in the middle of a review session, as 2 of the external reviewers were challenging the need to continue the prospective follow-up of this landmark study. As this was a cooperative project of NIMH in partnership with five University Centers, the Institute had invested a great deal of resources and funding into it, and therefore, had a vital interest in it. Actually, I was asked to write a 75 page "concept review" for then NIMH director, Fred Goodwin. Those were the public health priorities of the day, at that stage of the art and science of affective disorders. All of this is in the public domain.
- PC: I didn't realize that. By that time I had gone to Minnesota. We were starting to do the temperament stuff from the collaborative study, which you continued when you moved to San Diego with Dr. Judd, didn't you?
- HA: That's correct.
- PC: And you got Dr. Judd involved in outcomes? You did some very important papers together.
- HA: That was several years after my leaving NIMH. We examined the "microstructure" of mood disorders. We demonstrated mood disorders to be chronically fluctuating illnesses, not just episodes. That was a fundamental point to make with multiple data points over long periods of prospective observation. Only a carefully characterized large sample like the CDS had prospective data to lend credibility to this conclusion that has led to a paradigm shift on the necessity of uninterrupted treatment of mood disorders. Bipolar type II hypomania was the only condition in which there were some positive attributes, which is expected, but primarily with very mild hypomania.
- PC: Is there something else you would like to mention about your contributions to psychobiology?

- HA: Our work in the sleep laboratory in Memphis in the neurophysiology of depression. We studied a young man who was sleeping too much and thought to have narcolepsy or "characterologic depression". He was actually suffering from a chronic subthreshold depression, as we validated by his having short REM latency, but not SOREMPS. That started a series of studies on shortened REM latency in various conditions. It was largely limited to depression, which, in turn, led to pharmacotherapeutic trials. We did the first open study, published in the Archives of General Psychiatry in 1980. It would be impossible to publish something like that in the Archives today. There were many replications of our sleep studies in dysthymic and related low grade depressions - at least 10 - showing most classes of antidepressants to be effective in double-blind studies, as a result, millions of people suffering from chronic depressions worldwide have benefited from our research. This research has been recognized by many prestigious prizes and distinctions, such as the NARSAD, the Anna Monika, the Gold Medal of the Society of Biological Psychiatry, the Aristotle Gold Medal, and the Jean Delay Prize of the World Psychiatric Association, as well as several honorary doctorate degrees. For me the greater satisfaction is to have brought smiles to the faces of people with chronic depression. It's personally important for me, because I never saw a smiling face in my family when I was growing up. They were among the rare survivors, after exposure to the first genocide of the twentieth century during the last years of the Ottoman Empire.
- PC: I know you were influential in seeing that people with dysthymia were treated, but I didn't realize it stemmed from your sleep research nor did I know its personal significance for you.
- HA: If we hadn't found shortened REM latency, nobody would have believed that seemingly character disorders could represent veritable pharmacotherapy responsive affective conditions. You can use family history and course as external validators, but people will not be impressed because dysthymia doesn't look like depression. Sufferers look like chronic "complainers" or people with so-called character disorders.
- PC: I treated a medical student's mother with depression, and after about six weeks she came in and I asked, how do you feel? She said, better, you moved back my dreaming. That's just what happens, right, when someone gets well?
- HA: That we often hear, but it is a far more complex matter, because different classes of antidepressants influence REM and slow wave sleep in varied fashion.

- PC: The way patients describe their symptoms confirms what we think we are doing. I enjoy that part of seeing patients and it brings a smile to my face, too.
- HA: For twelve years, I was the research director of the sleep laboratory at the Baptist Hospital in Memphis and that was a remarkable experience, because for a psychiatrist to see relatively normal people from a psychiatric perspective is much of the job in a sleep lab. We would examine sleep apnea, hypersomnia and a lot of so-called psychophysiological insomnia - the terminology keeps on changing, though. I interviewed something like two thousand two hundred people, the whole spectrum from the poorest to the most accomplished people in terms of profession, including many famous musicians addicted to drugs. Regrettably, psychiatry lost its chance to have its neurophysiology laboratories. They have been largely appropriated by pulmonology as "rhoncology", snoring clinics, to evaluate sleep apnea.
- PC: Don't you think the key to doing good clinical research is seeing a lot of patients?
- HA: Absolutely. You become a psychiatrist by seeing patients, not by reading textbooks or making tapes and watching them.
- PC: I concur. I will add: Nor by talking to your supervisor.
- HA: I always made the student sit next to me when I saw patients. That's how I teach. That's how I supervise.
- PC: That's why you've won so many teaching awards. You won them at Memphis and won them in California, including best teacher of the year, right?
- HA: One was called "provocative" teaching prize, reflecting how residents felt. I was helping them thinking outside the box.
- PC: You went from NIMH to California where you rose to the rank of a distinguished professor. Do you have an international title too?
- HA: Joint appointment with International Health and Cross-Cultural Medicine. That's part of the Vice-Chancellor's program for International Health. For a decade I taught in seminar format on disasters, especially on community responses to earthquakes. I've had a very rewarding career and I am grateful. Medicine is all about having great disciples, to transmit our experience and excitement about innovation to be able to better help patients.
- PC: There are two other aspects that I want to talk about. More than any other psychiatrist in America, you have an international reputation, partially because you work with so many people in other countries. Have you ever thought about how many countries?

- HA: Ten countries in the long-term, and another twenty in the short-term, involving all five continents of the globe.
- PC: You really are an international researcher. In most of these countries you work with people on mood disorders. Is that right?
- HA: And temperament.
- PC: Have there been things that you've learned that you brought to your work here in the States?
- HA: This experience has enriched my perspective in many ways; it could fill several volumes! As we are on pharmacotherapy, I would like to mention that I learned from Italians that low doses often work quite well; collaboration with Guilio Perugi has been very rewarding.
- PC: You're talking about antidepressants in low doses?
- HA: For most medications, also the importance of rational "polypharmacy", again in small doses. My former fellow, the Brazilian Olavo Pinto, is a wizard when it comes to creative combinations of small doses of different agents. International contact is also vital, among others, because of different syndromes in different countries. The Japanese have very interesting syndromes. When I was first invited to Japan in 1992, they said to me, "Professor, living in Memphis, how did you learn about the Japanese personality, and what do you feel about the temperament that is devoted to work and to harmony, and is self-sacrificing and self-effacing, the dominant Japanese personality that underlies the cohesive structure of our society"?
- PC: They didn't understand the universality of it?
- HA: I guess they live in their own universe. They've got a peculiar, interesting and rich culture. The cohesive nature of their social order is quite unique, I must say.
- PC: And, you speak how many languages?
- HA: I can say few, brief, polite sentences in many languages, including Japanese. But as far as speaking, it is six.
- PC: Which are?
- HA: Armenian, of course, and Arabic, and I picked up some Turkish from my family, French and, of course, English. English was my fifth language. Italian, the sixth, I can manage as far as psychiatry, but not much beyond that.
- PC: And, you write in how many languages?
- HA: At least three.
- PC: English and...
- HA: French and Armenian. I can fill forms in Arabic.
- PC: Are there other things about San Diego I should know or we should have for your history?

- HA: Well, it's one of the most important departments in the country and we have almost "everything".
- PC: That speaks to Judd's leadership, doesn't it?
- HA: He is a master in recruiting talent. He was very patient with me; it took him 12 years to finally get me to move to San Diego. He recruits you to give you two jobs to start with, but you end up doing five or six, even though the salaries at UCSD are relatively low with respect to how expensive the real estate is.
- PC: How about your funding?
- HA: I've never been funded by NIMH extramural grants, even though I was there for four years.
- PC: Don't you think that part of the reason is you collect large samples and that always seems improbable to grant reviewers. They're always concerned that you're overly ambitious.
- HA: Ambitious it is, why be in academia if one will do mediocre work? I never listened to the advice to tone down the scope of what I was doing. I said, no, I can do this and I'll show you what I can do. And I've done just that. I'm one of the most cited researchers in ISI; I've been in the top ten.
- PC: One of the top ten psychiatrists?
- HA: Among Psychiatrists and Psychologists.
- PC: I want to switch to talk about the *Journal of Affective Disorders* because that's another of your major jobs and contributions, isn't it?
- HA: The other day I was making some decisions about manuscripts, and I thought this is the best job I ever had. Many people wanted to be editor-in-chief of the *Journal of Affective Disorders*.
- PC: When George died?
- HA: When he was very ill and someone said go and talk to him. And I said, no, I'm not going to talk to George, that's not a noble thing to ask a dying man to appoint me as his successor. However, I said to the publisher, Elsevier, if George decides I deserve to be his successor, I will seriously consider it.
- PC: They wanted me to be the editor and I said I wasn't good at that. I thought they should ask you. You seemed like the logical person.
- HA: I'm most appreciative because, it has helped me to not only continue George Winokur's legacy, and yours at the same time, but also to introduce innovations of my own. I take particular pride in helping young investigators whose name is unknown, and help them to get a publishable manuscript.
- PC: Is that right?
- HA: Yes, even against the reviewers' negative, sometimes "damning" comments. even though we caution them to avoid such language. Such

consternation may sometimes reflect something really innovative at the core of papers by novices in the field. Of course, there must be something salvageable in the submitted manuscript. I then help them over many months to reshape the manuscript.

- PC: That's wonderful.
- HA: I have done that from the beginning. Danny Freedman and, to some extent, John Nemiah were my models for introducing young talent. They made their handwritten suggestions on my own manuscripts, when I was young.
- PC: How many papers are submitted to the Journal of Affective Disorders?
- HA: It is a huge number and it is increasing exponentially. That, on the positive side, means the journal is enjoying great popularity because of its scientific rank, broad scope, and innovative contributors to our field. Unfortunately the peer-review system is in crisis, due in part to the proliferation of journals on the Internet with increased burden on the limited pool of reviewers. Often, the editor has to do the review himself if the paper is in his area of expertise. Fortunately mine is rather broad, and still I derive particular satisfaction examining in depth, the emerging scientific developments. That means these days I accept some without formal external review; I do many of those reviews myself. North Americans are relatively reluctant to review articles these days, compared with their European counterparts.
- PC: So, you're sending more of your articles to Europeans for review?
- HA: I tend to use relatively young researchers or scholars, who are more motivated to enhance their careers, from both continents, but I can sometimes get pretty good reviews from Japan and Latin America and Australia as well.
- PC: You usually send it out to two reviewers?
- HA: We endeavor to send to three.
- PC: And, you get it back from all three?
- HA: Rarely. Sometimes we are lucky to get one.
- PC: How long have you been doing this?
- HA: Since 1996. George Winokur was a no-nonsence editor, and his example and practical wisdom of running the Journal on a day to day basis guides my overall stewardship of the journal. His infectious laughter, even when facing tough situations is unforgettable.
- PC: What about the organization associated with the Journal; do you want to tell us anything about that? Are there other things about international psychiatry that we need to get down on tape? What is ISAD?
- HA: The International Society for Affective Disorders. It's for mental health professionals around the Journal interested in getting together and

networking. We try to get members initiated into affective disorders by joining. Many young clinical affectiveologists, I believe I have coined this term to refer to our specialty, are part of it and that's the emphasis I want. It's the pleasure of initiating young people into the excitement and elegance of clinical research, because we publish all kinds of articles in the *Journal of Affective Disorders*. It's not only biology or genetics, and neurophysiology; we publish clinical follow-up studies, epidemiology, social and cultural aspects, personality and temperament. I think that broad scope is extremely important. We periodically publish sponsored or editor-initiated special issues or supplements, focusing on special topics. I am responsible with this aspect of the Journal, whereas the European Editor, Professor Cornelius Katona from the UK is in charge of Journal logistics and the "political" governance of ISAD. We have had a very cordial relationship since the beginning, on the same wavelength on the major challenges facing the Journal and our broad specialty.

- PC: The ISAD used to meet just once a year. Now, are they meeting more often?
- HA: Once every two years and, then regional meetings, as well. Canadians have been very active in ISAD.
- PC: Okay, are there other things we should know about you?
- HA: I'm not very much of a political creature. I'm relatively easy to approach, though somewhat shy, except on the stage!
- PC: You did do poetry and art; I saw it in your CV.
- HA: I would say as a young person, many write poetry, especially when one falls in love.
- PC: I don't think that's true, but some people do.
- HA: When you fall in love, verses flow, it is like a natural hypomania!
- PC: That's funny. I have to tell you another story and I want you to talk a little bit about this before we finish. I had a patient, whom I'm sure you knew, too, who came to me one day and said he didn't want to be a bipolar type II; he wanted to be just a depressive. He resisted any other diagnosis and said "I am a hyperthymic obsessive-compulsive depressive". At that point I had not heard of hyperthymia, but he'd read the literature, and the patient said that's what Akiskal has described, and that's what I am. He was right. He was bipolar, but he certainly was hyperthymic, also. When did you come up with that concept, after cyclothymia or at the same time?
- HA: In 1976, I decided that the modification I'd made on our earliest outpatient diagnostic interview required something more than DSM-II personality constructs, and that histrionic, antisocial and cyclothymic and dysthymic were insufficient to describe the variety of human nature,

especially those with high energy and vigor and enterprising. Therefore, I decided to delve further into the German concepts and read Kurt Schneider again. In his opus Psychopathic Personalities, he uses the term "hyperthymic psychopath", psychopath in the sense of abnormal personality, purely in a statistical sense, with no moral judgment attached to it. Thereby, "hyperthymic" became part of our questionnaire and later the temperament scale; we operationalized Schneider's descriptive essay in order to quantify it psychometrically. So, these German concepts entered American psychiatry. That's a very good marriage, classical concepts in methodologically-driven American research.

- PC: I think the old classical nomenclature and some new biologic evaluations are going to be the key. We're going to extend it to another level, don't you?
- HA: I had a Rumanian-origin disciple in San Diego, Robert Bogdan Niculescu, who used to say "in the era of genomics, the phenotype will be king". I think the future is in the creative delineation of phenotypes and not in the largely committee-manufactured DSM-IV nosologic neologisms and constructs, which refer to over 400 ways in which one can loose one's sanity. We should endeavor to define them in their non-pathological versions such as temperaments and related affective and cognitive biases of responding. They should be detected early and one should endeavor to prevent those from becoming disorders. That's a future perspective and challenge to our field.
- PC: I think we want to do one more thing before we end. Tell me again what you mean by mood spectrum disorder. What does it encompass?
- HA: Mood spectrum is not my terminology, that's Angst's.
- PC: What do you call it?
- HA: Bipolar spectrum.
- PC: What does it encompass?
- HA: I will refer to several entities within the bipolar spectrum to highlight their clinical, pharmacologic and genetic significance. At the top of the hierarchy is schizoaffective, bipolar type; followed by the well-known "dichotomy" of type I bipolar and II; next comes type II and a half, these are cyclothymic. The next level of bipolarity is type III, hypomania, which is associated with medication, or ushered by somatic treatment. It is depression with familial bipolarity and which, in our experience, are not infrequently refractory to most treatments as they have been exposed to multiple antidepressants. We also refer to type IV, which is hyperthymic with or without depression, important because these people can be briefly and suicidally depressed, and kill themselves before anybody

knows about it as they can't tolerate any depression. The next entity is the type V, the unresolved question of recurrent "unipolar" depressions. They are often early in age at onset, and may originate from familial bipolar background and, we therefore, prefer to consider "pseudo-unipolar", especially when more than three major episodes have occurred, and subtle depressive mixed states have developed; in my experience, antidepressants do not do very well with these folks. The last one, type VI, has bipolar-like features, like activation, sexual indiscretions, in the context of dementia. This is important because they often respond to divalproex, but not agents used in Alzheimer's. To summarize, conceptually, the term "spectrum" simply refers to bipolar phenomenology of different degrees, which at one level overlaps with schizophrenia and at the other extreme with dementia. It is an attempt to map out a heterogeneous terrain, which, we have hypothesized, will reveal distinct underlying genetic bases. It doesn't mean that they're all due to the same genes, but there's a spectrum in the phenomenology. Here's the potential heuristic value of this concept. In their "dilute" expression these genes seem to harbor adaptive advantages. We must be very caring towards the mentally ill, not just for humanistic Pinelian reasons based on their being ill, but especially in the case of manic-depressive psychosis, they're. Kareen Akiskal and I submit, the carriers of genius or the genes of genius. Many are on the border of "insanity," it's an old idea; it goes as far back as Aristotle or perhaps much earlier.

- PC: That's wonderful. I think that's a perfect way to end, but I can't quite end here. I just want to do one more thing. Now, we've talked about your contribution to psychiatry, but from a personal standpoint, are your parents alive? Do they appreciate what you've added to the world?
- HA: My father, as already mentioned, died in a car accident when I was sixteen. I was in high school then. My mother died in 1986, so my mother knew something of my work and she was very proud to have given birth to me.
- PC: Did she die in Paris?
- HA: No, she died in Lebanon. She wanted to go back, because my aunt, her sister was ill, so she went back, and died there, also wanting to be buried next to her husband, my father. She knew about my career. One of my former professors she met in the States had said to her that I was by far the very best they had had, or something to that effect. And that was the best day for her, and for me, too because that professor had always been very critical of me, or at least he came across that way, and my mother to see a union of herself and my father, both genocide
survivors, contribute to this noble profession about the intangible mysteries of the human mind and the ways it can go wrong.

- PC: Are you an only child?
- HA: No, I have a brother and a sister, both older than me.
- PC: Where?
- HA: My brother, 12 years my senior. He also died in Lebanon.
- PC: Your sister is still living?
- HA: She lives with her husband in Los Angeles; she is retired from a lifelong career as a librarian.
- PC: And, then, about your wife, Kareen?
- HA: I owe much to her because when we were college students, she said to me, you're one of those people who can integrate science and art, and that's the ultimate aim of all human knowledge. I think that she saw something in me and predicted that my career would rise in a meteoric fashion. I don't know how she guessed; we were only seventeen, enrolled in college.
- PC: Then you came to the United States and she was still back in Paris, right?
- HA: Yes, I came in 1969.
- PC: When did you finally marry?
- HA: The Armenian Archbishop of Paris is a close friend of mine from high school. He once said to us, in front of God, a man and a woman are married when a man's eyes fall into the woman's eyes and merge with her soul.
- PC: That's beautiful, so you were married then. Is there anything else we should be covering?
- HA: I wish to conclude by thanking you for this opportunity to be forced to be narcissistic: You're very kind in your appreciation of the work I've done.
- PC: I've appreciated your career from the first time I met you. I think that you've made a major, major contribution to this field and continue to do so. So, thank you.
- HA: Thank you. You brought the best out of me.
- PC: I loved your summary towards the end, what personal factors motivated you.
- HA: Having known you and admired you for many years, I thought that you would be sensitive to it.
- PC: Oh, my goodness!

# **GEORGE S. ALEXOPOULOS**

#### Interviewed by Andrea Tone San Juan, Puerto Rico, December 8, 2003

- AT: My name is Andrea Tone and we are interviewing George Alexopoulos\* at the 42nd Annual Meeting of the ACNP in San Juan. Thank you for coming to the interview.
- GA: Thank you, Andrea.
- AT: Let me start with some general questions about your background. You were born in Greece. Tell me about your upbringing and your early education.
- GA: I was born at the end of the Civil War in Greece. I went to medical school in Athens and upon my graduation served in the Greek Navy, a mandatory service in Greece.
- AT: It is still mandatory, isn't it?
- GA: It is, but the service is much shorter. After the Navy, I worked as a country doctor in Mycenae, also a mandatory service. I enjoyed this work because it gave me the opportunity to practice general medicine. I had an internship in internal medicine earlier and a long rotation in neurology. Then, I came to the United States.
- AT: At what point did you decide you wanted to become a physician?
- GA: Oh, I wouldn't even remember. My family encouraged me to go into medicine. It seemed like the thing to do. My sister also became a physician.
- AT: And, what was training in medicine like in Greece? Would you say it varied from training in the United States?
- GA: No, it was pretty similar. I had excellent attendings during my internship. They spent a lot of time with me. They valued their trainees and enjoyed teaching. Even as an intern, we wrote a few papers together. In one of those, I was the first author. It was hard work but a very useful experience.
- AT: You mentioned that you had training in neurology. What was your exposure to psychiatry early on, and at what point did you decide to commit to becoming a psychiatrist?
- GA: I had no training in psychiatry. The debate in my head while in medical school was whether to go into a very practical field, like surgery, or to go into psychiatry, which was a broad and evolving field that would allow me use a wide variety of study methods. Growing up, I had interest in philosophy of science and I thought that psychiatry would allow this interest to be central to my professional work. It didn't happen. I still think it might happen at some point. Before I started formal training in

<sup>\*</sup> George S. Alexopoulos was born in Thessaloniki, Greece in 1946.

psychiatry, I had little exposure to psychiatric patients, essentially volunteering in a mental hospital, going to rounds with professors, etc. But I did not really know what mental illness is until I started my residency in the US.

- AT: How was mental illness viewed and treated at the time you were doing short hospital rotations?
- GA: That was in the early 1970's, and there was a lot of confusion about psychiatry in Greece and around the world. There were some people who believed in a rather naïve way in the power of the newly available psychotropic drugs and thought that everything else was unimportant.
- AT: Everything else being psychoanalysis?
- GA: Psychoanalysis and psychotherapy were felt to be unimportant by biological psychiatrists of that time. Most biological psychiatrists were working in mental hospitals, treating people with psychotic or severe mood disorders. In contrast, psychiatrists who favored psychotherapies would shun mental hospitals and preferred to treat people who were essentially well. They were treating them with psychotherapy or psychoanalysis with results that were neither measured nor standardized in any way. So, there were two different worlds. These two types of psychiatrists did not treat the same kind of patients and did not have the same vocabulary. They couldn't speak to each other. The integration of pharmacotherapy and psychotherapy that we see today was inconceivable at that time.
- AT: Was there a socioeconomic gap, as well? Were the psychotherapists treating largely the affluent population? Where there socioeconomic differences in those who were hospitalized and how did access to psychiatric services play out economically and socially?
- GA: In Greece?
- AT: Yes.
- GA: Well, most severe mental illnesses do not spare socioeconomic class. Those who had to be hospitalized were treated, mainly, by biological psychiatrists. The poor would go to community hospitals designed mainly for chronic care. They were part of the state hospital system. These hospitals had some acute units, but even the acute units had long stays by today's criteria, reminiscent of the institutionalization era. Privately owned hospitals were somewhat better staffed and likely to offer aggressive acute pharmacotherapy and ECT.
- AT: In the 1970s?
- GA: That's right.
- AT: What was health insurance like for psychiatric therapy?

- GA: In Greece, everybody was and still is insured in some way or another. There's no single carrier, but everybody was insured, through the State or through employers. The State was then a major employer and insured most of its employees and their dependents through two of its insurance carriers. Greece has been a semi-socialistic state, although democracy was interrupted by two or three dictatorships in the twentieth century. The dictatorships were hated by almost everybody in Greece.
- AT: You mentioned why psychiatry was appealing. Tell me more about your psychiatric training.
- GA: In Greece?
- AT: In Greece.
- GA: I just went to rounds with the various professors in one or two hospitals where I volunteered, so I didn't have much psychiatric training in Greece.
- AT: And, then, when you came to the United States?
- GA: I started my psychiatric residency at New Jersey Medical School in Newark. It was a wild place with about ten admissions per night and a length of stay of about four days. Many patients were discharged to state hospitals, because we had only a few beds. So we couldn't complete the treatment for many of our patients. Because of the difficult environment, good attending staff left the faculty within one or two years. I stayed there for a brief period of time and went on to finish my residency at Cornell. Dilip Jeste, another ACNP member, who subsequently had a career in geriatric psychiatry similar to mine, was a resident at New Jersey Medical School at the same time. He, too, left and went to Cornell. I stayed at Cornell after the residency where I had a research fellowship under Peter Stokes, and have remained at Cornell until now. Dilip went to NIMH and now is at the University of California in San Diego.
- AT: To back up a bit, why did you decide to come to the United States?
- GA: To learn psychiatry.
- AT: Just because there was nothing in Greece to support the training you wanted?
- GA: In Greece, psychiatry was one of the least developed medical specialties. A number of other medical specialties were advanced. Surgery, ophthalmology, and hematology had been traditionally very strong in Greece. A number of surgical techniques had been invented in Athens. Many hemoglobinopathies were first identified at the same university. But psychiatry was fragmented and individualistic. Psychiatrists felt free to design their approach to mental illness. They had no shared point of view that would have allowed psychiatry to advance as a serious scientific field. So, it was obvious when I decided to go into psychiatry that

I shouldn't stay in Greece. The question was whether to go to another European country, like Germany, or to go to the United States.

- AT: And, why did you choose the United States over a European country?
- GA: Because, I spoke English better than German.
- AT: So, when you came over here for training, had you already come to a decision about what you might want to specialize in or what were your objectives at the time?
- GA: My objective was to become sufficiently familiar with the main trends in psychiatry and see where the future lay. Since I was interested in philosophy of science, I tried to become familiar with psychoanalysis, the most controversial field in psychiatry. I went to a number of evening lectures given by eminent psychoanalysts and had long discussions with psychoanalyst supervisors. It took about a month to understand that psychoanalysis was not for me. The psychoanalysts made wild assumptions that did not fit most of the principles of logical positivism, Quine's holistic theory of science. Popper had the most explicit views about the non-scientific status of psychoanalysis.
- AT: Can you say a little more about it?
- GA: There were many assumptions that did not lend themselves to measurement and could not be experimentally tested. For example, the central assumption of psychoanalysis is that the unconscious influences behavior. There is nothing wrong with the construct of the unconscious. There are similar constructs in science that one cannot see or touch, e.g. no human eye has ever seen an atom. Yet unlike the constructs of other sciences, the unconscious, as conceptualized by psychoanalysis, did not permit measurement. Therefore, no scientist could construct a testable hypothesis related to the unconscious. Let me give an example from physics. The concept of "electrical conductivity" is almost as abstract as the unconscious. Yet, you can develop an instrument to measure the passage of electrical current through a metal wire and use the reading of the instrument as evidence supporting the construct of conductivity. The method to study the unconscious was based on analysis of free associations and dreams. These were not nearly as reliable as an instrument that detects passage of an electrical current through a metal wire. I don't suggest that there is no place for psychoanalysis. There may be. For example, psychoanalytic concepts may be used in literary criticism or in criticism of the visual arts. So it was my interest in philosophy of science that brought me to psychiatry and it was this same interest that steered me away from psychoanalysis. Another reason that made me turn away from psychoanalysis was my clinical exposure, which made it

clear that mental illness is a real illness with enormous consequences. It worsens medical illnesses, increases mortality, and destroys families and patient lives. You can play with your own ideas and become enamored with your assumptions in theoretical work, but when you are treating the sick you must take your work seriously. I felt that one had to be responsible and disciplined in studying mental illness. My early experience in Newark made me understand how severe mental illness is and steered me towards clinical/biological psychiatry. I saw the most neglected mentally ill patients there who lacked even the most basic resources and support. It was a human tragedy. Then, when I went to Cornell, I saw equally severe psychopathology, but occurring in people with more resources and an environment that allowed better study of their problems. In Newark, it was all emergency room psychiatry, whether you worked in the emergency room or on the inpatient service. At Cornell, once a patient entered the hospital, the doctor could sit down, catch his breath, and try to think what this person is about. There was a luxury of time and resources. So, I learned a different aspect of psychiatry at Cornell.

- AT: Describe your status when you first joined Cornell. What exactly was your position?
- GA: I was in the middle of my residency. After I graduated, I had a research fellowship in psychobiology with Peter Stokes, a pioneer psychoendocrinologist.
- AT: And, you were working at the hospital and also doing research?
- GA: As a resident, I did some research. The data collection for my first paper in an American journal was done during my residency in Newark. The paper was on the observation that patients with tardive dyskinesia do not report their mouth movements and are minimally aware of them. They did not complain even when the movements were disfiguring and made them dysfunctional. I thought that the lack of recognition of mouth movements by the patients was not a psychological phenomenon, but rather a neurological symptom, a type of anosognosia analogous to left body neglect after stroke. When I wrote the paper, this seemed like a wild assumption. But now it's pretty well accepted that tardive dyskinesia is often associated with neglect of illness. This was my first and only study in tardive dyskinesia.
- AT: Was this a pioneer contribution?
- GA: Let's not get carried away. It was beginner's luck.
- AT: What got you interested in geriatric medicine and in geriatric depression?
- GA: Several things. Some had to do with opportunity and some with science. After I graduated from my research fellowship on the biology of

depression, it was difficult to obtain research funding in that area. Dr. Stokes, my mentor at the time, said maybe you should try some other field within depression, but not just pure young adult depression.

- AT: Which was the hot topic at the time?
- GA: Depression was the hot topic. It was the area that attracted most researchers.
- AT: The 18 to 45 year age range was the targeted population?
- GA: I would say 18 to 55 or 60 years. So, I took a job in alcoholism and I started to study mood disorders of alcoholic patients. They were called, then, secondary mood disorders. The two years, 1978-1980, I worked in alcoholism gave me data to publish until 1988. In 1980, I went into geriatric psychiatry, which was an under-populated field. The scientific attraction was that brain lesions occurring in late life could serve as a laboratory of nature in which to study psychopathology. This was a rather simplistic thought influenced by my exposure to neurology. Another reason to be attracted to the relationship of brain lesions to psychopathology was that neuroimaging was evolving and lesions could be seen with some accuracy for the first time. The idea was that aging gives you brain lesions of various kinds but you don't have to surgically expose the human brain in order to observe a lesion-disease interaction. You can observe whether a lesion in the brain increases the likelihood to develop depression, influence its course or contribute to disability associated with depression. This was the scientific reason for going into geriatric psychiatry. On a practical level, a research career in geriatrics was feasible. The field was underdeveloped and many intelligent people went into geriatric psychiatry at that time. Another reason that may sound trivial, but it isn't, was that the field was increasingly populated by investigators who were very excited about what they did. They loved what they were doing and were respectful of each other. It was easy to interact with the giants of geriatric psychiatry without having to wait on line. If you wanted to discuss an idea or ask for help about a technique senior people were eager to find the time to help. I learned from both senior investigators and junior colleagues. It was and still is a good environment.
- AT: Why is it different from other sub-fields in the study of depression?
- GA: I don't suggest that other fields are less friendly than ours. I am saying that the field I know has been collaborative. It has been an environment of exchange and scientific sharing. Many geriatric psychiatrists would say the same. But there's a danger in being in a collaborative field. When you submit a grant or a paper your work might be reviewed by referees from another field, since collaboration with other geriatricians

creates conflict of interest. This is risky because non-geriatricians may be unaware of conventions and assumptions in the field of geriatrics. Every complex field needs to rely on some assumptions in order to create hypotheses that can be tested through the experimental means available at the time. The assumptions that geriatric psychiatrists make need not be the same made by those working in young adult depression. For example, an assumption central to my work has been that brain abnormalities underlying the cognitive impairment of geriatric depression confer vulnerability to depression and influence its course. Yet, many investigators of young adult depression consider cognitive impairment a confounding factor and exclude depressed patients with cognitive impairment from their studies. You can see here how a mismatch in assumptions can create confusion in the review process.

- AT: How many joined the field in 1980 when you hopped on this bandwagon and what was the thinking among psychiatrists, but also among other doctors, even the general population, about depression in the elderly?
- GA: Investigators, who were not in geriatric depression, thought it was a minefield. Because geriatric depression develops in people with medical illnesses or dementing disorders they thought that it was difficult to obtain a clean sample to study brain biology of depression. The classical experimental design in young adult depression was to "sanitize" the sample and study patients who had depression and depression only. They had to be otherwise healthy. They could not have another brain disease or concurrent medical illness. My view, when I went into geriatric depression, was just the opposite. I saw co-morbidity as an opportunity. The idea was simple and pragmatic. If a medical illness is known to cause depression, and we know the causes of that medical illness, we may begin to get ideas about what might be contributing to depression. For example, at the time, Dr. Arthur Prange was writing about thyroid abnormalities in young adult depression. As hypothyroidism is common in elderly men and in middle aged or elderly women, I was surprised that investigators were not giving an age dimension to the relationship between hypothyroidism and depression. The same concern is relevant to brain lesion research. It is difficult to study the relationship between brain lesion location and depression in young adults because patients with lesions were excluded from studies. Yet, in geriatric depression, lesions have been used to guide investigators in the search for those that influence the course of depression. So, what in research of young adult depression, was viewed as an obstacle, some of us in geriatric psychiatry saw as an opportunity.

- AT: Wasn't the thinking in 1982 that depression was just an inevitable corollary to getting old, almost a natural part of aging?
- GA: That was in the public's mind. I'm not sure that biological psychiatrists felt that way. Yet, many psychiatrists felt that old people don't improve with psychotherapy. It took many years and a number of well done clinical trials to show that standardized psychotherapies have reasonable efficacy in geriatric depression. The thinking of the time was influenced by Freud's view that psychoanalysis was ineffective after middle age because personality was consolidated and nothing could change it. As people say "old dogs don't learn new tricks". Except that depressed old people do respond to psychotherapy if you provide it.
- AT: Tell me about what you would consider to be the most important research you've done.
- GA: I have done two kinds of studies. One set of studies is looking at biological events that influence the course of geriatric depression. The second set consists of studies on the effectiveness of treatments for depression offered in the community. In the first area, a number of our early studies found that many patients with late-onset depression, meaning a first episode in late life, also had cognitive impairment and neurological symptoms and signs. These studies established a connection between cognitive and neurological findings with depression and supported the original idea that late onset depression may result from age related brain changes or diseases. An important question was who among depressed elderly patients was at the highest risk for dementia and who had a static cognitive impairment. To answer these questions we started with a study of depressed elderly patients with "pseudodementia". These patients met diagnostic criteria for dementia while depressed but their cognitive functions improved when their depression remitted. I should mention that most patients with depression and pseudodementia had their first episode in late life. We followed these patients for ftwo to three years and observed that about 40% of them developed dementia either of Alzheimer's type or a vascular dementia. We concluded that "pseudodementia" is not a "pseudo" state but, in most cases, an early stage of dementing disorder, which clinically becomes evident on follow up. And yet not all patients with pseudodementia became demented. Some had impairment in neuropsychological functions that neither progressed into dementia nor improved fully after remission of depression. Following this observation, I tried to characterize the type of neuropsychological impairment of depressed elderly patients and study its relationship to the course of depression. In an early paper, we found that late onset depression

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is less likely to remit than geriatric depression with a first episode in early life. But studies of depression onset have many methodological problems. I did one study which documented that ascertaining the age of a first depressive episode was not as reliable as the field thought at the time. Ascertainment of onset is particularly problematic when the first episode is not major depression. Knowing that most first episodes are of mild intensity, the lack of reliable ascertainment is relevant to the majority of geriatric depression cases. The other problem in age of onset studies is a conceptual one. Inherent in age of onset studies is the assumption that each depressive episode of the same individual has the same contributing factors. I argued that this assumption was unfounded. I found no compelling reason to believe that a depressive episode at age 18 had the same etiological contributors with an episode of postpartum depression or an episode of depression in late life after this same person suffered cerebrovascular lesions. Think of a young girl who goes to college. This is the first time living away from her family, she has to respond to a demanding curriculum, and the boy she likes does not even notice her. She develops depression by mid- October, but her symptoms subside during the Christmas holidays when she goes home and has the support of her family. Let's follow this young woman as she ages. She is now 32 years old, has her first child, and develops postpartum depression probably triggered by hormonal changes. Years later, our lady is 75 years old, has been hypertensive and overweight since midlife, and develops a third episode of major depression. Her brain MRI reveals white matter intensities in sub-cortical frontal areas. Do the episodes of depression in this patient have the same etiology? There is a good chance that they do not. In fact, we now think that depressive episodes occurring in early life, damage some brain structures critical for processing affect. If this view is correct, patients with depressive episodes since early life may have significant compromise in these structures. When vascular or other age-related lesions also occur in these structures in late life, patients with recurrent depression may become exceedingly vulnerable to depression. That is, more vulnerable than elderly persons who never had depression before. So paradoxically, depression starting in early life, increases the likelihood of developing depressive episodes in late life due to brain changes that once were thought to be the causes of late-onset depression, e.g., vascular lesions or age related brain changes. Based on these rather simple, clinical thoughts, I decided to abandon "age of onset" as a distinguishing characteristic of geriatric depression or as a predictor of the course of geriatric depression and

began to focus on cognitive impairment in geriatric depression and its impact on treatment response and course of illness. That was a critical turning point in my work. The first target of my subsequent work was executive impairment.

- AT: Please explain what that is.
- GA: Executive impairment is an impairment of a set of cognitive functions served by the frontal lobe. So it is the clinical expression of some frontal lobe dysfunctions. On a behavioral level, people with executive impairment cannot abstract easily, cannot set clear goals for themselves, cannot plan well, cannot initiate action towards achieving a goal, and cannot sequence their actions. Even if they achieve their goal, they tend to perseverate and continue to engage in actions no longer needed. My colleagues and I documented that about 40% of elderly patients with major depression have significant executive dysfunction. We also observed that severity of depression interacts with executive dysfunction and increases disability. Said differently, severe geriatric depression is likely to make a person disproportionately disabled if this person also has executive dysfunction. We observed, in three studies, that depressed elderly patients with a certain type of executive impairment do not respond to acute treatment with antidepressant drugs. Using different samples, but similar experimental approaches, these findings have been replicated by others. Interestingly, when our depressed elderly patients with executive dysfunction finally achieved remission, we noticed that they relapsed into depression early even when they received continuation treatment with the antidepressant nortriptyline. Although they stayed well for 4 to 6 months after remission, depressed patients with executive dysfunction were more likely to suffer a recurrence of depression than patients without executive dysfunction. Based on these studies, we concluded that geriatric depression with executive dysfunction has a slow, poor, and unstable response to antidepressants. In 2001, I described the "depression-executive dysfunction syndrome of late life". The reason to propose this syndrome was its heuristic value. That is, its ability to serve as an intellectual platform for specific hypotheses on the pathophysiology of geriatric depression. Following this logic, the next question was: "What are the brain abnormalities, underlying executive dysfunction, which lead to an unfavorable course of depression"? The studies I am doing today attempt to answer this question. The first set of studies focused on brain structures responsible for some of the executive functions. The anterior cingulate gyrus is one of these structures. The volume of the anterior cingulate gyrus may be smaller in depressed patients, especially on the left side, compared to

normal controls. This difference principally results from reduction of the white matter. An early finding that preceded this study was that microanatomical abnormalities, lower fractional anisotropy in white matter regions lateral to the anterior cingulate gyrus predicted a poor remission rate in a small number of patients treated with citalopram. We are now studying microstructural abnormalities in the whole brain in order to see which have specific relationships to treatment response. We use two MRI techniques for this purpose, diffusion tensor and magnetization transfer imaging distinguished depressed old patients from elderly controls. We also replicated our earlier finding of an association between frontolimbic microstructural abnormalities and non-remission of geriatric depression.

- AT: Do these abnormalities predict poor response to all antidepressants?
- GA: Our first study used many antidepressants as the probe to treatment response. Our only requirement was that they were given in adequate dosages for an adequate length of time. We now use only one antidepressant to minimize heterogeneity in the treatment. This strategy does not allow generalization to other antidepressants. I will report on some of the studies at this meeting. Changes in brain structure may inhibit antidepressant response by causing brain processing abnormalities. The next question then should be; what processing abnormalities are linked to poor antidepressant response? Starting from the observation that executive dysfunction contributes to poor antidepressant response, we now use probes of executive functions. This means we give a stimulus whose response depends on executive function, and we record changes in the electroencephalogram (EEG) in evoked potentials. At this point, we are studying the error negative wave the wave elicited approximately 80 milliseconds after the subject makes an error in a response inhibition task. We are also studying the error positive wave, the wave produced at about 300 milliseconds after committing an error. The generators of these waves are on or around different areas of the anterior cingulate gyrus. Our preliminary studies show that those depressed elderly patients who don't do well with antidepressant treatment have large amplitude in the error negative wave following a stimulus that requires executive function. So, that you can see, the sequence in our thinking, we started by characterizing the neuropsychological dysfunctions of depression and their relationship to outcome of treatment. We, then, used these findings to orient ourselves to the potential location of brain abnormalities contributing to poor treatment response, using structural neuroimaging to identify their anatomy. Now we are using electrophysiological approaches to identify processing

abnormalities. We started with clinical tools and ended up with more localizing studies, utilizing experimental technology as it is becomes available. You couldn't measure, in 1980, the micro-structural abnormalities in the white matter, nor did we know enough about executive functions to be able to do the electrophysiological experiments we're capable of doing now.

- AT: You mentioned that the field of geriatric psychiatry is very collaborative, very supportive. How would you say your work is different or unique, compared to the results of others looking at geriatric depression?
- GA: The studies I just mentioned were mainly done by our group. However, I consulted with several people over the years, including Kelvin Lim, John Foxe, Ranga Krishnan, Howard Aizenstein, Chip Reynolds, Yvette Sheline, Anand Kumar, and others. Many of our efficacy and effectiveness studies relied on close multi-center collaboration with competent colleagues. The psychotic depression study, the first treatment study of this syndrome since the mid-eighties, and the geriatric bipolar study, the first treatment efficacy study in the field, were led by Cornell investigators but relied heavily on the expertise and work of investigators of other centers. The PROSPECT Study was another example. I was the coordinating principal investigator, but the other participating centers were the Intervention Research Centers of the University of Pittsburgh and of the University of Pennsylvania. This was a unique collaboration. Research centers often are competitors and don't work with each other. But, in this case, Chip Reynolds of the University of Pittsburgh, Ira Katz of the University of Pennsylvania and I formed a consortium and did a study that was methodologically superior to what we at Cornell alone could have implemented. Each of us has been reporting data from the PROSPECT Study and I will be reporting new data at the International College of Geriatric Psychopharmacology meeting that immediately follows this ACNP meeting.
- AT: What are the general implications of your research for the every day treatment of depression in the elderly?
- GA: Identifying brain abnormalities leading to depressive syndromes with characteristic clinical presentation and treatment outcomes may allow us to sub-categorize depression according to biological criteria and use pharmacological and behavioral approaches to address specific brain abnormalities. Suppose we identify abnormalities in the frontal system, let's say the anterior cingulate, in a subgroup of geriatric depression which does not respond to conventional antidepressants. If the neurotransmitter systems of the cingulate gyrus are known, a logical next step is to use one of the available drugs that can improve the function of

the ailing neurotransmitter systems. This drug may not be thought of as an antidepressant and thus may not have been considered for use in depressed patients. Indeed, if this drug were used in all depressives, whether they have an abnormal cingulate or not, it might have been found ineffective, because a good number of depressives did not have an impaired cingulate gyrus and did not need this drug. I mentioned earlier the depression-executive syndrome of late-life. Based on evidence that patients with this syndrome have impairment in fronto-striatolimbic pathways, and knowing that dopamine is a central neurotransmitter modulating this system, it is reasonable to study the efficacy of a dopamine-acting drug in patients with this syndrome. And yet, if you use a dopamine-acting drug in a broader group of depressives, this drug may be ineffective because many depressives may not have a prominent fronto-striato-limbic dysfunction. Importantly, we have data showing that people with the depression-executive dysfunction syndrome of late life, while likely to fail antidepressant drug therapy, might be able to respond to problem solving therapy. Thus, a type of cognitive behavioral therapy, modified to address the behavioral deficits of these patients, can reduce the adversity they experience.

- AT: To summarize: your research has proven that geriatric depression is not a homogeneous entity and you can't have a one size fits of all treatment. Trying to connect this cutting edge research to the experiences of elderly Americans, what are the obstacles someone over the age of 65 faces when they feel depressed to obtain the kind of treatment you're discussing?
- AG: Well, public health is different than what we do. In most diseases, there's a gap between discovery of a treatment or an understanding of a disease and what happens in the community. There are at least two kinds of barriers to transfer of knowledge to community practice that are unique to geriatric depression. The first is the bias of elderly persons themselves about depression as well as the training of those who treat them. Old people often say, "If I lived my life without depression, who are you to tell me that I'm depressed or mentally ill"?
- AT: Depression is heavily stigmatized.
- AG: It is stigmatized. The second problem is that two-thirds of depressed elderly persons are treated by primary care physicians. The training of primary care physicians in recognizing depression varies. Some are as good as mental health professionals but others have limited training in mental health. Those with limited training may both miss cases of depression or overdiagnose depression where it does not exist. Limited training explains in part why antidepressants are both underused and

overused in the elderly. Another problem comes from physicians' training in psychiatric interviewing, especially interviewing patients who do not see themselves as depressed and need to be informed of their diagnosis in a way that would be acceptable to them. Physicians who lack such training may see this discussion as a confrontation and either avoid informing the patients of their diagnosis or avoid treating their depression altogether. Many elderly, especially the impoverished, don't even have primary care physicians. They go to clinics when they get very sick and they're treated as emergencies. So, the issue of access to care is of critical importance in geriatric psychiatry. My colleague, Marty Bruce, does studies of home healthcare patients. About 15% of patients in need of home healthcare have major depression and many others have less severe depressive syndromes. Marty Bruce trained drivers in a "Meals on Wheels" program to ask the question "are you sad"? Seniors, who answered, yes were referred for a more formal evaluation.

- AT: The "Meals on Wheels" driver?
- GA: They were trained to ask one single question. So there are clever ways of increasing access to care, but they need to be thought of, studied, and implemented. You asked me how to bridge the gap between treatment discovery or understanding of the biology of the disease and delivering care. In geriatrics, access to care is an important barrier that needs to be addressed. The other set of barriers exist at the primary care level. As I pointed out earlier, two thirds of depressed seniors are treated in primary care settings. Some seniors are referred to mental health specialists, but eighty percent of those referred never reach a mental health professional. They either resist or do not have the resources or the energy. Geriatric psychiatrists have rather limited impact on the direct care of depressed elderly persons. There are too few of us to make a difference. Most contributions, come from research and teaching, in geriatric psychiatry. Going back to primary care, I have served as the coordinating principal investigator of the PROSPECT study and had the opportunity to work with the principal investigators of the other two Centers, Chip Reynolds and Ira Katz, as well as many other accomplished investigators, including Marty Bruce and Charlie Schulberg from whom I learned a great deal about this kind of research. The PROSPECT Study compared the short-term and long-term outcomes of a care management intervention to usual care in depressed elderly primary care patients. The idea is that some primary care physicians don't have the time or the resources to follow depressed patients appropriately. They may identify depression and even prescribe the

starting dose of an antidepressant but not follow the patients with sufficient frequency and do not see whether they adhered to treatment, responded, or needed either higher doses or another antidepressant. Depression is a chronic disease requiring adjustment of dosages, prevention of future episodes, education of patients and families about the nature of depression, and the importance of treatment adherence. To meet these needs, the PROSPECT intervention relies on a care manager trained to assist physicians to provide appropriately timed and targeted intervention. The care managers follow a protocol based on the AHCPR treatment guideline modified to meet the needs of elderly primary care patients. They make recommendations to physicians after interviewing the patients and consulting the treatment guideline. The physicians make the final decisions. Our concern had been whether the physicians would accept their recommendations, but it turned out that the physicians loved the assistance the PROSPECT care managers offered and invariantly worked with them well. We completed the subject recruitment about a year ago and the follow up is about to be completed. We have submitted two papers, one to JAMA and one to the American Journal of Psychiatry. In these papers we report that primary care practices assigned to intervention had better outcomes than usual care, including less suicidal ideation, hopelessness, and overall severity of depressive symptoms and higher response and remission rates. We also began to identify predictors of outcomes in both the intervention practices and in the usual care practices. The value of these findings is that, if resources are limited, one may assign care managers to depressed primary care patients least likely to respond to usual care or most likely to benefit from care management. The question with the PROSPECT intervention, as with other interventions of this type, is who is going to pay for them? Who's going to pay the care manager or the back up psychiatric consultant? We talked so far about successful projects. But would you like to hear about one of my failures?

- AT: Yes
- GA: Well, the same group that did the PROSPECT Study applied and received a grant from the Robert Wood Johnson Foundation to negotiate with Medicare and plan a demonstration project that would allow us to test the fiscal feasibility of the PROSPECT intervention. The idea was that depression influences medical health and increases the utilization of medical services. A reasonable hypothesis was that giving good treatment for depression, as the PROSPECT intervention did, would improve both depression itself and reduce its medical consequences and, therefore, decrease medical expenses or at least break even. We

had a number of meetings with Medicare. We had the previous administrator of Medicare, Dr. Bruce Vladeck, who, for absolutely no pay and no personal gain, volunteered many, many hours over the period of a year to help us interact with Medicare. However, we were uniformly defeated. A year later, I sent the grant back to the Robert Wood Johnson Foundation because Medicare remained reluctant to proceed with a demonstration project. We had lost.

- AT: Why?
- GA: Perhaps because of our failure to understand how Medicare officers think and to what political pressures they are exposed to. It has to do more with public health policy and financial issues than clinical science. Even the process was unfamiliar to me. We met several times with different groups from Medicare, each of which was presumably empowered to make decisions. But each meeting was succeeded by a meeting with another different Medicare group. Every point of agreement in a previous meeting had to be re-discussed and renegotiated with the new group. So, it was one step forward, two steps backward, and it became apparent that we were not going to be able to advance. All of us who participated in this process concluded we lost. Clearly, I bear most of the responsibility for the failure. I know little about public policy and health finances. But I asked for help from health economists and public policy experts from the University of Pennsylvania, the University of Pittsburgh, Dartmouth, and Duke. Everyone I asked from the academic side came forward. It was a good feeling and substantiated the strong spirit of collaboration of our field. Of course to no avail.
- AT: So you identified obstacles that stand in the way of an elderly person with depression getting treatment that works, including the stigma, the patient not wanting to go to a doctor to discuss symptoms and the doctor likely to be a primary care physician, not a geriatric psychiatrist, so not trained to pinpoint the problem...
- GA: ... or not having the time to give appropriate treatment. On the one hand, we have advanced technology with brain scanning and genetics that soon may identify specific kinds of depression that may be targeted with specific treatments, but we have a care delivery system that doesn't have the resources to bring many of these discoveries to bear in the care of patients who need them. This is happening across the health field. Not just in the area of depression, although this gap is larger in depression because of stigma and bias. The response of the National Institute of Mental Health to this problem has been to create centers for intervention and services. I am referring to the Advanced Centers for Interventions and Services Research (ACISR). In the area of

geriatric depression, there are three ACISRs in the country, one at the University of Pennsylvania, one at the University of Pittsburgh, and one at Cornell.

- AT: What is your involvement in this process?
- GA. I direct the ACISR of Cornell. We have a continuum of research, from biological studies to understand and overcome the biological and clinical mechanisms of treatment resistance in geriatric depression, to treatment efficacy and treatment effectiveness studies. The PROSPECT Study is an example of an effectiveness study. It examines how a treatment of known efficacy performs in the community and how it can be made to perform even better. So, our ACISR's research program supports research ranging from the biological and psychosocial factors interfering with treatment response of geriatric depression, to transfer of knowledge studies that utilize findings of biological and psychotherapy studies, simplify them and introduce them into clinical care. For example, a neuropsychological battery examining executive functions may take two and a half hours to administer. Even if you find that abnormalities identified through such a battery predict poor antidepressant response, you cannot tell clinicians practicing in the community to use the whole battery. They would not have the time or the training. So, such a finding has limited value for direct clinical care. But if you start with a large battery and then you identify within it a simple test that predicts treatment response you have a better chance to introduce it into community-based practice. I think that the ACISRs can best fulfill their mission by working both on the side of clinical biology and on the transfer of knowledge from biological discovery to bedside and community practice. To paraphrase Kant's saying about theory and experiment: Clinical biology without application to community-based practice is empty and services research not rooted in clinical biology is blind. The application process that led to the ACISR made me think directly and consciously how to design experiments along this continuum. The extent to which findings of biologically informed health services research change community-based care is beyond what an ACISR can do. It is a matter of public policy at a national level. The Robert Wood Johnson project that we just talked about is perhaps the limit of what the three ACISRs can do. Although our first attempt failed, we don't have to continue failing. There's increasing recognition of the problem of depression and we may succeed in our next attempt. People of my generation, as they age, will bring along a different point of view about depression. We are much more aware that mental illnesses are real illnesses. I expect that

the baby boomer generation will advocate effectively about the need of better care for late life depression.

- AT: Right. There's almost a different intellectual orientation of the old generation. Some of our parents are in their eighties and I don't think they can stomach the diagnosis of depression. The 19<sup>th</sup> century belief that depression as a problem of the will, that you're to pull yourself up by your bootstraps and step back in the saddle is still alive in my mother's generation. But in my generation people are more comfortable with the concept of depression. I wanted to ask you something about prescription drug coverage and whether the absence of coverage for most of the elderly has a huge impact on the kinds of treatment available. How does the economics of that play out in the United States?
- GA: The economics of prescription drugs in the United States?
- AT: Yes.
- GA: It's a big obstacle. If elderly persons cannot afford medication, they won't take it and the more biased they are about a medical condition the less likely they are to buy medication for that condition. A second barrier to treatment of depression is its chronic nature, which necessitates long-term treatment that elderly may be unable to afford.
- AT: You know that people diagnosed with depression in their twenties, thirties and forties are more likely to be women than men. Does that ratio hold true for the elderly?
- GA: Yes and no. Men, as you know, die earlier than women, so, in that sense, there are fewer men to become depressed. On an epidemiological level, it looks as if the gap is not narrowing. But based on equal numbers of men and women, the gap narrows and a higher proportion of older men are afflicted by depression. The reasons for the increase in older men are not clear. A possibility may be that men are more prone to cerebrovascular disease and, therefore, more likely to suffer brain lesions than women. Ranga Krishnan and I, independently, proposed the vascular depression hypothesis, which postulates that vascular lesions in critical brain areas predispose to late life depression. This hypothesis may account for one of the reasons for the narrowing gap in the frequency of depression between older men and women.
- AT: If we flash forward to fifteen or twenty years from now, what do you think the situation will be in the diagnosis and treatment of geriatric depression, in a best case scenario?
- GA: I think it will improve. I believe that there has been significant progress in understanding depression among medical practitioners. There's recognition that depression is important. Similarly, there is an increase of scientific interest. As long as the intellectual leadership of medicine and

psychiatry is going in that direction, more discoveries will take place and the public will become more accepting and less biased about depression.

- AT: The work of Dennis Charney and others emphasized the extent to which depression is a debilitating illness that can increase one's vulnerability to diabetes, heart disease, Parkinson's, and Alzheimer's. Do you see this among the elderly and is there something that could be used to make the argument that it's cost effective to make sure that depressed elderly receive good care?
- GA: The relationship between depression and medical disorders is far better substantiated in the elderly than in the young. Epidemiological studies show that elders in the community are less likely to suffer from depression than younger people. But, if you look at elderly patients on medical services, primary care patients, or nursing home residents, you see a prevalence of depression two to five times higher than that of younger adults. What I'm saying is that in the elderly, depression is linked to medical illness. If you're not medically ill, you're not that likely to be depressed in late life. And, there's a reciprocal relationship between medical disease and depression. It goes both ways; if you are medically ill you are more likely to become depressed and depression itself worsens the outcomes of medical illnesses, as Dennis and others have shown. If you have depression you have a higher mortality and a likelihood of developing cardiovascular and perhaps Alzheimer's disease. Parkinson's disease causes depression, but it is unclear whether depression predisposes to Parkinson's. So, the relationship between medical illnesses and depression can be part of public education and serve to reduce the stigma of depression. A number of organizations have done a tremendous job and many investigators have joined them. A number of ACNP members are going directly to Washington at least once a year to speak to congressmen about the need for increasing appropriations, not only for research, but for public education on depression and other mental illnesses and interventions at the community level. So, there has been a lot of activity and I'm guite optimistic that things will change. They won't change in a day, but we're going in the right direction.
- AT: We talked about the difficulties that the elderly, who are depressed, have in getting access to the right doctors and the right treatment, including drug therapy. How motivated, in your estimation, are pharmaceutical companies to sponsor research to develop tailored drugs to treat various kinds of geriatric depression that can be tolerated by old people?

- GA: The most recently developed antidepressants are not more powerful than classical antidepressants but they have far fewer side effects.
- AT: The SSRIs?
- GA: Yes, the SSRIs, SNRIs, and bupropion. None of them is more effective than the tricyclic antidepressants or monoamine oxidase inhibitors. Yet, the SSRIs are safer and you can give them to a larger number of patients, including patients with contraindications to tricyclic antidepressants. The relative absence of side effects makes these drugs uniquely suited for the elderly although it would be a stretch to say that they were specifically developed for the elderly.
- AT: Do the elderly metabolize antidepressants differently than younger adults?
- GA: There are differences.
- AT: Can you say that different kinds of geriatric depression require unique different drugs that might not work for different populations?
- GA: The biological dissection of geriatric depression that I described today is based on very recent findings of my group. In young adult depression, there is a single study with similar findings, but little work has been done in this area. This work started in geriatric psychiatry and, hopefully, would be relevant to young adults, but I wouldn't generalize without direct studies.
- AT: We talked, mainly, about depression, and, yet, recent research has highlighted the very strong co-morbidity of depression and anxiety. Where does anxiety fit into this?
- GA: Where does anxiety fit into geriatric depression?
- AT: Yes.
- GA: Anxiety symptoms in depressed patients subside when the depression is treated effectively. The frequency of anxiety disorders independent of depression may be reduced in the elderly. It is uncommon to see a true panic disorder in an old person and, perhaps, there are reasons for that. The locus ceruleus, which is the center implicated in anxiety disorders, ages quickly, loses cells and becomes less capable of firing. Who knows? The prevalence of anxiety disorders is reduced in late life but depressed old people don't lose the ability to become anxious when they become depressed. One of my studies of the 1990s showed that old people with major depression have anxiety scores similar to those to younger depressed patients. But old patients with both major depression and dementia had lower anxiety scores.
- AT: My final question is an invitation to add anything not covered that you think is important for the record.

- GA: Oh, your questions have been well targeted. I have little to add.
- AT: OK.
- GA: Thank you very much.
- AT: Thank you so much.

## VICTORIA ARANGO

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

- AT: My name is Dr. Andrea Tone. I'm here, Monday, December 13th, for the 2004 ACNP Annual Meeting in Puerto Rico and it is my pleasure to have with me Dr. Victoria Arango,\* who will be discussing her contributions to psychopharmacology and psychiatry. Thank you.
- VA: You're welcome.
- AT: Why don't you start by telling us how you got interested in medicine?
- VA: I always thought I wanted to be a medical doctor when I was growing up in Colombia, South America. I went to the College of New Rochelle in New York and had the good fortune to do one year of research during my senior year. It was then I realized that I wanted to do research in basic science. From then on I abandoned my quest for medical school, although I had fulfilled all the requirements, and I applied to graduate school. I entered a program at Downstate Medical Center in New York and got my PhD in neuroscience and neuroanatomy. I got involved in psychiatry when I answered an ad for a postdoctoral fellowship, for which Dr. John Mann, a psychiatrist, and Dr. Don Reis, a clinician-basic scientist had joined forces. Dr. Mann had discovered that people who committed suicide had elevated numbers of receptors for serotonin, compared to normal controls. He was interested in finding someone who could handle the brain and follow through with those studies.
- AT: Was that you, and what did it require?
- VA: In those days, and we're talking about 1980 to 1985, the brain collections he had access to were either very small pieces of brain or whole brains that were frozen in their entirety. I couldn't study them without thawing them, which altered the biochemistry. We had to first figure out a way to collect brains that allowed me to identify specific anatomical regions in order to examine their cellular composition. Once that was accomplished, we started a twenty year fruitful collaboration with Dr. John Mann, a psychiatrist and Dr. Mark Underwood, my husband, a neurophysiologist. I feel very proud to have had an impact on the way postmortem research is conducted so that we can look at things that psychiatrists were not able to examine twenty years ago.
- AT: What has changed since you began this work in the mid 1980s and what kinds of projects have you been involved with?
- VA: During the entire twenty years I have been involved with this research, the main interest of our group has been to study people who die by

<sup>\*</sup> Victoria Arango was born in Medellín, Colombia in 1952.

suicide and to examine mental illnesses like depression and alcoholism that lead to suicide. We have made some interesting findings not only in the prefrontal cortex and higher cognitive areas but also in the primitive parts of the brain, such as the brainstem, which contains the cells that synthesize many of the traditional neurotransmitters. Scientific progress is slow but we have made discoveries about suicide, in addition to implementing methodological improvements in postmortem work including better methods of tissue collection.

- AT: What would you say the important finding today has been regarding suicide?
- VA: We know that suicide is a very complex behavior and has genetic components. Suicide runs in families. It also has environmental components in that stressors in life contribute to it. And the majority, over ninety percent, of people who commit suicide have an Axis I psychiatric diagnosis. The most salient reason for committing suicide is the presence of a psychiatric diagnosis but all these factors have to come together including biochemical predisposition, family history, genetic susceptibility and environmental stressors. People react differently to stressors; suicide in a kid could be triggered because they got stood up for the prom, or were afraid to bring their report card home. In an adult the triggers will be different.
- AT: And you were able to see some of that in the brain?
- VA: That's the clinical part of it. One of the most important things we've found is that when people commit suicide there are alterations in part of the brain that is right above the eye, called the orbital prefrontal cortex. It's the part of the brain involved in behavioral inhibition. When this area and its chemistry are intact, a person is able to control inappropriate behaviors, for example, not swearing in public or controlling the urge to insult somebody. Behavioral inhibition, some form of control, is necessary to live harmoniously in society but also includes being able to control the self-destructive behaviors like suicide. All the receptor and cell alterations we have found are in the orbital cortex and not in other parts of the brain. That is a major finding we have been able to replicate and we have studied over two hundred postmortem cases. The clinical finding from previous studies was less serotonin in the brain in suicide. And that's consistent with what we found in the cortex. The cortex has less serotonin. Remember, the cortex is the recipient of the neurotransmitters which are made in the brainstem in the back of the brain at the top of the spinal cord. We hypothesized that because there is less serotonin in the cortex there must be fewer neurons that make serotonin in the brainstem. But those who suicide

don't have fewer of those neurons, they have more. So we started to look at a number of other markers for serotonin, like messenger RNA and enzymes that make serotonin. Again we found that people who died by suicide had more of these markers, not less. It's as if the body, which is a wonderful homeostatic machine, is trying to compensate for the presence of less serotonin in the cortex. But not enough, because we still find a deficit in the cortex. The next question, in the years ahead, is to find the "station" in between both regions that is receiving more serotonin from the overactive neurons in the brainstem, but somehow preventing the serotonin from reaching the cortex.

- AT: Let me, ask a question from what little I know about suicide. There seem to be characteristics associated with the type of suicide. Men are more likely to commit suicide with a gun. Some people, perhaps, are more likely to jump from tall buildings. Does this influence your findings? You're not, I assume, able to examine a brain that's been blown to pieces or splattered on a sidewalk. Does that mean that there's a set of people who are excluded from the findings?
- VA: Actually, the main group that is excluded from the studies is not what the field refers to as "violent" suicides, but the people who take pills, who have the most intact brains. Because we are studying chemistry, it would be difficult to interpret whether our findings were the reason for suicide or the result of taking the drugs. So we exclude anyone who dies by overdose. We also exclude individuals who are on psychiatric medication. The brains we study have to be free of legal and illegal drugs. Regarding your other comment there has to be an intact brain in order to study it.
- AT: How does the brain end up in your lab? What are the different procedures in place to facilitate scientific research?
- VA: Presently, we're not collecting brains in the city where we work, but from Europe. In the past we would get a fax from the medical examiner early in the morning, with a list of people, the cause of death and the name of their next-of-kin. We would contact the relatives, obtain preliminary verbal permission and then mail them a detailed package including consent forms to study the tissue of their loved one as well as an agreement to an interview regarding the deceased at a later time. The interview was very important because having a brain without knowing anything about the person would be meaningless.
- AT: What proportion of relatives said yes?
- VA: I don't know the exact numbers. If the cause was suicide, they were more likely to say yes than if it was an accidental death, or the person was not psychiatrically ill. We need those accidents and non-psychiatric

individuals for control purposes and comparison with the suicides. It also depends on the ethnic background. I'm South American, and in my country, the stigma associated with suicide is much greater than in the United States, which is pretty great. And some stigma comes for religious reasons. Colombia is a Catholic country and suicides are not allowed to be buried in holy ground so even physicians go to great lengths to hide it, often omitting it from the death certificate. Also, some people do not want autopsies done. So, brain donation depends in part on your cultural heritage. One of the things we can do is to try to educate people about the importance and the need for donating brains to research, because it is the direct study of the brain that affords us the opportunity to see what is wrong in suicide using today's technology. In our research group we use Positron Emission Tomography (PET), for in vivo brain imaging to compare our postmortem findings with people who are depressed or have attempted suicide in an effort to be able to predict which individuals are at risk for suicide. At present it is very difficult clinically to determine which depressed patients are likely to kill themselves.

- AT: You were saying that people may be comfortable giving up their heart, but the brain is an almost sacred realm, the protected organ. Why is that?
- VA: I'm not sure, because if people knew how an autopsy is conducted, I don't think that they would have the same feeling for the brain. They want to bury their loved one intact, but the brain doesn't go back into the skull after an autopsy.
- AT: I didn't know that.
- VA: A lot of people don't know that. The brain doesn't go back into the skull, because if there is an open casket for viewing it is just going to leak. If people understood that they might be more willing to support the research.
- AT: Why are you forced to use European brains; what is the history behind that?
- VA: Can I say no? I don't think that should go on the record.
- AT: Will you take us through what a typical day is like for you? More so than with others I've interviewed, people viewing this tape may not really understand what you do on a daily basis.
- VA: OK. There are many people who work in my lab.
- AT: Is that Columbia in New York?
- VA: Columbia University. We start in the morning by sectioning a brain. I have an assistant who has been with me for ten years; I taught her how to section brains and she's absolutely wonderful at it. Following my

instructions from the previous day she goes to one of the twenty-seven ultra cold freezers where we store the tissue, selects the brain tissue and brings it to me on ice. We study a diseased and a normal brain, so we can compare them. And we do not take little pieces. We place a section of an etire hemisphere on a, three and a half by five inch glass slide. The machine we use to sections brains is called a Cryostat. It is two meters by one meter, and it consists of a freezer that has a slicer (microtome) inside, like a very thin meat slicer that is able to cut ultra thin sections only twenty microns thick; there are a thousand microns in one millimeter. I oversee this process and deal with any problems my assistant encounters. Another person conducts experiments on the large sections and someone else develops the X-Ray film, which is the ultimate product. This has images of the receptors which we quantify with a computer on our image analysis system. Then we have a statistical expert that guides us through how to look at all the multiple data points we get from these big sections. So that is what happens on a day when there is not a new brain coming into the lab. When a brain does come in now it arrives frozen in 1.5 cm thick slabs. It used to be a very different experience before when we had to be there to collect the brain and dissect it.

- AT: How many days or weeks, even, would it take to finish work on a particular brain?
- VA: That's an interesting point. We first remove the brainstem and the cerebellum and then cut the rest of the brain into the two hemispheres. The left hemisphere is used for neuropathological examination and we cut the right hemisphere into about ten pieces or blocks. In twenty years we have studied three of those sections from around two hundred brains, but we have never studied one brain from front to back. Only for teaching purposes have we shown pictures from front to back, but we did not get receptor numbers from the sections. It's such an incredible amount of work I do not see myself finishing a brain in my lifetime.
- AT: How long do you keep them?
- VA: I have brains that are as old as when I started.
- AT: I wonder if people would be more receptive to the idea of donating a deceased person's brain if they knew that, that person lives on through scientific research.
- VA: That's right. One of our biggest problems is if one of the freezers fails. We carry beepers and cell phones just so key people can be reached if one does fail. The integrity of the brain tissue is crucial. And the tissue is priceless. I don't even know how much the study of a single brain costs, but you have a whole clinical team interviewing the family and

multiple informants, taking information not only about the illness the person had but also reporting illnesses in the family, what we refer to as family history. We obtain very detailed information gathered by trained interviewers, including information about childhood, parents and what medications the person was on. There's a consensus conference to reach a diagnosis between a psychiatrist and a group of psychologists who use structured interviews with good inter-rater reliability. There is also an incredible effort involved by personnel in order to keep an updated inventory of tissue in the freezers. An individual brain doesn't take up much room but once it is sectioned the slides are placed in the equivalent of shoe boxes which take up much more space.

- AT: Do you think there's increasing public interest in this kind of work? I'm thinking about the success of Patricia Cornwall's novels and television programs like CSI that generate enthusiasm for forensic technology. Is there a way of using or capitalizing on that interest to promote your scientific research?
- VA: Just educating people about the need for brains to be donated and other individuals, like medical examiners, who need to participate in these projects, would be absolutely wonderful.
- AT: Is there a documentary interest in what you do?
- VA: There have been a couple of documentaries done in my lab. One of them was to aid the American Foundation for Suicide Prevention. They made a film about what is done in laboratories and there have been a couple of others. The local cable company in my town also, interviewed me with my husband.
- AT: How many people are there in the United States who do what you do for a living?
- VA: There may be a dozen.
- AT: Why aren't there more?
- VA: It's very slow painstaking work. You cannot really do experiments, per se. You look at static things, at the state of the brain when a person died. You cannot manipulate the system. When you take a live animal and identify a specific gene for something you can measure that behavior or answer certain scientific questions. Well, it's not easy to answer questions doing postmortem work. There is very important, but limited, knowledge that we can acquire from dead human tissue. In today's scientific climate postmortem work may be negatively viewed as descriptive science. I think it still should have a very important place, because there are so many things we still do not know about the human brain. Another reason is that this research is very expensive because you have to use extra caution. You don't know what kind of problems the dead

person could have had. There's a fear of slow viruses, or non-viruses, or hepatitis; it's not like working with a mouse. The equipment is expensive. A Cryostat to section a human brain costs eight times more than the one to section a mouse or rat brain. To do tissue staining, or to do different reactions, the containers have to be custom made. You cannot buy the slides from a catalog. Everything is custom made.

- AT: I just have a few more questions and you add whatever you want to include. We're here at the ACNP meeting. How welcoming have scientific psychiatric associations been to you as a non-psychiatrist?
- VA: Oh, very welcoming. I have been coming here since 1988, I was accepted for membership in 1994, and I really love this meeting. I have always had a very good reception from the psychiatric community. And, I think it's a very good mix.
- AT: I see they've got you on committees, so, clearly, you've been integrated. I feel I have to ask this question. Some people might think what you do is morbid. How do you feel about your work?
- VA: Actually, it is not morbid. Everyone in the lab has the utmost respect for the brain we are holding in our hands and we are really grateful to the families, who had the courage to donate the brain of their loved ones for such a good reason. It is not morbid. During my five years at the University of Pittsburgh I personally collected the brains from the coroner's office along with my husband. We don't do that anymore but it was just very sad to see why people die. There was the inevitable death from disease, but we also saw the people who died because they were drinking and driving, and the young kids that were reckless with motorcycles. There was nothing morbid about it. There was something very sobering; you just want to make sure that everybody you know is wearing a seatbelt; that nobody you know is going to get in the car after drinking. There's a sense of having learned more caution in life and how to prevent fatal accidents that happen so easily.
- AT: I imagine studying death would make one more respectful and reverential of life.
- VA: That is right.
- AT: Final question and please add on. Twenty years from now or fifty years from now, what do you hope that the work you've begun will help us to understand?
- VA: I hope that we have enough ligands or very specific chemicals that can be used in vivo to study patients, so that our findings could be translated directly to the clinical situation. Let's say a patient comes to the clinic and has a PET scan and the doctor is able to say, oh, my goodness, this person has all the abnormalities that we have seen in

people who killed themselves, even though, this person doesn't appear suicidal, we really have to watch this person. They should be hospitalized, or given medication to reduce the underlying depression. That's what I hope to be able to accomplish; to give something to the field so that suicide can be prevented. The only other thing that I hope to accomplish is that people will not view suicide as a stigma, but as just a complication of an illness. It's like having pneumonia after you get a cold. And, if we could start on that basis, if we could teach, starting in medical schools, the public, everyone that suicide is just a terrible and unfortunate outcome of poorly treated mental illness, and by treating the underlying mental illness we can reduce the risk of suicide. If we can get those things done in the next twenty to thirty years it would be absolutely wonderful.

- AT: That's great. Thank you. Is there anything you'd like to add?
- VA: I cannot think of anything, Andrea.
- AT: I'll be talking to you again, I'm sure. Thank you very much.
- VA: Thank you.

### DAN G. BLAZER II

#### Interviewed by Andrea Tone San Juan, Puerto Rico, December 14, 2004

- AT: My name is Dr. Andrea Tone. We're at the 2004 ACNP Annual Meeting in Puerto Rico and it is my pleasure to be able to interview Dr. Dan Blazer\* for the ACNP Archives. Thank you so much for joining us.
- DB: Good to be here.
- AT: Let's start with some basic background about you. Tell us about your upbringing and how you got interested in medicine.
- DB: I was raised in a family that was not involved in medicine at all. But, when I was about sixteen, I read some books on medical missionaries and became very interested in medicine with the idea of becoming one. In one of his books Tom Dooley wrote that after he finished service in the Navy, he went to Southeast Asia and worked there. I became very intrigued with that possibility and went to medical school with the idea of being a primary care physician and then doing mission work.
- AT: Let me take you back a little bit. Why did you choose the particular medical school that you went to and tell us about the training at that time?
- DB: I had no idea, having no background in medicine, what I wanted to do but I had heard that the University of Tennessee was a school that trained primary care physicians so I applied there. I only applied to one medical school so that's where I went.
- AT: Confident! You did some school work in Nashville, didn't you?
- DB: Yes. I went to Vanderbilt to undergraduate school and worked toward a Master's Degree in Religion, prior to medical school. I wanted to combine the two, because of what I thought was going to be a life long career in Africa, which did not turn out to be the case.
- AT: What religious affiliation did you see yourself being a part of?
- DB: This was the Church of Christ. We had a hospital in Nigeria and I had planned to work there with a man, whom I had known since I was a small child. After medical school I did go to Africa for two years as a missionary, but it was just after the Biafran War; the political situation was very unstable, and so I had to return. At the time I was beginning to get interested in psychiatry but the experience in Africa also led me to develop a very strong interest in public health and epidemiology.
- AT: Tell us a little bit about what it was like to be a medical missionary. I think people watching this tape would be interested to learn more about this.

<sup>\*</sup> Dan G. Blazer II was born in Nashville, Tennessee in 1944.

- DB: In some ways it was fascinating and in some ways it was very boring. It was fascinating to be in another culture. We were very isolated. This was prior to cell phones, to e-mail, to television. Where we were located we had electricity and short-wave radio, but beyond that, we were pretty isolated although I had a wife and child at the time.
- AT: They went with you?
- DB: They came with me.
- AT: Wow!
- DB: We went with a small team and worked in a mobile clinic, not in a hospital, most of the time. I drove a Land Rover, five days a week to different villages with a nurse, a pharmacist and a couple of other people. We set up a clinic and saw somewhere between one hundred fifty to four hundred patients a day then turned around and drove back.
- AT: So, you don't have any sympathy for the doctors today that say, "Oh, I have to see too many patients"?
- DB: Well, I have some sympathy for them if they want to talk to their patients, because we really had almost an assembly line. That was the part that was somewhat boring. We had very little time to talk because of the burden of care that was necessary. I did learn the language, a variety of English, which they call "Pidgin" English, but it was very hard to converse for any length of time. We had no doubt that we were doing something good. We treated a lot of infectious and parasitic diseases but we also encountered things we couldn't treat at all. Interestingly, we saw very few psychiatric problems, but the ones we did see we could do nothing about.
- AT: What were the kinds of psychiatric problems you saw?
- DB: We would see some very psychotic disorders including a few severe postpartum psychoses, and schizophrenia more frequently. We did not see much depression probably because we were not looking for it. Those individuals probably would not have come to our clinic. Because we were treating physical illnesses they went to native healers to get psychiatric care, so we were invisible to that group.
- AT: What did you do when patients presented with schizophrenia or postpartum psychosis?
- DB: We had a little antipsychotic medication. It was chlorpromazine (Thorazine), which we tried to use occasionally. I don't think we were very successful, but the interesting thing was that the communities managed to take care of their schizophrenic members. In any village of a hundred or two hundred people, there would always be one or two who were, what they would say, "different", for whom, the village provided considerable support. An interesting lesson we learned was

that the environment in which the schizophrenic patient lives makes a big difference in how well that individual can be cared for. They had no psychiatric hospitals in the entire country in Cameroon so there was no choice for treatment except what we were able to do pharmacologically and that was minimal.

- AT: That's interesting. So, you came back to the United States and already had a burgeoning interest in psychiatry.
- DB: I'd become interested in medical school and applied for a residency at Duke in psychiatry before we went to Africa. Because we knew there were political problems we had planned on spending two years in Africa, then, coming back to a residency. While I was in Africa I had sent over about a hundred books on psychiatry and managed to read them all.
- AT: Take us back to how psychiatry was understood at that time.
- DB: It was very heavily influenced by psychoanalysis. Social psychiatry was also in its' heyday during the 1960s. Biological psychiatry and psychopharmacology were just beginning to have an increase in importance and emphasis. Among the books I took to Africa and read cover to cover, was a seminal text, *The Theory and Practice of Psychiatry* by Danny Friedman and Fritz Redlich, Later on I got to know and admire them for their pioneer work in biological psychiatry. Most of the other books I had available were related to psychoanalysis.
- AT: I'm curious. When you decided that psychiatry was an interesting field did you envision embracing psychopharmacology or see yourself as becoming more of a psychoanalyst?
- DB: I did not see myself doing either. I became intrigued with the epidemiology of psychiatry, why people got ill and what societal factors may contribute. The other thing, related in part to the use of medications, was how to help and treat people with psychiatric disorders on a larger scale.
- AT: So, tell me about your psychiatric training.
- DB: I came back to Duke and began my psychiatric training. Having been in Africa for two years, it was almost more of a culture shock to come to Duke than it had been to go to Africa. I felt like a bush doctor coming into this high tech medical center. I realized that I was very much behind by not being familiar with some of the more modern techniques, even though I knew how to take care of patients, which was a real plus. Duke, at that time, was a program that was eclectic. This was still an era where psychoanalysis was very strong and many programs around the country were antagonistic to psychopharmacology. But Duke had some excellent psychopharmacologists. One was Bob Friedel, who was one of my supervisors. Another supervisor, Bill Wilson, was a certified

biological psychiatrist, who'd done a lot of work with electrophysiology. I was fortunate to be in a program that had doctors who were very good at taking care of patients but also used medications and a variety of other techniques to treat people with mental illness. It was excellent training. However, I had this nagging thought in the back of mind while we're treating these individuals one at a time that wouldn't it be nice if we could look at the bigger picture? So, my epidemiology interest also began to grow during my residency training.

- AT: Tell me more about that, when you say "we're treating one at a time, wouldn't it be neat if we could look at the bigger picture", exactly what do you mean?
- DB: Well, this is a lesson I learned when in Africa. There was one village we went to where we drove across a swamp and I would treat maybe a hundred persons with malaria in one day. Then while I'd driven right back across the swamp I realized there were mosquitoes in that swamp and if it could be drained perhaps malaria could be eliminated or, at least, decreased significantly. But, for two years, once a week, I drove back and forth across that swamp to treat at least a hundred patients a day, one at a time.
- AT: So, you were looking for a social-political solution that would be prophylactic against malaria?
- DB: Well, if they'd had the ability and political will to drain the swamp or provide some kind of mosquito protection in the area that would have solved the problem.
- AT: At the time you were thinking about epidemiology and psychiatry, did you have a concrete idea about how this might be applied to help people or prevent mental illness?
- DB: I've always had the idea that mental illness was very much related to the unique constitution of the individual, and the impact of the environment on the individual. I was particularly interested in the social environment, but over the years, I've recognized the importance of the physical environment, as well. So, we have this environment person interaction; that's certainly not new; we hear it at this meeting all the time. People talk about it continually. But I think we may be neglecting the environmental side as we pay attention to the individual side. One thing the pharmacological revolution has led to in psychiatry, in my view, is that we are able to do things now that we just could not do before and that's very much a positive influence on our field. But we may be beginning to reach some of the limits of the pharmacologic level, because we're not dealing with the environmental side. Look at the rest of medicine. Take obesity. We don't, in our society, just say, let's give a drug or do

gastric bypass surgery and that will solve the problem. We realize we need to get the message out that society has a problem with fast food We're serving too large portions and consuming high calorie levels. We need to post calories on food products; we need to make the public aware of what they eat; we need to offer behavioral programs that will help individuals control weight. We have a range of interventions that we can use for treatment of obesity. The same is true of cardiovascular disease. Yes, we have wonderful medications that can lower cholesterol but we also emphasize the importance of diet, of lifestyle, and of trying to resolve personal and environmental interactions, especially in the workplace, that will reduce stress and lead to better care of the individual in ways that decrease cardiovascular disease. Across the spectrum of medicine we intervene at all three levels of the environment. behavior and biology. In psychiatry we need to have the same kind of mind set. Granted, we know much less about the environmental factors that contribute to mental illness than we would like. That's been the area that I've studied for most of my career and we need to do more. That doesn't decrease the importance of the medications and what we can do with them. I just don't want us to neglect this other part. I think we'll reach a limit where if we don't pay attention to the environment, we're going to have some real problems.

- AT: Yes, several people I've interviewed this week have made the point that it's unfortunate that psychiatrists, especially research psychiatrists, spend more and more time dissecting the brain into tiny parts and forget that its part of a whole connected to a human being, connected to a larger society. We can't just look at illness as an isolated occurrence. It's all part of this whole.
- DB: Yes. I just finished a book that's coming out in the spring which I began on sabbatical at Stanford a couple of years ago. It's called, *The Age of Melancholy: Major Depression and Social Psychiatry.* In it I emphasize the social origins of mental illness. The reason I concentrate on major depression is that sometimes when we label a disorder we automatically assume that it is only a biological disease with no social or psychological impact in terms of its' etiology. So, I'm on the same track.
- AT: This meeting, in particular, it does seem to favor the other approach. Let's take you back to Duke and tell me about your training there.
- DB: It was a great training experience. As I mentioned before, one of the things that I really appreciated was the eclectic orientation at Duke. There were good people in just about every area and that was unique for departments of psychiatry at the time, especially, in the south. As we talked before we started the tape, I do have a pronounced southern
accent. I am a Southerner, and that was important. Two things at Duke that I think were very important. One, they had an emphasis on aging and much of my career has been focused on disorders in the elderly. Secondly, they encouraged us to be independent in taking control of our own careers and destinies. And, I really appreciated that. Many of the trainees at Duke were going into psychoanalysis and that was considered the thing to do. I had no interest in that at all.

- AT: How come?
- DB: It just did not appeal to me. I thought psychoanalysis was interesting and had cultural importance but I could not see any value therapeutically. I could never see myself treating people that way. It seemed there was a larger task to be addressed. Instead, I took the opportunity to go to the University of North Carolina and meet with an older woman, who'd worked in Africa as a psychiatric epidemiologist. Her name was Dorothea Leighton. Both she and her husband, Alexander Leighton, were the premier psychiatric epidemiologists in the world. While my colleagues were going for their analysis four times a week, I was going once a week to Chapel Hill. She gave me things to read, then we'd talk about them and that really got me interested. There was no one in psychiatric epidemiology at Duke when I started out but they gave me the opportunity to develop that interest.
- AT: Sounds very interesting. So, you left your psychiatric training intending to do what?
- DB: I was very much in flux, like many people at that stage in my career; I wasn't exactly sure what to do. I also had some interest in psychosomatic medicine at the time so I went to New York to do a Consultation-Liaison Fellowship. That turned out to be a wonderful experience, not so much because I learned a lot about Consultation-Liaisons psychiatry, but more because I got to interact with a new group of individuals who were formative in helping develop my career. We were supposed to have psychotherapy supervisors in this program and I was assigned to the Chairman of the Department, Herb Weiner, who was a giant in the field. He had about as little interest in supervision of psychotherapy as I did and so we spent an hour a week for a year talking about psychiatric research. I already had the interest in epidemiology and was beginning to think that I'd like to do something in that area, but knew nothing about it except what I could read in a book. So I did something very odd. I'd applied for a grant to go back to Africa to do an epidemiology study of older persons in Africa. Thankfully that was not funded. But then Herb said, "You can turn this around and make it into a career development award and learn something about research." So while I

was still in New York, with Herb's help, I applied for a career development award. I remember sitting around a table with the site visitors and they said, "We like you, but we don't like your grant. Do you want to be a social psychiatrist, an anthropologist or an epidemiologist"? I answered, "I really want to be an epidemiologist". So then they said, "If you want to be an epidemiologist, you have to go back to school. Rewrite the grant and put yourself in school". So that's exactly what I did. I rewrote it with the idea of getting a Master's in Public Health, resubmitted it, and it was funded. I went to school at the University of North Carolina and did both my MPH and PhD. It was a wonderful way of getting me tracked into research. Remember, there were no doctors in my family and no academics. I was a Southern boy who grew up in a blue-collar family. People like me didn't do research. But I had an intuitive interest in research and one thing I appreciated about Herb Weiner was that he was the first person who told me, you can do research, and that really helped.

- AT: Why all the extra degrees? I can understand MPH, but why do a PhD on top of that?
- DB: There were a couple of reasons. When I was in college, I wasn't a great student but I applied to get a Master's degree at another institution while I was an undergraduate at Vanderbilt. The admissions officer said, "You're not a strong student. We're not going to admit you as a Master's, but I want to give you some career advice". He continued, "You just are not smart enough to get a Master's degree. I'm not sure how you got through Vanderbilt as it is. I would really encourage you to just get your degree from Vanderbilt, be very thankful that you even got it and go to work". When I finished my Master's degree, we took a qualifying exam, and I passed at the PhD level. All I had to do to get a PhD was a dissertation. Remembering that story from the past, I thought "I'm going to get my PhD and show that guy". He died several years before; I completed my PhD in a year.
- AT: Wow!
- DB: I had the data and knew what I wanted to do.
- AT: What was your topic?
- DB: I did a paper on, Social Support and Mortality in an Elderly Community Population. To this day my dissertation is the most cited paper in my resume.
- AT: Fantastic! Tell us about your early career then.
- DB: Even before I started my degree work I took an administrative job as the Associate Director of the Center for Study of Aging at Duke. It was kind of a fluke. Somebody had left on sabbatical and they needed a person

to fill the position. So, I came back from my fellowship in Consultation-Liaison Psychiatry and took over the position in the Aging Center. That made no sense and was not a particularly good year. A year later I received my Career Development Award and immediately started back in school for the next four years of my time at Duke. During the final year I did halftime clinical work and was working halftime on my PhD. I was also writing papers on a community survey that had been done at Duke. That allowed me a chance to do some secondary data analysis back in the days of the old computer cards. It was an interesting time and a great learning experience as I saw my career beginning to come together. But now I was about to get my PhD in Epidemiology what was I going to do with it? Then an interesting thing happened. A colleague, Linda George, who was a sociologist, walked into my office one day and said, "Look here, they've got these research proposals for large scale epidemiology studies". Some of the giants in the field of psychiatric epidemiology were involved. Lee Robbins was the principal investigator, Myrna Weissman was an associate principal investigator and Ernie Grunberg was principal investigator at John Hopkins, another giant in the field. So we applied a year before I finished my PhD and our application was funded two months after I had received the degree.

- AT: Did you have any patients at the time?
- DB: I started out spending half my time seeing patients but then it dwindled. I still see some.
- AT: Once you realized that research could be very exciting, did you always feel a continuing commitment to clinical work?
- DB: Absolutely. I saw the two inter locking. I had that identity as a doctor and I wanted to continue to see patients because I enjoyed treating people.
- AT: Can you tell us more about why you chose to specialize in geriatric psychiatric disorders and what was the thinking about mental illness in the elderly at the time you started out?
- DB: Two things influenced me. One was, when I was in Africa, the older people seemed to be doing very well. Their survival rate was not great but once they aged they seemed to do well. When I came back to the United States I heard all this talk about the older you get the more difficulty you have with mental illnesses of all types. So I couldn't understand why. That was an intriguing question. Secondly, Duke had a premier program for aging so it was a great environment in which to study the elderly. The question I'd brought from Africa, coupled with the environment at Duke, got me started on my interest in aging. One of the things we showed, early on, was that the frequency of mental

illness in late life was actually lower, except for Alzheimer's disease, compared to other stages of the life cycle once you control for other factors, such as physical illness. That interested me. Why are, older people less depressed, compared to younger people? I had always thought that older people were more depressed.

- AT: I've always thought they were more depressed, too. Was that the thinking at the time?
- DB: Oh yes, absolutely.
- AT: You were considered a pioneer in Africa, finding the elderly had lower rates of depression?
- DB: And we were curious about why.
- AT: What was the answer?
- DB: This is where having a biopsychosocial approach is very important. There's no question that older people have some unique biological vulnerabilities to depression. Work that George Alexopoulos and others have done has pinned that down very well. There may also be some biologic protective factors, but they haven't been identified yet. In an under developed country older people may develop psychological protective factors, what some people might call wisdom that help deal with problems of survival and stress in ways that younger people have not yet learned. That might contribute to a lower frequency of depression in people who survive. In addition, if you look at the types of problems older people face, they tend to be problems that are predictable, as opposed to younger people. For example, if you're thirty-five and a spouse dies that's not only horrible, it's unexpected. If you're seventy-five and a spouse dies, it's equally terrible but not unexpected. If you're forty and develop significant arthritis, that's difficult to adjust to. If you're seventy-five it's difficult to adjust to but it's not a surprise, because you see others your age developing similar problems. With age comes the ability to anticipate the kinds of problems you may have and rehearse how you might handle them. There is not one woman seventy-five years of age who has not thought about what it's like to live without her husband if he dies before her, as most men do. That ability to look ahead is an important protection against depression. I think there may be a maturing process that also contributes. As I said, there may also be biological protective factors against depression later in life that we are unaware of.
- AT: I interviewed George at last year's meeting. One of the things he suggested is that depression and other disorders are very different entities in the elderly than they are, say, in children and late adolescents. We can't talk about depression as though it presents the same way at

different ages. What do you think about that? Are we talking about the same beast?

- DB: George Alexopoulos and I have talked about it at some length and it's very clear from his work and the work of others that there are some unique varieties of depression. I'm not sure that covers the waterfront of the types of depression that older people feel. There is a unique geriatric depression mostly driven by biological factors without sadness but associated with executive dysfunction. But there are other individuals who are perfectly cognitively intact who become significantly depressed in late life that is no different than individuals who are thirty-five or forty.
- AT: So interesting, because it seems that a lot of the attention paid to mental illness is to emphasize how it's under-diagnosed; it's under-treated and you have a much more up-beat message.
- DB: For political reasons we may keep pushing the issue of the importance of looking at mental illness in late life, because it is under-treated. There's also no question we need to temper that with the idea that older persons are quite adaptive and may manage things better than we give them credit for.
- AT: In my research on the history of the treatment of anxiety among the elderly I found that doctors have, on occasion, given aged patients so many benzodiazepines that they have become groggy and their memory fails. They are more likely to fall when they are medicated, a problem that increases the need for and incidence of hip replacemnent. So, there's a real risk associated with over medicating an elderly cohort.
- DB: Yes, very true.
- AT: Looking at your research, what would you say, at this point in your career, your key contributions have been?
- DB: One was documenting the lower frequency of depression in the elderly and making people think about this. Clinicians, whether they're biological psychiatrists or clinical psychologists, need to look at the empirical data regarding the frequency of depression across the life cycle and use that as a stimulus to understanding the phenomenology of depression in the elderly. Second, the work we did in bringing social risk factors into the study of our older persons and health outcomes in general. My most cited paper, *Social Support of Mortality*, has nothing to do with psychiatry, but with social epidemiology. This has certainly been a major contribution. A third area that we received a lot of attention for early on was looking at existing epidemiologic data to help understand the basis for the DSM–IV and upcoming DSM-V diagnostic categories. It's important to let statistical approaches help understand

how symptoms cluster and how those clusters play out over time as opposed to the intuitive thoughts of clinicians for diagnostic categories. Just this month, there's an editorial by Lee Robbins who worked with us in the ECA studies, about the importance of using epidemiologic data to help inform our diagnostic nomenclature. Finally we've been very interested in the association of depression with mortality in older persons. Most clinicians think depression increases the risk for mortality in the elderly but we've been a little more cautious. In well controlled studies there is no difference and other factors may modify the effect of depression. Untangling those interactions to understand the relationship between depression and mortality is important so we've done a number of studies along those lines.

- AT: The DSM system is a very controversial way of understanding psychiatric illness. Could you give me an example of how epidemiological data might better inform these diagnostic categories?
- DB: For example, DSM-IV has nine symptoms that are the basis for a diagnosis of major depression. These symptoms were derived by committees of clinicians based on their experience. Suicidal thoughts were included but not constipation, although both can occur in depression. The problem is these categories have not been validated. The ECA study would be a good example of the epidemiologic approach to validating diagnostic categories. That study included fifteen thousand people in the community. We asked about every DSM symptom plus a lot of others such as somatization, anxiety and obsessive compulsive disorder. We then used various statistical procedures to find symptoms that clustered naturally together, including grade of membership, latent class and factor analysis. Unlike clinicians these make no assumptions about the data. In addition we have ECA data on individuals at two points in time, a year apart. We can track symptoms over time to determine which hold true or are more important. Every symptom in DSM -IV for depression can now be rated equally. We now have an opportunity to look cross- sectionally and longitudinally at how people in the community really present. We could also compare this data with other large clinical studies, such as a psychobiological depression study, to see how they differ.
- AT: How do you see the field as having changed since you first became a psychiatric practitioner?
- DB: DSM-III was a major breakthrough. It moved us from having a much more subjective, fuzzy, albeit humanistic, approach to a solid empirically based science. And then the advent of psychopharmacology enabled us to do efficacy trials of treatments to determine what helped or did

not. Along with that came shorter term psychotherapy, cognitive behavioral therapy and interpersonal therapy. Together these brought psychiatry back into medicine, where it belongs. But we also know much more about what works and what doesn't so we've become much more honest about outcomes than we used to be. On the downside we've had a huge mountain to climb to get to where we are since the late 1970's and the field has devoted its' interest to massive numbers of studies on molecular events, descriptive efforts and clinical trials. We've made tremendous progress but we've lost our broader perspective. During this period other fields of medicine have become more humanistic and paid more attention to psychosocial support and prevention than has occurred in psychiatry. We've had so much to learn over such a relatively short time that we've been just preoccupied with the biological. Now we need to complement that with increased interest in other neglected areas without losing the impetus that biological studies have made.

- AT: What's your prognosis? Do you think that's likely to happen?
- DB: That's a tough question. Eventually, it has to happen. Psychiatry has been on a tremendous period of growth and influence, but the promise of the field may be greater than the reality of what we're able to deliver. The public is asking for patients to pay attention to psychiatry but the public is also interested in a lot of other things that contribute to illnesses. I mentioned obesity and cardiovascular disease, but we could look at many other areas and see similar patterns. Psychiatry needs to pay attention to other medical specialties. It's not the detailed descriptions, but how different diseases are dealt with and managed. We could learn a lot from cardiology and from how cancer centers are run and from endocrinologists how they manage diabetes. Psychiatrists might be very surprised as to how that field looks today.
- AT: One of the concerns the *New York Times* has expressed is that so much of psychiatry and research seems to be dominated by the pharmaceutical industry and whether that's right or wrong, I wonder if discounting social and cultural factors has to do with how psychiatric research gets funded and who profits from a biological orientation. Or is that too cynical a view?
- DB: I have thought that is somewhat too cynical. It's an easy view to take if you're on the outside looking in. We would not be where we are today in psychiatry if it were not for the pharmaceutical industry. There's no question in my mind about that. To say we'd be better off if we had not had the influence of the pharmaceutical industry over the last twenty or twenty-five years is a foolish and almost a dangerous thing to say. On the other

hand psychiatry is too enmeshed with the pharmaceutical industry now and both psychiatry and the pharmaceutical industry need to talk seriously about the good of the patients. This is not easy in a market driven economy. There's so much competition and need for growth that it's hard to get people to think about that. It's not just the pharmaceutical industry that wants people taking more pills in order to make more money with more products that are patented and expensive. Academic departments of psychiatry are in the same situation. More grants, more studies, more papers written, so we can bring in more money. We do have a major challenge that the pharmaceutical industry and academic departments of psychiatry and the field face. That is the incredible influence of the market economy and consumer society we live in. At one level people are looking for a more holistic approach to medicine and, at another level, they want a pill for guick answers and guick solutions to their problems. At the same time the field of psychiatry has seen dramatic growth and continues to think it needs to expand while we also have an industry that is driven by profits. It's time to think about that whole process, try to disentangle it, and see how we can deal with it within the constraints we are working with. It's important to get that dialogue going with people on different sides debating this complex issue.

- AT: What advice would you give to someone who is very young and entering the field?
- DB: First of all, I think it's a very exciting field. Everybody says that, so that's not anything new. I would say, read outside the field. Don't get tunnel vision so that all you read what comes out in the *Archives of General Psychiatry* and *American Journal of Psychiatry*. Read novels; newspapers; commentaries and books as if you're going to write about the history of anxiolytics. Read, David Healy's book, *The Antidepressant Era*. Find out what's going on around you. Psychiatrists, when I was in training, read more than any other group of specialists. I'm not sure that's true today.
- AT: That's very interesting.
- DB: I would like to see young people widen their views and one way to do it is read broadly.
- AT: The person I interviewed right before you, Andrew Winokur, said that his undergraduate degree at Yale in American Studies in some ways was the best training he received, because it made him view things as part of a much larger whole. Why would reading broadly have an impact on people, not just psychiatry?
- DB: When you are with a patient and see a cluster of symptoms, you have an algorithm in your mind of what you need to do. If you don't have

anything to balance that against, you tend to always follow the same road. One of the problems with psychiatry is that if we keep going the route science may be exciting but the practice can be boring. Go back to my experience in Africa; two or three hundred patients a day, one after another, quick judgment, quick delivery of medications. At one level, it was very exciting, all these different exotic illnesses I was seeing. At another level, it was very boring, because it was so automatic. Reading, which is what I did in Africa, helps you step back from that automatic behavior, reflect on it, and consider what you might do differently.

- AT: To choose a corporate cliché, you're thinking outside the box?
- DB: I guess I am.
- AT One of the interesting transformations that have occurred with psychopharmacology is that more and more psychiatric illnesses are being diagnosed and treated not by psychiatrists, but by general practitioners and family internists. What do you think about the fact that has happened?
- First of all, it's a reality, because psychiatric illness is very common and DB: these people are naturally, going to be treated in primary care settings. I am concerned because we have suggested it's so easy to treat psychiatric illnesses that any primary care physician can do it. A number of studies show that is not the case. Primary care physicians are treating most psychiatric illnesses, but not treating them optimally. We need to pay attention to that. The question is what is the role of psychiatry? There is some very interesting work by Jurgen Unutzer, Wayne Kayton and others which suggests that putting a psychiatric nurse practitioner into a primary care office helps develop the delivery of mental health services either as a primary therapist for individuals, providing consultation, or improving access to psychiatrists. However, I would hate to see psychiatry moved to the periphery for the common psychiatric disorders so that we are squeezed into just treating the complex disorders. I have a personal experience about why this is so important. I was out walking for exercise and noticed some tightness in my chest. After it happened, a couple of times, I had an appointment for an annual physical with my primary care physician. He's a very good doctor and I said, "I think I probably need a stress test". My son who is a physician, training in surgery, had already suggested that. My primary physician agreed but also recommended a cardiac catheterization. I felt this was going too fast. So I called a close friend, who is a cardiac thoracic surgeon. I told him the story and he said, "I think you need a cath" and referred me to a cardiology fellow who saw me the same day. He examined me

very closely, looked at a rhythm strip, and said, "Yes, we need to get this stress test and see what it shows. We might need to do a 'cath' but I'm not so sure. Let's just take this a step at a time". You do not know how much more comforting it was to hear somebody, who I thought was an expert, talk that way about my little simple everyday problem. Well, I did the stress test and it was fine. I went back to my friend and he told me I did not need the "cath". I saved money; I felt better about what happened; and I was educated into what to look for. A lot of things happened that would have not happened with my very good primary care physician. That experience, in some ways, is analogous to a patient with your garden variety depression, who walks into the primary physician's office. Ultimately the person is going to be managed right there, but, on the other hand, the patient is losing something, because I think psychiatrists, have a lot more to offer. And it might be cost effective as well.

- AT: Do you think the problem is largely, or in part, a political one because of the way we've set up healthcare delivery in this country?
- DB: That contributes immensely to it. The pharmaceutical revolution has led to the false assumption that because we have drugs, treating mental illnesses is simple Which is not true, anymore than having Zocor (simvastatin) makes cardiology a simple specialty.
- AT: Final thoughts, fnal comments on where you're going, what you've achieved, where psychopharmacology should be going.
- DB: I took a nine-year hiatus out of my career and did some administrative work as Chair of our department for a couple of years. I was also Dean in Medical Education. Basically, I ran the medical school for several years. About five and a half years ago I stepped down from those positions and needed to decide either to continue as an administrator for the remainder of my career or go back to research. I was somewhat nervous about the idea of going back to research, because I knew the field had moved on and I hadn't moved along with it. I made a couple of false starts in terms of areas I thought I might get into, and I just realized I was not cut out to do that. Then I went back to some of the original work that I had been doing and sort of rejuvenated that. So I've enjoyed my career over the last five years, probably more than any time in my life. Not that I didn't enjoy my time in administration and not that I didn't enjoy my career prior to that, but now I am learning new things. Mostly about new statistical modeling procedures, taking advantage of existing data sets, and trying to do the kind of thing that Lee Robbins suggested, sorting out symptoms and disorders, looking at how disorders change over time. I'm having a great time doing this. Some colleagues are working with me but I don't have a big operation right now, by design. I'm very fortunate to have an

endowed chair and that permits me flexibility in how I spend my time and I'm taking advantage of that. We're publishing important things and I'm having a ball doing it. I really feel like I'm just a young faculty member again. There is plenty of work to do for the next ten years, at least, and I'm excited about the possibility I've got my own area that I get excited about, but there are many different areas across psychopharmacology and this meeting has just been fantastic. I came to learn and I go to as many events as I can. I'm learning new things. I'm just sitting there and my eyes are wide open. I love it. You know this exciting stuff that people are doing. I have the advantage of not feeling that I am constantly under pressure, to think more creatively about what I'm doing, I'm just not sure our younger investigators and faculty are going to have that opportunity, so I have real concerns about how they can be protected. And, it's not just time protection. We talk about that all the time in academics, but I think it's more the need for intellectual space to think. You said, outside the box. I just say, think. You know many faculty members do not go to seminars where they share and try to understand what others are doing. They don't have the time. I wish we could find a way to reinvigorate the intellectual environment of our psychiatric departments and get more cross fertilization and discussion that's not so task oriented. Ultimately, that would stimulate the field. How do we do that? I'm not sure. I really don't know. Sometimes I've thought that one way it could be done would be to bribe a faculty member. I love bribes! Give a faculty member five thousand dollars at the beginning of the year to attend eighty percent of interdisciplinary seminars over the year with no conceived agenda. It's based on a model the MacArthur Foundation use very successfully and I'd like to see it tried in academic departments of psychiatry. It's an exciting time in science, but I think there's a group of young faculty, who may be denied the excitement, because they feel under so much pressure.

AT: We have a course at McGill that's in the faculty of medicine and it's called, Medicine and Society. It's for fourth-year medical students and it meets several times a week for about four hours over a month-long period in February and March. I am one of many leaders of a group of twenty medical students. I have a co-leader, who is a grad student, but most co-leaders are social scientists and humanists; there`are`historians, sociologists, anthropologists, philosophers, etc. This year we will read David Healy's book, *Let Them Eat Prozac*, along with myriad articles and a lot of other secondary articles. The point of this course on medicine in humanities is to give doctors a chance to reflect about how ideals, theories and real-life policies and pragmatics interact. They think about medicine in this larger context. They think

how religion plays into how people understand and communicate about an experience of illness. I haven't taught it before, because I'm new to McGill, but it sounds fascinating and I understand that the students themsevves have come to appreciate it.

- DB: I could not agree more. I have an interest in spirituality in medicine, of really taking some time out to think, but, hopefully, that's not just something you do at one point of your career. You do it throughout. Probably, one of the best things that ever happened to me was the time in Africa that was sort of down time. There was no TV, there was no radio, there's not much social life. So, I actually had a chance to read and I read everything I could get my hands on. It was a very, very productive time in the sense that I got started reading and have never stopped. I've always been able to find time to do things outside work. I've been extremely fortunate in my career to have those kinds of environment to work in. I spent something like eight or nine years with the MacArthur Successful Aging Network and that was great time, because we really did share ideas. We did not come in there with agendas and problems, and we all loved it. I also spent a year of sabbatical studying Behavioral Sciences at Stanford and that was a great year because we could sit at lunch and talk about and share ideas. That kind of opportunity is so easy to create
- AT: Is there anything that you wanted to add, any final thoughts?
- DB: No, you've asked a lot of questions. I have one final thing that's kind of interesting. This is my first year as a member of ACNP.
- AT: Congratulations!
- DB: I'm glad to get in. I wrote some people and said this seems odd. I'm a psychosocial epidemiologist. Why would you want somebody like me around? But I think the ACNP has widened its' spectrum, I'm not your traditional member. It's not only very important and very rewarding to me personally, because I've had a thoroughly enjoyable time at this meeting, but I think it's probably good for the organization. They need people like me.
- AT: I think so, too. And, I do think you're right, that they're trying to expand the boundaries. Yesterday we interviewed an anatomist, a woman who, actually, dissects suicide in brains. But, it was interesting and she said, I feel so welcome here, even though, I'm not a psychiatrist, and I have been asked to contribute. We're getting bigger.
- DB: Yes, I think so.
- AT: Well, we're delighted to have you.
- DB: Thank you. It's been fun to be here, good luck on your book.
- AT: Thank you,

## THOMAS N. CHASE

## Interviewed by Thomas A. Ban San Juan, Puerto Rico, December 7, 2003

- TB: This will be an interview with Dr. Thomas Chase\* for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the college in San Juan. It is December 7, 2003. I am Thomas Ban. Let us start at the beginning; where and when were you born? Could you say something about your education?
- TC: I was born in a small town near New York City called Westfield, NJ, in 1932. My family consisted mostly of lawyers and business or financial people. Not a single one was an academician, a physician, or a scientist. So I had no real background in those fields. Early on, I became interested in how things worked and I would love to take apart mechanical and electrical gadgets. I was particularly fascinated by radio receivers and transmitters, and later by television. I became an amateur radio operator and maintained an interest in electronics as I grew older. When it came time to decide what I wanted to do for an education, my family declared that I would go into business and start with an engineering degree. In those days, around 1950, children pretty much obeyed their parents. So I said. OK. and since I liked things electrical. I chose to train as an electrical engineer. Then I had to decide where to go to college. That turned out to be rather easy when my girlfriend selected Wellesley. The only engineering school in the Boston area that I knew about was MIT. And so that's where I applied. Fortunately, they acted on recommendations from my high school principal and a prominent local alumnus so I was spared the risk of taking examinations. During the first few years at MIT, I became interested in potential engineering applications to medicine and particularly in how circuits worked in the brain and whether one could apply electrical engineering principles to the understanding of central nervous system function. I devoted my college thesis to how, what was then called cybernetics or feedback theory, might relate to cognitive processing. Studies of human cognitive functioning have continued to fascinate me.
- TB: Are we in the early 1950s?
- TC: This was around 1953 and 1954. I wondered about how people communicated with each other and how brain neurons transferred information through its neural networks. As these thoughts progressed, it became clearer that I didn't really want to do ordinary engineering, but rather the biological applications of engineering. Nevertheless, after

<sup>\*</sup> Thomas N. Chase was born in Westfield, New Jersey in 1932.

graduation from MIT, I felt obligated to return to the Singer Sewing Machine Company, where I had worked during summer vacations and which at that time employed some 75,000 people around the world. My experience at Singer was informative, since it reinforced my evolving thoughts about not pursuing a standard engineering career. I was assigned various projects, like improving the delivery of lubricants to the gears of a sewing machine, which were not very challenging. I was also disappointed to find out how this once great company functioned in terms of product development. For example, they designed the mechanical process by which cloth is stitched together purely empirically. The company had no clear understanding about how the thread tensioning system and the caming surface of the shuttle actually worked to form a stitch. They simply gave a block of steel to a toolmaker and asked that he file it so that it throws off the thread in a way that the hook catches it and makes a knot that neither sags nor puckers. I was disillusioned and wondered why I should spend my life with a company that seemed to have so little interest in what it was doing. When I asked about how Singer went about updating their products, an official took me to a room where sewing machine parts were laid out on tables. All these components came from competitors. It was appalling to realize that the Singer approach to improving their machines relied mainly on copying their competitors. Finally, let me tell you about one other disillusioning experience I had with the Singer Company. I lived at a men's club in Bridgeport, CT, and one of the other residents during much of the workweek was a man who served as the Singer vice-president for research and development. We often had dinner together and from these encounters I learned a lot about the issues of greatest concern to the company's upper management. To my dismay, I found out that one of the major problems at the time was to decide whether sewing machines should be painted brown or green. How sad,I thought, to have such a smart and successful engineer end up having to bother with such trivial matters. I knew that this was not the direction I wanted to go and began to look for a way out.

The army rescued me. I had been an ROTC student at MIT and upon graduation I was commissioned a second lieutenant in the Signal Corps. After completing military training in New Jersey, I was shipped off to the Korean War zone where I took command of a platoon responsible for maintaining telephone communications between the country's airports. This assignment proved to be a challenging and sometimes alarming experience. When I joined the platoon I discovered that much of its equipment was missing. When I asked the senior supply sergeant why, he said the platoon had been overrun in battle, many of the troops were injured or killed, and most of the equipment was lost. So here I was, a naïve young man from small-town America, suddenly confronted with the awesome consequences of war. An armistice had been signed and organized fighting had ceased. But the devastating consequences of war were everywhere. It's with unending sadness that I now recall the awful plight of the civilians around us. The battalion to which I was assigned occupied portions of a small village south of Seoul. The village consisted mainly of rice paddies surrounded by small thatched houses and a bombed-out textile mill. The troops lived in Quonset huts, but the officer's guarters were set up in a section of the mill. Although mostly in ruins, it was still the nicest place in town. Detachments of my platoon were spread across the county, near the various airfields. Thus my job allowed me to travel the length and breadth of the land. The main interairbase communications system depended on copper wires strung on telephone poles. That turned out to be a big problem. Landline communications relied on a commodity of compelling commercial interest to the impoverished people surrounding us. So we played an interesting game. Each day my linemen would string new wires and each night the locals would take them down. As you can imagine, it was a rather hectic life.

Several informative experiences during my time in Korea remain etched in memory. First, I made friends with two Korean high school students. The deal was that on weekends I would drive them anywhere in my jeep if they would choose interesting places and serve as informed tour guides. They did and I learned a lot about their culture and how different civilizations approach similar problems. To this day, I maintain contact with both men, who went on to highly successful adult lives. A second experience concerned techniques to inspire others to do what needs to get done. The work of our platoon was basically tough and dangerous. Most serving in Korea were not there by choice, but had been drafted into military service. Getting soldiers to perform well in such a demanding situation is challenging. Military discipline helps, but it's not enough. The situation forced me to learn how to be a better leader and the lessons learned have helped ever since. Finally, while in Korea I had time to think about what I should do with the rest of my life.

Having decided that a business-engineering career was not for me, what else could I do? My thoughts returned to an early fascination about finding out how things worked. This interest began to focus on nervous system function while choosing a topic for my undergraduate thesis. Now I began to read medical books and show myself medical

training films, not a difficult task since one of my responsibilities was to supervise the movie depot for our troops in Korea. I also had an opportunity to work in a nearby Leper colony, which gave me a glimpse into what the practice of medicine was like in such a needy group of individuals. By the time my term of military service was over, I had firmly resolved to go back to school and become a doctor. Going back to tell my father of this decision was a little rough. He sort of shook his head saying you can't make money off sick people. Impetuously, I fired back that I didn't intend to charge any sick person for providing medical care. And to this day I have kept that promise. My father eventually struck a deal with me. He offered a small allowance, I don't even remember what it was, but otherwise I was on my own. Getting married helped solve the financial problem. But dealing with the emotional problem of having little family support was harder. Often during those initial years I wondered about the wisdom of my decision. Now, in retrospect, I can tell you I made no mistake. I made a choice that was exactly right for me. And ultimately my family seemed proud to see me graduate from medical school and pursue a career in neurosciences research. To get ready to apply to medical school proved to be a bigger challenge than I had expected. I had taken none of the traditional premedical courses and began attending night school at Columbia University to fill in the gaps. I was officially labeled an "atypical applicant" by the Columbia premedical program, which alarmed me and made me realize the whole venture could end badly. But the schoolwork proved easy and I got good enough grades to essentially pick my own medical school. The maturity gained since college also helped. I recall one rather hostile medical school interviewer who seemed to enjoy asking rather demeaning questions. At one point he asked whether I had chosen to be a doctor to get rich. Fortunately, it was my practice to spend time in the school library at each place I interviewed. And so I knew about what this young instructor of surgery was earning. It was less than I had been paid at Singer. When I put out my hand and asked whether he was willing to bet that I'd already earned more than he did, the interview suddenly turned rather collegial and in due course I was accepted at that school for admission. But my interview with the Dean at Columbia Medical School was the most memorable. I had read about Dean Rappleye and knew that he had enjoyed a distinguished career in medical education. He was a large and imposing man ensconced in an impressive office. I approached him anxiously. Since this was my school of choice, I asked why he bothered to see me, since Columbia was well known to accept only

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typical applicants from the top of their class. A gracious and perceptive man, he answered by reviewing what I had done in college in a most complementary way. He particularly liked my interest in applying engineering principles to medical problems. My confidence was restored and we began a lengthy and wonderful conversation. At one point, I kidded him about his school's strict dress code. All Columbia medical students wore identical, immaculately starched, white coats and looked like they came from the same cookie cutter. There followed an engaging discussion about uniformity versus individuality in medical education. Several years later an acquaintance, an Assistant Dean at Columbia, told me that Rappleye spoke to others about how impressed he had been by our conversation. I, too, was excited by our encounter, but that didn't convince me about the merits of conformity. For that reason and others, I chose to go to Yale rather than Columbia. Yale seemed to have a uniquely mature attitude towards medical education. The school assumed that anyone they admitted would take responsibility to learn the basic material. No class attendance or exams were mandated. And plenty of time was left for individual study and research. Upon entering Yale, I assumed I would gravitate towards neurology and the neurosciences. But it didn't take long before I realized that my original ideas about using engineering principles to solve neurological problems were hopelessly naive. I did a little lab work with two neurophysiology investigators, but found their research to be uninspiring. So I ended up trying to apply some engineering approaches to a study of protein cross-linking in relation to arterial elasticity and blood pressure regulation. Unfortunately, the mentor I choose was a cardiac surgeon, interested in pumps, but not in the problem I wanted to study. It was just as well because the work never amounted to much. But it did expose me to the thrill of laboratory research and I was forever hooked. I also came to the realization that primarily seeing patients might not be all that satisfying. While the practice of retail medicine held many attractions. I thought wholesale medicine might be better for me. I thought I'd rather spend my life trying to figure out how to improve the practice of medicine rather than just applying what was already known. So I decided by the end of medical school that I really did want to go into neurology, both from a clinical and research point of view, and to focus on pharmacology and experimental therapeutics. In the mid 1960s, neurology strongly emphasized diagnostics and had relatively little interest in therapeutics. At the time, "diagnose and adios" was the humorous characterization of neurologists. This attitude seemed a bit defensive, since few effective treatments were

available and prospects for improving that situation seemed daunting. Drugs then available for brain disease had largely been discovered serendipitously. The concept of trying to figure out how the nervous system worked, how disease altered normal function, and on that basis developing a rational intervention was not seriously discussed. The Chair of Internal Medicine at Yale was Paul Beeson, one of the all time greats of his profession. I was a medical student in his department and served under him as a medical intern. During these periods he influenced me in many important ways. Not the least of these was his advice to go to Harvard and the Massachusetts General Hospital for neurology residency training. He said during our last meeting, while handing me his autographed textbook of medicine, that he had written his very best reference letter and now it was up to me. Looking at the other top neurology residencies at the time convinced me that he was right. So I moved to Boston and started work at the Mass General. The clinical part was demanding but made entirely worthwhile because of Raymond Adams. In retrospect, I would certainly place him as the most distinguished neurologist of this time. Encyclopedic in his knowledge and logical in his reasoning, he was always kindly and discerning in his approach to others. He quickly understood his patients and his students. He allowed me time to explore the rapidly emerging world of neuroscience at Harvard Medical School. At the end of my clinical training, I told him that I thought I had some beginnings of understanding about what the practice of neurology was all about, but that I really didn't want to go in that direction. Caring for neurologic patients was a source of great personal satisfaction, but I wanted primarily to devote myself to research in neurotherapeutics. To my surprise, since he was a neuropathologist and rarely spoke much about therapeutics, he became very interested. He said my plan was right for me and suggested that I go to NIH and spend some time learning to do research and then come back to Boston. He advised me to see either Sidney Udenfriend or Seymour Kety. I went to Kety. He had come to Harvard to give a lecture during my residency that impressed me enormously. Up to that point, it seemed most neurologic researchers were simply measuring things, what ever their assays allowed, and then looking for correlations between their measurements and various clinical attributes. Today, we would call these plodding efforts fishing expeditions. Kety took a much more scientific, hypothesis testing, approach. He showed how it might be possible to study linkages between specific brain dysfunctions and particular clinical symptoms using chemical and pharmacologic techniques. He illustrated this possibility by describing how

abnormalities in certain neurotransmitters might relate to depression. It seemed like a generalizable concept. And it related directly to therapeutics, since drugs might be designed to selectively correct either too much or too little transmission in a particular system. When I met Kety,

he expanded on these ideas and suggested I discuss them with others in his group, especially Julie Axelrod and Irv Kopin. By day's end, I was excited about the potential of what was then called transmitter pharmacology and had decided to join Kopin's lab. I started working on animal experiments, but with an eye towards clinical applications. It was an amazing time since there were so many smart people around from whom I could learn. This was NIMH and most in Kety's group were focused on the problem of depression and to a lesser extent on schizophrenia. But, of course, my inspiration came from neurology. I was particularly interested in transmitters in the basal ganglia and how they might relate to parkinsonian symptoms. At the time, Arvid Carlsson was beginning to publish his classical papers on dopamine and serotonin and motor function. The discovery of levodopa for Parkinson's disease by George Cotzias also occurred during my training at NIMH. Clearly, the opportunities to apply transmitter pharmacology to neurologic disease were wide open and NIH seemed like the ideal place to take advantage of these opportunities. It amuses me today to think about the simple administrative procedures that sufficed to gain NIH tenure in the 1960s. One day, just two years after beginning my postdoctoral training, the NIMH administrative officer approached me in the lab and asked whether I would like to become a regular government employee. I was then paid by an NIH fellowship that still had another year or two before expiring. The last thing I was thinking about was finding a job. My initial reaction was that I didn't want to become a civil servant and would eventually prefer an academic appointment, especially the one promised at Harvard. But Hazel Rhea was an imposing woman, not used to taking no for an answer. She told me that accepting a government appointment would increase my salary and that I could resign on just two weeks notice. So I soon became a permanent NIH employee with none of the paperwork or committee reviews that so encumber the tenuring process today. Interestingly, I maintained contact with my former bosses at the Mass General, and they initially implied that when I came back it would be at the instructor level and without tenure. The next time this matter came up, they said when you come back you'll be an assistant professor. Soon I caught on that because I was spending full time doing research and publishing a lot, I was advancing faster in the Harvard system than

I would have if I had actually stayed there. The work at NIH was exciting and I decided to remain for the time being. Thirty-five years have now flown by and I've yet to regret that decision.

- TB: Could you tell us about your activities at NIH?
- By all usual standards, my career was upside down. My research went TC: well and two years after accepting tenure I was promoted to the level of Section Chief. In that position, I was assigned a lab technician and a part time secretary. I spent my time doing clinical research using several assigned beds and related pharmacologic studies in a nearby one-room lab. Then two years later, in 1974, as my own independent research was just beginning to pick up some steam, I was unexpectedly called to Don Tower's office and told that I had been selected to serve as the Scientific Director of the National Institute of Neurological Disorders and Stroke (NINDS). He explained that I would take responsibility for all the Institute's intramural research efforts as well as a number of off site projects. I had little idea about what scientific directors did and the thought of having 600 scientists and support people reporting to me, most far more senior than I, seemed a bit overwhelming. But the prospect of taking charge of what was then the country's biggest neuroscience program was irresistible. Spending full time on my own research would have to wait. The mid-1970s were a great time to be at NIH. Resources were plentiful. Scientific productivity and prestige were at their peak. The bureaucratic superstructure was still lean and committed to promoting the scientific enterprise, not the other way around. NIH attracted the best and brightest young scientists, although it must be conceded that this was partially due to the fact that many sought to avoid the military draft by working at a Federal institution. Among the senior staff, many were world leaders in their fields. Excitement and morale ran high and prestigious prizes and other forms of professional recognition came frequently. Members of the National Academy of Science were everywhere. An NIH intramural researcher received a Nobel Prize nearly every other year during that period.
- TB: Was the Nobel laureate who worked in your group at that time Gajdusek, or Axelrod?
- TC: Carleton Gajdusek was the one in my group. He received the prize in 1976 for work on Kuru, a spongiform encephalopathy due to prions. Just a few years before, soon after my period of working with him, Julie Axelrod had also won a Nobel Prize. His prize, as you know, was for studies on synaptic transmission mediated by catecholamines. Many of the approaches he took seemed directly applicable to studies of dopamine and Parkinson's disease as well as to other neurologic

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disorders where pharmacologic manipulation of synaptic mechanisms might be a rational approach to therapy. He also taught me, like so many others in contact with him, if you can't prove your hypothesis in a four-rat experiment, then it's probably not biologically worth pursuing. Julie and Irv had a big influence on the directions I wanted my own research to take when I transferred to NINDS and began to organize a neuropharmacology laboratory. At the start of my tenure as the NINDS director of intramural research I had a number of short and long-term goals. At the top of my list was a commitment to launch an experimental therapeutics program. I felt that clinical neurology was seriously behind in this area and that the NIH offered an ideal environment for this work to flourish. But before expanding on this, let me mention a few other initiatives that I now recall with special pride. Overriding was the opportunity to recruit outstanding young scientists and begin new research programs. One of these involved brain imaging, which when I started the NIH effort, involved just positron emission tomography (PET) scanning. Early on, it served as a model for establishing extramural PET centers across the country. Another was to organize an international effort to standardize brain banking. NIMH helped with this work, which involved getting the neurosciences community to establish standards for collecting and assaying CNS tissues so that human post mortem findings from one lab could be reliably compared with others. I also had the opportunity to begin or rejuvenate NINDS research operations at the Marine Biological Laboratory (MBL), in Woods Hole and on Guam where pioneering studies on the local forms of Parkinson's disease and amyotrophic lateral sclerosis (ALS) had been conducted. A decade later, when I had stepped down from the Scientific Director's job, the NINDS intramural program had doubled in size and in citations to its publications. There are so many other things that I should mention about this, but before time runs out let me return to my interest in neurotherapeutics. My goal upon joining NINDS was to organize a lab that was vertically integrated. By this I mean a research group that attacked the same general problem with various technologies and at various levels from the basic to the clinically applied. The NIH structure was well suited to this concept, since the 526 research beds at the Clinical Center were surrounded by related lab facilities. Geographic proximity facilitated the efficient transfer of ideas and materials from bench to bedside and back again. Some research problems are best begun at the clinical level. Others lend themselves more to experiments at the molecular or cellular or whole animal levels. I started a lab that spanned the entire spectrum but focused on the medical needs of patients with

neurodegenerative disease. Today this approach is no longer uncommon. Now it's called translational research. While my interest in amine pharmacology derived from my experiences with Kopin and Axelrod, my attraction to Parkinson's disease began much earlier. During residency training, I had been affected by the plight of parkinsonian patients and those with similar movement disorders. I was impressed that they had a rational treatment, the anticholinergics, even if the effect size was small. One of my most memorable teachers at the Mass General was Bob Schwab. He was full of interesting ideas about the pharmacotherapy of movement disorders. He had done pioneering work with apomorphine and with amantadine. And he was also among the first to develop a scale to quantify motor disability in Parkinson disease. So Schwab had a big influence on my choice of career directions. At the time my NINDS lab was beginning, following close upon the classical preclinical studies of Carlsson, George Cotzias discovered how to turn the earlier observations of Birkmayer and Hornykiewicz into a practical and effective treatment for Parkinson's disease. Immediately, the race was on to extend and perfect the concept of transmitter replacement in neurologic disease. For Parkinson's disease, the big problem was that levodopa did not replace the depleted neurotransmitter, dopamine, in a very physiologic way. For that reason, patients who did well initially eventually began to loose benefit and develop a syndrome called motor response complications. A disabling hypokinesia was replaced by an equally disabling hyperkinesia and other motor abnormalities. Early on, most working in the field attributed motor complications to pharmacokinetic issues. Before long, however, it became clear to me that pharmacokinetics could not explain the entirety of this problem. Another popular view, even to this day, has been that motor complications reflect denervation supersensitivity of postsynaptic dopamine receptors, even though the data give scant support for this simplistic idea. My thought was that the periodic administration of levodopa only restored striatal dopaminergic transmission episodically. But the nigrostriatal dopaminergic pathway functions largely as a tonically, not phasically, active system. And so began a line of research that I have pursued to this day. I wanted to figure out whether my hypothesis that the nonphysiologic stimulation of the nigrostriatal dopaminergic system was responsible for the motoric adverse effects of levodopa therapy, and if so what were the consequences at the neuronal level as well as in downstream networks, and how could we give dopaminergic treatments in a more physiologic and thus less detrimental way. I felt the answers to these questions might have relevance to other transmitter systems and other brain disorders,

including those where therapy might involve the inhibition of synaptic transmission. Some of our earliest studies involved the continuous parenteral infusion of dopaminomimetic drugs to parkinsonian patients. Since the dopamine system fires off fairly constantly at about five Hertz and since, as a first approximation, the amount of dopamine released into the striatum is a function of the rate of nerve impulse activity, it follows that the amount of the transmitter in contact with its postsynaptic receptors normally remains guite stable. On the other hand, treating a parkinsonian patient with levodopa produces marked fluctuations in striatal dopamine. With each oral dose, dopamine levels shoot far above the physiologic range and then soon fall back to sub-physiologic concentrations, since both extracellular levodopa and dopamine are rapidly metabolized. So, with standard therapy, you're chronically pulsing, a neuronal system that normally functions continuously. To test our hypothesis and determine, whether continuous transmitter replacement might prevent or reverse the motor complications syndrome, we gave patients constant infusions of levodopa or dopamine agonists for days or even weeks. It worked. Motor complications abated. And in primate models of Parkinson's disease we later found that initiating treatment with continuously administered agonists actually prevented onset of these complications. So now I was sure that motor complications were a consequence of chronic nonphysiologic stimulation.

- TB: In looking for effective treatments did you work with the pharmaceutical industry?
- Early on, we established a close working relationship with Merck. TC: Nowadays, NIH regards such collaboration between government and industry with suspicion, and the easy opportunities to hasten clinical development of innovative products by joint efforts of this type have largely disappeared. Merck was trying to develop levodopa formulations that reduced GI intolerance and improved convenience by prolonging their duration of action. The company seemed most concerned about their patent and marketing position. Our interests lay in finding better approaches to therapy and in evaluating the continuous versus intermittent stimulation hypothesis, which then was little known or understood beyond our lab. The first levodopa improvement involved the addition of a dopa decarboxylase inhibitor, which we found reduced the initial nausea and vomiting and thus allowed a far more rapid dose titration. But it didn't significantly prolong levodopa's duration of action. And neither did the next upgrade, the various controlled release formulations, which we also contributed to in major ways. Both levodopa improvements were clinically useful and led to a product that remains

the gold standard for the treatment of Parkinson's disease. Both helped patients, although not because they reduced the problem of intermittent dopaminergic stimulation and resultant motor complications. The search for pharmaceutical strategies to deal with that problem, including the development of longer acting dopaminomimetics, continued for many years. Progress was slow and my lab made relatively few contributions. My duties as Scientific Director prevented spending much time on my own research, which in any event had now turned in other directions to avoid competing with my newly recruited Clinical Director, Don Calne, an internationally recognized expert on Parkinson's disease. Eventually, several dopamine agonists with very long half-lives were discovered by industry. Other approaches to more continuous dopamine system stimulation that my lab subsequently worked on, that ameliorated this problem, included miniature wearable pumps, subcutaneously implantable polymers and skin patches. We launched the initial proof of concept trial for what could be the first transdermal preparation approved for Parkinson's disease. The tortuous story of its development is interesting since it illustrates the enormous time and effort needed to bring a drug from discovery to market. In the mid-1980s, my search for a dopamine agonist suitable for continuous administration led to Alan Horn's lab at the University of Groningen. He proudly showed me a series of recently discovered aminotetralins that were potent dopamine-D, agonists. But an overlooked characteristic of one of these drugs immediately got my attention. It appeared to be highly lipid soluble and thus might work as a transdermal preparartion. So I helped arrange its acquisition by a small California company that named it N-0437 and began work on formulation. Over the next 10 years, the drug struggled through 4 or 5 underfunded and under-skilled companies in several countries before being finally ready to try as a patch in humans. We found that it successfully reduced response fluctuations and the preparation should soon be approved for marketing as rotigotine. Neurologists initially tended to be skeptical about our intermittent versus continuous stimulation story. Thus I'm pleased that the newer long-acting agonists have been shown to significantly delay onset of motor complications in patients just as we had earlier predicted based on studies in animal models. And now patch technology also appears to be on the verge of clinical utility. Clearly, the trend towards more continuous dopaminergic replacement has benefited all those suffering from Parkinson's disease.

TB: In addition to helping patients how did your work illuminate mechanism of action?

TC: I'd like to say something about the pathophysiology of the motor complication syndrome and how fundamental studies of these mechanisms have enhanced our understanding of CNS function. In the late 1970s we began to look at the role of GABA and glutamate mediated functions in the basal ganglia and how these transmitter systems influence motor function. Some of our earliest studies looked at the relation of these striatal systems to the motor dysfunction in tardive dyskinesia. But soon our efforts returned to the Parkinson's disease problem and began to focus on the medium spiny neuron. These remarkable cells make up the vast majority of striatal neurons. They express both D, and D, dopamine receptors and receive input from the substantia nigra. They also express glutamate receptors and receive input from all areas of cerebral cortex. And spiny neurons project directly and indirectly via gabaminergic terminals to the major output nuclei of the basal ganglia. Clearly, the medium spiny neuron must be critical to basal ganglia function and we needed to know how this worked. Soon we discovered that something was happening to the sensitivity of ionotropic glutamate receptors on spiny neurons in response to changes in dopaminergic input. Our studies began to show that both N-methyl-D-aspartase (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazoleproporionate (AMPA) receptor blockers could alter the effects of dopaminergic drugs on motor function. Slowly the details of these interactions emerged from our work in rodent models. Since various forms of neuronal plasticity were mediated by glutamate transmission via the NMDA receptor, we examined the effect of MK-801 (dizocilpine) and other NMDA receptor blockers on the development of motor complications during chronic treatment of parkinsonian rats with dopamine agonists. Tom Engber and others in the lab found that pretreatment with MK-801 both prevented and reversed the motor dysfunction mimicking motor complications in parkinsonian patients. These results were later confirmed by Stella Papa in the primate 1-methyl-4-phenyl-1,2,3,6-tetrahydroxypyridine (MPTP) model of Parkinson's disease. Finally, as the culmination of all this step by step work we launched a clinical trial of amantadine, then the only NMDA antagonist available for human use, in patients with intractable motor complications. In 1998, Leo Verhagen Metman and others reported that amantadine significantly improved levodopa-induced dyskinesias and motor fluctuations. Amantadine remains today the standard pharmacotherapy for motor complications, even though it's long off patent and has never been promoted by any drug company. The results of our small yet well-controlled trial, since replicated by many other groups,

had a major impact on the lives of those with advanced Parkinson's disease.

- TB: This seems like an excellent example of what you referred to earlier as translational research.
- TC: It is. The discovery that amantadine benefits parkinsonian patients with response complications was particularly important to me because it reinforced my view that truly novel treatments can be found by small groups through the painstaking application of fundamental scientific principles. We started with insights at the molecular level and proceeded to evaluations in rat and non-human primate models and then finally in man. The basic idea arose from our observation that dopaminergic input to spiny neurons affected the sensitivity of co-expressed glutamatergic receptors. This led to studies of the bidirectional signaling between D1 and D2 dopaminergic receptors and ionotropic glutamatergic receptors. We found that the nonphysiologic stimulation of dopamine receptors altered the phosphorylation state and channel characteristics of nearby NMDA and AMPA receptors. These changes reflected the aberrant activation of kinases or deactivation of phosphatases that control the amount of phosphorylation at particular sites along the intracytoplasmic tails of these glutamatergic receptors. The receptor alterations increased their sensitivity to cortical excitatory drive. As a result, striatal output evidently changes in ways that favor the appearance of parkinsonian signs and response complications. Clinically, we now know that although other NMDA antagonists attenuate the motor complication syndrome, those that are non-selective for all NMDA receptor subtypes are not very useful. So our attention turned to drugs that target the NR2B subtype of NMDA receptors. These drugs appear to be very effective in our animal models, and clinical trials of NR2B antagonists should begin soon. In addition, we are now finding evidence suggesting that NMDA and AMPA receptor antagonists may have additive effects in rodent and primate models. Perhaps a cocktail of both antagonists would prove safer and more effective than either given alone. Hopefully, a clinical evaluation of this possibility will start in the not too distant future. Our studies thus suggested that sensitization of NMDA and AMPA receptors expressed at the dendritic tips of spiny neurons play a crucial role in the pathogenesis of motor dysfunction in Parkinson's disease. Since protein phosphorylation serves as an important regulatory mechanism for these receptors, the differential changes in the phosphorylation state of certain tyrosine and serine residues that we found occurring as a result of nigrostriatal system degeneration or

intermittent dopaminergic treatment likely contributed to their altered synaptic efficacy. These thoughts raised the possibility that we might be dealing with one aspect of a more general phenomenon. At the time, little was known about signaling in medium spiny neurons or about how these neurons integrate inputs from their various receptors. Extending our observations about how signaling between dopamine and glutamate receptors functioned, we began to look at whether similar mechanisms might be operative at other transmitter receptors expressed on these striatal efferent neurons. If the way one receptor was stimulated regulated the synaptic efficacy of others then, we wondered, could this be a way that neuronal dendrites approach the challenge of synaptic integration? The implications of this concept for the treatment of motor dysfunction seemed obvious. Could blockade of other, nondopaminergic and nonglutamatergic, transmitter receptors expressed on spiny neurons affect motor function and, more specifically, ameliorate symptoms due to a decline in striatal dopaminergic input or chronic exposure to nonphysiologic dopaminergic replacement? If some of the various transmitter receptors expressed on spiny neurons modulated the way cortical glutamatergic input influenced striatal gabaminergic output, then drugs that interact with these receptors might treat motor dysfunction due to disease or treatment related abnormalities involving one of the other receptor systems. To make a long story short, we have been exploring these possibilities in relation to the adenosine  ${\sf A}_{_{2a}}$ , the serotonin  ${\sf 5HT}_{_{2A}}$ , and the  $\alpha_{_2}\text{-}$  noradrenergic systems. In each case, it now appears that selective blockade of one of these receptor classes ameliorates Parkinsonism or motor complications or both. These studies were started in rat and then primate models, and we have already started, or we are planning to start, clinical proof of concept trials. These strategies open up an entirely new approach to the treatment of Parkinson's disease and perhaps other neurologic disorders as well. Rather than the traditional approach of replacing the deficient transmitter, it may sometimes be safer and more effective to pursue novel pharmacologic strategies that prevent or reverse subsequent reactive changes. In Parkinson's disease, we might no longer be limited to simply replacing dopamine at spiny neurons, but rather have the option of pharmacologically modifying other systems with countervailing actions at these neurons. More generally, we might no longer be constrained to think only about directly correcting the malfunctioning transmitter system, but could consider pharmaceutical interventions that tend to reverse the downstream consequences of the original malfunction.

- TB: When did you do this work?
- TC: These are experiments mainly carried out over the past five years, although the concepts had been percolating within the lab for a bit longer. What I've been describing are examples of the general concepts that have long guided my research at NIH. I sought to apply and extend what is already known about neural mechanisms, especially interneuronal transmission and more recently intraneuronal signaling, to the discovery of better pharmaceuticals for the treatment of brain disease.
- TB: You started treatment of Parkinson's disease with anticholinergics. What is their status now?
- TC: Before the discovery of levodopa, the anticholinergics were all that was available to treat Parkinson's disease. But they confer only meager benefit to early stage patients and can cause confusion and somnolence. The pharmacology of anticholinergic therapy of Parkinson's disease hasn't really advanced since the 1950s. The drugs we have today are essentially the same as those we had then. Usage is low. Nevertheless, much more has now been learned about CNS cholinergic receptor subtypes and it might be useful to go back and see whether selectively targeting a particular subtype might improve their therapeutic index. It's an area that warrants future attention.
- TB: What is the current status of MAO inhibitors in the treatment of Parkinson's disease?
- TC: A fair amount of work has been done on monoamine oxidase inhibitors. Drugs of this type have relevance to Parkinson's disease for two reasons. For palliation, MAO inhibitors provide modest symptomatic relief as monotherapy in early stage patients and they may also help a little in smoothing out motor fluctuations in later stage levodopa treated individuals.
- TB: Type B inhibitors, or all MAO inhibitors?
- TC: Selective inhibitors of the MAO-B isoform are used clinically for safety reasons. The second reason that parkinsonian patients receive drugs of this type is because of their disease modifying potential. Interestingly, there is evidence suggesting that their neuroprotective activity in animal models could reflect mechanisms other than MAO inhibition. But the results of clinical neuroprotectve trials have been hard to interpret. A big problem has been in trial design, particularly the lack of outcome measures that accurately reflect the underlying disease state. All studies to date have failed to prove that MAO-B inhibitors are neuroprotective. But, on the other hand, they didn't rule out that possibility. So, the work continues.
- TB: In the United States?

- TC: In the United States and elsewhere in the world.
- TB: In the course of your research did you have any contact with psychiatry?
- TC: My first seven years at NIH were spent at NIMH, where I was surrounded by talented psychiatrists and their exciting work in psychopharmacology. My initial lab experiences included sharing a bench with Joe Schildkraut and Saul Schanberg, and later sharing an office with several psychiatrists including Chris Gillin and Keith Brodie. Biff Bunney's affective disorders group, which then included Fred Goodwin and Dennis Murphy, was nearby. Dick Wyatt got me interested in the relation between monoamines and sleep. John Davis started me to think about psychosis and monoaminergic mechanisms. Interactions with these and many other individuals taught me a lot about how to approach the clinical study of brain disease and shaped the directions my future research would take. Like many around me at NIMH, I began to use drugs as tools to selectively manipulate brain transmitters, especially those measurable in spinal fluid, and specific clinical functions, especially motor and cognitive function. Using this pharmacologic approach, one could infer a great deal about the relation of specific transmitter systems to particular clinical behaviors. Soon I was attracting others to work with me and was able to begin the first NIH clinical aroup focused on neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease. Although most who subsequently came to do clinical research in my group were neurologists, I also had the privilege of training a number of psychiatrists, at least three of whom went on to chair their own academic departments and one who became a president of the ACNP. Just now I'm preparing for an upcoming NIH celebration for all the young people who have passed through my lab. It was surprising to find out that the total is now somewhere around 120 and to realize how many had already made extraordinary accomplishments and risen to positions of high responsibility in the academic, government and industrial worlds.
- TB: Your years at the NIH have shaped both the lives and careers of others and your own.
- TC: Due to my experiences at NIMH I have always had a strong interest in disorders at the border of neurology and psychiatry, such as Alzheimer's disease, and Tourette syndrome and Huntington's disease. In relation to Alzheimer's, Norm Foster and I were among the first to map the cortical distribution of neuronal hypofunction using early PET scan technology. Most investigators at that time thought that the disease mainly affected the prefrontal cortex. But our results pointed more to involvement of the parietal and temporal association cortex. They seemed to

fit the most typical clinical picture as well as the distribution of cortical neurofibrillary tangles. Interestingly, when I first presented these data to an imaging conference in Stockholm they were politely ignored. When I presented them several weeks later at a meeting in Bethesda, they generated rather heated criticism. Then a few months later, I listened in New York while a competitor presented what was essentially a concurrence with our findings along with the claim of precedence. Fortunately, we had already submitted our findings to the Lancet and Neurology. And our pictures must have been attractive, since several drug companies later made use of them, without attribution or permission, in advertisements for their cholinesterase inhibitors. In the case of Huntington's and Tourette's disease, our work failed to make much progress towards finding better treatments. But my interest in these disorders did afford the opportunity to try new ways to stimulate clinical investigators to perform more scientific and less descriptive studies. In cooperation with the relevant patient advocacy organizations, my trick was to organize large international symposia to which leaders in research disciplines that could be important for a particular disorder were invited. The first was on Huntington's disease in 1972. Most of the invitees had never actually worked on the disorder being discussed. But, as hoped, many were tempted to apply their technology to have some results for presentation at the meeting. And publication of the proceedings of these symposia served as a stimulus to both investigators and granting agencies. I know these efforts were effective, since Pub Med Citations invariably spiked in their wake.

- TB: So in the course of your research you have become involved with cognitive function in neurodegenerative disease?
- TC: Yes. I've already mentioned our imaging studies in Alzheimer's disease. My lab was also among the first to perform clinical studies with cholinergic system activators and inhibitors in Alzheimer patients as well as in those with progressive supranuclear palsy. But I think your question was referring to my earlier comments about an interest in cognitive processing. In that regard, we have done some work, although not nearly as much as I would have liked. For example, Alan Braun and I conducted several cerebral imaging studies in Tourette's syndrome, which attempted to link regional changes in neuronal function with the severity of various behavioral abnormalities. Perhaps the most interesting finding was an association between obsessions, compulsions and coprolalia with hyperactivity in the orbitofrontal cortices. In the late 1990s Chris Randolph and Eric Mohr and others in my group devised a neuropsychological screening battery known as the Repeatable Battery

for the Assessment of Neuropsychological Status (RBANS) that is now used in the assessment of cognitive disorders of various types. Now, aetting back to neurodegenerative disease, our early work focused on the application of transmitter pharmacology to the development improved palliative treatments. But more recently our emphasis has shifted towards disease modifying, rather than just symptom modifying, treatments. Current molecular and cellular biology offer lots of powerful new tools and approaches to study neuroprotection and neurorestoration. I think the field is beginning to make some real progress, especially at the basic science level, even if the results from the large clinical trials of protective interventions have been uniformly discouraging. I've been putting together a list of pharmaceuticals that are available for clinical use and that have recently been found to act on mechanisms that could benefit some neurodegenerative disorder. These drugs, often older ones that are now off patent, would thus lend themselves to repurposing as novel disease modifying agents. Our focus has been on pharmaceuticals of potential interest for Parkinson's and Alzheimer's disease. The list includes more than 30 drugs.

- TB: Was it as many?
- TC: I came away with the feeling there are too many, not too few. There were more approaches to test than resources for testing. How could we rigorously prioritize all these possibilities? The drugs we first chose to work on had to act on a plausible disease mechanism and in a valid animal model, if one existed. They also had to act in the human brain in ways that could be measured noninvasively. It was essential to be able to establish acutely whether a safe and tolerable dose was able to exert an adequate effect on the putative target mechanism. Only then would it be reasonable to invest the huge amounts of time and money that even a pilot neuroprotective trial takes. In the case of Alzheimer's disease, we are now looking at drugs that block a particular kinase, GSK (glycogen synthase kinase) 3, which mediates the phosphorylation of the microtubule associated protein tau at certain sites. The hypothesis is that the hyperphosphorylation of tau at these sites initiates a potentially injurious process of self-assembly into neurofibrillary tangles or impairs axoplasmic flow. Although Alzheimer's disease is clearly multifactorial and heterogeneous, one or both of these mechanisms could contribute to the degenerative process.
- TB: Are you working on this in your laboratory these days?
- TC: Yes. We are currently looking at the ability of several common drugs, including lithium and valproic acid, to block particular GSK3 mediated phosphorylation reactions. Clinical trials in this area are beginning

elsewhere, although I am dubious that any one of these GSK3 antagonists alone will confer clinical benefit to Alzheimer patients. It may be necessary to combine these drugs, or some additional drugs, in order to safely alter phosphorylation at critical tau epitopes in human brain. Working more with biologic markers, in this case tau in spinal fluid might be a good way to start evaluating these therapeutic hypotheses, before launching a clinical trial. Mechanisms affected by these drugs could also be important for the treatment of other neurodegenerative disorders.

- TB: Let me switch now to another topic. Could you say something about how you got involved with the ACNP?
- TC: When I joined Irv Kopin's lab I noticed that nearly everyone went off to some tropical paradise in December to talk science. The ticket for admission was merely a poster, which was easy to prepare if you were doing full time neuropharmacology research. I found out that the meeting was organized by the ACNP and the next one was scheduled for Palm Springs. And so I did what was necessary and went to the meeting and learned and enjoyed. And since then I have done what was necessary so I never, or hardly ever, missed a subsequent meeting. Although the focus was always on psychopharmacology, I have never attended an ACNP meeting that was not full of exciting new brain science related to therapeutic issues of interest to me. In most ways, psychiatry has lead in the development of better treatments for brain disease. Neurologists have much to learn from these successes.
- TB: Is there anything else you would like to add? Is there anything we did not cover?
- Well, there are always more things to talk about. Now perhaps they are TC: best left for another time. But before ending I should mention that I have been heard to complain that neurotherapeutics wasn't getting its fair share on the ACNP programs. The ACNP leadership usually responded by asking why I didn't propose sessions that would attract neurologists. So I tried, once or twice, with little success in getting participants. Of course, there was a circular problem. If there's no neurology, then there are no neurologists, and if there are no neurologists, then there's no neurology. The ACNP was doing just fine the way it was operating and I was enjoying their meetings. If I wanted more emphasis on neurotherapeutics, then I would have to find another venue; which is eventually what happened. In 1997 I founded ASENT, The American Society of Experimental Neurotherapeutics, which joins the academic, government, industrial, and advocacy communities to facilitate progress in developing new therapies for those with neurologic disease. The

organization is doing well, largely because it copied ACNP's successful formula.

- TB: What would you like to see happen in the future?
- TC: I think that trying to figure out what causes CNS neurons to die prematurely is very important. Neurodegenerative disorders can be regarded as a rate phenomenon. In Parkinson's disease, the difference between someone who evidences no Parkinsonism throughout a normal lifespan and one who manifests parkinsonian symptoms at age 60 is that the rate of degeneration of the latter individual's dopamine cells has increased by a factor several folds. The implication is that in Parkinson's disease, and presumably in other neurodegenerative disorders, just slowing down this accelerated rate could confer real benefit. Preventing onset or totally stopping progression is not immediately essential. I think the chances of discovering a way to achieve a modest degree of benefit are excellent in the near term. One or more of the newly emerging leads will soon begin to show efficacy. And even an initially modest success will transform the field of neurodegeneration, just like transmitter pharmacology did for psychiatry 40 years ago.
- TB: I hope it will.
- TC: I'm sure it will.
- TB: And on this note we conclude this interview with Dr.Thomas Chase. Thank you very much.
- TC: Thank you. My pleasure!

## PAULA J. CLAYTON

## Interviewed by Thomas A. Ban Waikoloa, Hawaii, December 9, 2001

- TB: This will be an interview with Dr. Paula Clayton\* for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the American College of Neuropsychopharmacology in Hawaii. It is December 9, 2001. Could you tell us where you were born, something about your education, early interests and how you got into psychiatry?
- PC: I was born in St. Louis, Missouri in 1934, the third daughter of two parents who both went to college. The fact that they both had college educations was important. My mother decided, very early on, that I should be a doctor. She was an energetic woman who helped me pursue that goal. It never occurred to me that I wouldn't become a physician. When I graduated from high school, I went to the University of Michigan, graduated and then entered medical school in 1956 at Washington University, which was in my home town and where I was one of only two girls in my class. I felt they took me because they needed a second girl. It happened that I chose a medical school that was intensely interested in research, so we had to do research in our freshman year. Then, in our sophomore year, a very funny thing happened. We were just beginning our first course in psychiatry and the man in charge of teaching burst into the room and said, "We've just been approved for a rotation in psychiatry; now we've got to teach you about psychiatric diagnoses. We want you to come to class! You can't take it lightly! We're going to lock the doors if you're not here on time". That man was Eli Robins. That was in 1957. So we went through a systematic approach to diagnosing patients for illnesses from depression and mania to schizophrenia, alcoholism and so on. Eli would say things like, "The first thing you've got to decide when you see a patient is whether they have 'the big C'. We all looked at him, dumbfounded, and he said, "Whether they're Crazy or not, because if they're Crazy, and that's the layman's word for it, they can only be depressed, manic, schizophrenic, organic or maybe have alcoholic hallucinations. That's the first thing you've got to decide." We were taught intensely about psychiatric diagnoses. That was certainly to my advantage, yet totally fortuitous. When we went into the clinic in our third year in 1958, the faculty was beginning to use imipramine. So we were not taught about psychotherapy. I only learned about making a diagnosis, basing a treatment on the diagnosis and following the

<sup>\*</sup> Paula J. Clayton was born in St. Louis, Missouri in 1934.
improvement of a patient's symptoms. A classmate of mine, who was first in the class, experienced a serious depressive episode. We were on the same rotation. You could just see him becoming less and less capable of answering questions directed to him. He was treated by a department member and after several failed drug trials, he was treated with ECT in his junior year. He graduated with our class. That shows how somatically oriented the department was. Before I graduated, I thought I wanted to go into internal medicine, but because psychiatry at Washington University was so similar to medicine, it became a possibility. I liked the people, Eli Robins, Sam Guze, George Winokur and Lee Robins, in psychiatry, so I wondered if it would be a better area for me than medicine. I talked to my husband and to the faculty and decided, on the day I graduated, that I would do a residency in psychiatry. It was not something I went to medical school to do.

- TB: It seems that your first encounter with psychiatry through Eli Robins had a major impact on your career.
- PC: Right. And the lecture by Sam Guze on depression and suicide also had a major impact. The idea that we should ask patients whether they were suicidal when depressed, and plan a treatment based on that, was so foreign. Not just to me, but to all in the class. Everybody else said one should not put ideas like that into the patients' heads, but at Washington U, they were insistent that every depressed and alcoholic patient had to be asked these questions.
- TB: So, you were taught direct interviewing to derive a diagnosis. Everyone had to be asked specific questions?
- PC: Yes, you had to ask questions. It was unique. The other unique characteristic was that we were taught that when dealing with inpatients, we should always interview their relatives before seeing the patients themselves. For really ill patients, relatives were considered more reliable sources of information about the patient's condition. There were only three of us who went into psychiatry and we were probably the first generation of students exposed to that kind of thinking. When I began my residency it was imperative to do research. No resident was allowed to graduate without a research project. I was encouraged and decided to do research on bereavement, because I knew what depressive patients admitted to the hospital looked like and I wondered how that state differed from that of those who were bereaved. First I interviewed relatives of patients who died at Barnes Hospital. Then I wrote a grant to do a bigger study, identifying people from death certificates. Even though Washington U had a good reputation, they'd never obtained a grant to study a clinical issue before. So, they were very

pleased that I did the project. Another important thing was that Eli, who was the chairman of the department, got intimately involved with evervthing we did. He was able to do that because by that time, he was ill with multiple sclerosis, which limited his ability to travel. So he taught me how to design a questionnaire for widows and widowers. He said, "Never ask open-ended questions. Think of all the possible answers, so that you give people an idea of what you want". That was interesting because the only open-ended question I did ask produced all kinds of answers that I couldn't put together in any quantitative way. He also taught me how to analyze data. At that time there were no computers. so we did all of our "p" values by slide rulers. Because I was interested in depression, I also got involved in research with George Winokur, who at the time was doing a big follow-up study. From data collected in that study, we derived the diagnostic criteria for mania, which outlined the three main symptoms of the illness: a manic mood, push of speech and overactivity. That was my first paper.

- TB: When did you publish with George Winokur the diagnostic criteria of mania?
- PC: In 1965. Then we did a follow up of those patients and wrote a book on *Manic Depressive Disease* that was published in 1969. There were no computers but George Winokur loved to work by hand in the card sorter.
- TB: So you worked, at that point in time, mainly with George Winokur?
- PC: Right. He was my major mentor. We also published the first American paper on the division of bipolar and unipolar depression.
- TB: Didn't your book with George have a third author?
- PC: That was Ted Reich. He was the junior author. I was the middle, and George was the senior author. Ted was a geneticist. He was born in Canada, studied there, trained at Washington U. and then went to England, I believe, to study genetics. He did the studies that showed bipolarity runs in families and that there are hypomanic gamblers and obsessional patients in those families. I was always most interested in treatment and wrote the clinical descriptions and treatment section in the book. At that time lithium was already used; in fact, I used it first in 1962. We had a manic minister, kind of like Elmer Gantry. He'd written bad checks. George read about lithium in *The Lancet*, and after the patient was given multiple ECTs and trifluoperazine, but was still not well, George had the pharmacy make up lithium pills, because nobody produced them. We gave lithium for mania in 1962 even though it wasn't marketed and approved by the FDA.

- TB: It took quite a long time after the first paper was published on the effectiveness of lithium in mania before it was approved for clinical use in the United States.
- PC: Right. But the first paper was written by Cade in 1949.
- TB: Then, there were several papers published on it in the 1950s by Treutner and his group in Australia, and Baastrup and Schou in Denmark.
- PC: Right. I was always interested in treatment; probably more because of George's mentoring than Eli, who was a therapeutic nihilist. For his entire career, Eli probably only used psychotherapy and Sodium Amytal (amobarbital).
- TB: Could you say something about Eli Robins? He was a very important figure in American psychiatry.
- PC: I did not know him when he wasn't ill, so I can't comment. But women who knew him before then said he was a very handsome, outgoing, charming man. He could talk to you at a party about the movies you'd seen, or the last book you'd read. He was an intense thinker who studied at Harvard in the early 1950s and brought the scientific method to Washington U. His team of Sam Guze and George Winokur promoted a different approach to psychiatry than others did. They were not popular. I remember I was a resident and went to a meeting in Chicago in 1962 with another colleague of mine, Dick Hudgens. They were promoting community mental health programs, saying that we needed to develop services in the community to prevent mental illness. Everybody agreed that pregnancies could be prevented with birth control and that infectious diseases could be prevented with vaccines, but my colleague stood up and said, "But we can't prevent mental illness. How in the world are you going to prevent mental illness"? It was that kind of approach that made everyone angry because we asked piercing guestions that people couldn't answer. Our Grand Rounds and Research Seminars were that way too. You had to present research every year, and Eli would sit there and listen. He was sick and he couldn't hold his head up. Then, suddenly, he'd lift his head and ask a question that you were amazed at. You thought he was sleeping and then he asked the most pertinent question. And you'd say, "Well, I'm sorry, I don't know the answer". Then, you'd go back and analyze your data to find the answer. It was a very provocative, enriched environment in which to be a faculty member. And it was very open. Except for those times when we had an outside speaker, we never had Grand Rounds without interviewing patients and discussing them. Eli would interview the patient or, when he got too sick, other people would. We'd discuss the treatment with everyone involved and you learned that there's no

perfect treatment. Depending on where you're coming from, you might treat the patient in very different ways. So, it was a helpful, nurturing environment.

- TB: What about George Winokur? Could you say something about him?
- PC: Yes, I told him once that I don't think he could have survived in the late 1990s, because he was so direct, to both men and to women. He could say the most awful things to you and then laugh and get away with it. When I was a resident, he said to me, "We'd like you to be chief resident". That was, in 1965. I hadn't thought of that, and I said, "Why should I do that"? And, he looked at me and he said, "Because it'll make a man of you". And then he laughed. He couldn't have said that in 1995. He was in charge of the in-patient service, so he also interviewed every new patient the residents admitted to the hospital. He was also in charge of recruiting residents. I remember one of my junior colleagues telling me that he was interviewed by George, and at the end of the day, George called him into his office and said, "You know, you're not the best resident candidate we've ever seen or will ever see, but we'll take you". He was so direct that he would throw everybody off-guard. I saw him interact with a colleague who was a dyed-in-the-wool analyst, and he'd say the most terrible things and get away with it. You certainly learned to be open and honest with George, and to admit when you didn't know something. I think the skills he taught me did me well when I became chair in Minneapolis. It was Sam Guze who represented the medical model in psychiatry for us. He was an internist before becoming a psychiatrist, and we learned from him the ways to validate a psychiatric diagnosis by information on clinical course and family history, treatment-response, outcome, and biological tests. He was also more serious. Once, I asked him if he wanted to have lunch with me. And he replied, "Only if you won't talk about your children". I was shocked, as I didn't think I talked much about my children. However, by the time he became Vice Chancellor at Washington U. he learned to be more tolerant of trivial talk.
- TB: Could you say something about the relationship between Eli, George and Sam?
- PC: They got along well. I think George and Sam lived in the same area of St. Louis and for many years carpooled to work and, I assume, talked about psychiatry constantly. When Eli got sick, George and Sam decided they would have to go to meetings and carry Eli's message. It was hard to tell, though, from whom the message truly originated.
- TB: So, it was hard to tell from whom the message originated.
- PC: I couldn't be sure. You know, by the time I was there each had his defined area. We all read Kraepelin. So Kraepelin was our Bible.

- TB: Do you know which edition of Kraepelin's textbook you had to read?
- PC: I think the 1899.
- TB: The one in which he introduced manic-depressive insanity and dementia praecox?
- PC: Yes. And the department paid for the book to be translated into English. And then we read things from Strömgren, Bleuler and all those people. We were only taught evidence-based psychiatry. Every paper we read was based on data. We were not taught to be psychoanalytic, to think in terms of the unconscious or dreams and things like that. So it was unique and I always felt lucky.
- TB: You were very lucky.
- PC: I was lucky also that I was one of the few women. Eli Robins' wife, Lee Robins, was in the department as well. She was a sociologist and did a very famous follow-up study that probably was Eli's idea. Lee became a real hero in her own right, but I don't know where she, or I, for that matter, would have been without being in that atmosphere. There was also another woman in the department, who eventually left. So, I was one of the few women and it was an advantage. They put me on the lunch brigade with every speaker. And we had speakers from all over the world, a lot of Englishmen, people from this country, and Canada. I went to have lunch with them, being the token woman.
- TB: Would you like to mention a few people whom you met?
- PC: Well, Jules Angst is one. I later collaborated with him. Bob Kendall and David Goldberg from England are others.
- TB: What about John Wing?
- PC: Yes, I did meet him as well. We collaborated and interacted with many people, including basic scientists, in several countries. Eli supported a basic science laboratory in the department originally with two basic scientists and residents and faculty who worked with them.
- TB: What did they do in the laboratory?
- PC: Blake Moore worked on protein chemistry and Bill Sherman worked on phosphoinositides and the mechanism of action in lithium. They had a mass spectroscope. So we did original research on the relationship between dosages, blood level and treatment response to first-generation antidepressants. I'm an author of a paper that reported that of all of the first-generation antidepressants, nortriptyline was the one that you could depend on the most in terms of dose, blood levels and outcome.
- TB: Kragh-Sorensen in Denmark had similar data. Did you collaborate with him?
- PC: No. His study and ours were parallel studies. I knew him, but we did not collaborate.

- TB: I suppose by the time of these studies the therapeutic nihilism in the department was gone?
- PC: Well, Eli was really the only nihilist. John Biggs and another set of people did those studies.
- TB: Are we talking about the late 1960s or early 1970s?
- PC: I would think the mid-seventies. We would look at these drugs on the mass spectroscope and see which were dirty and which were clean. I learned at that time, mainly through nortriptyline, to think about drug metabolism by the liver, because if you gave somebody 50mg of nortriptyline, the most common blood level you'd get was 50 ng. But if you gave somebody the same 50mg and they ended up with 100 ng in their blood you realized they must be a slow metabolizer.
- TB: So, you and the department got involved in psychopharmacology and especially in pharmacokinetics?
- PC: I never thought about it that way, but you're absolutely right. We started attracting residents who wanted to do these kinds of studies. Sheldon Preskorn and Matt Rudorfer came to Washington U. to train and took their own ideas forward. We also trained people like John Olney, Dave Dunner, John Feighner, Marc Schuckit, Steve Zalcman and Ted Reich. Some of the people in the department got together and wrote up our diagnostic criteria so they could be published.
- TB: You are referring to the St.Louis criteria that Robins, Guze and Winokur formulated and John Feighner put in writing in 1972.
- PC: Absolutely correct. And, I think John would admit that. I was reading those criteria as a medical student in 1957.
- TB: Were you involved in the preparation of that paper?
- PC: No. I would have liked to have been, but I wasn't. They met in Eli's office every Wednesday for months. Without John Feighner, that project wouldn't have been done, because Eli was ill and the other two were busy doing other things. It was John who said, "We really have to get this into writing". So, they met every Wednesday and wrote the paper.
- TB: The paper was written at those meetings?
- PC: Exactly. Another interesting paper that Eli did was on the biochemical basis of psychiatric disorders. He wrote it with Boyd Hartman. Boyd went on to do wonderful research on norepinephrine in the brain, showing that it's frequently on blood vessels. He got cows from the slaughterhouse to study their brains.
- TB: Were you encouraged to do biochemical research?
- PC: I only did pharmacokinetic research, but others, depending on their interests, did basic research. I left in 1980, but I can say that from 1956 to 1980, during the years when I knew what was going on in the

department, we never did a drug company study. We were frequently invited to participate in these studies because we knew so much about clinical diagnoses, but we never accepted. On the other hand, the two collaborative studies of depression, one of which was a drug study, were the basis of my entry into this society.

- TB: When was that?
- PC: I would guess in the late 1970s; just before DSM-III was published. DSM-III was the product of many consultations. So Spitzer and Endicott came to Washington U. frequently, and would stay for three or four days at a time talking to Eli about it. I became a member at the time when neuropsychopharmacologists realized they needed an understanding of diagnoses. Many of us were admitted in those years as members in this College, so that we could be the critics of papers that dealt with clinical psychiatry.
- TB: Were you involved in the development of the concept of external validity of psychiatric diagnoses?
- PC: Eli gave a speech in the mid 1960s on external validity. I don't know from whom the concept comes, whether it was Eli's or Sam's or George's. But certainly by doing cross-sectional, follow-up studies, we all strived for external validity. Another thing that happened in the 1970s was that Eli got very involved as a consultant in both the clinical and biological collaborative studies of depression. There's still a part of a project going on, on follow-up of those patients.
- TB: Were you involved in those studies?
- PC: Yes, because I was Eli's legs. He couldn't move; to go to a meeting was very difficult for him. So, he always had to have a collaborator go and I was his collaborator on that project.
- TB: But were you involved in those studies as an investigator?
- PC: Yes, with the clinical study, but not the biological one. Eli had such an active mind. He also started a study on schizophrenia. It was about the time that Bob Heath in New Orleans put electrodes in the brain of schizophrenic patients to stimulate them. Then Arnie Friedhoff reported on a pink spot in the urine of schizophrenics and Eli decided to follow it up. He started it when he was well and I followed those patients. It was amazing the criteria he used in the 1950s to gather this group. When we followed them up years later, if they had not committed suicide, they were still all schizophrenic. I remember going into the home of one woman and interviewing her. She seemed so normal. She was a mother and had children in school. I was using our structured questionnaire and when I asked her if she ever felt that people interfered with her, she said, "Yeah, I really don't like to have people that close". And

I said, "Why? What do you mean"? And she said, "Well, I don't like those people who come into my house and comment on me and tell me what to do". I had interviewed her for an hour and did not realize that she was psychotic. But once I got to psychotic symptoms in the questionnaire she had every one. I didn't understand how she was able to function. It was amazing how she did so with those strong auditory hallucinations and delusions in the back of her mind.

- TB: They didn't seem to bother her?
- PC: No, and her family seemed to accept it. I don't know whether she had any further treatment. The first part of the interview was general questions like,"Have you been in the hospital"? When I completed that part I thought, well, this is the one patient that Eli really misdiagnosed; she is not psychotic. But there she was, psychotic.
- TB: So the use of the structured interview helped.
- PC: We were taught how to administer a structured interview and used one with every research patient. There were several competing structured interviews used in the department. However, the one that became the most well-known was the Diagnostic Interview Schedule (DIS).
- TB: Were you also taught general psychopathology?
- PC: We were taught psychopathology. I still have Fish's book and use it to teach residents.
- TB: Didn't Fish come over to North America to give a series of lectures on psychopathology?
- PC: Not that I know of. We were taught many things written by those descriptive psychiatrists. They were colorful and it was wonderful but we never knew who was right.
- TB: Let's get back to your research. Your very first research grant was on bereavement, right? And you did this research sometime in the 1960s.
- PC: Right, it was in the mid-1960s.
- TB: Could you tell us more about that project?
- PC: I found the people by using death certificates and identified the ones to be interviewed by using a random numbers table. We would call the people we wanted to be included in the study and then we would go to visit them within the first month after their loss. Then we followed them up a year later. We found they had all the depressive symptoms that other depressed patients have, except as Freud already recognized, they did not have guilt feelings, they were not self-incriminatory and were not saying, "It was my fault", and that kind of thing. But they had sleep disturbances and weight loss. Some of them would lose 40lbs. They also had trouble concentrating and poor memory. They described their first response to the loss as numbness, which I think is the first

response to any kind of stress or shock that could last from a few hours to a few days. Then they developed a severe depressive syndrome. They did not eat or sleep. The depressive syndrome dissipated in a year or so, although 10% of them remained depressed. These displayed a sort of a major depressive disorder without self-incrimination and suicidal thoughts.

- TB: Then you analyzed, wrote up and published your findings. Was there anyone else at the time that did similar work?
- PC: There was no one else at the time. But we had a group of depressed in-patients who were being monitored. So I did compare my findings to what is seen in depressed patients in the hospital. They had similar symptoms except they also had guilt feelings and self-incrimination.
- TB: You mentioned before that the first response to the loss was a kind of stress response?
- PC: I feel that bereavement provides a model for studying the response to stress. What we learned was that stress increased alcohol intake in some people. People, who took pills, took more; they took their own and their deceased spouse's pills as well. And people who were inclined to overeat were eating more. Whatever characteristic behavior the person had under normal circumstances was increased once they were under stress. In spite of their increased smoking and drinking, the mortality rate of the widows and widowers was not different from the general population. To be able to study that, we had a control group of people who were in the same voter registry book, and of the same age. We had permission from the city to do that and identified them at the time the person died. They were in the same community with the survivors, sometimes even on the same block. We followed them for a year so that we could compare the mortality rate of widows and widowers with that of this group. The sample was small; it wasn't thousands, only 109. But there was no difference in mortality. So, we were interested in all aspects of bereavement. Since only 58% of those we identified allowed us to do an interview, we also had to prove that the people who refused were not systematically different from the ones we interviewed. After comparing them on all the things we could find in the death records, I thought maybe the people who refused were sicker and would die sooner. So I called them and said, "Hello Mrs. So-and-so, I'm calling from the Post Dispatch", which was our newspaper, and asked if they'd like a subscription to the paper. They'd either say, "No, I don't want it" or "I already get it", so at least I knew they were alive. There were four people whom I couldn't find because they did not live in the same house any longer. My data showed that if all of them had

moved out of town and died, there still would have been no increased mortality among those who refused an interview.

- TB: How was your report received?
- PC: It got mixed reviews. Danny Freedman accepted the first report or the Archives without sending it out to reviewers. There was some controversy because one of our papers showed that Lindeman's idea of acute death and the syndrome that followed was not valid. Another study on anticipated versus unanticipated grief showed no differences, which was upsetting to some.
- TB: Did your finding stand up over time?
- PC: Yes, absolutely. And it's important that it is a model for stress.
- TB: Stress caused by death?
- PC: Yes. I recently wrote a paper titled, *Why People Should Use Death as a Model for Stress*. I have never understood why animal researchers didn't take a pair of animals, remove permanently or kill their mate, if that is acceptable, and study the animal's physiologic responses. There's one nice study on norandrenaline responses in men whose wives were dying of cancer. Some of the wives died and some didn't, so it was possible to study bereavement response.
- TB: Did you look at sex differences in the bereavement study?
- PC: We did. We looked at everything. We looked at length of marriage, sex differences, religious affiliation. There were very few sex differences. Women had a little bit more insomnia but the overall responses were amazingly similar. Men cried less frequently than women, but for the most part they had the same responses.
- TB: So you eventually moved from studying stress and bereavement to studying manic-depressive illness and genetics?
- PC: Actually, I was doing those projects simultaneously. I did the study on stress and bereavement on my own; the one on manic-depressive illness was in collaboration with George. I was also involved in the cross-sectional and follow-up study of 500 randomly selected outpatients. I have to say that Washington U had a very different model of education than most universities did at the time, in that they thought that young people needed to do research and the older people should do the teaching, because younger faculty needed to make their mark in research at a young age. So we were allowed a lot of time to do research and had very few clinical responsibilities, which is totally different from what universities do now. Now, what the residents do is mainly clinical. What we did at Washington U. was good. And there is something I have not mentioned yet I had three children and didn't work full time to begin with. It was really fortunate that I didn't have any strong ongoing clinical

responsibilities, because I wasn't there half the time! They couldn't assign me to a ward to take care of patients, because I only worked Tuesdays, Thursdays and Fridays.

- TB: Weren't you chief resident at Washington U at the time?
- PC: Yes. Actually, my ex-husband should be given some of the credit for that decision. When they asked me to be chief resident, I went home and said, "Gee, they've asked me to be chief resident. Do you think I should do it"? And he said, "Well, they're awfully nice people". He thought it was a good idea. I hadn't thought of staying in academia before that happened, because the natural course was that if you were chief resident, you would go on to become a member of the faculty.
- TB: What did you intend to do?
- PC: I hadn't really thought beyond residency. I don't think I ever thought about practice and I certainly didn't think about being chief resident. I might have thought about staying to help somebody do research. You could do that. But then I got involved in the follow-up study on mania.
- TB: Did this happen when you worked halftime? When did you actually work halftime?
- PC: Maybe from 1965 to 1972, or something like that.
- TB: Didn't you write your first book, *Manic Depressive Illness,* during that time?
- PC: Yes, it was published by Mosby in 1969. There are many research findings in that book that have been reconfirmed over the years.
- TB: Could you tell us something about the book?
- PC: It was based on a follow-up study of 61 patients, all with manic depressive illness, who we had identified. George had done the work originally. I did the follow-up. My former husband was also helpful at the time. He was an attorney and asked me, "Why would anybody drive from Springfield, Missouri to interview with you? How can you ask these people to come back"? I said, "I really don't know, but they do"! Then he said, "They want to tell you their story". I realized he must have been right. It was an interesting adventure and I learned that followup studies are essential. That was the other thing that Washington U championed.
- TB: Didn't that follow-up study draw attention to the fact that psychotic symptoms in mania are indistinguishable from psychotic symptoms in other psychiatric disorders?
- PC: My first paper based on that study dealt with psychotic symptoms in mania and it showed that manic patients have as many psychotic symptoms as schizophrenic patients do. When it came to diagnosis, there was nothing pathognomic about psychotic symptoms. In the book, the

study clearly showed that psychotic symptoms are not unique to schizophrenia and that they also occur in mania and depression. We also did a follow-up study and a family study. We interviewed every member of the patients' families and wrote the book on the clinical picture, clinical course, family history and treatment of manic-depressive disorder; but first, we did a thorough review of the literature up to that time. The book is especially informative because the course of illness was less influenced by pharmacological treatments at the time. We found that one-third of the patients had their first episodes before age 20, none after the age of 50. Most of the family members were depressed.

- TB: Is there anything else you would like to tell us about Washington U. before we move on to the next chapter in your professional life?
- PC: Two things, actually. One, we were a very social group the department members threw lots of parties at their homes for faculty and residents. Two, we were always encouraged to go to meetings. Not only were we encouraged to attend, but Eli actually paid for us to go to them. I remember the first meeting I went to in England, where I presented on bereavement. I presented annually at the APA and at many other prestigious meetings. I met a lot of people. Then, when Sam Guze became Chairman of the department, he said to me, "You know, I really think you should be a chair person". When I asked why, he said, simply, "Because I think you'd make a good chair person"! By that time, I was sort of "second in command" in the department; he was both Chairman of our department and Vice President of the University. I was the one in the department to whom people would complain. It was also Sam who told me, "You've got to go and interview for jobs, even if you don't want them. You've got to interview. You can go once and find out about the job. Don't go back if you're not interested, but go once and learn the process". So I did that. I went to Buffalo, to Irvine and maybe a third place, but I felt the problems in those departments were insurmountable and I didn't go back to any of them. Then I was invited to go to Minnesota. It had always had a tradition of research and they had a good department of psychiatry. Don Hastings had been an earlier Chairman and he'd taken care of a lot of important people. He had a special research budget for the department. Len Heston did his early research on schizophrenia and Alzheimer's there, and since the department was in a place that used to be a psychopathic hospital, they also had a budget from the state. So the department had a very hefty budget.
- TB: Was Hastings the successor of Bert Schiele?
- PC: No actually Bert was never a chair. Bert had retired by the time I went, but when he was there, he had a research unit. There were studies

going on on anorexia under Elka Eckert and Heston. They had a really good research program that I could identify with. I went back for the second time and finally decided to accept and become the chairperson.

- TB: When was that?
- PC: That was in 1980 and I did that for 19 years. Actually, Gerry Klerman told me that he had interviewed for the chairmanship; evenutally they hired a person from the army who succeeded Hastings. This interim chairman, whose name I won't mention, was a good clinician but not a researcher. He had no interest in research. At the time he took over the chairmanship he asked Bert Schiele, "Well, why do you get grants to do studies when the state will pay your salary"? He couldn't understand. He had no concept of research. When he left, we re-started research. But, in the meantime, the psychologists had been very active in the department. Hathaway, who devised the Minnesota Multiphasic Personality Inventory, was there. Paul Meehl was also in our department. We had a whole host of strong researchers. So we reinstated psychiatric research in the department, I think successfully.
- TB: Did you continue your research in pharmacokinetics or any other area of psychopharmacology?
- PC: I really have to say, I did not pursue that. I've always been more of a clinical epidemiologist, and so the grant I wrote in Minnesota was to study elderly depressed people, because I wanted to learn what kinds of activities they were engaged in. I didn't get that grant. They thought it was too ambitious. After that, I mainly pursued psychopharmacology through the ACNP and work with pharmaceutical companies. I did not do drug studies myself, but our younger faculty members started to do clinical trials. I remained interested in the genetics of psychiatric illnesses but I didn't pursue that line of research either. I was also still involved in the data analysis of all the studies I had worked on at Washington U., so I continued to write manuscripts.
- TB: Didn't you do some studies with the dexamethasone test in anxious depression?
- PC: Yes. Max Hamilton was another good friend and it was evident from his questionnaire that anxiety is a very significant part of depression. So I used collaborative study data to write about anxious depression and then, collaborating with Bill Miller, used Iowa data in a study in which we compared dexamethasone suppression in anxious and nonanxious depressed patients. We used a scale derived from the SADS items. We found that anxiously depressed patients were the most consistent suppressors of the morning rise of cortisol. That shouldn't have been too surprising. The HPA axis reflects anxiety and not just

depression. I pursued clinical ways to validate diagnoses, but not any neuropsychopharmacology.

- TB: Could you tell us something more about the collaborative study you just referred to?
- PC: It was an NIMH collaborative study, an enormous undertaking. It was pivotal in developing assessment instruments that are still used today. It was difficult because there were five centers - Chicago, Boston, New York City, Iowa and St. Louis - as well as NIMH. We were five sets of strong investigators and we did well. Gerry Klerman was a wonderful leader because he was so tolerant. He would listen to everything and then make a decision. He had a tendency to get a little impatient, so the discussions couldn't go on forever. It was a very important study in confirming the age of onset and course of bipolar and depressive disorders. It also established lack of difference between different subtypes of depressive disorders. Marty Keller was part of that study and, of course, Bob Hirschfeld. Bill Coryell and Nancy Andreasen were also involved, as were Bob Spitzer, Jean Endicott and Jan Fawcett. It was a study that taught people about research. Marty Keller was a resident when I first met him and now he's the Chairman of the Department at Brown. All of this is important for appreciating the scientific value of that project.
- TB: Didn't you do some research with Jules Angst in Zurich?
- PC: Yes and that was wonderful. This month, we will be publishing a followup of his original bipolar and unipolar cohorts. He has been collecting data on these patients from their first intake interview to their death. And he has already shown that in each depressive episode there is an equal chance that the patient will commit suicide. An interesting part of that study was related to clozapine. In spite of the reported cases of agranulocytosis in Finland, clozapine was not taken off the market in Switzerland because they found it so useful in hospitalized patients in Zurich. Angst's studies show that if bipolar and unipolar depressed patients are maintained on medication, that includes lithium, antidepressants and antipsychotics, their suicide rate is enormously reduced.
- TB: You worked with him on this study.
- PC: I collaborated with him on this and on another study. In the other study, he administered a German personality inventory, in which many dimensions were measured, to all men inducted into military service in the canton of Zurich, Switzerland at the age of 18 and followed their psychiatric history throughout their service. We went through all of those records and used Feighner's criteria to re-diagnose those patients who got psychiatrically ill. We also looked at their personality traits. It turned

out that unipolar depressed patients, prior to the onset of illness, had personality traits characterized by more aggressiveness than controls, whereas the personalities of bipolar depressed patients were not different from those of controls.

- TB: Did you work with him on any other projects?
- PC: No, these were the only two in which I collaborated with him.
- TB: What are you doing these days?
- PC: I retired in July of 1999, moved to Santa Fe, New Mexico and began teaching in the outpatient clinic as a volunteer. Last year I decided I was not doing well with retirement and needed to get back to work. I missed being mentally stimulated and thinking about research issues. In September of this year (2002), I started to work halftime at the University of New Mexico and I'm a Professor in the Department of Psychiatry. I drive from Santa Fe to Albuguergue and teach in the outpatient clinic, see a few patients and then try to mentor residents, mainly women. We just wrote a grant to study the treatment of depressed bereaved patients with Lexapro or with a placebo. There is another group in the US involved in the same kind of research; if we get our grant I think we will write a proposal for a collaborative study and try to get funding from a pharmaceutical company. Since September 11<sup>th</sup>, it has become very important in cases of death and trauma to determine when psychiatric medications are necessary and what treatment is most appropriate for each patient. It's a very timely grant at this point.
- TB: It seems that you are trying to get back to research?
- PC: I started with research and I'm going to end with research. All I did in between was administration, and I didn't find that pleasing.
- TB: Seventeen years of administration?
- PC: Nineteen. When I first went to Minnesota, I asked the head of surgery, "What do you expect of a psychiatrist"? And he said, "I want them to see my consults on time". That was not at all what I expected him to say. By the time I left, people appreciated the significance of psychiatry in medical school. The Dean told me if he had to do it over again, he would have become a psychiatrist. I think they did finally feel that psychiatry was a part of medicine and could bring in research dollars. Our budget in Minnesota went from three hundred thousand when I started to eleven million by the time I left.
- TB: It sounds like you were a very successful Chairperson.
- PC: I just had good people. You hire some good people and you hire some bad. That's what Tom Detre taught me. He said, "Paula, for every eight people you interview, you'll get one good one". So you hire them and you really try to support them.

- TB: What do you consider your most important contribution?
- PC: I would say establishing the definition of mania and the book on bipolar disorder, published in 1969 which was really George's idea but we executed it together. The whole idea of studying normal people in bereavement to find the psychological response to such an event and the subsequent outcome was also very important to me. Those would be my two. I wrote the first paper on schizoaffective disorder in this country. Some people still ask me to come and speak on schizoaffective disorder, but it's not a subject I've pursued. I also published on depression in women physicians. Another interest of mine is anxious depression. Those are my favorite subjects.
- TB: What was your last publication?
- PC: My last paper was with Jules Angst on his bipolar study; I'm a middle author on that article. My last sets of papers were on anxious depression; on the family history, treatment response, and things like that from the collaborative study, and then on the biologic markers in that study from the Iowa data. One other thing has dawned on me in recent years, about entering academia - I really feel it's extremely important. It's sad that people don't enter academia, particularly women. I was married to a man who had to go to work every day to make a living. He was not salaried and he taught me how fortunate we in academia are to get a monthly salary and benefits. He said, "Well, Paula, I can't go with you on your trips. If I don't work, I don't make money". In academia we can do all this traveling and have all this freedom because we have people to back us up. We are salaried and encouraged to do those things. It's a very wonderful life. It gives you a lot of freedom. It's worthwhile to take these lower academic salaries and have this enormous freedom compared to having a higher salary and getting stuck in one place forever and ever. So when residents come to me and say they like academia and research and especially if they have published a paper, I say to them, "Try academia if you can afford to do it. It really is a wonderful job and you meet all these wonderful people and you're on the cutting edge". I have never felt that I made a mistake in my decision to become an academic, and it wasn't because I thought it through. It was just being in the right place at the right time. I believe that more people, especially women, should go into academia.
- TB: So it was people like Eli Robins and Sam Guze who stimulated you to become an academic?
- PC: And George. I think it was George. George was the one who asked me to be the chief resident, in his crazy way, and that was my entrance. My early research with him played an important role. He was my mentor. He

had a way of teaching. We had rounds with him three times a week to present new patients each time, at the end of those rounds, he assigned one of us a subject that we had to read and report on. I said to him one day, after presenting a depressed patient, "How does this patient differ from what you feel if you lose someone"? And he said, "I don't know. Go read about it". And, of course, I went and read Lindeman's work, because he was one of only three major contributors to the area, along with Freud and Abraham. When I presented what I had read to him and the group, he said, "Well, that would be a good project". That was to become my research project as a resident.

- TB: As Chairman, were you involved mainly in administration?
- PC: I couldn't do much research. I didn't have time.
- TB: How did you support the research units in your department?
- PC: Through grants and donations.
- TB: How much teaching did you do?
- PC: That's a good question. When I became chair in Minnesota there was only an elective clerkship in psychiatry. So, the first thing I did was work on getting a six-week clerkship. That was important. I had a very good faculty teacher whose father had been a teacher of chemistry. He was a very bright guy who didn't do a lot of research but was extremely scientific in his approach to questions. And he took charge of teaching. I always lectured in the freshman course and lectured in the second year on depression or mania. So I did do some teaching. I also interviewed all the prospective residents. And of course, I always taught residents in various rotations.
- TB: Did you use the model of Washington U?
- PC: Yes. I established Grand Rounds, where we discussed clinical cases and at times, brought in scientific speakers.
- TB: Did you encourage residents to combine research with their clinical work?
- PC: I couldn't quite adopt that model but I tried. When I was half-way through as chair, we established a clinical track and I called all my faculty on the tenured track together and said, "I think we should hire people to do the clinical work so that you have more time to do your own research, but the only way I can attract people to do that is to pay them more. Now, what would you think if I hire an assistant professor in the clinical track who makes \$20,000 more than you"? They assured me that that would be acceptable to them. So we did it, and that freed up the time for people on the tenured track to do more research.
- TB: How much clinical work did you do while you were Chairperson?

- PC: As Chairperson, I was involved in clinical work with the residents. Each of us spent two months a year on the inpatient service. I even spent one month on the eating disorders unit, a clinical area I had little knowledge of. After we started an outpatient clinic I worked half a day in the clinic every week. I also started a mood disorder clinic, where I supervised residents. I also saw a number of patients for medication combined with psychotherapy; probably five or six every week.
- TB: So, you were involved quite a bit in clinical work?
- PC: Right. I've never stopped and I've always seen patients. Another thing I did in Minnesota was what Sam taught me, which was that there would always be grateful patients and so it's very important to think about asking people, in the right way maybe through the alumni offices to give money. We did raise money for two endowed chairs and two professorships and some other things.
- TB: You mentioned that currently you are mentoring, and I felt that you were emphasizing that you were mentoring women psychiatric residents?
- PC: I was hired because women comprise half of most faculties now, and those who are good don't have time to supervise. There's a wonderful woman professor at the University of New Mexico, but she's busy. She cares and is a great teacher, but she's busy doing everything else. So she felt that I could have the freedom to do this. I think women need more encouragement, mainly because they're caretakers. Women are by nature and by nurture caretakers. It is easier for them to take care of patients than to do research. They may not be quite as competitive or as thoughtful about the world out there, so they need more encouragement to do research. That's why I stress the point.
- TB: Is there anything else that we didn't cover? I have one other question that is related to your involvement with ACNP. You have served on several committees of the College; could you tell us something about that?
- PC: ACNP is run by people actively involved with the organization, so I was one of them. I had been a member and chairman of the membership, ethics and education committees. I was on the council for several years. And I was involved in a long-term project that evaluated what training psychologists – PhDs – might need to be able to prescribe medication. That was quite a commitment. We went to Washington and all over the country. As I said, I've been very active.
- TB: Aren't you also involved with other organizations, like the American Psychopathological Association?
- PC: Yes; I am actually a past president of that organization, as well as the Psychiatric Research Society and Biological Psychiatry. The only

other one I have been active in is the APA. I'm on a whole host of APA committees.

- TB: Weren't you involved in the editing of the APA journal?
- PC: I was, but not anymore. But I have been on the committee that works on practice guidelines for some time now.
- TB: Is there anything else you would like to add?
- PC: Although I have mentioned my ex-husband and my children, we haven't talked about the fact that I was in medical school when I got married and had my first child. My mother was over 40 when I was born and as a consequence, was not as involved in my life as I would have liked. I got it in my head that I wanted to be a young mother. I had my second child during residency, and my third at the end of my residency. At the time, I felt like the people around me accepted it. Now when I talk to my former teachers and I ask them how they felt about it, they say, "Oh, we had long discussions about whether you could be pregnant and be a resident"! I was shocked. It was something they thought might be difficult, but it was possible. Now I have five grandchildren and two of my three children are married. One is a doctor and two are attorneys. My life is proof that you can do all of these things. But you have to prioritize what is important to you, and I learned that very early on. I once was asked to do a computer program for a lot of money, early in the 1970s, and I said that I would do it. I sat down one weekend and tried to write a program, but I didn't like it - I thought, "I'd rather be with my kid". So I called them up the next day and said, "I'm sorry, I can't do this". Around the same time, I was asked to be President of the Missouri Psychiatric Society, which would have meant driving to Jefferson City from St. Louis, so I said no. I think you have to prioritize, especially if you want to be both a mother and an academic.
- TB: On this note, we conclude this interview with Dr. Paula Clayton. Thank you very much for sharing this information with us.

## **C. KEITH CONNERS**

## Interviewed by Burt Angrist Waikoloa, Hawaii, December 10, 1997

- BA: I am Burt Angrist. I'm interviewing Dr. Keith Conners\* for the ACNP History Task Force. Dr. Conners is Professor of Medical Psychology at Duke University Medical Center and very well known for his many contributions, particularly in ADHD. Am I right?
- KC: That's been the main focus of my work.
- BA: I'm looking forward to an account of your career. Why don't you just tell us what's happened?
- KC: I'll start with my early interest. When, I was a student at Oxford, I had the chance to take a course in psychology and physiology; I spent two years duplicating all the classic experiments, and met some of the well known people at the time like Frederick Bartlett, who was studying memory. Up to that time I'd wanted to be a philosopher but after my experience with psychology I applied to clinical programs in the United States and spent a year at Stanford. It wasn't, clinically, what I was looking for, so I transferred to Harvard where I did my PhD. In the course of that experience, I had an internship with children and that's what got me started. My first experience after graduate school was a serendipitous one because John Money at Hopkins wrote to me while I was doing a post-doc and invited me to study hermaphrodites. I wrote back and said I wasn't sure what those were, but I wasn't interested in making a career of it. He passed my letter on to Leon Eisenberg, who was then Professor of Child Psychiatry at Hopkins. Eisenberg was just beginning the first real controlled trials in children with psychotropic drugs, so he asked me to come and work with him. The first thing that I did was to analyze data they had collected from a study in a school for delinquents. They had randomly assigned kids to either Dexedrine (dextroamphetamnie) or placebo in this training school for delinguents, which consisted of a number of separate cottages. Some cottages were assigned to placebo and some to the active drug. Almost everybody in the placebo cottages got into trouble. Those on Dexedrine suddenly showed an interest in going to school; the amount of bed wetting went down and the most interesting thing was that the number of aggressive and behavioral incidents declined.
- BA: Oh, my! That was dramatic.
- KC: Very dramatic. I'd had an internship with children, where I'd seen conduct disorders. I spent a year in psychotherapy with some of these

<sup>\*</sup> C. Keith Conners was born in Bingham, Utah in 1933.

kids and never saw anything change. To me, this was quite a dramatic experience. From there we began other controlled trials. At that time, in 1960, there was no child psychopharmacology and the field was a relatively new one for adults as well. But, any drug that happened to be used in adults, we thought we should try with children. The next thing we did was to try meprobamate. This was to be a crossover study where half of the kids started on meprobamate and half started on placebo and then crossed over. What happened was that every kid who got meprobamate and every parent whose child got meprobamate refused to continue the experiment. This was the opposite of the Dexedrine experience.

- BA: But still powerful in demonstrating the impact of medication in children.
- KC: Very powerful. And, there was one other feature that was interesting. Leon Eisenberg and I learned that practically every kid had anxiety improved very quickly, no matter what you did. So, we would exclude these kids from drug trials. Then we had a group of kids who were essentially very hyperactive but not anxious. That, also, led me to do some experiments to see what would happen if you gave stimulants to anxious kids and we found that anxiety seemed to interfere with treatment response. But if you took anxious kids out of the sample then the rest responded very well.
- BA: That was with Dexedrine?
- KC: Dexedrine and then, shortly after, Ritalin. But, essentially, we began a series of trials with kids who were today what we would call ADHD, without co morbidity, because they did not have anxiety, obsessive compulsive disorder or depression. It was a fairly selective sample and we got such striking results with stimulants. That encouraged us to submit grants to the NIMH.
- BA: There must have been some fairly astute and careful clinical observations leading you to define your target population. It's not a trivial thing to have picked that up.
- KC: I think there was a tradition at Hopkins. Leo Kanner had retired a few years earlier and Leon had taken his position and Like Kanner, Leon also had a very careful observational approach. Kanner's textbook was very descriptive and had chapter headings for different kinds of kids. So, when we began these studies, I took the chapter headings and made a rating scale out of them. That was the way we gathered data on the kids, sorted them and selected those of interest. This began the other part of my career, which has to do with rating scales.
- BA: Right. But, there was this tradition of very careful documentation of clinical material.

- KC: Child psychiatry in those days was basically psychodynamic and there was no documentation, so when we did these drug trials we had no tradition of what to measure. But the psychotropics being studied in adults suggested we ought to have some symptom descriptors or rating scales.
- BA: So, these were to become the first rating scales used in child psychiatry.
- KC: Yes. There were scales derived from other work but this was the first time, as far as I know, that scales had been used to document treatment outcome. We began by doing randomized trials, collecting ratings before and after. We found clusters of items with very significant changes and that was one my first publications. It had to do with the effect of stimulants on these rating scales.
- BA: It was an interactive effect. Psychopharmacology created a need for quantitative documentation and once you had the quantitative documentation it advanced the psychopharmacology.
- KC: Yes. The measurement part had a life of its' own. The tools we had to develop became, in some ways, much more important than the psychopharmacological effects and became widely used. I came out of an experimental background interested in performance measures. So we began to look around for other performance measures and that was when I got into the Continuous Performance Test (CPT), as a measure of attention. We also began to look at learning, using the Impact of Recovery from Startle, as a possible measure of whether we were dealing with a cortical or sub-cortical phenomenon. These were essentially habituation to startle studies. We found that if you asked these restless and anxious kids to make a controlled motor response when they were given a very loud startle, using a starter pistol, of course they jumped. Then we repeated that and asked them to try and make a smooth controlled motor response. Eventually they habituated and got control over the motor behavior. It was a paradigm of cortical control or voluntary motor response. The involuntary response didn't really differ between anxious and restless kids, but the voluntary response did. It looked like these hyperactive kids had a deficit at the cortical level of voluntary motor control, not at the subcortical or involuntary level.
- BA: The habituation to startle issue has taken on a life of its' own in schizophrenia research.
- KC: I had been exposed to Tinbergen and Morintz at Oxford in ethology who, talk about habituation as the basic form of learning. It seemed natural to study it as a measure of how drugs impacted learning.
- BA: When you say a basic form of learning, it's almost on the level of reflex, isn't it? I mean something between physiology and psychology.

- KC: Yes, it is at a very primitive level of adaptation to stimuli that had no adaptive consequences. In other words, if you were to reinforce that response, you could prevent habituation. If you provide novel stimuli, it changes the response. But, when you have a repeated stimulus that has no consequences for the organism then the response very quickly drops out.
- BA: In these populations of impaired kids were the changes in habituation population specific, or symptom specific?
- KC: We did a paper called *Habituation of Startle in Anxious and Restless Children* and showed differences in the rate of habituation for the anxious and the restless kids. I haven't pursued that much; although we did subsequent studies with autonomic habituation. There's been confusion in the literature about that. Some people say these kids don't differ in the rate of autonomic adaptation. We did a definitive study of that, and found that if you mistakenly included kids who were anxious, you didn't get this failure to habituate. The anxious kids habituate very differently from the hyperactive. Taking them out of the sample you find that if you do a drug - lacebo study and look at the effect on habituation the drug accelerates tremendously the rate at which they habituate. That doesn't happen if you include anxious kids in the group. So, we felt that something in the brain was very definitely prolonging the attention to irrelevant stimuli.
- BA: In psychopharmacology there's been a constant refinement of methodology. Has that been important for your work?
- KC: Yes. I was curious to know what measures were sensitive to these medications, so we had a lot of them and gradually weeded out those that seemed to be drug insensitive. There was quite a bit of work looking at which measures are responsive to drugs and which ones are characteristic of kids with a particular diagnosis.
- BA: Always, in the background, relating the measures to clinical response as well?
- KC: Yes, this was one of the themes I felt was important. Let's suppose you have something like reaction time and you show that you give a stimulant drug and the kid now has faster responses. That's well and good, but unless you show some relationship with clinical behavior, it doesn't have much practicality. It doesn't mean much. So, we always tried to have measures that describe the clinical state, and that's where the ratings came in because kids are brought by parents or referred by the teachers. Parents and teachers are the natural measuring instruments for assessing the impact of the drug. We did a certain amount of work with interviewing the child and looking at their performance in response

to the treatments, but it was pretty clear that the clinical significance had to do with the child's behaviors as they impacted the parent and the teachers. So our parent-teacher rating scales really became the anchor for these studies.

- BA: Did the parent-teacher rating scales originate with you?
- KC: I think so. It had not been done previously. Working in an outpatient setting we saw that a fairly significant number of kids were referred by teachers or the parents brought them because of school problems. Once you did a basic clinical work-up, you found there were both home and school problems in most of them. So it seemed reasonable that we would get parents' impression of how the kid was behaving. We also asked the kids but they were not very good informants, very unreliable. We would get kids that were being kicked out of school but if you'd ask, "how are you doing in school", they'd say, "fine".
- BA: It really means, "I don't want to talk about it".
- KC: Parent and teacher measures became the core of assessment and eventually impacted DSM- III. When I started we had DSM-II which characterized these kids as a reaction to psychological or parental stress. Because we demonstrated that parent and teacher phenomena were involved the new criteria required the presence of symptoms in both settings.
- BA: Those are the only two settings? There is a social ecology as well, that is equally important in the development of these disorders.
- KC: That's the ecology of the situation.
- BA: So, those are the basic diagnostic criteria in DSM-III?
- KC: I think our rating methods had a lot of influence. Some of the items in DSM-III were taken straight out of our ratings. But it was the drug trials themselves I thought of as experimental tools. I was mildly interested in the therapeutic outcome but more interested in the mechanisms causing change. This sort of dramatic phenomenon when a stimulant changes behavior gets you thinking about what the mechanism is. I think I was one of the first people who looked at cortical responses as a measure of what's going on in the brain under these treatment conditions.

I did a fair amount of work for the next twenty years or so in cortical evoked responses and was interested in whether there were laterality effects and whether there were differences that predicted drug effect. One of the conclusions that I came to was that this broad group of kids, whom we were thinking of as a single diagnosis, were really quite heterogeneous. So, we did some work, which I presented at the New York Academy of Sciences, where we used a variety of rating and

performance measures as well as learning and vigilance tests to do a cluster analysis of a fairly large sample. We found we could identify five or six different clusters. When we looked at those clusters to see what the drug placebo differences were like, we found that some showed very large drug placebo differences and some showed no differences at all. For example, in one group that was predominantly characterized by parent complaints there were no abnormal neuropsychological tests or any other indication that anything was wrong. Those kids showed no drug placebo difference. There was another group we would now characterize as having frontal lobe problems who performed poorly on the Porteus maze and other tests that involve frontal executive function. They showed tremendous differences with no overlap between drug and placebo. If you used that as the selection criteria you'd get a pure group of drug responders. I've been interested all along in this idea that within the broad mass of kids that we characterize as disruptive there are some groups that are biologically distinct. Some of the evoked potential and other work I've done has been directed toward looking for markers for those sub-groups and that's continued to the present day.

- BA: So you've seen the drug effect and then become interested in methods for measurement in particular neurophysiologic measures, before going after etiology?
- KC: Yes.
- BA: Interesting progression. You were using drugs as tools, in a sense, to separate out groups. Fascinating!
- KC: There were two lucky things in my career. One was latching onto a phenomenon that was real and the other was accidentally creating tools that other people found useful.
- BA: I'm sure it wasn't just an accident. It took a lot of thought.
- KC: I guess it's a combination of making the observations at the right time.
- BA: And seeing what was needed to sharpen up the observations?
- KC: At that time it was an open field, so it wasn't done consciously with the idea this is going to be an important thing. But my rating scales have turned out to be among the most cited papers in the literature. That was because I made a useful tool but that was very accidental. It was designed for a very specific purpose but turned out to have general usefulness. Another thing that influenced me is that I have always seen patients. I wasn't only in the laboratory. Working with patients gives one some appreciation of the complexity of conditions surrounding each of these kids. At this point I've developed the notion that there are many pathways to get to this one condition and our job is to find what clinical features are unique to these pathways and what treatment they

respond to. I've also been interested in brain imaging because every study seems to find something positive with ADHD kids. What's interesting is that they are all different. They have very different brain loci, which are affected. In the last few months we've had a paper in which we reported on cerebellar involvement. My feeling is that, as clinicians, we've rushed to the idea that this is a disease entity and it really isn't. It's a function due to a series of disease entities that we haven't sorted out. like the time when fever was considered a cause for everything. If you had fever, you got a treatment, but it didn't progress beyond a very superficial characterization as to what was wrong. I think that's the state we are now in. Just recently, for example, we repeated that clustering study, using a neuropsychological test that involves drawing a complex design and then copying it from memory. We scored that for a number of executive functions and other measures and found our sample was composed of three very distinct subtypes. One group was very impaired on this measure, one was not at all impaired and another was impaired in a very different way from the first group. The groups were also very different in the presentation of ADHD symptoms. One of them was very hyperactive and one was a very inattentive group. We also found that if we used some of our more experimental measures of visual attention they differed there, as well. So, it just reinforced my feeling that this is a heterogeneous group and we haven't yet found the biological marker that differentiates the different subtypes.

- BA: Was there a difference in treatment response or dose needed for therapy in these three groups?
- KC: That's something we are currently looking at. The treatment side of this condition is interesting because you may know that the last five years we've been involved in a national collaborative study with NIMH. Six different university sites have joined to study treatment outcome in ADHD, and the design involves drug only, psychosocial treatment only, and a combination, with an untreated community control group referred to their family doctors. That study is now being completed and analyzed. I think we'll find that drugs work, psychosocial treatment works and the combination works, but we'll also find that there are a lot of kids who don't respond to one or the other of these treatments and that this is a heterogeneous group.
- BA: Do you have some of the measures like drawing a complex design and other experimental measures on these kids?
- KC: Unfortunately, very, very little. We do have some genetic measures. Jim Swanson, one of the collaborators in the study was looking at the dopamine  $D_4$  transporter gene in these kids. Unfortunately, the measures

that were used were chosen by a steering committee, and when you do a scientific project by committee you get a traditional camel. Some of us who are pretty biologically oriented wanted to have neuropsychological measures but there are very, very few. This is the largest clinical trial ever run by NIMH and so we have a tremendous amount of data, but I'm afraid we're going to find similar outcomes.

- BA: Because the treatment groups were not characterized in ways to pick up heterogeneity within each group?
- KC: Right. We can only characterize them at the surface level by behavior or symptomatic measures. We don't have imaging or neuropsychological tests that would get at something more biological. We don't have frontal lobe measures or any other ways that sort them beyond the traditional clinical measures; interviews, rating scales and the like. The stimulants are not diagnostic, because they improve everybody. They seem to have a general toning effect on the brain, but nothing specific to this disorder. We've had a dopamine theory, a norepinephrine theory, a serotonin theory and all three in various combinations but nothing has been replicated or substantiated as a basis for a biological understanding of this disorder. I think it's because we've done the thing upside down. Instead of taking biological measures to sort these people and then doing the treatments we've taken the clinical measures and sorted them on symptoms like hyperactivity and inattention. But those are final common paths for too many different things.
- BA: I guess you can have very large groups but if they are heterogeneous it's going to be tough to get anywhere.
- KC: That depends very much how they're sampled. In the neurology clinic kids diagnosed as ADHD tend to be weighted with the referral characteristics; kids with motor problems, kids with tics, the sort of things that neurologists like to work with. They wouldn't be exclusively that way, because pediatric neurologists see some of the same kids that we see in our outpatient clinic, but that sample is going to be biased. Similarly, in a university health clinic or a clinic that is getting all it's referrals from school you're going to have kids who are characterized by learning disorders and academic failure. The result is that any sample is going to be some unknown mixture of these different subtypes and the power is generally not large enough, even if you separate out the subtypes with these small samples to find differences. So, it seems to me that you have to take large samples and sort them on hypothesized biological variables that might be able to predict effects. This is what I think we've been showing. It's very clear, for example, that if you took a test that doesn't discriminate ADHD from non ADHD or some of the time it does

and some of the time it doesn't, even good investigators don't get consistent answers dealing with different samples. This is an area where the power of the human observer to differentiate disease is very limited.

- BA: Again, like fever.
- KC: Like fever.
- BA: Very interesting. Are there other things you'd like to bring out? Are there any people who had a particular impact on your career? Would you care to concisely say how you see your contribution? It's certainly a lot about methodology, a lot about sub-typing on a clinical level, and a lot about going after etiology. Am I putting you in a corner?
- KC: Whatever my specific contributions, the most important was the belief children are biological entities and that behavior disorders are kind of a big mish-mash. Delinguency, conduct disorder and ADHD can be resolved into meaningful characteristics but that has to include a developmental trajectory. It's not just the same approach that we use in studying adult psychopathology. I happened to come into this business at a time when there was no science of child psychopathology and if I've had any impact, it has been with the idea that we can do biological treatments of these kids and there are biological causes for the disorders. That was not always obvious. When Leon Eisenberg and I started, it was unpopular to say those things because child psychiatry believed things evolved from the matrix of child-parent interaction. What we're seeing is that the parent-child interaction is often, if not always, the product of biological interactions and so my contribution has been to help establish child psychopharmacology and a biologically oriented psychopathology.
- BA: Was there active resistance by some members of the psychiatric community?
- KC: Very active, and among the public as well. Maurice Laffer, who along with Eric Denhoff did some of the earlier work with hyperkinetic kids, was shouted down in meetings by students and in the sixties we had a lot of very vocal opposition. What's interesting, sticking around long enough, is to see how this becomes cyclical so that the Scientologists are doing the same kinds of things, raising the same kinds of issues, saying this is all demonology.
- BA: We're drugging our children.
- KC: Now we're drugging children. Then, what we were doing wasn't popular either. It was very much against the predominant educational patterns in the field. Child psychiatrists were taught you don't use drugs and don't do descriptive psychopathology. Get down on the floor and play with the kids. And, everybody got the same treatment. I was

somewhat of a pioneer in that time, and whether right or not, I guess we will ultimately find out. I was with a few stalwart colleagues from the beginning in a minority, eventually becoming within the main stream, but now being attacked as part of a that main stream.

- BA: You can't win! Goodness, gracious! Do you have any thoughts about the future?
- KC: We have some scary things going on. I feel the lack of thoughtful analysis. What I see is that child work has been absorbed into adult work, with the same approach using a catalog of descriptive symptoms, a DSM categorical approach in which you have so many symptoms to qualify. If you have them you've got it, and if not, you don't. That approach has become a hindrance and one of the results is that kids are prescribed too many drugs. Just recently, one of the epidemiology studies on the prevalence of ADHD in a large western country study by Angold and associates found that 3.2 percent of kids had ADHD but 7.5 percent were prescribed Ritalin, almost double. So, there's no relationship between the diagnosis and the treatment. In the future, we're going to haother ways of diagnosis than categorical approaches which seem to be so vague and loose that anybody can qualify as having the disorder. Now I've been pushed by people to say if it's safe and it works why not give it? It becomes a moral and not a scientific issue, a value judgment. In the future, we're going to have to decide how we draw boundaries around these conditions in such a way that they fit with the rest of our value judgments about children. We have gone from a period when no drugs were prescribed to being over prescribed. Maybe that's true of adults as well.
- BA: Maybe. Are there other things you'd like to bring out this point?
- KC: One thing struck me, I happened to be here when you were being interviewed by David Janowsky and one of the questions that came up was research funding. It seems that to be a scientist you have to be very light on your feet because you need to be opportunistic when funds are available for something you want to research. Funds were not always available for the topics I was interested in. It would have been very nice had there been a little more stability in the funding so that one could follow a line. On the other hand, in the early stages of science, funding can stimulate research. For example, we got into the effects of foods on behavior because there was a period when the Feingold diet was considered a valid treatment. We did controlled clinical trials to look at that and began to find some interesting issues. This led to studies on the role of sugar in behavior of kids. We learned a lot about that, not that I had ever planned on doing those particular kinds of research.

Sometimes, you just have to do what's available at the moment in order to keep being a researcher and avoid being driven out of the field. In my career I've been lucky to have grants when I needed them but at times I had to go the round about way.

- BA: And sometimes something even came out of it?
- KC: Sometimes things that came out of it were unexpected. I think that kind of sums it up.
- BA: It's been a pleasure. I've enjoyed it.
- KC: Thank you very much, Burt.

## THOMAS B. COOPER

## Interviewed by Thomas A. Ban San Juan, Puerto Rico, December 9, 2003

- TB: This is an interview with Thomas Cooper<sup>\*</sup> for the Archives of the American College of Neuropsychopharmacology. It is December 9, 2003; we are at the annual meeting of the College. My name is Thomas Ban. Please tell us where and when you were born, and about your education?
- TC: I was born in England in 1935. After my initial education, which was in medical laboratory technology and later in biochemistry and biochemical pharmacology, I came in 1960 to the Rockland Research Institute, which later became the Nathan Kline Research Institute. I came for two years. Forty-two years later I am still here. I came at a time when psychiatry was on the brink of moving away from psychoanalytic theory towards a more biological orientation. Nathan Kline was one of the very few people who believed in the biological aspects of psychiatry. As a young neophyte, for me this was a given, and it wasn't until I had been to meetings about two or three years later than I realized that we were either on a cutting edge or way out in left field, whichever way one wants to look at that. It was a marvelous time in research because there was a lot of money and not too many people trying to get it. To give an example, Jonathan Cole telephoned me in 1964 and asked would it be possible for me to take my first grant three months early. He would fund it for the extra three months because they had to get rid of some money in a short time. My naiveté was such that I said I would have to ask Dr. Kline whether this was acceptable. Jonathan Cole, with that marvelous belly laugh of his, said, "Well, I think it will be". So I duly went to Nathan Kline and got a quiet smile with an affirmative that I could certainly accept the money ahead of time, especially the extra money! That was my introduction to grantsmanship. I must tell you from then on it has gone downhill steadily. It is much harder to get grants. But that was how I came into psychiatry. Rockland Research Institute was a program within a major state institution. When I arrived there were 9,000 patients on campus. There is now something like 380. Unfortunately, as we all know, there are still patients who are on the streets and homeless. But the bottom line is that the hospital campus on 680-odd acres is now very small but the Nathan Kline Research Institute still thrives there.
- TB: You came in 1960?
- TC: Yes.

<sup>\*</sup> Thomas B. Cooper was born in South Shields, England in 1935.

- TB: How did you get to join Nate?
- The Institute advertised a position in England. I picked this up and was TC: interviewed by George Simpson. I lived in Newcastle, in the northeast part of England. It's a good place to leave in terms of the climate. So I wasn't unhappy when I came to New York and saw sunshine. George Simpson apparently liked what he saw, I was offered the job, and came over. George was interviewing me for the job at the Institute with a. Dr. Cranswick who turned out to be an Australian. When we arrived in the US in March in fourteen inches of snow, we were met by Drs Simpson and Cranswick the latter wearing an open shirt, a pair of shorts, sneakers and no socks! Frankly I didn't know whether I should turn around and go straight back! But he turned out to be a delightful fellow, a psychiatrist and endocrinologist and bright as could be. So I was recruited by Kline, and gradually over the years became extremely friendly with him. I had and have tremendous respect for what he did. I was very lucky.
- TB: Could you say something about your work at Rockland State after your arrival?
- TC: When I arrived at the Nathan Kline Research Institute I lived on the campus with my wife. We were directly involved with patients who lived in the same building where we worked. Nate Kline and I think he was absolutely right about this, said that young researchers should be exposed to who they were studying to see what a patient's life and their illness was like. I came to the Nathan Kline Institute to work on the thyroid physiology aspects of mental illness. Dr. Edward (Ted) Cranswick had a penchant for building his own multiple channel radiation detector equipment long before such equipmet was available for routine clinical use. In that context, we had contact with patients over many days when they were given small doses of radioactive iodine, and we looked at uptake and turnover of compounds produced by the thyroid and the effects of psychotrophic medication on these measures. We also had close contact with the patients in simple things like collecting urine and making sure blood collections were correct. That was my first exposure to this type of patient and population. There were many other basic scientists and psychiatrists working at the Institute, and we all worked in close proximity to the patients. There was Dr. Vestergaard a psychiatrist and endocrinologist interested in steroids. He developed methodology for measuring steroids that was way ahead of its time. He was one of the first people who had an almost totally automated liquid chromatography system for urinary steroids across the whole spectrum. He would spend hours and days working with patients, collecting consecutive

24hr urines over months and in some cases several years. There are many amusing stories about that. We had some patients who didn't really want to have their urine collected. We had others who collected urine and put their ball point pens in the urine. I remember a patient who was extraordinarily bright. He came in one day with a bottle that was full. The urine was a dark blue in color so Dr. Vestergaard asked "What have you done to this urine"? The patient reared up imperiously, and said, "Dr. Vestergaard you are the chemist". There were many, little vignettes like that. I found it an enjoyable and productive area to work in, simply because I knew everything that was going on. We had meetings regularly. Nate Kline joked, that he traveled a lot and when asked, "Who does all the work when you're away" his reply was, "Exactly the same people who do it when I'm there". And, this was truly his attitude. If he thought you were good enough, he left you alone, to get on with whatever you wanted to do. I found that terrific.

- TB: So you worked after your arrival in the thyroid laboratory. Weren't you in charge of that lab?
- TC: I took over the thyroid laboratory in 1964 because Dr. Cranswick died. He had a cardiac infarction and died six weeks later.
- TB: He was in charge of the thyroid lab before?
- TC: Yes, After I took over George Simpson and I worked for about two years on the differences Ted Cranswick had observed and because we developed the capability to measure total iodine in plasma we realized that a lot of the findings we had were due to the patient's high iodine diet. Because of that their thyroid function looked as if it was reduced, when in actual fact it was not. We found that there were no major changes in the function of the thyroid in these patients. During that time, we developed methods for iodine analysis, which in the early 1960s, were very difficult assays to do. We were paying a commercial firm something like \$25,000 a year to do the assays, and, at that time, I was earning about \$6,000 a year. So I suggested that if I did the assays and split the \$25,000 I would be ahead of the game. After Ted Cranswick's death, which was a tremendous loss, Nathan Kline first made me acting director, then after I gave a talk about the thyroid findings he suddenly said, "OK, you've got this department. This is your lab. Go ahead and work with it".
- TB: What were the initial findings?
- TC: The finding initially by Dr.Cranswick was turnover of the iodine in the thyroid gland was very slow in chronic schizophrenic patients. We did these measures every three months, on and off drugs. The drugs in those days were not as esoteric as they are now. Then we found that

the hospital supplemented the diet with iodized salt and this created the misrepresentation of low thyroid function, when in actual fact a lot of iodine was going into the gland. We didn't understand the low activity we had found until we were able to develop analytical methods which measured total iodine, and then we realized that these patients had enormous amounts of iodine circulating in their blood, and therefore the uptake of the radioactive iodine was extremely low. So the results after a number of years work were really negative and there were no major thyroid abnormalities in these patients. The rationale for looking at the thyroid in the first place was a syndrome called myxedema madness, in which patients who had major thyroid abnormalities could manifest psychiatric symptomatology. This lead to the idea that perhaps there was some basic thyroid or endocrine abnormality in schizophrenia which we could examine.

- TB: Didn't you study periodic catatonia?
- TC: Per Vestergaard was working with periodic catatonic patients. Nathan Kline brought together a group, which designed a study protocol to examine the interaction between endocrine systems and psychotrophic drugs in schizophrenia. We joined this group and studied thyroid drug interactions. The periodicity in steroid output collected over many years in a relatively large patient cohort was published but in my opinion never got the attention it warranted
- TB: Did he try to follow up Gjessing's findings with thyroid administration?
- TC: Yes. He was inspired by Gjessing's work and followed that for a very long time. The work clearly showed that there were patients who were periodic catatonics. He tried interventions; one that worked was using cortisol. But most of the treatments he tried did not work. Catatonia nowadays is something that a lot of young psychiatrist's claim they have never seen. But to see it at that time was quite devastating.
- TB: We are talking about the 1960s.
- TC: Yes. Slowly in the thyroid lab we began working with Dr. George Simpson who had an early clinical drug evaluation unit. We started looking at psychotropic drug levels and drug metabolism in schizophrenia. First in the urine, because that was all we could look at, then gradually, as gas chromatography, liquid chromatography and mass spectrometry became available we were able to develop methods of sufficient sensitivity to look at tissue and blood levels of the drug and many of the metabolites. Now, I'm jumping forward a 20-year period. At the beginning, we were able to measure very little, and progress was really slow.
- TB: So you started with measuring urinary metabolites of psychotropic drugs?

- TC: This is just because we had the metabolites that were present in large quantities quite often.
- TB: Could you tell us the drugs you studied?
- TC: Phenothiazines, and antidepressants a little later. We didn't get much work in antidepressants until the 1970s, mainly because of the patient population. It was only when we were doing work with Dr. Kline and Dr. Simpson outside of the hospital that we started looking at not just chronic depression, but acute depression.
- TB: So, first, you worked with antipsychotics?
- TC: Yes. The findings are well known now, but then were very surprising. Most people at that time thought that if you looked at dosage of a medication and outcome that was all you needed. The initial findings were very clear that patients metabolize at different rates. For instance, with the phenothiazines, we confirmed that there was a 30 to 40 fold variation in the metabolism of the compound; that one patient given 100mg could have 1ng per ml in the plasma, and another patient given 100mg could have 200 or 300ng per ml at the exact same time point and dosage. It became very clear that to simply say that 300mg or 600mg of chlorpromazine was an adequate dose was totally inaccurate, because the patient can metabolize the drug extensively in the gut before it ever reaches the systemic circulation. This was, at that time, a major finding. We also were able to show that there is a very strong correlation between the total concentration of the drug in plasma and brain. What is surprising is that these drugs were highly bound to protein. Yet if we looked at brain levels in animals and in humans, we found that the brain levels were 20, 30, 40 times higher than the plasma levels. So even though the drug was highly bound, it moved across the blood-brain barrier very quickly, and the bound material became free very quickly. So we had equilibrium between brain and plasma. That data has held up over many years. We have the glorious images of PET now, and clear data which show that if you look at the plasma level of haloperidol, and the occupancy of the D<sub>2</sub> receptors in the living human brain, the correlation is extremely high. In collaboration with Adam Wolkin, et al at NYU our first experiments involving PET demonstrated that D<sub>o</sub> occupancy reaches its peak at about 15 ng per ml of haloperidol, and that is exactly what one finds in terms of clinical efficacy. You get very little benefit from going higher than that, and doubling the dose doesn't give double the efficacy but increases the side effects. The development of these assays has been a good part of my research life and experience. I don't quite know how that developed. I really don't. We got more and more interested as we went along. I think this is where I owe Nathan
Kline a great deal; he believed in the interaction between clinicians and so-called basic scientists and I benefited from that. I do a considerable amount of work with many collaborators across the country, and indeed in other countries. I think it benefits me and them. We bring to a study a level of laboratory expertise which many clinical units could not develop because it is too costly. Clinical studies are very time consuming and therefore one institution can only focus on a limited group of patients. To function as a core laboratory for several clinical research centers increases our scope and is intellectually stimulating. This, I find, very satisfying.

- TB: When did you start to work with antidepressants? Didn't you start sometime in the 1960s?
- TC: We started working with antidepressants in the late 1960s. At that time the methodology was extremely crude. Many people were trying to measure these compounds and, I must admit, not very successfully. If one looks at some of the early data, reports were of imipramine being present in microgram per cc. amounts, where in actual fact they are 1,000 times less. This was due to the non-specificity of the methodology. As things progressed, we got into gas chromatography with nitrogen detection, and found that we could quantify exactly how much imipramine, and metabolites were present in plasma. The nitrogen detector came out in 1974 and we were fortunate because we got the first nitrogen detector in the country. We read about this in a paper, telephoned the company who built the machines, and they said they had just one which we could have provided we bought it, which we did. That was one of the great moments in my career in terms of instrumentation, because I was suddenly able to look at a chromatogram and see that this simple detector resulted in a 40 to 50 fold increase in sensitivity. I also had far more specificity in that most compounds which don't contain nitrogen are not detected by this system. Thus the peaks on the chromatogram contained nitrogen e.g. imipramine and metabolites, all other compounds gave little or no signals. That started about 1974 and from then on we continuously developed methods for the antidepressants, both first generation and second generation. We've developed methodology for the phenothiazines, the new antipsychotic drugs and blood, spinal fluid and tissue assays of all of these compounds.
- TB: What do you consider your most important finding?
- TC: With antidepressants, the strongest findings are with imipramine and nortriptyline. If you have imipramine plus the metabolite, desmethylimipramine, which is also an antidepressant drug, and the sum of these is around 200ng, that is the optimal therapeutic level. With less than that

when the patient is not responding well, raising the plasma level can increase the number of patients who respond by about 20%. There are, however patients who do not respond to imipramine no matter what the blood level. Glassman and Perell were the first group to describe this threshold of 200 – 220ng per mil. It is worthwhile noting that this helps understand why some patients require a very large amount of medication, which physicians may be reluctant to give without knowledge of the blood level.

- TB: What did you find with nortriptyline?
- TC: Nortriptyline seemed to have what we call the inverse tea cup or U-shaped curve, a level above which you must reach to get clinical efficacy. As you move further on, you reach the point at which clinical efficacy deteriorates, with toxicity coming in, and then full toxicity if you go high enough. The Scandinavians were the first to demonstrate that nortriptyline is the only drug where you have hard evidence that if you get a patient up to about 80 to 100ng of nortriptyline, you are in the optimal situation for that particular patient. The range varies from different findings, but is about 50 to 150ng. If you get up to around 180 to 200ng, you start getting toxicity and side effects including cardiac effects. So with imipramine we had a lower threshold, but no apparent upper threshold except obvious toxicity. With nortriptyline, we have a lower and an upper threshold. This meant to me that blood level monitoring really had a place in treatment in psychiatry. We went on to the antipsychotics. The Scandinavians did an enormous amount of work on chlorpromazine, showing that lower dosages seemed to be as efficacious and had fewer side effects than high doses. To give examples of that, when I first went to Rockland, to see a patient receiving even 2 grams of chlorpromazine a day was not unusual. You might see a little old lady who weighed 50 kilos taking that much chlorpromazine who didn't bat an eyelid. We would draw blood on patients like this and find their levels were extremely low. It turned out that chlorpromazine is one of those compounds which, like many others will induce its own metabolism. The gut metabolism can be induced to an extent that you virtually don't have any chlorpromazine present in the plasma, and therefore in the brain. So this little old lady we're talking about, in actual fact, was getting a very small dose of chlorpromazine. She was simply metabolizing it so fast that it was probably useless. The classic example we have of that is a patient of George Simpson's who was on butaperazine, in the middle 1970s. No matter what was given the patient responded for a week and then the response disappeared. In frustration, he was put on the butaperazine, and we did kinetics, collecting something like

10 bloods samples over a 48-hour period. These showed a very nice kinetic curve with the peak at about three hours. Eight weeks later, even though his medication had been increased to twice the maximum permissible dose, he had no clinical effects whatsoever and deteriorated. When we did a second loading dose, we couldn't find any butaperazine. We looked at similar kinetics with chlorpromazine, and found exactly the same thing. But when he was given intravenous drug he had a profound effect immediately. So getting medication past the gut enabled him to benefit. This patient has done well on a long-acting intramuscular injection that's not metabolized by the gut. But every time he is given oral medications, it doesn't work.

- TB: Did Hilary Lee work with you on these projects?
- TC: Hillary Lee worked with George Simpson and me. She worked with you also before that.
- TB: What happened after George Simpson left the Institute?
- TC: There was the usual period when I thought maybe I would go and work with him but that didn't happen for a variety of reasons. One, he was working in California, and the California housing costs were astronomical. So I decided I could still work here. Nate Kline always had been extremely supportive. We had become much closer in our relationship over those years, but at the same time I was recruited by Columbia University to go to the department of psychiatry when Edward Sachar had taken over as Chairman, and Don Klein was there. Nate agreed to this. I didn't want to leave the lab, because I had a lot of people working with me and many were women with children who would not have moved. So a deal was made that I would work part-time at Columbia and part-time at Rockland and, in fact, that still exists today.
- TB: When did you start to split your time between the Nathan Kline Institute and Columbia?
- TC: In 1980. Nate agreed to all of that and then unfortunately died in 1981. I started doing collaborative work at Columbia which opened up a whole area in which I had not been previously involved namely child psychopharmacology, working with Drs. Greenhill and Shaffer. That has been particularly productive because we have looked at methylphenidate and methylphenidate enantiomers. In fact, our lab has done all of the kinetic work on the enantiomers which has demonstrated that the D-methylphenidate enantiomer can be given to patients at half of the dosage of the racemic mixture with comparable clinical efficacy. This enantiomer is now marketed All of the laboratory work was done at Columbia including bioavalability studies and full kinetic profiles of the D and L enantiomers in animals and children. We are now looking at the

development of new drugs used in children and psychopharmacology. But for many years, children were forbidden to be in studies of new drugs. So we have an enormous backlog of non-information, where drugs have been used in children, but we have no documentation, no evidence of the kinetics or even whether the drugs are useful. We have anecdotal evidence, but not hard data.

- TB: Didn't you continue working with George Simpson after he left?
- TC: He and I have worked closely since I first arrived in the US and for all of the years I have been here. He moved to USC in 1978 but we still do collaborative work and are in contact roughly once a week. Jan Volavka came to the Nathan Kline Institute about two or three years later and took over the schizophrenia program, and he and I have worked together closely since then. I suggested to him that we look at controlling treatment by blood level as for example, looking at haloperidol and controlling the treatment by blood level and not by the dose. We obtained years of grant support in that area. We were able to show that if you got patients into the 5 to 15 nanogram per ml. range that was therapeutic but if the level went higher you didn't achieve anything additional.
- TB: When you say excessively high doses of haloperidol, what are you talking about?
- TC: We had patients who were getting up to 70mg a day of Haldol, which by my standards is an enormous dose, and yet when they were brought slowly down, most of them didn't deteriorate and quite often got better. There was the occasional patient who showed massive deterioration on these very high doses. But there are other aspects to those patients including that they could be rapid metabolizers with drug not reaching the central nervous system. As well as working with Jan Volavka I worked with Don Klein at Columbia. We started lots of collaborative studies with Drs. Klein, Quitkin, Rifkin, Stewart, McGrath and Rabkin. I have also worked with John Mann at Cornell, Pittsburgh and now at Columbia on his suicide studies. This involves a lot of tissue work, levels of drug in the central nervous system and spinal fluid.

Of course, I don't just do drug metabolites. We've moved on into looking at neurotransmitters and their metabolites in the central nervous system. We have a large biochemical pharmacology laboratory, which covers a wide range of compounds of interest in biological psychiatry. We do a lot of steroid hormone studies; cortisol, prolactin, growth hormone including the metabolites of these compounds. We have capabilities in gas chromatography, mass spectrometry, liquid chromatography and various immunoassay procedures. This gives us powerful precise tools to look at what is going on with these compounds. We've moved from urine, which was the only thing we could measure, to blood, spinal fluid, tissue, and we are now measuring hair concentrations. It turns out that hair grows roughly one centimeter per month, and drug is deposited in the hair but doesn't get out because of certain pH conditions. So you can get a chronology of what's going on in a patient. We can section the hair into one or two month sections, depending on hair length.

- TB: Isn't hair used for the detection of some drugs of abuse, for example PCP?
- TC: Yes. One of the groups that work with me is Marc Larouelle's group engaged in PET imaging. Some of their studies involve patients who are abusing PCP or ketamine. If you look at the blood or the urine that gives you a picture of what has happened over the last couple of days. But if you look at the hair, you can get a picture of what has happened over the last six months again depending on the hair length.
- TB: Which are the drugs you have the methodology to study in the hair?
- TC: We can do it in pretty much all psychotropics now. All of the second generation drugs we have routine methodology for and it's running continuously.
- TB: All the different classes of psychotropics?
- TC: Antidepressant, antipsychotic and anxiolytic.
- TB: What about the enhancers?
- TC: We don't have much because I've not been asked to collaborate with people who are doing that. We do a lot of collaborative work with Dan Javitch now at the Nathan Kline Institute. We are looking at the cycloserine, D- serine and lysine work which he has developed. We've not done much in terms of the blood levels of the enhancers. But, technically, they're not that difficult. If we had projects we would develop the methodology.
- TB: Were you involved in research with monamine oxidase inhibitors?
- TC: We were involved with monoamine oxidase inhibitors with Donald Robinson and Alexander Nies. This was late 1970s and early 1980s. Robinson was at the University of Vermont, and heard we were measuring antidepressants. He had done this beautiful study with amitriptyline. Robinson came to me with the Rosetta stone; he had a completed tightly controlled fixed dose study with more than adequate plasma samples for each and every patient. We had just received the nitrogen detector, so we were able to do amitriptyline and nortriptyline and the hydroxyl metabolites easily. We had two or three hundred samples. We analyzed these and gave the results to Don Robinson. He came back with terrible findings. There was no correlation whatsoever between

plasma level and a single outcome. We didn't believe this, and tried to analyze it as many different ways as we possibly could, but it just didn't work out. After that it turned out Robinson and Nies had done some of the pioneering work in monoamine oxidase inhibitors, and so we started looking at the methodology to measure these compounds. And they were not easy to measure. We focused on phenelzine, and eventually we were able to measure it using a mass spectroscopy method and deuterated standards. Then we tried to look at the monoamine oxidase level versus the inhibition, measured in the platelets. Robinson and Neis had shown that to get a full effect you had to have inhibition at 80% of the platelet monoamine oxidase. And that held up very well in clinical studies. We looked at the blood level of the monoamine oxidase, but one has to realize that monoamine oxidase binds irreversibly and so, once it's bound to the protein, it is actually degraded with the protein. It never comes off.

- TB: Was any of the clinical work of that project done at the Nathan Kline Institute?
- TC: No, they did that up in Vermont, and came to me to look at the metabolism of the compound. That's where my reputation was established, when people began to realize that collaborative studies were possible, and you didn't have to have a lab of your own. Don Klein and Ed Sachar at Columbia realized that if they put resources in place at Nathan Kline Institute and my lab, this would work to the benefit of both of the Institute, the psychiatric researchers and also to me. It was a very nice moment for me because that's the first time I had access to a mass spectrometer, purchased by Columbia.
- TB: What was the technology you used before? Was it paper chromatography?
- TC: Yes, you're right. The first grant I ever had was on iodinated amino acids, and I used paper chromatography. Now we're working with capillary columns which are 30 meters long which have separating powers I could never have dreamed of in the 1960s.
- TB: Remind us what year did you get your first grant?
- TC: In 1964.
- TB: What about grants later?
- TC: I've had grants in my own right. I got contract grants. I always have four or five collaborative grants where I am a co-investigator.
- TB: Did you have a grant together with Jan Volavka?
- TC: Yes. Jan is psychiatrist and electrophysiologist and has been interested in the blood levels of drugs. He has also developed an interest in violence and aggression. I first met Jan when he was at Manhattan Psychiatric Center running the violence ward. That was my first real

exposure to a ward with patients chosen because of their violence. We collaborated with EEG work. He looked at drug levels, and we extrapolated to the brain. But the electrophysiology was 100% Jan and not me.

- TB: What was the drug he monitored, haloperidol?
- TC: Yes.
- TB: Was there a linear relationship?
- TC: That was specific for haloperidol, but we have done it for many other compounds. We try to keep ahead of the drugs that come onto the market. That was pretty easy in the 1980s because not too many drugs were introduced. It became a little more interesting with the advent of the SSRIs and the new generation antipsychotics. We are able to measure all of the antipsychotics and SSRIs on the market at the moment.
- TB: Before they get to the market?
- TC: Sometimes before, sometimes after. We do some work with drug companies where we look at Phase II studies and blood levels. With methylphenidate we looked at the early Phase I trials and early Phase II trials. We looked at initial kinetics in children. That was very interesting work, because it turns out that methylphenidate has two forms; the D form is active, the L is not.
- TB: When did you do that research?
- TC: This was done in1994-1995. The drug came to market in 2002 and I understand, it is effective and doing well. What we found, which was very interesting, was when a patient is given a mixture, which is normal, the D level in blood is quite high, and the L level is virtually non-measurable. So there is extensive metabolism of the L form in the gut before it gets into the systemic circulation. That was a complete surprise. People were doing PET studies where D and L were given intravenously, and were looking at the effects of both forms. We were able to show that the L form didn't really reach the blood. What they were looking at with L only pertained to intravenous metabolism and not to gut metabolism. And no one gives methylphenidate by injection.
- TB: Did FDA at a certain point in time become interested in bioavailability?
- TC: We did a lot of work in the late 1970s and early 1980s on bioavailability of drugs for FDA studies. The FDA was put into a situation where there were many drugs on the market which have never been examined in terms of the kinetics and their bioavailability. The ACNP, about 15 years ago, had a whole symposium on the topic, because when a generic drug came onto the market they were finding that it showed something called super availability. The new generic formulation was better than the old because more of the drug was available per unit dose. The conference

was about how do you handle that but it was never resolved. When imipramine came to the market and was used extensively there was no kinetic work because there were no available measures.

- TB: Any other research in pharmacokinetics you would like to mention? Didn't you do some research with lithium?
- TC: I've done a lot of work on the kinetics of drugs, and one of the things we found was we could predict dosage required to reach a certain blood level. We discovered this with lithium. We gave a single dose and 24 hours later we took a blood sample and showed the lithium level was highly correlated with what a patient would achieve on a fixed dose, and I emphasize a fixed dose. Once you had achieved that you could adjust the dosage to bring that patient into the range you wanted which at that time was between 0.82 and 1.2mEq/I. Since then it has dropped considerably, but the methodology works. It has been used since 1972 when we first published this data and is still mentioned in the literature today. Some people say it doesn't work. Some people say it does. Some clinical laboratories can't use this technology, because many of the instruments cannot measure lower lithium levels.
- TB: When did you do that work?
- TC: We did that in 1971 and we published after we presented our findings at the ACNP. It was the first presentation I made at the ACNP.
- TB: When was that?
- TC: I gave my first paper here in 1972, and then pretty much presented a paper every year at the ACNP. They are wonderful meetings where one can interact with people and scientists, both at the basic and the clinical level.
- TB: What year did you become a member?
- TC: I became a member in 1983.
- TB: Are you still active in your research?
- TC: Yes. I'm excited at the moment because PET is here. PET has been around for 15 years, but didn't really produce very much. There were nice pictures, but we didn't have the ligands or the technology that we have now. I would like to be able to continue to contribute in the area of plasma level monitoring, hair monitoring, and looking at spinal fluid, both drug metabolites and also neurotransmitters and steroids, in conjunction with PET studies. That is probably the most exciting area because we are looking at a living human brain. We can give it certain challenges, and look at the consequences biochemically.
- TB: I think we should conclude on that note this interview with Thomas Cooper. Thank you very much.
- TC: Thank you.

### **ERMINIO COSTA**

#### Interviewed by Stephen H. Koslow Waikoloa, Hawaii, December 11, 1997

- SK: I'm Stephen Koslow and on behalf of the ACNP History Task Force, we are doing an interview with Professor Erminio (Mimo) Costa.\* Mimo, how did you get started in psychopharmacology?
- EC: I'd like to start when I entered the United States, because there is a strong connection between psychopharmacology and my immigration. I was born in Cagliari, Sardinia, in 1924 but as an Associate Professor of Pharmacology in Italy I saw there was not much opportunity to do real science. It was after the Second World War, in the early 1950s, and reconstruction was the main goal, so science was in the background. I applied for a scholarship and came to Chicago where I worked in the Department of Physiology on dogs to measure a factor that was known to cause hypoglycemia. When I presented this data at a meeting a man approached me who worked on the metabolism of glucose in the brain and the action of insulin. He was Harold Himwich and he invited me to work with him for a few months at his Institute at the Galesburg State Research Hospital in Illinois. After I did some work on LSD and serotonin, published a paper, and had developed a good relationship with my sponsor he asked if I was interested in immigration to the United States. I accepted and returned with my wife and two year old son, Max.
- SK: What did you work on after you settled in the United States?
- EC: I became interested in the distribution of serotonin in the human brain. Why was serotonin present in the brain of many animal species and also present in bananas? There was skepticism that something present in bananas could have a very active action on the human brain. Just about this time Kuhn, in Switzerland, had made the astute observation that a new drug, imipramine, benefited depression in patients. I was among the first to study the drug's action on serotonin in the brain. I presented the findings in 1958 at a meeting of the Society of Pharmacology in Florida and it attracted the interest of Dr. Brodie with whom I had shared a taxi from the airport to our hotel. This began a relationship that lasted until Dr. Brodie died. Eventually he invited me to join his lab in Washington and, although I was reluctant, my wife was attracted to life in the city so eventually we moved. It was the best decision in my life, because Brodie was an extraordinary person. He was trained in organic chemistry, not biology, but was always trying to

<sup>\*</sup> Erminio Costa was born in Cagliari, Italy in 1924. Costa died in 2009.

learn biology from his collaborators. I was learning from him how to think, and he was learning biology from me. This lasted for five years and I became his deputy chief of the laboratory. At that point, I realized it was time for me to move, because I needed to find my own way. I moved to Columbia University which had just received a fifteen million dollar endowment to build a new research center, primarily devoted to Parkinson's disease. I created a research group and over a three year period we made major contributions to the understanding of neurotransmitters and their turnover in the disorder.

- SK: You have had a really distinguished and productive career and have been visionary, and very creative in your research. Was there a major hypothesis behind your thinking or was it your capability to assimilate and integrate knowledge that was already out there?
- EC: In life nothing stays as it is; it changes continuously. Even something that you measure like serotonin is turning over continuously. This was always my guiding principle in creating new ideas. Dynamic equilibrium, the regulation by enzymes, the induction of enzymes; these all evolved from the same idea. The idea of regulation applied to the receptor accounts for all of the innovations I brought about. In research, you have to have some guiding principals. I learned the importance of methodology from Brody. He knew its importance very well, because he had created a new method in neuroscience for the measurement of serotonin
- SK: When you look back on your career, what do you think were the most significant discoveries you contributed to?
- EC: The most significant discovery was the recognition of a need to surround myself with stimulating young people who wanted a career and were ambitious. I had to create new ideas for them in order to help form their careers. I think I made important contributions to the identification of factors involved in receptor regulation. In another arena my willingness to promote my ideas and defend them, was an important contribution.
- SK: What have you been involved in more recently?
- EC: The last two years I have spent trying to understand the problem with schizophrenia. I am fascinated by the possibility of two things. First of all, that schizophrenia appears in puberty and is associated with a dilation of the ventricles that does not progress with the disease, which means there is something that happens early on in development that is important but not sufficient for developing schizophrenia. So I began to look at possibilities that disrupt development. For instance, brain circuitry is created by the position of the neurons. If the position is

wrong, the functional outcome will be different. During development neurons migrate from the ventricular membrane to the upper part of the cortex and there is evidence now that there might be a defect in migration in schizophrenia. My idea is to examine the brains of people with schizophrenia to see if we can identify and develop a method to measure the messenger that creates this defect. Another important area of research involves the detection of genetic mutations in the embryo that may induce alterations in the development of the brain in people who become schizophrenic. This has been my most important research and will continue for as long as God gives me health and the ability to do this interesting work. I want to be on record as one of the happiest men alive, because research provides satisfaction that keeps you happy, interested in life, and what happens around you. What contributes to this happiness is that I have had three hundred and twenty people working with me during my tenure at the laboratory. The influence of Brodie and the young people around me have been the two most important things in my life.

- SK: You have had a major impact on lots of people, including me. When you look back and into the future how should people make the best of their capabilities to do research? You've worked in many different environments; in the government, in private research, in universities. The world is more complicated and competitive today. If you had some new postdocs, what advice would you give them?
- EC: When I got my first research grant as Director of an Institute at age 72, I discovered that to work on a grant is very interesting. This process of creating a grant from nothing forced me to study psychiatry, psychology and neurodevelopment biology, because the job I have is to integrate people. In contemporary neuroscience, research cannot be done if you don't have a group with different skills. In molecular biology if you want to know the meaning of a gene you have to put together a biochemist, a physiologist, a pharmacologist and a molecular biologist.
- SK: Where do you see major breakthroughs in terms of drugs? What major change is going to allow new therapies?
- EC: The major change has to do with the pharmacology of gene expression. First, I thought that brain function was regulated by neurotransmitters. Then I discovered that no transmitter regulates a particular function; most of the time it speeds up or slows the rate of firing but not the behavior. Next I thought the answer was receptors, but one receptor does many other things than just the one thing that you are interested in. If you analyze the history of schizophrenia research, the first thrust was to produce drugs that were more and more specific to a particular

receptor. Now, the drugs that are successful are those that target three or four receptors. I believe that the recognition of gene receptors, or proteins made from genes, will be the next big step. We know already that you can have a mutation in one part of a protein that does not allow the protein to be secreted. This may be the case in schizophrenia. To identify where the secretion is faulty could be a good approach to drug therapy. Another approach would be to identify the site of disruption in the cascade of events during protein synthesis and develop drugs that modify this process.

- SK: Great ideas, as always. In closing what role have you played or has the ACNP played in your life?
- EC: I was involved early on with the ACNP. There was a big meeting in 1958 after Brody and a few other senior persons met and said why do we have to go to Europe every two years to the CINP meeting to get together? Washington, DC, is the place where the ACNP was formed. In the beginning we had the meetings in rented bedrooms at a hotel. Eventually we went to Puerto Rico, because it was far away and everybody liked to go there in December. For four years I was a counselor of the ACNP with the important role to promote legislation favoring research. The other important aspect of these meetings is gathering young people in one place where relationships can develop for future collaboration. You should never under estimate the importance of a young mind activated in the proper environment. This is the greatest treasure of research and the ACNP.
- SK: Good point. It has been fun to have this interview. Would you want to say anything else about your career, the college, or science in conclusion?
- EC: I think I've talked about myself too much.
- SK: That was the purpose. It was great to hear what you had to say. Thank you, Mimo.

# SVEIN G. DAHL

#### Interviewed by Andrea Tone San Juan, Puerto Rico, December 16, 2004

- AT: I'm Dr. Andrea Tone and we're at the 2004 Annual Meeting of the ACNP in Puerto Rico and it is my pleasure to interview Professor Svein Dahl.\* Tell us about your upbringing, how you got interested in medicine.
- SD: It was a coincidence. Other people say they see a very clear path to where I am now, but I don't see it like that. I was always finding things that seemed to be fun and taking different twists in my career. Maybe they are right, when I look back on it. I was born in the town of Tromsø, Norway, in 1942 and grew up there, but when I was ready to start my university studies there was no university at the time. So I went to Oslo to study chemistry; I got my degree, somewhere between a Master and a PhD, in physical and structural chemistry.
- AT: Had you always been interested in this, as a boy?
- SD: We had a teacher at school and he got me interested in chemistry. He was a devoted teacher, and an original character; he had very advanced views. Forty years before the molecular biology era he said that kids should learn more about DNA.
- AT: That's wonderful.
- SD: Yes. He could even explain the periodic table in a way young kids could find exciting.
- AT: What year was this?
- SD: That must have been in 1959.
- AT: Very much ahead of his time.
- SD: He was, and that made me decide to study chemistry. When I came to the last of my six years of study in Oslo, I decided to do structural chemistry and got interested in the relationship between molecular structure and action; why compounds act the way they do and to explain that. I had used computers, already in 1966, having started learning FORTRAN programming.
- AT: I remember people in my university learning that.
- SD: You had the program and for each line one had to punch a card until you had a stack of cards you gave to the computer operator. He would read it into a mainframe computer and you got the printout a couple of hours later; you corrected the program by punching a new card for each line and fitting the new card inside the stack.
- AT: Very laborious.

<sup>\*</sup> Svein G. Dahl was born in Tromso, Norway in 1942.

- SD: It was. But, that gave me a background in the use of computers, which has been useful ever since. Many people at this time only worked with computers but for me, it was a tool to assist my research. I have used many different computers up to the Cray supercomputer but always to pursue a biological problem.
- AT: When you were studying chemistry, were you already thinking about doing work in pharmacology?
- SD: No, I didn't know the word pharmacology and I had no medical training, not even biological training. It was physics, statistics and chemistry. But then, I got a job in a pharmaceutical company.
- AT: That's very interesting.
- SD: That was, indeed, very interesting because I reported directly to the CEO and my job was to go through all the different departments of that company, called Nycomed. It was later bought by Amersham and now it's called Amersham Health Care. In that organization, I had to see how the flow of information went within and between the different departments. Like everybody now does with computers; when you take something out of stock, the message goes to those who are responsible for supplies so all the information in the whole organization is linked. I did an analysis of this and proposed a plan for starting to use computers, informatics. That was in 1970, twenty years before that was something everybody did.
- AT: You weren't doing work for the pharmaceutical company in the lab?
- SD: No, I was doing this analysis, interviewing the heads of departments and the people who did research on contrast agents or made pharmaceutical formulations. They were pharmacists, and had heard about pharmacokinetics. It's a mathematical way of describing how the body treats drugs.
- AT: That's a great definition. What was the state of the field at that time?
- SD: The field was just emerging. In pharmacology, we divide the field into two areas. One is pharmacodynamics, what the drug does to the organism, and pharmacokinetics, what the organism does with the drug. But, at that time I started doing pharmacology, people were only studying pharmacodynamics; the specific effect of drugs in isolated organs, but were not aware that what the body does to a drug is as important for the effect as what the drug does to the body. If the body, somehow, prevents the drug from getting to its target, you have no effect.
- AT: That makes sense. So, that field excited you.
- SD: I got an understanding of pharmokinetics when I went to a course in Basel, Switzerland in 1970. All the big shots, mostly Americans, were there as teachers. They were pioneers in the field, and described the

different aspects of pharmacokinetics in a one-week course. I took a lot of notes and, some weeks later, I heard about clinical pharmacology from someone else who gave a lecture.

- AT: Who were the big shots at that time?
- SD: The biggest one was John Wagner. He was with Upjohn, but was also a university professor in Michigan, and Milo Gibaldi, Sidney Riegelman, Lucius Dettli from Basel and Leslie Benet, who's still very active. He was one of the younger generation.
- AT: And you were impressed?
- SD: I liked it because I understood it. I had to spend weeks and weeks, going through my notes, before I understood it clearly. Then I heard this guy talking about clinical pharmacology, which was a way of analyzing how the body treats drugs. You take blood samples, for example, and see how high the concentration of the drug is in the blood. If you have a drug which is accumulating in the body that is excreted by the kidneys and you have kidney failure you find high concentrations in the blood.
- AT: When you were thinking about moving into this field, was there a set of problems you wanted to tackle?
- SD: Yes. It happened like this; I worked for this pharmaceutical company, with computers and information analysis. When I heard about clinical pharmacology I thought this was extremely interesting. So I gave up my job and started a new career in a field that I knew absolutely nothing about.
- AT: What did you think you might be able to contribute to pharmacology? Were you thinking that depression was the great problem in human society you needed to tackle or were there other things more important to you?
- SD: Let me tell you how it happened. By chance, someone said, "There's an interesting lecture in clinical pharmacology. You should come and hear". So I went and was fascinated by what I heard. I spoke to the lecturer afterwards and said I would like to do some research in this area and eventually I got a Fellowship. The area he proposed was antip-sychotic drugs, studied from the clinical pharmacological point of view. There was no pharmacokinetic information on chlorpromazine.
- AT: Break this down for me. We see chlorpromazine as a great breakthrough drug that finally allows institutionalized schizophrenic patients to be cared for by the family in the community, but how would a patient's body shape the way that drug affects him?
- SD: Chlorpromazine and other drugs used to treat psychosis, all have side effects and some patients do not benefit from them. In some cases, you

can either reduce the likelihood of side effects or increase the likelihood of getting the response you want by adjusting the dose of the drug individually. These drugs are converted to other chemical metabolites in the liver which may, also, be active. This process can proceed at a varying rate in different patients. The way to find out is to take a blood sample and analyze the concentrations of drug and its metabolites in the blood. That was the problem we were facing. At that time, there was no method for the analysis because the concentrations were so low. When you give the drug, most of it goes out of the blood stream into the body, to the brain, but also to other parts. We had to develop a method for analyzing the drug in blood plasma. Then we could look at the pharmacokinetics.

- AT: What was the method you developed?
- SD: It was gas chromatography. I did that with my thesis, something like a PhD. I worked for six years on that.
- AT: What was your thesis on?
- SD: It was on the clinical pharmacology of chlorpromazine and levomepromazine.
- AT: What did you find?
- SD: Several things. Some patients, who fainted due to orthostatic hypotension when they stood up abruptly, had higher plasma drug levels than the others. If you gave the drug in a dose that produced a fairly high peak, then they were likely to have this side effect.
- AT: How would you eliminate the side effect?
- SD: You had to reduce the dose or give a slow release formulation, but that wasn't available at the time. We also found, by chance, when we measured the metabolites of levopromazine in the blood that a particular metabolite had higher plasma levels than the parent compound. I then asked the question, could the metabolite contribute to the beneficial or side effects of the drugs? That led to another series of pharmacodynamic studies on the activities of the metabolites. Mostly we got them from a pharmaceutical company but some I was able to produce myself. We knew that these drugs could sometimes cause cardiac side effects, so we did classical pharmacodynamics studies. We used rats, killed under anesthesia, dissected out the heart muscle, made it beat in an organ bath and added the drug or metabolite. We could then measure how, in this isolated system, they affected the heart rate and the strength of the contractions.
- AT: I had always wondered how rats were sacrificed, if it was under anesthesia or not. Doesn't one have to worry about the interaction of the anesthetic agent and chlorpromazine?

- SD: That's a good question. You have to worry about it, but we concluded that it was not likely to have an effect in this system.
- AT: Looking at your career what would you say are the key research contributions you've made?
- SD: Pharmacokinetics was a new field and I was often asked to give lectures around the world, concerning plasma level monitoring of antipsychotic drugs. I was appointed Professor of Pharmacology in the School of Medicine, where I am still, because I made a unique contribution by promoting knowledge about pharmacokinetics in Norway.

At the Karolinska Institut in Stockholm we had terminals linked to computers via telephone lines and I wrote programs to do pharmacokinetic calculations. Then we could determine parameters, like the halflife of the drug.

- AT: One of the things I've learned, during this conference is how much programs in pharmaceutical and neuroscience depend on technology; you can only do so much until computer technology and brain imaging develops.
- SD: That's also true for running a pharmaceutical company, as we talked about earlier. Information processing is now involved in every aspect of the way companies run. In 1970 we saw that as a possibility, but it took twenty years because the technical development wasn't that far along. When we did the pharmacokinetic studies, there were, in the back of my mind, some lingering questions. I had studied these drug metabolites, identified them in the plasma of patients, and studied them in isolated rat heart preparations but there were discrepancies in what we found. Some compounds did not behave like others and we couldn't explain why. That was about ten years after my PhD thesis in structural chemistry. I had not worked with x-ray crystallography but I had the basic training from earlier, so I went to a crystallographer at our university and said, "We have these drug metabolites that differ in their activity and it would be interesting to look at their structures". That was also the time when receptor binding studies started as a new discipline, so I also used that to characterize metabolites, which few other people had done. From receptor binding and other studies, the crystallographers got interested and we did a series of studies, all on drug or metabolite molecules. There were differences in the three dimensional structures that could explain the differences in their action.
- AT: Were you always more interested in psychiatric drugs?
- SD: That was because Sten Jacobsen, who got me interested in clinical pharmacology saw that the clinical pharmacology of psychotropic drugs was almost non-existent at that time. Remember, that was in 1970. If

you look at all the papers on pharmacokinetics and metabolism, most of them were published later and reflect technical achievements. It was difficult to analyze these drugs, and I struggled for two years with the gas chromatographic method.

- AT: When did scientists figure out the way to measure a drug's half- life? You mentioned this as one of the contributions that you made.
- SD: It was about that time. First of all, they had to define half-life and understand the concept. Half-life is linked to first-order kinetics. If you look at the literature, all these concepts evolved around 1968-69.
- AT: It does seem so recent and, yet, it's absolutely imperative to helping patients and doctors figure out what treatments are best. Determining how long a minor tranquilizer stayed in a patient's body was absolutely instrumental in figuring out the kinds of drugs that would be hardest to withdraw from.
- SD: I did some reviews on anxiolytics and on benzodiazepines. One was published, I think, in 1973 but unfortunately, only in Norwegian, entitled *Accumulation and Elimination of Benzodiazepines*. I listed all the information available on half-lives of the drugs and active metabolites and how long they would accumulate in the body. The result was that Hoffman-LaRoche asked me to work for them. I heard, later, that they said,"There's this young Norwegian fellow that nobody has heard about, and he knows more about our drugs than we do".
- AT: But you decided not to take the job?
- SD: No, because I realized I had the possibility of completing my doctoral thesis on chlorpromazine.
- AT: This work was only published in Norwegian?
- SD: Yes. It's a pity, because later, other papers were published, which were essentially the same.

When I visited Hoffman-LaRoche, there was my article in German translation. Later, a friend of mine in Sweden asked if I was working for Kabi, a pharmaceutical company in Sweden. They had published my article, without asking me, in their house journal, called *Ronden*.

- AT: One of the interesting things about your career is that most of it has been spent in Norway. I wonder if you can still walk us through the extent to which the science that you do is international or the ways in which it developed differently, because you're in Norway. I'm trying to figure out how much being in Norway mattered.
- SD: Quite a lot in one way because, unfortunately, the resources for doing research are very limited in Norway. I'm sorry to say that. It's one of the richest countries in the world, because of oil revenues, and politicians generally agree that they want to increase research budgets at least

up to the average of the OECD countries. It was the plan to do that over a five-year period but it's still not the case when we look at the annual budgets. Economists have a lot of influence in the Department of Finance, and their idea is you cannot put too much money into the Norwegian economy, because it will heat up and cause inflation. We have had very, very limited resources to do research, compared to Sweden and Denmark. But, my work was always quite internationally oriented. Since I came to Tromsø in 1976, I've spent about eight years abroad, mostly in France over several periods and I spent one year in the USA at San Francisco. I've been privileged in that I have often received invitations to talk at different meetings and become a member of different societies, like the ACNP. But I'd like to tell you more about my work, because what we've talked about, so far, is just the beginning.

- AT: Yes, please.
- SD: We did the studies on the crystal structure of the phenothiazine drug metabolites, and the receptor binding studies. Those metabolites that didn't act as expected, or like the others, appeared to have a different three-dimensional structure. I thought that was guite interesting, but left it at that. Then I went to a meeting in Sicily in 1983, in a wonderful place called Erice. It's on top of a mountain in an old village where there was a School of Crystallography. It was a two-week course on receptors, structure and activity. There were about one hundred and five people and one hundred and two of them were chemists; only two or three were pharmacologists. The two other pharmacologists didn't say anything, so I felt very lonely. It was a different environment. I had left chemistry thirteen years earlier and these people were talking about structures and molecular graphics. I would like to mention one pioneer in the field; his name was Peter Kollman. Unfortunately, he died three years ago. He was a giant in molecular modeling and calculations of molecular structure, but there were also several other pioneers of the field that I met. That meeting, in 1983, together with the meeting in 1970 on pharmacokinetics in Basel, was the turning points in my career. In Erice, I heard about molecular graphics; immediately, I saw this as a new tool, what we now call bioinformatics, for studying the problem I'd been interested in all the time, namely, to study the relationship between activity and structure by studying the relationship between the activityo of the drug and its metabolites. I had a sabbatical coming up, and was invited to spend that year as a visiting professor at the University of California San Francisco from 1985 to 1986. I plunged into a completely new world, the world of calculations of molecular structure and of molecular graphics. Of course, one of the first drugs I tried to model

was chlorpromazine. That was the good old drug that I knew a lot about, and other drugs, too, antipsychotics and their metabolites. I learned about something else I'd never heard about, molecular dynamics. Molecular dynamics is the study how molecules move, internally. For a protein or any molecule to have a biological activity or a pharmacological activity, it has to move; function requires motion. If these molecules were completely stiff, they wouldn't work. They don't work in a crystal state. There's always some kind of motion going on and this is one way of studying it. This opened up a completely new world to me, so I learned about molecular modeling, calculations of structures, and how you could do molecular graphics to look at the structures to get a deeper understanding.

- AT: Your computer background helped?
- My computer, pharmacological and structural chemical background, all SD: merged together. When I came back, I started something that nobody else had done. First of all, I needed about eight hundred thousand Norwegian kroner for equipment, and our annual budget for the department was forty-three thousand. I raised half a million in contributions from my colleagues at the university and from different foundations, including the Lundbeck Foundation in Denmark. Then, this company in Oslo I had worked for was excited when I offered them a post-doc in our lab in return for some computer equipment. Today, it would only cost about 10,000 Norwegian kroner but, at that time, a Micro-VAX cost 300,000 Norwegian kroner. So, I got my funding and a little group of people and we started working on these drugs. Then, in December 1988, a publication came out from Olivier Civelli's group. People had started cloning receptors, and they had cloned the dopamine - D, receptor, so that the amino acid sequence of the protein was known. So I started making a model of the dopamine - D<sub>2</sub> receptor, very crucial but very primitive. It was the first model of any of these receptors that anybody made.
- AT: Tell us why it's crucial to see the structure.
- SD: Because the structure explains the function, just as the double helix structure by Watson and Crick started molecular biology. Then people understood how genes worked when they saw how they were built. In the same way, if you understand how the receptor is built, 3-dimensionally, then you can understand its function. I was working on that the whole first three or four months of 1989. I had a group of three or four post-docs working with different drugs. I did the receptor work myself, because it was difficult. By that time, luckily, e-mail had just started. I needed to have discussions with my colleagues in San Francisco who

were nine hours behind me in time, so we used e-mail. One of them came from San Francisco to Tromsø, and installed the system and helped me make it work.

- AT: That's very interesting.
- SD: I didn't go any skiing that Easter, I was only making the dopamine D<sub>a</sub> receptor until I had a three-dimensional model of the receptor, which was, of course, completely wrong. I mean, all models are wrong, but some may be useful. But, still, it explained certain things. There are certain amino acids, one which was deeper into the cell than others, and when people saw that they said, "Ah hah, that explains why". I first presented it at the Annual Meeting of the Scandinavian Society of Psychopharmacology in April 1989, and later at the European College of Neuropsychopharmacology. I think that was in September of 1989. Floyd Bloom, the President of the ACNP, was at that meeting of the European College, and invited me to come to the ACNP and give a plenary lecture. The meeting was in Hawaii in 1989. I had made a video in addition to making the three-dimensional model, which was very inexact but still explained how the protein has negative and positive charges. We saw that immediately and it has been proven to be right. All these drug molecules have a positive charge when they are in solution. At the outside of the neuron, where the receptor sticks out of the cell, the receptor is negative, so it pulls the drug by electrostatic charges. At the beginning we saw all that and, in addition, we did molecular dynamics simulations. Today, somebody came and talked about that video, because it demonstrated that drugs were flexible and how they moved; that, apparently, made a big impression because it was a new way of thinking. The only reason we could do that, at that time, was that there was a supercomputer available, a Cray computer in Trondheim. We were linked to it, so we could do our simulations, because it requires a lot of computer power. Now people understood something they hadn't understood before about the structure of the receptor. In many of the lectures at this year's meeting, receptor models are shown and people take that for granted. The concept that things have to move is important. The big news at this meeting is the allosteric modulating drugs that affect how parts of the receptors move, in relationship to each other. Before 1989, pharmacologists thought that drugs and receptors were like locks and keys. But they're not something rigid. That's not the way it works. I was very pleased that I was asked whether I would like to be nominated to be a member of this college. So, I became an ACNP member in 1990. Little by little, what had been a kind of left hand project grew into the major activity of our group.

Maybe my major contribution to the field has been the use of combined structural chemistry, bioinformatics and pharmacological knowledge to make these models of receptors and other drug targets. I remember my friend, Peter Kollman, who hosted me when I was a visiting professor in San Francisco. When he saw what I was doing, he said, "This is quite interesting stuff". He saw it was a new angle he hadn't thought about previously.

- AT: Where do you think the field is headed?
- SD: We are getting new protein models and more exact models. In order to make these models, we need to have a kind of a template. Up to a certain number of amino acids, say, eight to ten, you may be able to simulate the three-dimensional structure, but for a receptor that may have four or five hundred amino acids, you cannot calculate the threedimensional structure. A researcher called Anfinsen who got the Nobel Prize, I think in 1973, postulated that all the information about the folding of the protein lies in the amino acid sequence, but no one still has been able to do that. You have to have some kind of a template, which is normally a crystal structure of some protein, and this crystal structure can be more or less exact. There are big consortia who try to use modern robotics and experimental technology to solve the crystal structures of classes of proteins, so that in each type of three-dimensional shape, you have at least one crystal structure and can use that as a template to model the others in the same family. It seems that is where the field is heading. A breakthrough occurred in 2000, when the light receptor in the retina of the eye, a large receptor called rhodopsin, was crystallized, and it's used as a template model for many of these receptors. There will be more of these models coming. In 1990, we took up another line of research, because just as the receptors had started to be cloned in the 1980s, in 1990-91, a number of transporter molecules were cloned. These are molecules that pull some of the neurotransmitter substances, the signal substances, into the neural cell when it has been secreted into a cleft between two neurons. Some of the substance is taken up in a kind of a reuptake process by a protein called a transporter. When these transporters started to be cloned, we made a very speculative three-dimensional model of a transporter. The receptors go through the cell membrane seven times but the transporters go through twelve times, so they are bigger. Later on, newer templates came in that area, also. A doctorate student in my lab did her thesis on transporters. When she had submitted the last publication, written her thesis and sent it to the committee, then, suddenly, a crystal structure came out. The crystal structure, by and large, confirmed the transporter model that we had,

which was interestig for us and we were very pleased. That was only last summer. That field is heading, obviously, towards more and more crystal structures of these types of proteins. The problem is that they're sitting in the cell membrane and in order to make a crystal, one has to pull them out of the membrane and preserve the structure. That is very hard to do. As we get more and more of these crystal structures, bioinformatics will take over, you just need starting points, or anchoring points which is what we lacked. We had something but it was very inexact.

- AT: Do you see yourself as a scientist, who was in the right place at the right time?
- SD: I probably was, but I cannot let this interview go without telling you one little story. I thought that the chlorpromazine molecule was very beautiful when I saw the calculated structure, so I made a couple of photographs, fairly big ones, and framed them. I have one in my home, and gave one to Peter Kollman, who introduced me to molecular modeling. Who was the other obvious person to give the structure of chlorpromazine to? Whom would you think? I can say that it was a Frenchman.
- AT: It couldn't have been Heinz Lehmann?
- SD: No, but the one who discovered the drug that Heinz Lehmann started studying, Pierre Deniker.
- AT: You gave it to him?
- SD: I sent it to him and I got a very, very warm letter back from him, appreciating the work. He was later joking and said he might use it as a flag on his sailboat!
- AT: Do you know if he did?
- SD: No, I don't think so. I had met him before when I gave a seminar in 1978 on plasma level monitoring of antipsychotic drugs at the CINP Congress in Vienna. The chairmen were Pierre Deniker and Paolo Morselli. Deniker must have been maybe in his seventies already, maybe not, but he was not a young man. He was sitting there listening to state-ofthe-art lectures on plasma levels and pharmacokinetics. He didn't say much, so I thought that he was invited as a kind of honorary person, just to be there. The other chairman did everything, introduced the speakers etc. At the end of the session, after four or five speakers, Pierre Deniker took the microphone and gave a summary of the whole session, crystal clear, absolutely to the point, fantastic. I was impressed. I met him again at the World Congress of Psychiatry in Athens in 1989. We had a chance to chat.
- AT: Why is the chlorpromazine structure beautiful?

- SD: I don't know. You can see it. I can send you a copy. It's very beautiful. I put it on my home page and you judge it for yourself; it sort of flows in space there. You'll see. It always struck me as very special, maybe because I knew the history.
- AT: Yes. Beauty is such an individualized subjective thing. Are there other things that you wanted to add?
- SD: We have a system at our university where we can take a sabbatical every fifth year and my first sabbatical was in France. The university where I work was founded in 1968, when the decision was made in parliament to have a university in Tromsø. I think that the official starting date was in 1971. I went there in 1976. It was my hometown, but I hadn't lived there for fifteen years. The salary of a professor or a senior lecturer was the same everywhere in Norway, regardless whether one was in medicine, or in theology. Now, it's more individualized. Back then, they needed to do something to attract people to come to this new university in a very remote location, because it's north of the Arctic Circle. The whole population of Norway is only four million and only four hundred thousand live in the part that stretches to the north. There was no academic tradition and I think I was only the second full professor who came from the region. Some clever person realized that one way to attract people was to offer more frequent sabbaticals and, politically, they could justify it because of the remote location. That's how it was from the beginning and still is. You work four years and if teaching is taken care of, then, you may have a sabbatical every fifth year. In addition, if you go to the United States, you don't pay any taxes in that year. Almost all of my colleagues went to the States but I was fascinated by France, so I went to France. I didn't know the language. I had to pay income tax, but I liked France a lot and I learned to speak French.
- AT: French is listed as one of the languages you can write and speak. You must be a quick study.
- SD: It took me a while, but I spent a lot of time and effort on it. I had taken French in school for three years, but, when I came to France ten years later, I had forgotten every word. It came back, but it was hard. I read newspapers, understood maybe twenty-five percent at the beginning, and asked my colleagues how to say this and that, and little by little it came. I have now lived seven years in France, so I ought to be able to speak it. After the first sabbatical in France I did the next sabbatical in San Francisco. Then, another sabbatical in Paris, as a visiting professor and, then, I worked for a pharmaceutical company, as the Head of Research, in Paris.
- AT: Sounds the ideal way.

- SD: Yes, it's been nice.
- AT: Any burning projects you're working on now?
- SD: You did ask me about where I think the field is heading. The whole discipline of clinical pharmacology, measuring plasma levels, was based on the fact that patients needed individual doses, and pharmacokinetics became popular and important because it was understood that variation could explain part of the individual response to the drugs. Clinical pharmacology as a discipline is essentially founded on that, and doing plasma level monitoring on different drugs, a whole range of different drugs, is fundamental to clinical pharmacology. We always knew that part of the variation in response is due to the other side of pharmacology, namely, pharmacodynamics. Again, we have the dualism between what the drug does to the body and how the body treats the drug. In pharmacodynamics, people thought there was some variation but it wasn't well known, and now, with genomics, and the human genome research, a new field of pharmacogenetics, is evolving, and people start to understand it in a different way. In other words, you can pinpoint from a genetic point of view how a certain patient should react differently from another, even if you correct for the pharmacokinetic variation. If a dose gives them exactly the same concentration of the drug in the body, they may still react differently. I think that's an important evolutionary field in the future. There have been lectures about that at this meeting, pointing to a new way of improving individualized therapy. My contribution probably will be, when we know more about genomics, to translate that into a structural knowledge. Once you have a model of a structural target for a drug, a transporter or a receptor protein, and you know that in certain patients the genetics is slightly changed, then it's fairly easy with the model to see how genetic changes affect the target molecule where the drug acts. You can explain the different molecular mechanisms of action in light of that variation. You can say the mechanics clearly work a little differently in this patient than in that one, because of this trait inherited from the parents.
- AT: It will facilitate individualized and much more efficacious care.
- SD: Yes, with that and the other dimension, the pharmacokinetic dimension. When I teach pharmacology to medical students, I say, you must take all of this for granted but when I started receptors were just a concept used to explain the relationship between dose and effect. When I started in pharmacology in 1970, nobody knew what a receptor was. Now, everybody knows the molecular structure and they take it for granted. Having seen that evolution has been fascinating.

- AT: It's like studying history; at some point we don't take things for granted quite as much.
- SD: Exactly. If you don't have the historic way of seeing things you don't understand their importance. It's easy in life to say what is right and wrong, but to say what's important and what's not so important is not so easy; history can help you do that.
- AT: Thank you so very much. If there's anything else you want to add?
- SD: One of the most rewarding things in my career has been the fact that this work has given me good friends all over the world; in America, France, Germany and many other places. When you have seen colleagues for twenty-five years, you develop a kind of friendship, which is unique. The fact of being able to travel around the world, often among friends, is something that I appreciate a lot. I think that's really one of the major privileges in working as a scientist in the international field.
- AT: Thank you, that's great.

## DAVID L. DUNNER

#### Interviewed by Thomas A. Ban Waikoloa, Hawaii, December 13, 2001

- TB: This will be an interview with Dr. David Dunner\* for the archives of the American College of Neuropsychopharmacology. We are at the 40th anniversary of the college in Hawaii. Could you tell us when and where you were born, something about your education and how you got into neuropsychopharmacology?
- DD: I was born in Brooklyn, NY on May 27, 1940. My father was a general practitioner in Brooklyn, and just before the war he decided to join the Veteran's Administration. He asked to go to the east coast, and not to a mental hospital. So, they sent him to the Menlo Park VA. At the Menlo Park VA, which is a mental hospital in California, he had guarters on the grounds. One of the patients asked, "Would you like some calla lilies in your garden"? He said sure. So, the patient transplanted the manager of the hospital's prize calla lilies to my dad's garden, and dad was promptly transferred to the Livermore VA. I grew up on the hospital grounds. Dad was active in TB research and involved in clinical trials with streptomycin. When I was ten we moved to St. Louis for three or four years, and my father became head of regional TB studies for the VA. In 1954 we moved to Washington DC when he became director of research for the entire VA. He lived in the Washington area until he died. So, I went to high school and college in the area. I went to George Washington University, and then to medical school at Washington University in St. Louis. I graduated from there and then took a one-year rotating internship at Philadelphia General Hospital.
- TB: How did you get into psychiatry?
- DD: When I went to medical school I thought it might be nice if I was an internist and did research. I immediately took a disliking to both. Then I thought maybe I should be a pediatrician. My first patient in pediatrics died. I decided that was not for me. I remember sitting in my dormitory room at the end of my third year at medical school flipping through a catalog of medical specialties wondering what would become of my life, and did I want to be an anesthesiologist? Then I came to psychiatry. At that time, the Department of Psychiatry of Washington University was run by Eli Robins, and was very medical, non-Freudian. Psychiatry was the furthest thing from my mind when I went to medical school but these patients came in the hospital sick, got better with ECT, and were

<sup>\*</sup> David L. Dunner was born in Brooklyn, New York in 1940.

discharged within a few weeks. There was really an improvement so I decided I could do that.

- TB: Did Eli Robins have any impact on your decision?
- DD: It was the whole department being non-Freudian and medical. Having decided to be a psychiatrist and to train at Washington University, I went out of town for a year to Philadelphia for an internship, and then came back to Washington University to do my three-year residency. Right around that time, men had a draft obligation in the military. You could defer it to become a specialist through the Public Health Service or the army. I applied for both and was accepted to both, and then decided to do the Public Health Service because my parents and my wife's parent both lived in Washington DC. So, it would be going home and spending time with our families.
- TB: So you went back to Washington?
- DD: Right. I finished my residency in 1969 and went from St. Louis to NIMH for two years. Because I was going to go to a place that specialized in research on manic depressive illness I talked to George Winokur, who was one of the teachers at Washington U. I said, "George, I need to know more about bipolar disorders so I don't look like a fool when I go back east". So, I did a little research with him, which wasn't published, on the effect of ECT in the treatment of acute mania. Around that time lithium was first being used. I remember we would have patients sign a consent form saying that they agreed to take the experimental drug, lithium carbonate, and the side effects included nausea, vomiting, diarrhea, tremor and death. We went to the pharmacy where they had these huge bottles of lithium carbonate, and asked them to make up capsules to give to patients. Lithium was exciting, and George Winokur, Paula Clayton and Ted Reich were doing studies on the genetics of bipolar disorder. So, I ended up at NIMH worked with Biff Bunney and Fred Goodwin, and was paired with Elliot Gershon.
- TR: As a resident, did you do any research?
- DD: Not their research. I had summer jobs back in Washington DC in a laboratory.
- TB: What did you do?
- DD: The first job was at the Mt. Alto Veteran's Hospital where I worked on tubeless gastric analysis with doctor Sun. He published my first paper in a GI journal.
- TB: What year?
- DD: Probably around 1966, when I was a medical student. Then I did another summer research project with a person trying to look at antibodies that developed to TB and sarcoidosis. I was playing around in her lab

staining pine pollen because there was a theory it had something to do with sarcoidosis. I found out that pine pollen was acid fast and we published a paper. That was number two. Number three came early in my days of NIMH. I happened to have lunch one day with Julie Axelrod. We got to talking, and he had a young person in his group, Cal Cohn, who had been working on an assay for catechol-O-methyltransferase (COMT). So we did a study looking at COMT in the blood of patients with depression, schizophrenia and controls. The results showed that the groups had different values. Julie, being a good scientist, did not believe it and asked us to replicate it. We got more blood, replicated it, and published the results in *Science*. It was the first publication that Julie had after his Nobel Prize. So from 1969 to 1971 I was at NIMH.

- TB: So you participated in research on catechol-O- methyltransferase?
- DD: Right. I did the assays if Cal Cohn was busy but my primary job was to get blood from the patients.
- TB: Did you find increased activity in any of the groups?
- DD: No. There was decreased COMT in depressed women.
- TB: What about in schizophrenic patients?
- DD: Schizophrenic patients were no different from controls. My interest in bipolar disorder and clinical genetics stem from interactions with Elliot Gershon and having just come from Washington University where Winokur, Clayton and Reich had published their book about the genetics of bipolar disorder. Elliot was somewhat skeptical about that but we had access to patients at NIMH. First we reviewed all the charts of the patient's who had been admitted over the previous ten years, and divided them into unipolar depression and bipolar disorder. In doing that we found a group of patients who had depression and hypomania but weren't bipolar because they had not been hospitalized for it. They weren't unipolar so we put them in a separate category, and that is how bipolar II got delineated. It turned out that those patients had a very high suicide attempt and suicide rate. We identified that group around 1969 and presented the data at a meeting in San Francisco in 1970. It took forever to get that paper published because I do not think people were quite ready for a subtype of bipolar disorder.
- TB: Was that before or after Angst and Perris published?
- DD: Angst and Perris had written their reports around 1966, but they had bipolar and unipolar patients. We were interested in replicating bipolar versus unipolar, and found this bipolar II group.
- TB: Could you tell us something about the place you worked at NIMH?
- DD: It was a 15 bed locked research unit. There were inpatients with mania, acute mania or depression who volunteered for research studies. There

was a series of offices. Biff's and Fred's offices were on the left and I shared one with Elliot Gershon on the right. There were some secretarial offices. When we were second year clinical associates and Bob Post came in as a first year clinical associate, we moved across the hall and had a window office. Further into the unit, there was a day room, a nursing station, and down the hall there were patient rooms. What we were studying was the chemistry of bipolar disorders and treating patients with L-DOPA and  $\alpha$ -methylparatyrosine. We were studying cerebrospinal fluid (CSF) and using probenecid trying to block the outflow of 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA) then measuring their accumulation in CSF to see if we could show chemical effects of drugs or differences in patients. We were also looking for COMT and dopamine B-hydroxylase enzymes in blood as they were being discovered. We were collecting urine and looking at MHPG, a forgotten substance these days. The patients were all volunteers and stayed on the inpatient unit at NIMH for sometimes about a year. After being part of a study, they would be treated and discharged back to their community.

- TB: By that time you did this research you had discovered bipolar II?
- DD: By that time I had discovered bipolar II.
- TB: What else did you work on at NIMH?
- DD: I was working on some early genetic studies with Elliot Gershon. Around the end of our first year at NIMH, Gershon and I proposed a family study of bipolar and unipolar depressed patients, interviewing relatives, and drawing blood for enzymes of interest. We invited the regular faculty of NIMH like Bunney, Goodwin and Axelrod to join us in this project but they thought we were kind of crazy. No one believed that these were genetic disorders at the time, and the notion that you would interview relatives did not appeal to anyone as having scientific merit. To get ahead a little bit, Elliot went on to Israel and I went on to work in New York with Ron Fieve to do those studies. These early studies on the genetics of bipolar disorder did not arouse great scientific enthusiasm because everybody thought the illnesses were mainly psychosocial.
- TB: So you were back to bipolar illness that you first became interested in at St. Louis?
- DD: It started in St. Louis because I knew I was headed to NIMH. If I had been heading to NIMH to work on schizophrenia I probably would have wanted to be more involved in schizophrenia in St. Louis. Washington University was one of the few places in the country at that time that diagnosed bipolar disorder. So, I learned the Washington University

diagnostic system, which was the forerunner of DSM-III, when I was a first and second year resident.

- TB: Could you say something more about the program at Washington University?
- DD: It has always been called a biologically oriented program. The preferred word was medical. It wasn't that they didn't believe in psychotherapy, they didn't believe in anything. They had what was called an agnostic approach which was data driven. So, if you had data to support a position, then you had some way of conversing with other people. Otherwise, it was all supposition. The diagnostic system in use at the time was DSM-II, which had paragraphs of descriptions with no exclusion criteria. That diagnostic system was, by and large, ignored by the faculty at Washington University who instead relied on their book of research papers. These involved descriptive, follow-up and family studies. Eli Robins and Sam Guze had written a paper around 1960 or maybe 1970, on, how you differentiate one schizophrenic syndrome from another. Eli Robins used to have a meeting once a week with all the residents. We would present a case, and he'd expound upon whatever he wanted to expound upon for as long as he wanted to expound upon it. He was the professor, so we just sat there. He was encyclopedic in terms of his knowledge, and a wonderful man. At that time, he was still walking. The disease that ultimately took his life had just begun, but he was still very mobile. His wife, Lee Robins, is one of the premier epidemiologists in the world. There were several other important people in the department. George Winokur was in charge of the first year residents and we presented cases to him regularly. Sam Guze was very active in the outpatient department and consult service and we saw him more as a second or third year resident, Paula Clayton was an assistant professor at the time. She just had a couple of children and was mostly teaching in the outpatient department. Ted Reich was a resident who was a year ahead of me. Bob Cloninger was a resident a year behind me. John Feighner was in my residency class. John went on to do wonderful things in psychopharmacology. Dennis Cantwell who died a few years ago, the famous child psychiatrist, was in both my medical and residency class. We had a very large group of co-residents. Other people who were there include George Murphy, who was the primary person who taught us psychotherapy. He went on to do some cognitive behavioral psychotherapy studies at Washington University. A fellow named Bob Woodruff joined the faculty from Harvard around the time I was a second year resident, and unfortunately died six or seven years later. He was a wonderfully warm, bright person who was another kind

of no nonsense Washington University person. If he didn't have data he just could not talk about a problem realistically.

- TB: He wrote the book on Psychiatric Diagnosis?
- DD: Right! And he was really loved by all of the trainees. The interesting thing about Washington University is that it was so different from American psychiatry which was dominated by psychoanalysts. We thought we knew the right stuff. Everybody else thought they knew the right stuff, so we would go to meetings and nobody talked the same language. We were data driven and descriptive while other psychiatrists were analytic and impressionistic. We were using treatments, including medicine and ECT, and were well trained in how to use the medications of that time. That was minimized in most American training programs in favor of analytic therapy. We used different, non analytic, therapies. I remember treating a patient who had fetishes using skin shock behavior therapy. We used other forms of behavior therapy that were just coming out. We were also taught by people who were Freudian. Ed Gildea, the chairman before Eli, had a wife who was a Jungian analyst and she taught us. The difference in Washington University from other places was that there wasn't a dominant therapy that everybody adhered to. When we didn't know we had to find out and that meant research. So, all of the faculty were active in research.
- TB: Tell us something about the research done by the faculty.
- DD: Lee Robins, and her work in sociopathy is a good case in point. She studied conduct disordered children to determine which behaviors were associated with the disorder and with adult sociopathic behavior. "Deviant children grown up", was a description of adult sociopathy. We used our own diagnostic system with disorders like primary affective disorders. Schizophrenia was a chronic disorder. We had mania; it wasn't even called bipolar then, and alcoholism. There wasn't that much street substance abuse at that time; it was mostly alcoholism and barbiturates. Rarely would we see anybody with heroin abuse. Sociopathy and Briquet's syndrome, hysteria, were both identified through follow-up studies. The goal was to have a descriptive psychiatry so that if you saw a patient and they met criteria for a diagnosis you could predict the treatment and outcome based on follow up data. That also left a group of patients who did not fit into the system very well so about 20%, were called undiagnosed. We had 10-12 major diagnoses summarized in a paper authored by John Feighner in 1972 called, Diagnostic Criteria for Use in Psychiatric Research. These were the clinical criteria we were using as residents. Follow up studies on the undiagnosed patients found that they stayed undiagnosed over time.

So there was stability in that category also. You didn't have to diagnose everybody.

- TB: Didn't they use external validators?
- DD: There wasn't any good way to externally validate anything. I am not sure there are good ways to externally validate diagnosis but if you have a laboratory test that can help. But descriptive, follow up and family studies were what really drove Washington University and the different disciplines that contributed to structured interviews. As a resident I was doing the Renard structured interview, which was a collection of instruments that later became the Schedule for Affective Disorders and Schizophrenia (SADS). The Research Diagnostic Criteria were the forerunners of DSM III. Washington University went on to develop its own Diagnostic Interview Schedule. (DIS), but we were doing this kind of stuff as residents. We would ask patients to go through checklists of symptoms because that helped us with diagnosis and prediction of outcome. Then we could tell the family if a disorder might become recurrent or chronic. It was a very exciting time, and I think Washington University and lithium have contributed greatly to contemporary psychiatry in the United States. Washington University because it recognized mania and developed ways to diagnose people with bipolar disorder became important for American psychiatrists to diagnose and treat bipolar disorder with lithium. The evolution of DSM-III from DSM-II was a major contribution by Washington University pioneers like Eli Robins, Sam Guze and Bob Woodward. They, in turn, influenced others like Bob Spitzer and Gerry Klerman leading to the development and use of structured instruments such as the SADS and RDC in clinical practice and research. We still had some differences of opinion. The DSM criteria for diagnosing schizophrenia required only two weeks of illness but at Washington University it was six months because our follow up data showed that duration predicted outcome. The lengthy illnesses we called schizophrenia usually didn't recover. Others call the Washington University approach "biologic", but I would call it descriptive. It was data driven and if the data changed we would modify the criteria. An example is Briquet's syndrome, which is now somatization disorder. It went from a checklist of about 60 symptoms divided into 10 different categories to the current DSM-IV system, which is probably 30 symptoms in five or six categories. My understanding is you can get the same degree of reliability in diagnosis with about 10 symptoms if you are positive about a certain sub group. Washington University was never very good about treatment studies. It wasn't their thing. We used amitriptyline, lithium, ECT and chlorpromazine but weren't doing treatment outcome

research or clinical trials. It was descriptive, and later became more image-driven using techniques developed by Mallincrodt. When I was there psychiatry had the third largest biochemistry laboratory department in the medical center, and the most labs after pharmacology and biochemistry. Psychiatry was very active in basic research including Eli Robins' work with brain proteins. He was an excellent clinician who also had a research laboratory. Not everybody on the faculty worked in a wet lab, but everybody did some kind of research. All the residents had to have a three or six month research component to their training, and most published papers. I did not. I worked with Lucy King in her lab and did research on rat brain epinephrine and norepinephrine in sleep deprived rats. We didn't find anything worth publishing. That was one of the few research areas that I never published in.

- TB: What was your background in research before you joined NIMH?
- DD: My first exposure came through my father who was active in research. Then, at Washington University, psychiatric research was just what we did. If you wanted to find an answer you did research. Inquiry was important. After that the focus on mood disorders came with the choice I made of going to NIMH with the Public Health Service and being accepted into a group that was studying the chemistry of manic depressive illness. I think the reason I was selected at NIMH was my background in diagnosis at Washington University. At the end of my first year of a two year commitment it looked as if I might go into private practice. Keith Brodie was chatting with me before he left to go to Stanford after finishing his two years at NIMH. He suggested I consider working with Ron Fieve in New York and continue my studies on bipolar disorder. I didn't want to live in New York but Peggy and I visited and got offered a job. We ended up finding a house in New Jersey within easy commuting distance. I spent the next eight years at New York State Psychiatric Institute working with Ron Fieve at Columbia University in the Lithium Clinic. He had several hundred patients that he was treating with lithium and antidepressants. He also had an inpatient research unit which I was in charge of and we continued to do spinal fluid and treatment studies including the use of L-DOPA and L-tryptophan. Ron was working on rubidium, another metal in the lithium chain that seemed to help depression. Unlike the NIMH, we had a very large outpatient clinic where we did studies. Using the Washington University approach to diagnosis I wanted to see if clinical, family or biological factors could distinguish primary affective disorders from bipolar disorders and depression from manic depression, looking at bipolar II as a subtype. We published a large family study at that time. It was an exciting time

for me scientifically because Ron was very helpful in introducing me to people like you. I went to my first ACNP meeting in 1972, and joined the college around 1974. I don't remember the exact date, but at that time meetings were mostly in Puerto Rico, though occasionally California. I met people like Max Hamilton. Our group at Columbia was right next door to Joe Zubin, a wonderful person who had tremendous influence on American psychiatry. He was a psychologist who helped developed the DSM-III system and Bob Spitzer had worked in his lab. Joe was very sympathetic toward research and less so to analytic psychiatry. We were doing research that made sense to him so we became friendly. I remember having lunch with Joe and Max Hamilton, and meeting this grumpy, old English man who never seemed to have a nice thing to say but with a little twinkle to his sneer. It was exciting for me as a very young person. ACNP at that time had maybe 200 members. It was easy to have lunch with a basic scientist or another clinician, and much less complicated than it is now where you have to hunt for people or make appointments to see them. There were fewer sessions, and a coffee break that everybody went to so one could easily find people to chat with.

- TB: Were the meetings still at the Sheraton?
- DD: At the Caribe Hilton more than the Sheraton. While at Columbia I wrote about 50 papers and started to do national talks. I always tried to present at Biological Psychiatry, the APA and ACNP. Those were meetings I targeted, and I tried to write a paper for each occasion. One year, when I wanted to get promoted to associate professor, I wrote something like 14 papers. Both my wife and I felt that New York was not a forever place for us, and I started looking around. It's easy to leave angry, but hard to leave friendly. It was important to me that I leave Ron in a friendly way, which I did. We are still close and do collaborative work because he was very important in developing my career.
- TB: Could you tell us something about depression research at Columbia?
- DD: We were interested in differentiating depressive subtypes looking at bipolar I, bipolar II and unipolar diagnoses from family data and symptom differences in clinical studies including psychological and personality tests. We did treatment outcome studies, and it was through those that we developed the concept of rapid cycling. In the early 1970s lithium was used a lot. It had gotten positive reviews in Europe but had been very negatively viewed in the United States where it had actually been taken off the market because it had been used as a sodium substitute in cardiac patients and deaths occurred.
- TB: That happened long before.
- DD: That was before. But in the early 1970s, there was this turmoil about whether to treat mental disorders with medications or psychotherapy, and most departments were dominated by people who were psychoanalytically oriented. There were a number of early drug trials in depression using tricycle compounds like imipramine or amitriptyline. Haloperidol was starting to be used right around the early 1970s for acute mania, but while there was some interest in what became psychopharmacology, it wasn't a big part of many training programs. Ron Fieve's major effort was to get wider acceptance of lithium. When patients from our lithium clinic went on vacation it was difficult to find physicians they could consult who knew about the drug. The positive side of lithium was a driving force for Ron while I looked at those who didn't respond well. He called me the negative guy in the department. To decide what it was about people who didn't respond to lithium we started looked at their age, age of onset, gender, family history and prior episodes. We rated episodes in the two years prior to lithium treatment and found that had great predictive value. People who had four or more episodes, in the two years prior to lithium treatment were most of the lithium failures; people who had fewer episodes generally did better. We published that paper, and that is how rapid cycling got started. It turned out we weren't the first to identify that group. There was a Canadian psychiatrist and others before. Bunney's group at the NIMH was studying 24 hour cyclers. Anyway, we got the credit with our paper. It was published around 1974 and titled Clinical Factors in Lithium Carbonate Prophylaxis Failure. Ron and I were the authors.
- TB: Who was the Canadian psychiatrist?
- DD: I will get his name later.
- TB: Was he Paul Grof?
- DD: No, it wasn't Paul. At that time I was going to more meetings and talking about bipolar and unipolar distinctions in lithium treatment. Sid Malitz and Sandy Glassman's group at Columbia, down the hall from us, were treating mostly unipolar depression. We had a large clinic with a lot of students. We helped train people like John Nurnberger, Norman Rosenthal and Mike Liebowitz who wrote their first papers with us. Steve Roose worked with us early in his career. Part of their training at Columbia would sometimes involve research and time with our group. I always made sure they got a paper out of it because almost anything you studied revealed something new that could be published. I once had two papers in the same Archives issue. We were writing and publishing a lot, it was exciting and I felt good about mentoring people. I became involved more with teaching, lecturing and continuing

medical education (CME) presentations. Prior to the mid 1970s I didn't travel very much, but all of a sudden I began to get invited. It was very exciting. But it came time to leave. Mark Schuckit, who was a resident at Washington University a couple of years behind me, suggested I look at the University of Washington in Seattle. Carl Eisdorfer was chair and they were recruiting to replace their psychopharmacologist, Bob Friedel, who had just left. I never thought of myself as a psychopharmacologist but more as a descriptive psychiatrist who does clinical trials to study patients and their outcomes. Anyway, I looked at the job but it wasn't quite right. Seattle seemed OK, Mark was there and it was a nice department. I liked the people. They had another opening as chief of psychiatry at Harborview Medical Center and asked me to look at that. My wife Peggy liked Seattle and I saw things in the job that were very positive. It would enable me to continue research in bipolar disorder, and I could set up the kinds of things that I had been doing with Ron in family studies, but broaden it to do more teaching. Also, there was some interest in anxiety disorders. Pete Pitts, who was at Washington University when I was, had done lactate infusions in panic but, when Pete's son developed leukemia, he dropped out of research. That idea got buried for a while, but Don Klein picked it up and was starting to do lactate-infusions at Columbia. I was really very interested in looking at children who might become ill. Again, assuming that panic was a genetic disorder in which children would develop the illness later maybe we could develop family studies in anxiety disorders. When I took the job at the University of Washington, became professor in the department and head of psychiatry at Harborview, there was a small clinical trials program that Eisdorfer was running. His area was ageing but he had contracted to do a study in anxiety. He was going on sabbatical and asked if I would take over those clinical trials. At that point, he had one or two ongoing trials, a part time research coordinator and a doctor looked in on the patients. While he was gone, we developed an immense clinical trial program at Harborview. Within five or six years we had 26 ongoing studies in areas like schizophrenia, depression, panic disorder, generalized anxiety disorder, smoking, dementia, and sleep. We developed a huge staff, using the money to fund younger researchers at the University of Washington.

- TB: In what year?
- DD: I moved there in 1979, and was chief of psychiatry at Harborview for a little over 10 years. Those who were involved with me were people like David Avery who was hired to do ECT and research studies, Steven Dager who has become an excellent neuro-imager, Debra Cowley, who

is our training director at the University of Washington, Deb and Steve were residents together, and collaborated in studies on panic. We did get a couple of grants to look at high risk children with depression and panic, working with child psychiatrists, Bob Reichler and one of his colleagues, Carrie Sylvester, who is now at the University of Illinois. We put together a program funded primarily from psychopharmacologically driven trials through industry, and used them to get patients to do family studies similar to what I had been doing in New York, except that the populations were obtained from clinical trials. The high risk studies never panned out, but people from the group went into neuroimaging, like Steve, or back to depression and bipolar studies, which I focused on in the mid 1980s. I set up The Center for Anxiety and Depression because we had a lot of faculty expertise in Seattle, and developed a consulting service for local clinicians, and also a way to do research using structured assessments of patients. That era really led into more clinical trials and a big bridge with the community in terms of being the primary person in Seattle for consultation on treatment resistant patients. Now I am the clinical expert in bipolar disorder and treatment resistant depression in the Seattle area, involved in clinical trials mostly in mood disorders but still wanting to do family studies. We are trying very hard to get funded for a family study dividing unipolar depression into subtypes. We continue some interests in bipolar disorder, but I like to go where people haven't been because it is more fun.

- TB: Didn't you collaborate with John Feighner on fluoxetine?
- DD: John Feighner was a residency classmate of mine. He developed this excellent clinical trial group in San Diego, and drug companies were interested in having him study new drugs. One of them was fluoxetine, and he had contact with Paul Stark, who was a PhD and worked for Lilly. We studied fluoxetine, until it was approved by the FDA. We had, I think, a quarter of the Prozac patients involved in Lilly's clinical trials, not all of them positive. Our primary work was with Upjohn on alprazolam (Xanax) in panic because they were funding our lactate infusions and studies of mitral valve prolapse. So, patients who were undergoing studies with Xanax were actually part of the research on lactate infusions and echo cardiograms for mitral valve prolapse. If the subjects had children we put them into our family study. Upjohn was funding us to a much greater extent than Lilly although we went on to do a whole bunch of studies with other companies. We were involved in clinical studies of every single drug on the US market at least once, if not many times.
- TB: All kinds of psychotropics?

DD: Antidepressants, anxiolytics, and early on in studies of an approach for dementia. When I was at Harborview, because we had an inpatient service, we looked at some new neuroleptics, some of which have never come to the market, and some like risperidone, did. We also got involved in doing some psychotherapy studies. That came a bit later. I took over the outpatient department at the University of Washington around 1990 where residents learn how to treat outpatients and do psychotherapy. In most psychiatry outpatient clinics, residents learn psychotherapy from the head of the clinic who is a psychotherapist. I wasn't doing any psychotherapy and hadn't seen a patient in psychotherapy since 1976. But now people were getting certified to be therapists using techniques like CBT and IPT. I thought if we weren't going to teach them to do what I did, we would at least teach them to do something that was data based. We began to certify faculty in CBT and IPT, so we could teach manualized psychotherapies to our residents. That is still going on at the University of Washington. We took things like the Barlow Manual for panic because we could expose residents to data that supported the treatment. This isn't very different from my earlier training at Washington University. If you have data to say something works you go with the data. Around that time, we developed studies in CBT and dysthymia. Nobody was studying dysthymia much so we got interested in that. I did a fluoxetine and CBT comparative trial in dysthymia. Earlier I was a co-principal investigator with Joe Becker on an application for the collaborative treatment of depression, which the University of Washington didn't get. I am going to talk a little bit about psychotherapy. Not that I am a psychotherapist, but I like research. For years there was a famous psychologist at the University of Washington, Neal Jacobson, and we had been having meetings every year about doing some collaborative studies. Finally, about five or six years ago Neal wanted to do a study comparing his psychotherapy, behavioral activation, to CBT. We collaborated on that project, which was federally funded. It was a four cell design where depressed patients got behavioral activation, CBT, paroxetine or placebo. I was in charge of the psychopharmacologic part. Unfortunately, Neal had a heart attack and tragically died two years into the grant. I then became the principal investigator, which I am today. Through that I became involved with other psychotherapy studies. Marty Keller was doing a large trial in chronically depressed patients that was funded by Bristol Myers Squibb looking at metazodone and a new cognitive behavioral analysis system of psychotherapy (CBASP). We became one of the study sites and trained psychologists in our outpatient clinic

to be certified in CBASP. I like that therapy, it is interesting. There is no perfect or single way to help patients and if combined treatment works so much the better. By the way, the name of the Canadian scientist who first identified rapid cycling is Harvey Stancer.

- TB: Harvey Stancer from Toronto?
- DD: Yes, he published a paper about a year before ours which described lithium failure correlated with more episodes. But he never got the credit for it. I am not directing the outpatient clinic anymore, instead I direct the Center for Anxiety and Depression, doing clinical trials and descriptive studies. At present we are trying to get funding for a very large family study of unipolar depression.
- TB: You mentioned the study you collaborated on with Keller.
- DD: The studies that we did on dysthymia and the Keller study led us to work extensively on people with chronic depression. When you deal with treatment resistant depression all of the patients are chronic with illnesses lasting two years or more. Psychiatry these days is really dealing with treatment resistant chronic depression. So, it is important we learn more about it, but, having said that, I came to the belief that DSM-IV splits categories too much. It makes more sense to combine the different forms of chronic depression into one category. Right now we have chronic major depression, dysthymic disorder, dysthymic disorder complicated by major depression, and a chronic form of depression that begins with a major depressive episode, but people don't get better even if they lose the criteria for major depression. That is called major depression in incomplete remission. To me all of these are similar. The four entities are not that different and in many ways they are confusing for clinicians. It is simpler to simply see a patient who has been sick for a long time. Unipolar depressions could be separated into acute and chronic forms. We are doing studies that we hope have some interest for people working on DSM-V to differentiate these subtypes and their course of the illness. This is the kind of work that I enjoy and like to do using a very structured history on the large number of patients I see in clinical trials.
- TB: What would you say was your single most important contribution?
- DD: Training people who have gone on to do great things. I mentioned a few of them, and I am very proud of my association with them.
- TB: What about research contributions?
- DD: The bipolar II and rapid cycling concepts are probably the things most identified with me. Those are descriptive concepts. They are not biologically or family based but they describe groups of patients and their longitudinal outcome. I am disappointed that we have never identified

the "bipolar gene". I started off with Elliot Gershon 30 years ago to find the gene for manic depressive illness, which we hoped discover that summer. I realize now how complicated it is and how naïve we were. Very good people are now looking for the genes, not a single gene. I am not going to be the one to find them, but it would be nice to know that there really are genes when patients ask, "Is this a genetic disorder?" and I can only say, "Well, we think so". At Washington University if we don't know we are not going to make it up. People ask me how drugs work and I tell them I don't know. I can tell them what we think but in real life we really don't know. That is OK with me because our treatment outcome studies prove they do work.

- TB: Could you mention some of your important papers?
- DD: I mentioned the rapid cycling paper and the paper on bipolar II. It was written with Elliot Gershon and Fred Goodwin, and took forever to get published. We presented that data in 1970 at APA and it was turned down by a couple of journals for reasons nobody really understood. People did not recognize bipolar and unipolar, let alone bipolar subtypes. It was a very good paper and was finally published in *Biological* Psychiatry in 1976. We also did a longitudinal study of lithium and placebo treatment in bipolar II, and found effects for mania, but not depression. Don Klein came to the Psychiatric Institute shortly after that, and we gave him our computer program for analyzing data. The computer was almost as big as this room. It was a complicated analysis, but Don found something wrong with the program and asked us to retract the paper, which we did. But in the course of reanalyzing the data over two and a half years rather than one year we showed that lithium also had maintenance effects against depression in bipolar II patients. That information was buried in a letter to the Archives when we corrected the first paper but expanded it. So nobody knows about it but it was an important contribution. The other thing that I have enjoyed doing has been to be at the crest of the wave in psychopharmacology. I alluded to that this morning. I was always in the right place at the right time. I was at Washington University when we worked on diagnosing mania but nobody else knew how to do it. I was at NIMH when we developed the concepts of bipolar II and did family and linkage studies that others only started doing later. We also did biological studies in mania and depression when there weren't a lot of things like that going on in the country. I was in New York with Ron Fieve when lithium appeared in what has been called the psychopharmacologic revolution, and I was right in the middle of it. I was knowledgeable about drugs and began to do clinical trials to study new drugs and psychotherapies. I was on the front lines

and it was exciting. Later, my career shifted to more administrative activities, which was okay because I still was able to do research, which I find fun. I still like to come to the ACNP. I always have a poster or a paper, and I presented a poster at this meeting. I like to do that.

- TB: What was your last paper on?
- DD: I have one coming out next month on citalopram treatment of dysthymic disorder. This past year we had one on sub typing chronic depressions and I have written a couple of review articles on chronic depression.
- TB: So your current work is focused on chronic depression?
- DD: Right now it is though I still have a good deal of interest in bipolar disorders and mania. In the 1970s everybody was interested in studying mania, but around 1980 people became interested in studying depression and anxiety, and very few people were doing anything in mania. It has only been in the last couple of years, especially with valproic acid, that people became interested in studying mania again. We have still been doing descriptive studies in rapid cycling and in bipolar disorder. I have two things I am working on now. One is a study of who becomes hypomanic in response to antidepressant treatment, and the other is about defining the term chronic. Is it two years of illness or, in our data, it appears one year might suffice? Both of these studies have some implications for DSM-V.
- TB: Did you publish any books?
- DD: I edited a textbook, *Current Psychiatric Therapy*, which went through its second revision. That was a lot of fun. When I was President of the American Psychopathological Association (APPA) I designed the meeting and edited a book that was titled *Relatives at Risk for Mental Disorders*. The meeting focused on high risk. For six or seven years I have been coeditor with Jerry Rosenbaum on an annual volume called the *Psychiatric Clinics of North America Annual of Drug Therapy*. I am the editor of *Comprehensive Psychiatry*, a journal that actually fits my interests because it is a journal of descriptive psychopathology, which is what I am and what I do. I am also on the editorial board of about 10 journals.
- TB: Have you received awards and honors?
- DD: I got the Samuel Hamilton Award and the Morton Prince Award from the APPA. I received the Robert Jones Lectureship from the Canadian Psychiatric Association. This spring I am going to be receiving the Ward Smith Award at the annual meeting of the West Coast College of Biological Psychiatry, a 25-year-old organization that Biff Bunney founded of west coast mental health researchers. I have been president of that. I have been president of the American Psychopathological

Association, president of the Psychiatric Research Society, president of the Society of Biological Psychiatry, and a fellow of ACNP.

- TB: Let me ask you about your activities in ACNP?
- DD: ACNP has always had the problem that we don't know how to appoint new members. When I was elected they created a category of scientific associate which I became. A few years later they decided that didn't make any sense because some really prominent people were scientific associates, and so it made all the scientific associates members. I have been on a bunch of committees, and I like to do that when I am part of an organization. So I set up a symposium, I was on committees but in order to be a committee chair you had to be a fellow. In the early 1980s.I was appointed chair of the education training committee. I was really excited by that because I knew it meant I had been elected to fellowship. I have only missed one meeting since 1972 and I think I presented at each meeting I attended. For the last several years I have usually nominated someone for membership, and I have been on a number of committees and task forces for ACNP. I love coming here. The organization is a lot bigger than the original 200 people, but you learn an awful lot coming, sitting and talking with people.
- TB: Is there anything else that you would like to add?
- DD: I think family is something that never gets covered. My wife didn't come with me during the early times when we were in New York because we had young kids at home and it was right before Christmas. But since we moved to Seattle Peggy has come to just about all the meetings and that has been a very integral part of enjoying them. You structure your life around meetings and this one is on my calendar for the next couple of years.
- TB: Well, thank you very much.
- DD: Thank you very much.

## **BURR S. EICHELMAN**

## Interviewed by Thomas A. Ban San Juan, Puerto Rico, December 9, 2003

- TB: This will be an interview with Dr. Burr Eichelman\* for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Tell me about yourself, where and when you were born, and something about your education?
- BE: I was an only child, born in one of the Chicago suburbs, Hinsdale, and grew up in Downers Grove, another suburb. My parents wanted me to be a physician and started me on piano so I could be a good surgeon. I appreciate that, although I didn't become a surgeon. Their expectations fortunately meshed with my interests in biology and in medicine, and I proceeded in that direction.

In terms of college studies, I went to the University of Chicago and, looking back, appreciated a general education, so that even though I had an interest in biology and in science, I was forced to read the classics in the process of my college education. While at the university, I became interested and fascinated in the synthesis of morality with biology and behavior as I saw others involved with these mind-brain kinds of issues. Such research was becoming very exciting, particularly in the areas of limbic function. For example, one could control sleep or appetite or sexual behavior by stimulating or lesioning parts of the brain.

- TB: Did you do any research as a student?
- BE: In that context, I began to work with Dr. Robert McCleary, who was an MD, PhD trained at Hopkins. He was a professor with appointment in biopsychology at the University of Chicago. I enjoyed his college course and was accepted at the medical school in an advanced placement after completing my bachelor's degree in biopsychology in three years. In the summer hiatus between college and medical school, I worked in his laboratory. There, I believe serendipity played its first role in my career.

At that time there were some papers published out of Illinois Wesleyan College on pain-induced fighting in animals. If one provided a painful stimulus to rats, snakes or monkeys the animals would attack each other. Dr. McCleary suggested I find out about this and explore it in the laboratory. I went there and learned the procedure and, on my return, I did limbic, amygdala, lesions in the rat and reconfirmed in this model what had already been noted in other studies that amygdala lesions modulated aggressive behavior.

<sup>\*</sup> Burr S. Eichelman was born in Hinsdale, Illinois in 1943.

This research and preliminary findings "stayed on the shelf" while I went to medical school where I was accepted into probably one of the first public health supported MD/PhD training programs. So the federal government and the university played a very big role by supporting a married medical student, and by assisting with tuition and a living stipend. The University of Chicago also allowed an overlap in my medical school and graduate school courses, so that many of my PhD. courses could also count for medical school and vice versa. I completed my preliminary examination during the four years of medical school, actually during my third year pediatric clerkship, and then spent an additional year working up this model of pain-induced aggression in the rat in the context of limbic lesions. This led to my first publication in the Journal of Comparative and Physiological Psychology as a lead article. During that time Danny Freedman had come to Chicago as Chairman of Psychiatry and it was clear that biology was going to play a major role in psychiatry. Though the neurosurgeons had coaxed me into a senior elective sub internship, Freedman's very compelling personality and mentorship really won out and directed much of my post-MD training.

- TB: What year was this?
- BE: I completed my MD degree in 1968. Danny must have come to the university in 1964 or 1965. I met with him to ask for advice about "what to do next". He advised me to do a pediatric internship to see normal development at the same time as I was learning additional medicine. As a consequence, I matched at the University of California, San Francisco, in pediatrics. In that same intern class was Phil Berger who has been another member of the College. He was a co-intern with me. Three of our eight interns subsequently went into psychiatry.

On the day I passed my oral PhD exams in Chicago, the movers arrived to relocate my wife, son, daughter, and myself to San Francisco. I stayed for that academic year in San Francisco, learning general pediatrics. During that year, I had applied for a post doctoral fellowship at the NIMH, which was at the time a lock-step career development pathway for young clinician researchers interested in an academic career. I had been accepted into Dr. Fred Snyder's Laboratory of Clinical Psychobiology. This was a sleep research laboratory that Herb Meltzer, president of our college, as well as Chris Gillam, a past editor of our journal, and Dave Kupfer, another ACNP past president had worked in. TB: What areas of research did you work on at the NIMH?

- BE: During my internship, Fred had called and asked what I wanted to
- BE: During my internship, Fred had called and asked what I wanted to work on. I replied that I would like to resume the rat work that I had been doing on aggression. I had shifted to the study of injecting

neurotransmitters into brain regions which Pete Grossman at Chicago, and Sarah Leibowitz at Rockefeller had been doing with feeding behavior. Fred agreed that I could continue this research at the NIMH.

I arrived in the summer of 1970 at Fred Snyder's laboratory. Shortly after, Irv Kopin's group spoke to Fred about some aggressive rats in their lab and how to evaluate them. These were rats that had been fed a carnitine-free diet. So Fred suggested I look at the rats. They were perfectly docile. In fact, in all the time that Irv continued with this research, he never saw the aggressive behavior again. However, in the cages above these carnitine-deficient rats, were some rats that had been treated by Larry Ng, with 6-hydroxydopamine. These were huge 750 gram rats, sitting up in their cages. I suggested to Larry that we just test them in my paradigm for shock-induced fighting. He agreed, so we wheeled them up to my lab.

These animals were about three to four times as aggressive as control animals even though they didn't look like it when handled. This started my behavioral neurochemistry collaboration with Irv's laboratory. At that time Nguyen Thoa, a Vietnamese pharmacologist was there with Larry Ng, a neurologist, and Friedhelm Lamprecht, a German post doc. Redford Williams, also a fellow of the college, was there as an internist. It seemed at that time that everything we touched was statistically significant.

- TB: Can you tell us about your findings?
- BE: We published work with catecholamine depletion using neurotoxins. I did some work with Redford showing that sympathetic activity differed if the animals received stress when they were shocked, versus when they had the opportunity to attack another animal, suggesting that the attack paradigm was less stressful. We did some work with Friedhelm showing that animals stressed and immobilized for a month and allowed to recover so that their blood pressure reverted to normal, and they looked normal to handlers, remained two to three times as aggressive as non-stressed controls. Moreover, they had durable changes in brain enzymes such as dopamine- $\beta$ -hydroxylase.

We did some genetic work and showed that various strains of rats had significantly different levels of aggressive behavior. This returned me to the question of how do brain chemistry, genetics and environmental stress lead to issues of human aggression, law and morality. With this work, my two years at the NIMH ended.

- TB: What did you do next?
- BE: I guess I could have stayed for an intramural career, but I have always straddled the clinical and basic science spheres so I accepted a

residency in psychiatry back at Stanford during the tenure of David Hamburg, who had been working with stress and aggression. It seemed like a natural environment for me. I had negotiated with Stanford to do two years of clinical psychiatry and a third year of residency in the laboratory, working with Jack Barchas, also a fellow of the ACNP.

Shortly after my arrival I was informed that the department had lost their training grants and I would need to be doing clinical work during my third year, not fulltime research. Jack was nevertheless very gracious with his laboratory support. At that time Roland Ciaranello and Donna Wong, also past and present members of the ACNP, were working in Jack's lab.with catecholamines and phenylethanolamine-Nmethyltransferase (PNMT). It was a natural fit to continue my research on aggression and biogenic amines in that environment. So, during my residency, while I was seeing patients and taking call, I continued work with tricyclic antidepressants and aggressive behavior as well as looking at second messengers with cyclic AMP that Elaine Orenburg was researching. I also examined the effect of caffeine and other thioxanthines on rodent aggression while I completed my psychiatric residency.

- TB: You certainly accomplished a great deal during three years of residency.
- BE: I also learned a great deal even though I was looking forward to working with aggressive and violent patients and trying to understand their behavior in the context of their biology as well as their environmental stressors. During my residency at Stanford, Leo Hollister was also there. I recall one of my first days on call. I was asked to consult on a patient with scleroderma who was taking tricyclic antidepressants. The medical service wanted to know whether this patient could continue with the medication since it was anticholinergic. I hadn't the faintest idea as to how to answer the question. In Palo Alto, when asked a clinical psychopharmacologic question you couldn't answer, you called Leo Hollister. That was my first contact with him. He was very gracious about being pestered by a first year resident, and said go ahead and tell them it's better to treat the patient for depression.

There were a lot of resources in Palo Alto, not only on the biological side. I had the privilege of working with the Hilgards, particularly with Josephine Hilgard, and learned from her psychoanalytic skills. I worked with IrvYalom who was my group therapy supervisor. All that time, either to the detriment or to the benefit of what I was doing, I kept one foot in the clinical camp and one foot in the laboratory.

- TB: After all that learning and research what was your next move?
- BE: At the time I completed my residency, which would have been in the summer of 1975, there were a number of chairs open and recruitment

didn't seem to be heading to where I wanted to live. Consequently, I remained for another year at Stanford, funded by a Kennedy Fellowship in medicine, law, and ethics. This was a fellowship that the Kennedy-Shrivers, Eunice Kennedy in particular, had created. I took some ethics courses at Berkeley, worked with the bioethicist Al Jonsen at UC San Francisco, and audited some law courses at Stanford. All this was done with an eye towards moving into clinical research with aggressive and violent patients and having sufficient legal and ethical underpinnings to proceed in a reasonable way. During this time at Stanford Arnie Mandel put together a symposium on aggression which was my initial exposure to the ACNP. The first meeting for me was in San Juan in 1973. I presented much of the work that I had done at the NIH and some that I had continued at Stanford.

- TB: Where did you go after this additional year at Stanford?
- BE: At the end of my fellowship year, I looked at a number of departments of psychiatry, including the University of Wisconsin. Madison felt comfortable as a new Midwestern home. The department and graduate school was generous in funding my start-up and my salary was "hard money" as Chief of Psychiatry at the affiliated VA hospital. So my wife, I and our two children made another move which felt much closer to being "back home".

In Madison I established a Laboratory of Behavioral Neurochemistry, looking at biogenic amines and second messengers involved with aggressive behavior, utilizing rodent models of aggression. Initially, I had a Pakistani biochemist, Asaf Qureshi, working with me and subsequently one of Paul Greengard's post docs, Linda Hegstand, became the biochemical director for our laboratory. We had technical and post doc support during those years. Kathy Kantak, who went on to a faculty position at Boston University was part of our lab.

- TB: What lines of research did you work on in your new environment?
- BE: We continued the line of research with aggressive behavior, working principally with rats and to some degree with mice. We studied primarily predatory and defensive affective aggression. We examined enzyme systems such as tyrosine hydroxylase in attempting to localize where biogenic amine affects were initiated. We did a fair amount of work with dietary restriction, tryptophan deficiency, showing that no matter how you deplete serotonin by p-chlorophenylalanine, neurotoxins, electrolytic lesions of the raphe, or by a tryptophan-deficient diet, you can push the aggression system(s) in brain to enhance aggressive behavior. We looked at receptor systems and showed that an alteration in  $\beta$ -adrenergic receptors led to a correlative change in aggressive

behavior. We demonstrated that if you create a super-sensitivity of  $\beta$ -adrenergic receptors and then withdraw the  $\beta$ -blockade, for the first 48 hours you have more super sensitive receptors and you have an increase in defensive aggressive behavior.

- TB: What were the implications of your animal research for human behavior?
- BE: Not all, of the laboratory changes we observed translate directly into clinical correlates. Certainly, we do not have evidence that patients discontinuing their β-blocker treatment for hypertension become aggressive. Similarly, though we demonstrated an increase in defensive pain-induced aggression in the rat with chronic antidepressant treatment in docile Sprague Dawley rats, we do not generally see this in patients treated with antidepressants. Though, there are a couple of papers reporting this in the human literature.
- TB: Were you trying to find out where the differences between animal and human behaviors come from?
- BE: We were trying to look at a balance between neurotransmitters. We had the sense that the serotonin system functioned in an inhibitory manner in a number of different rodent models. We also felt that increased catecholaminergic, noradrenergic-turnover facilitated or increased defensive aggression. We had replicated Jon Stolk's findings that the alkaline metal cation rubidium increased aggression as did immobilization stress and sleep deprivation stress. All of these behavioral findings were associated with increased norepinephrine turnover. There was the sense that in organisms with enhanced catecholaminergic activity certain types of aggressive behavior would be increased. This adrenergic story was much less clear than the serotonin story.

The research work continued with VA and NIH funding. During that time investigators working in the area of aggression research were concerned about the scientific and political milieu for such research. Utilizing my bioethics background, I undertook a National Science Foundation funded study of aggression, looking at whether research in this area was being constrained on the basis of ethical or political forces. This was in the period between 1976 and 1980. The outcome of that study demonstrated that in those times, there was no particular problem. Institutional Review Boards (IRB), were developing but did not appear to be affecting preclinical research.

- TB: Did some of the ethical concerns limit your own research?
- BE: During that time I continued to, within the VA system, see a number of aggressive patients. We looked towards setting up protocols to study these behaviors. This was really difficult because of the issues of informed consent and because of the episodic nature of serious or

intense human aggressive behaviors. Consequently, most of my clinical work took the form of consulting and collaboration. During this time I was asked to see a patient with Cornelia-DeLang syndrome. He was a mentally retarded young man who engaged in a great deal of self-injurious behavior. His clinicians had measured whole blood serotonin which had been reported to be altered in some mentally retarded patients. His was significantly low. The clinicians asked for consultation in managing his behavior with available resources. At that time, tryptophan was still a food product available at health food stores. In the pre-SSRI era, the only serotonin-enhancing agent with significant specificity was trazodone. So, we suggested enriching his diet with tryptophan and treating him with trazodone. When this was done, the patient showed a major increase in his whole blood serotonin levels and his clinicians could document that his self-injurious and aggressive behavior significantly diminished. We published this correlation as a letter in The Lancet. Serotonin in mentally retarded individuals still appears to be an under-researched area, including the phenomenon of abnormal peripheral levels of serotonin. It appeared to us at this time that the most feasible manner of clinical exploration of human aggression was through natural single subject experiments occurring in the clinic. much as this situation materialized.

- TB: Were there any other reports of the use of trazadone in aggression?
- BE: Our trazodone effect was in conjunction with the use of tryptophan. However, there have been other reports in the literature, particularly in geriatric populations, using trazodone to attenuate aggressive behavior. However, placebo controlled studies are, I believe, non-existent. Even with fairly familiar clinical situations such as delirium, where we use trazodone with small doses of atypical antipsychotic agents, controlled studies have yet to be completed.
- TB: What was the reason that you left eventually Madison?
- BE: The difficulties in implementing clinical research with seriously aggressive patients, funding constraints in the 1980s at the NIMH and personal issues all were involved in my decision to close my behavioral neurochemistry efforts at the UW. I went through a divorce at that time, which takes a lot of energy. In conjunction with remarrying, I inherited not only a new wife, but four stepchildren. Now we're talking about a total of six children. All of this took a fair amount of energy away from my research. Coincident with this was an academic offer to my new wife, an appointment at UNC in Chapel Hill. So we moved.

David Janowsky, a member of the college, was chair at UNC and Bernie Carroll, also an ACNP member, was chair at Duke when I

approached the move. I talked with both of them as colleagues and comembers of the college. David really had the best opportunity for me to continue some of the clinical work on aggressive behavior by taking on a role as Medical Director of one of the state hospitals, Dorothea Dix Hospital in Raleigh. This hospital had one inpatient program of 40 to 50 beds for psychiatric patients who were repetitively aggressive. During that time I was also consulting with pharmaceutical houses that were attempting to address the issue of aggressive and violent patients.

- TB: What line of research did you pursue in your new setting?
- BE: There is a problem with American psychiatry in that we can diagnose depression as an affective disorder and we can diagnose thought disorders, but we have no nosology for incorporating into clinical practice something that clinicians struggle with all the time, namely the affective disorder that incorporates aggressive and destructive behavior.

During those years in Carolina, we attempted to address that issue outside of the DSM. We published papers on what we called the Carolina Nosology for Destructive Behavior, attempting to focus on the problems of a nosology for human aggressive behavior, a task that addressed biology, typology and other differing elements. Is clinically relevant aggression in a particular patient associated with abnormalities in biogenic amines? Is it associated with epilepsy? Is it driven by social stressors? We posited that with a clearer description of clinically relevant violent behavior, the creators of the DSM or even leaders within the FDA would allow for more than just a single diagnostic category of Intermittent Explosive Disorder. We live in a medical culture that affirms that if a disorder doesn't exist, then there is no attempt to understand or treat the condition. Research monies are limited and the pharmaceutical industry does not focus on it. Clinically relevant aggressive behavior, again, becomes a neglected child of medicine.

- TB: Did other clinicians or researchers follow up on your concerns?
- BE: Despite the championing of a research diagnosis for aggressive behavior by such as Coccaro, of our college, this has continued to be a durable, unmovable problem. During those years I was a consultant to Duphar Pharmaceuticals in Holland. They were researching in their preclinical labs a class of compounds called "Serenics". These were 5HT<sub>1A/1B</sub> agonists. Duphar wanted to study these drugs in an aggressive clinical population. They packed me off to the FDA in the US for a meeting to determine how they could best demonstrate the efficacy of these agents and get them eventually marketed. It was a very disheartening meeting at the FDA with Paul Lieber. He essentially said to Duphar that you need to have a disease, not a symptom. Even though

we treat hypertension, even though we treat angina, even though we treat headache, for "aggression" we need to have a disease. He illustrated how Upjohn had assisted in developing and essentially created Panic Disorder as the disease for treatment with alprazolam. He took the problem one step further into the political arena and indicated that in this country it would not be politically feasible to create a disease hallmarked by aggressive behavior and market a product targeted for it. My read about this was that it was un-American to treat aggression with a drug. In all honesty he did not say this directly. I believe he really meant that it was un-American to treat assertive behavior with a "pill" and this would be politically unpalatable.

- TB: What was the outcome of your visit to the FDA?
- BE: Duphar packed up their bags and stopped the idea of developing or researching these drugs in the United States. They attempted to show efficacy in European populations but my understanding is that they had great difficulty with their control placebo populations and the agents were never developed. Since then, we only see an occasional poster on valproic acid or aripiprazole targeting clinically relevant aggressive behavior. Coccaro has done some work with SSRIs. However, without a clear "disease" there is no clear research mandate and no bona fide treatable population for Pharma to market to. This field, in contrast to research on the mental health problems of HIV or autism, has remained stagnant. The energy for one investigator or institution to develop a sustained effort in this area has not been forthcoming. Folks, who publish in this area, have continued to do so by virtue of having some other funding stream where they can piggyback this kind of research. This has been very problematic.
- TB: What did you do next?
- BE: Even though Carolina is a very beautiful place, we decided that we really were Yankees after all. I was offered the Chair of Psychiatry at Temple in Philadelphia and my wife, who is a PhD. attorney, was offered a position at the law school. We thought it would be great to return north and we moved to Temple before I had the time to develop the clinical research at UNC and Dorothea Dix Hospital. Time may have been a factor, but it also seemed to me that the "writing was on the wall". Bringing to fruition the dream I held for a research program geared to the study of clinically relevant aggressive behavior was not likely to happen given our current clinical and political environment.
- TB: Before moving to Temple you completed the Carolina Nosology.
- BE: We did develop the Carolina Nosology for Destructive Behavior, using "destructive" as more politically palatable than "aggressive". It's a

multi-axial nosology which gets cited from time to time when clinical aggression gets cyclically resurrected. We then moved to Philadelphia. It is now 1990.

- TB: What plans did you have for continuing your research?
- BE: As you note, I did not move my behavioral neurochemical lab from Wisconsin to UNC. I did piggyback some rodent research onto the work that David Janowsky was doing and that a Fogerty Fellow of mine, Olgierd Pucilowski, was doing after he moved to UNC. During those Carolina years we did some work with aggressive behavior in alcohol preferring strains of rats and some work with calcium channel blockers. However, I clearly was shifting toward administration and clinical work.
- TB: How did this and your background equip you for your position at Temple?
- The department at Temple had been predominantly a teaching depart-BE: ment for medical students and, to some degree, residents. With the exception of Charlie Shagass and Donald Overton, also a college member, the department had a more public health or community mental health vision with a limited biological and psychopharmacologic research perspective. There was a lot of work to do to change the medical school teaching and bring Temple medical students face to face with the changes in behavioral neurosciences that were impinging on psychiatry. We remade the first year psychiatry course into a neuroscience course. There now was clearly "testable" content. Unprepared for this "new psychiatry" a third of the medical students failed because they thought this was "just psychiatry". They believed you only had to learn how to "feel" about patients instead of learning about receptors, neurotransmitters and brain regions. This was a time of significant transition, and the medical students in subsequent years came along.
- TB: Were you able to pursue or encourage any research as Chairman?
- BE: We continued to try to enrich the research aspects of the department and urged our residents to do some scholarly work and present this at a Grand Rounds. Even if this revolved around a case report, it was geared to review the literature and consider publication.

Funding issues in psychiatry, for any department of psychiatry, were excruciating during those years. They still are. There were issues of mobilizing complacent faculty to see patients and to generate revenue, if they were bringing in their salary on a research grant. The "free ride" or the payment for teaching exclusively as a salary support was ending in academic psychiatry. There was a great deal of angst during those years. It was very difficult, not just for me, but for all department chairpersons to maintain departmental fiscal survival while trying to meet the departmental mandates for teaching, for making new discoveries or contributing to our medical knowledge base, as well as provide top notch, conscientious care for our patients.

During that time, I didn't have the time to do controlled studies, to get outside funding for research. However, I consulted at a residential facility for clients with developmental disabilities. Temple operated this facility and we saw a fair number of aggressive, mentally retarded clients. From that experience, though not published, were some interesting single case studies using  $\beta$ - blockers as well as SSRIs in autistic, aggressive patients. We would have a steady baseline of aggressive behavior cataloged by the psychologists on the units, then introduce the pharmacologic agent and show a reduction in aggressive behavior. If the medication had to be withdrawn for a side effect or if another clinician discontinued the medication, we would usually observe an increase to baseline of the aggressive behavior. We could demonstrate good correlative findings.

We also had a very interesting "natural discovery" at that facility where the dentist refused to do dental care on these patients unless they were anesthetized for fear of being bitten. The parents would not consent to general anesthesia, so these clients had very bad dentition. A new dentist came to the facility and agreed to see them as long as they didn't bite her. She took care of their dentition and, remarkably, when they had their root canals repaired, the aggression ceased. With a medical student, we went back to these patients and showed, using an estimated pain scale from the School of Dentistry, that there was a statistically significant correlation with what would have been the expected pain for these nonverbal patients and their aggressive behavior. This did underscore what we know clinically and teach, namely, that there are other interventions besides biochemistry or pharmacology for modifying aggressive behavior.

Academically, during that time, I mostly did reviews of the literature. I also served on an NIMH study section in the areas of PTSD and aggressive behavior.

- TB: So your time at Temple was more in administration and teaching. Where did you go next and were you able to return to research?
- BE: After seven years as Chairman in Philadelphia, both my wife and I felt it was enough and we returned to Madison. So, I am back in Madison at the University of Wisconsin. I am no longer doing aggressive behavior research. I am mostly teaching and providing clinical service. I head the consultation/liaison and emergency psychiatry hospital services there.

I suppose some people would say, well, all of this research training and why haven't you persevered? Why aren't you publishing papers? When I come back to meetings such as the ACNP, I ask myself that question. At the same time, I really believe that the research portion of my life allowed me to become both a better clinician and teacher to a new wave of predominantly generalist psychiatrists. It is critical to make them aware of how to read research papers and how to use clinical situations as a way of triggering curiosity and posing questions that can then be taken into either the research or basic science laboratory for study. I'm having fun with that right now.

- TB: When did yo leave Temple?
- BE: We left Philadelphia in 1997. For a period of time there was a hiatus in my academic career. I'm not certain that it is obvious on my current curriculum vitae, but maintaining one's self in the academic arena can be difficult, especially if you only want to live in one city. I did not have an immediate jump back to the UW faculty in Madison. I did some insurance consulting during the interim. This was a strange world to be in for an academic psychiatrist. But I followed another ACNP member, Barry Blackwell, into a behavioral health medical directorship, for a company based in Milwaukee. Subsequently, a position opened back at the UW and I returned full time in 2001. And now it is almost 2004.
- TB: Before movig to that would you like to say anything further about your research and publications?
- BE: We published some papers much like Mike Sheard's group at Yale. Michael was another person who was a psychiatrist, worked with animals, but also worked with patients. He published significant work with lithium in both rodents and aggressive prisoners. He, too, had difficulty with American science and morality being in conflict. I recall him telling me about his proposal to treat male domestic abusers with lithium. He went to the Yale IRB to do this; this is apocryphal, but I think it is accurate. He was told by the community representatives on the IRB that domestic violence is a "moral issue", not a "biological one". These abusers are bad people and clinicians shouldn't be helping them or giving them a "biological" excuse. They should go to jail. The community representative to the IRB contended that studying lithium in this population was inappropriate. I don't believe that this study has ever been done, although a number of us have used SSRIs, lithium or other agents, untested in blinded studies of domestic abusers, and found this helpful without obviating the abuser's legal or moral responsibility, but helping them to conform, their behavior to the law.

We also did studies with lithium, rubidium, cesium and the alkaline metal cations. The two that really altered aggression in our pain-induced

model were, of course lithium, and remarkably rubidium. It would have been dramatic to have had the ability to videotape the behaviors we observed. For example, in terms of brain lesions, a rat with large lesions of the septal nuclei is a very irritable rat. You can blow on this rat and it jumps out of the cage at your face. In terms of alkali metal cations, rubidium-treated rats are incredibly aggressive animals, an effect first reported by Jon Stolk, a past member of the ACNP. What occurs in the brains of these animals to change their affect, to make them so aggressive? I don't think we know yet although we do know that norepinephrine metabolism is increased.

Ron Fieve from New York Psychiatric Institute had attempted clinical protocols with rubidium as an antidepressant, as it had been used in uncontrolled treatment in Russia. Since its therapeutic effect for depression at safe dosing was not dramatic, the research did not proceed. I don't believe it was ever used at doses comparable to our animal studies, so to my knowledge there was never any report of it inducing marked irritability. It is fascinating and remarkable that you can give as simple a compound as a chemical salt to an organism that has been bred for generations to be docile and induce dramatic irritable and aggressive behavior.

- TB: But you never reproduced these effects in patients?
- BE: I have worked with repetitively aggressive individuals, whose closest DSM diagnosis would be intermittent explosive disorder. I have worked with mentally retarded folks. I worked for a period of time as a consultant to the Philadelphia Geriatric Center, treating aggressive, demented, adults. For whatever reason, be it administrative demands, my conscious or unconscious choice, my abilities or my inabilities, I did not commit those patients to systematic study such that I could publish it in the academic literature. I did publish some open case reports in the *American Journal of Psychiatry* and in *The Lancet*.
- TB: You were clearly frustrated in your research efforts. What might have made a difference?
- BE: I believe it really would have been helpful for moving the field along if there could have been an endowed chair for aggression research where NIMH or some other organization funded a responsible investigator in a program to study a clinical condition that needs to be addressed. Fund it substantively for five years and see what comes out. The issue is of a magnitude sufficient to justify this approach. We essentially did this for AIDS and we did it for AIDS dementia at the time that HIV was becoming epidemic.
- TB: What do you think why this did not happen in research on aggression?

- BE: One of the major impediments to such clinical research is the issue of informed consent. Somebody would have to provide informed consent by proxy for many of these patients, particularly the developmentally disabled or the demented. I believe there could have been greater research contributions to the field and to the practicing clinician if there had been a societal mechanism to oversee ethical research around this topic, weighing the risks of research with the benefits of attenuating aggressive behavior that often leads to more restrictive living conditions. Right now, clinicians have few controlled clinical studies to rely on in the treatment of the destructive behavior of their patients. They are essentially flying by the seat of their pants.
- TB: Are there valid, reliable measures of aggressive behavior, such as the Buss-Durkee aggression inventory?
- BE: The Buss-Durkee inventory doesn't measure the assaults. Probably the one that gets used the most is the Stuart Yudofsky's Overt Aggression Scale. Coccaro modified that. Our Carolina Nosology was a way of compartmentalizing or cataloging patients so that you don't mix the demented aggressive patient with the mentally retarded patient, the patient with autism or the aggressive patient with mania. These populations need to be separated so that if you are going to do pharmaco-therapy or behavioral interventions, you don't lump everything together. Clinically relevant aggressive behavior is a heterogeneous issue.
- TB: Do you conside aggression as as a condition co-morbid with a specific disorder, or do you consider it to be independent from diagnosis?
- BE: Certainly it can be co-morbid. When I was working with the developmentally disabled population, I evaluated a young woman whose mother had just died. This client was non-verbal. She looked depressed, and she looked as if she might fit Fava's aggressive depression characteristics. I had been asked to see her because of temper tantrums and assaults toward peers and staff. We started her on trazodone which we had been using in this population. Well, we flipped her into mania. The next week, when I returned to the facility, she was running around and singing songs. She wasn't crying anymore, but she was equally as assaultive. What was needed for her, as her diagnosis was clarified, was a mood stabilizer; to have her primary biplar diagnosis treated first.
- TB: Do you think trazadone should be systematically studied in any particular disorder where aggression is a common symptom?
- BE: I used a lot of trazodone in geriatric patients. It would be an interesting and useful study, particularly in patients with Lewy body dementia where there is a risk in using typical or atypical antipsychotic agents. Even to take a population into an open study could be valuable. But the

probability of obtaining funding is quite limited given that trazodone is off-patent and the agent doesn't fit a theoretically defensible construct to garner federal funding.

- TB: Does the aggression of a schizophrenic patient different from the aggression in a geriatric, demented patient in responding to trazodone? Would you think that aggression in a schizophrenic patient would respond better to another drug?
- BE: Well, Jan Volavka tried a study with tryptophan supplementation in schizophrenia. This was done before tryptophan was taken off the food market. If I recall the paper correctly, one or two patients responded positively, but most of them did not. He did not do that study in combination with other drugs that might have made tryptophan more effective, such as we did in our *Lancet* paper.
- TB: So both ou and Volavka used tryptophan supplementation to increase serotonin to control for aggression in schizophrenia.
- BE: However, its toxicity, secondary to impurities of tryptoaan halted this approach.
- TB: What drugs were you using in your animal research for controlling aggression?
- BE: We worked mostly with drugs to modify neurotransmitter systems. So we were particularly involved with ways of enhancing or depleting serotonin and noradrenergic systems. That was the focus of the lab. We also looked at whether strain differences or other influences, such as environmental mental stress, could push these systems in a way to change aggressive behavior.
- TB: What animal models did you use for studying aggression?
- BE: We worked with Karlis' model of predatory aggression and mouse-killing behavior. A certain number of rats will spontaneously kill mice. This can be modified through brain lesions or brain chemistry changes. There is also a murine model of cricket-killing. Similar to rats and mouse-killing, mice will kill crickets.

We also worked with pain or shock-induced fighting in the rat as a model of affective, defensive aggression. And we begun to incorporate Micek's intruder model of affective offensive aggression, but this was just at the time I was moving to Carolina and I did not reestablish my lab there. We also carried out general rating scale assessments on more naturalistic behavioral situations, but most of our publications focused around pain-induced or shock-induced fighting.

- TB: Weren't you involved in conditioning research?
- BE: We did not do conditioning experiments in this model. The closest we came, and it really is not conditioning, was the work I did with Redford

Williams at the NIMH. Redford was a behavioral internist interested in blood pressure, hypertension, stress, and emotion. He proposed we record blood pressure in these rats using a non-invasive tail blood pressure measurement. Interestingly this led to a paper in *Science*. When the animals are paired and receive foot shock, their blood pressure goes down, probably due to a peripheral vascular effect. This is highly replicable and statistically significant. However, if you take these same rats and give them the same foot shock alone in the cage they do not have the coping behavior of fighting and the tail blood pressure goes up significantly. The physiology and chemistry of these two responses is different. The increase in tail blood pressure is linked to the adrenal gland. Adrenalectomized rats do not show this effect. The decrease in tail blood pressure is a central effect and can be blocked in the centrally catecholamine-depleted rat that is treated with 6-hydroxydopamine.

Even more fascinating to us was the observation that if you put the rat in the cage, alone, and give it just enough shock to induce a flinch, you see the same increase in blood pressure. If you put two rats in the cage and provide a foot shock sufficient to induce a flinch, you see the opposite effect, reduction of blood pressure. This serves as a prototype or model that the social environment of an organism makes all the difference in the world, not only in the context of behavior but also in terms of their physiological response. How little we know about how these social cues affect our human physiology and how this differs from individual to individual!

- TB: Have you done research in the non-pharmacological influences on human aggression?
- No, we just did it in the context of our animals. Clearly, however, when BE: you teach about managing aggressive behavior in clinical populations you need to look at the environment and what's happening to the organism within that environment. Let me give an example that might illustrate this. Because of my interest in aggression, I have done forensic consultations and was seeing a prisoner in Wisconsin who was an arsonist. He had previously been treated with lithium but discontinued it and set another fire. Under Wisconsin law he was clearly responsible for his action and was not going to be excused by the State. The same day that I saw him, the Archives of General Psychiatry came out with an article by Matte Virkunin from Finland, reporting low CSF levels of 5-hydroxyindoleacetic acid (5HIAA) to predict recidivism in arsonists. I wasn't going to be able to assay this gentleman's 5HIAA in cerebrospinal fluid (CSF), but I would bet he had a low level and would fit into Virkunin's high risk population.

This leads us to the issue of how much of our behavior is driven by our biology. It even takes you back to Original Sin and Predestination. What does it mean for us as humans to think and talk about free will or morality and at the same time know that there are biological processes that drive us to more impulsivity, deliberation or anxiety, making it easier or more difficult for us to function in a "moral environment". I don't have an answer to this complex problem, but I think this is one of the great human questions. As one gets older one spends more time pondering these questions.

- TB: Do you think biological measures, such as 5HIAA, would help identify who is at risk for aggression?
- BE: Low levels seem put you at risk. The question is shouldn't we know about the biology of our patients or even our prisoners. Marku Linoilla, another, now deceased member of the College claimed it was criminal not to know what the CSF level of 5HIAA is in any depressed or violent patient because it is a significant risk factor for completed suicide and serious violent behavior. Why shouldn't we evaluate that any less than measuring elevated blood pressure in assessing risk factors for health and safety. Just as with hypertension, shouldn't be 5HIAA level an indication for early medical intervention?
- TB: Is there sufficient evidence for that?
- BE: I believe it would be a reasonable medical and social project to assemble and follow a population longitudinally, and measure the predictability of low 5HIAA on human behavior. But in this country we have a lot of difficulty putting needles into people's backs, especially those who may be violent and may choose not to consent. So it would be wonderful if we could develop non-invasive techniques to measure compounds like 5HIAA in the CSF. We do spinal taps in children with meningitis and the lifetime risk of harm due to aggression may be just as grave in individuals with low levels of 5HIAA.
- TB: Do you have any suggestion about selecting medication to treat aggression?
- BE: It depends upon the individual. Our social database is crude right now. Coccaro's work suggests in people who have an intermittent explosive disorder, serotonin-enhancing agents like SSRIs can attenuate their aggressive behavior. This is also consistent with Mike Sheard's work with lithium. He suggests that the effect may not be directly on "anger" per se, but rather on the impulsivity and the "hair trigger" evident in certain individuals. In conversation, he noted that aggressive prisoners on lithium reported that they were just as angry, but had some time to

think about whether they wanted to go into solitary confinement or not, inhibiting their aggressive behavior.

The literature concerning brain-injured patients treated with high doses of  $\beta$ -blockers such as propranolol is also compelling, probably also affecting impulsivity more than anger. I've seen this intervention effective for patients that have preexisting head trauma. There is compelling literature that argues for the use of low doses of antipsychotic agents, particularly the newer atypical agents, in managing aggressive behavior in clinical populations. We would do better both with compliance and demonstrating efficacy if we characterized these patients with greater specificity. This comes back to the fact we don't have a nosology within DSM to define aggressive patients in day to day clinical practice. We don't know which populations would do best with behavioral interventions alone in combination with pharmacotherapy, such as in the treatment of post traumatic stress disorder. Until we have homogeneous populations in which to test interventions, it becomes very much "catch as catch can".

- TB: Let's go now to some of your most recent activities.
- BE: I'm not doing research now. I miss that, but I'm also very busy clinically and I'm busy with ten grandchildren, so there's a personal life that is very rich. Certainly there are some natural opportunities. On the consult service we've encountered several patients with aggression and Lewy Body Dementia. I should be thinking more of developing and using single patient protocols for psychopharmacologic discovery. However, the reality is that those of us in the clinical arena are very time-strapped providing services to poorly funded programs.

I do a lot of consultation with the transplant teams. We see psychiatric and behavioral problems with liver, heart-lung and kidney-pancreas transplant patients. I don't talk with my transplant colleagues about reimbursement. They work very hard but American medicine is set up to reward "procedures" which are substantially more remunerated than psychiatric practice. It would be delightful if the funding resources were greater so that I could share my role with a colleague. This would allow me time for scientific development and protocol writing to improve the clinical condition of the aggressive patients we see and more effectively guide our clinical interventions.

- TB: Let me switch topic. When did you join ACNP?
- BE: I don't remember. I suspect that it was in the late 1970's. Leo Hollister and Jack Bachas were my main sponsors. As I said earlier, Arnie Mandel invited me first to the College in 1973 to participate in a plenary session on aggression.

- TB: What would you like to see happen in the future? You mentioned a couple of things you would like to see occur.
- BE: American psychiatry needs to come to terms with clinical reality. There are many patients who are disenfranchised. They are being treated at more intense levels of care, more restrictive levels of care, than they would need to be if their aggressive behavior were in better control. American psychiatry, the APA and the NIMH need to recognize this is a significant clinical and human problem with major economic and personal costs. It is not a criminal problem. There is a criminal problem too, but I am referring to the clinical problem. These patients are being sometimes appropriately, sometimes inappropriately, but most of the time not at all, treated for their aggression, which DSM doesn't recognize as a disorder. This is a disorder that alters lives which may already be impaired by head injury, mental retardation or by dementia. As a clinical problem area, psychiatry and the whole of behavioral health need to look at this. They should recognize it and develop a moral, ethical and clinical strategy for intervening. This requires the organization of information we already have. It also requires testing hypotheses to improve these peoples' lives. It is very difficult because many of them cannot provide informed consent. If you turn that around, though, why should a person who cannot provide informed consent be disenfranchised from research opportunities that a person with a panic or depressive disorder has access to? I think that is not only unfortunate, but morally wrong. We should develop some type of national effort. This is not mind control. It is not social control. But it could benefit a very large population who are isolated, disenfranchised, and often imprisoned by their aggressive behaviors.
- TB: That is a passionate summary and I think we have probably covered everything we need to. Thank you very much.
- BE: Thank you.

## JEAN ENDICOTT

## Interviewed by Darrel Regier Boca Raton, Florida, December 2007

- DR: I am Darrel Regier and I am the director of research at the American Psychiatric Association. I am very pleased to introduce Professor Jean Endicott.\* Jean, why don't you start from the beginning, in terms of where you were born and your early life experience?
- I was born and lived in a series of small towns in northeast Texas. My JE: father worked for Humble Oil Company and, from the beginning, I was interested in science and doing experiments. I will always remember that I wanted to see what would happen if I planted seeds from beans in my father's worm bed, which he used for worms to go fishing. Of course, they took over the worm bed completely and climbed up the tree. I ended up having my own worm bed, so I could grow cantaloupes from seeds. That meant everything to me. In high school I took as much science and math as I could. When I graduated I was planning to be an organic chemist. I had even explored the programs at the University of Texas. However that summer I worked in the county emergency room at John Sealy Hospital in Galveston. I started wondering, did I really want to be a laboratory scientist or did I want to do something with people? An emergency room in a sea port town is a good place to learn about people. So, when I went to the University of Texas I was in an honors program that allowed you to take any course you could talk the professor into letting you do. I took all the chemistry, biology, physics and math that I could, but I also talked my way into a graduate course on abnormal psychology. I was totally hooked. This was what I wanted to study and where I wanted to go. So, when I transferred to the University of Connecticut, I majored in psychology and minored in zoology. I also did as much in the way of science as I could and, then, got into Columbia University Teachers College for the clinical side of psychology
- DR: What year did you graduate from the college?
- JE: I graduated in 1958 and worked for six months in Connecticut as a social worker at Long Lane School for Girls. I did a little bit of research there, too, getting the girls to fill out various kinds of questionnaires. Then, in the spring, I started graduate school at the Teachers College in the clinical psychology program.
- DR: So, that was your first introduction to Columbia University?

<sup>\*</sup> Jean Endicott was born in Jacksonville, Texas in 1936.

- JE: Yes. I didn't tell them that my husband I got married at the age of eighteen, after my freshman year of college was going to have to go into the Air Force under the Berry Plan, after he finished his residency in psychiatry. I didn't tell them because if you tell them you are going to leave after the first year, you are not going to get into a PhD program. So, it was a sin of omission! I also did some extra work because I thought if you are going to have thirty hours of graduate courses, you might as well get your masters. I did that and then I asked my advisor; "What do I have to do to get back into the program after my husband finishes his Air Force term"? He replied "You have known the whole time that you were going to go, righ"? I said, "Yes, but you wouldn't have let me in". He agreed but told me to send him a letter or call, which I did two years later. So we moved to Manhattan, I finished my graduate work and got my degree in 1964.
- DR: That was at the beginning of the Vietnam War. So your husband was in the Air Force during the war?
- JE: He was in the Air Force for two years. Egland Air Force Base was a psychiatric receiving center, so there were about eight or nine psychiatrists and for a brief period they thought they might have to extend their service. Everybody had already lined up jobs and we were watching the news very closely, but he was discharged in July of 1960.
- DR: So, you went back to Columbia?
- JE: Yes. In the meantime, my husband and I had done some research while he was in the Air Force and we were busily writing papers. He was the leader in that, but I was learning a lot about research and the practical realities.
- DR: Tell us about your experience through the rest of the doctoral program? What did you focus on?
- JE: The program was very strong on measurement and assessment. Dr. Schafer, who was head of the clinical psychology program, taught an excellent course where you read papers and summarized them on five by eight cards. I always remember those five by eight cards. You summarized the aim, the method, and the findings and then you critiqued the paper. It was fantastic training in critical thinking. The big issue was did the method really address the question? Did the authors have the measures to even try to address the question? There were also very good courses in statistics related to measurement and assessment. When I graduated I met Bob Spitzer at a cocktail party of a mutual friend. I had done my internship at the Psychiatric Institute, and he knew I had been there. He asked what I planned to do after graduation so I told him I would be looking for a full time research job. He

enquired what kind research and I told him that my best training was in measurement, assessment and clinical description. He had a new grant starting in September and asked me to see him the next week about a possible job. I have been there ever since.

- DR: What year did you start?
- 1964. He had developed the Mental Status Schedule and I was hired as JE: a research assistant to interview patients. After a year or two, he and Joe Fleiss were talking about developing a scoring system. It was a small office and I could hear everything and I thought they were reinventing the wheel. So I went in and said, "There are standard procedures and methods to go through when you're developing scoring systems; there are choices that you have to make". Bob looked at me kind of funny and Joe Fleiss said, "So what"? So I replied, "I didn't get a PhD to be a research assistant the rest of my life, and if you are going to develop a scoring system I would like to be involved". Joe immediately said, "That makes sense", and Bob said, "Yeah, sit down". So I continued to interview patients, but got very involved in the factor analysis and cluster analysis of the data. The first thing I learned with factor analysis was that it makes a difference who your subjects are. We got a factor, and named it by content, "Alcoholic Depression". We had data from a bunch of investigators, so I called up one and said "The primary diagnosis of your patients is depression; were a lot of them alcoholic"? He replied, "This is a drying-out-farm; they are all alcoholics". So you get different factors, different clusters, depending upon what patients you study. Also, I learned about the issue of stability. We split our two thousand subjects, odd and even, and did the factor analysis with different kinds of rotation and different numbers of factors and, then, repeated it. The issue was which of these factors are stable and which dissipate?
- DR: Some members of our audience may know this, but at that time this marked the development of some seminal instruments for the entire field of psychiatric research. You were developing major tools for clinical assessment in some of the biggest studies that were going to be supported by the NIMH. Could you say a little bit about the range of the instruments that you developed at that time?
- JE: Initially, after the Mental Status Schedule, which measured mainly symptoms, we wanted an instrument for function, so we developed the Psychiatric Status Schedule. It had broader coverage and roles such as wage earner, homemaker, parent and the like. But it was a very lengthy questionnaire with many dichotomous items and clinicians were not favorably inclined to use it. We used our experience with that to develop the Current and Past Psychopathology Scales (CAPPS),

which had six point scaled items of the same concepts that were covered in the Psychiatric Status Schedule. At about that time, the potential for a large collaborative diagnostic study was being discussed at NIMH and there were issues about what scales would be used to evaluate the patients. The Feighner Criteria had been developed by Eli Robbins and the group in St. Louis. So, there was a preliminary grant. I think Joe Mendels and Bob Spitzer were the principal investigators at the two facilities and, initially, we were just going to modify the CAPPS. It immediately became apparent that we had problems. One was that we needed diagnostic criteria for additional conditions, not just for the Feighner Criteria. So there were discussions with Eli who felt there was no evidence for those other conditions. Our argument was there never will be if we don't develop criteria and methods for evaluating them. Maybe they won't hold up, or maybe they will; but we ought to expand the Feighner Criteria. So we developed the Research Diagnostic Criteria (RDC) with Eli and a lot of input from colleagues. We would meet with people about a syndrome and ask what the defining characteristics that could be judged reliably were. We developed the RDC, the Schedule for Affective Disorders and Schizophrenia (SADS) and the Family History Diagnostic Criteria, because we know that the family members are excellent sources of information. We knew we also wanted to get some family study data, so we developed a lifetime version of the SADS to interview relatives about themselves. These scales were tested in a four facility pilot study to see if we could get reliable clinical evaluations. We also collected some other data for initial validity. Then, the Collaborative Depression Study was funded and that was a five facility study. We had to show cross-center reliability. Intake on that study started in 1978, went on to 1981 and we are still following those subjects.

- DR: It is important to note that the whole development of the RDC formed the basic framework for the DSM III. The SADS instrument that was used in the psychobiology of depression collaborative study was one of the prototypes of structured interviews that could be used in clinical settings and the SADS-L became the major prototype for epidemiologic studies since it had a lifetime measure. That was an incredibly important period for classification, the defining of disorders, and for the development of methods for assessing disorders in large scale studies.
- JE: During that period, also, I was very lucky. First, I got to come to ACNP a lot as a guest of Joe Zubin or Bob Spitzer. Also, because of the measurement issues and the importance of measurements in the assessment of patients, I became a member of the FDA Psychopharmacology

Advisory Committee. I always made sure that I sat next to John Davis because he helped educate me. Of course, I was attending the ACNP meetings, and it was partially because of that FDA experience that I became a member of the ACNP. I always say I was very lucky that I came along in the seventies because when I look at who is getting into the ACNP now it probably wouldn't happen to me. That was at a time when measurement was a big issue.

- DR: Well, it was an incredibly important stage where measurement was an issue for all the new clinical trials that were starting. The New Clinical Drug Evaluation Unit of NIMH (NCDEU) worked closely with many of the ACNP investigators. Perhaps you can say something about the functional assessments that you did with the Global Assessment of Functioning or the GAF scale and the like.
- We realized that the instruments we were developing were giving us JE: measures of dimensions or syndromes, and functioning in one particular area. But clinicians tend to talk about the severely, mildly and moderately ill and we could make discriminations that were better on a six point scale. Jack Cohen had always told us, never dichotomize anything, and don't try reducing the scale points unless you absolutely have to; the more points that clinicians can reliably discriminate the areater the sensitivity. So we looked at what the global measures were and the Luborsky measure was available. However, one of the problems with Luborsky's measure was that some of its anchor points used diagnosis, so with schizophrenia you couldn't get higher than a certain level but if you had certain other disorders you couldn't get a score on the whole range. We knew if you were following patients over time, regardless of lifetime diagnosis or even current diagnosis, there could be a great variety of levels of symptoms and functioning. So we basically took Luborsky's scale and changed some of the anchor points and developed the GAS (Global Assessment Scale) which was later incorporated into the DSMs as the GAF with some slight changes. We found, as many investigators did, that the GAS was an incredibly sensitive and good predictive measure. Philip May would give patients with schizophrenia a medication and, then, do a twenty four hour GAS which was the best predictor of how they were going to do. What was wonderful was that when we developed a new measurement tool many investigators were willing to put them in their studies and make the data available to us. That was very good feedback.
- DR: It was a very important time for me because I was at the NIMH developing a Primary Care Research program. We had a major study at the Marshfield Clinic in Wisconsin where we had David Goldberg's GHQ as

a screening measure and then used the SADS-L with the RDC criteria and the GAS. We found that the most predictive measure for service use on either inpatient or outpatient for specialty or primary health care was the GAS; better than any single diagnosis. It was on this basis that I encouraged Bob to drop Axis V in DSM III and insert the GAF or GAS in the DSM III R. My experience was replicated by many others that this was a major step in bringing a dimensional measure to diagnosis. It's really the only dimensional scale in the DSM.

- JE: In the nomenclature now.
- DR: Yes
- JE: It is interesting when you talk to clinicians. Initially they say I'm not sure I can do that; it's too broad or vague. But, then, they find they can make good ratings.
- DR: One of the things we wanted was to get your kind of research career off the ground. Can you tell us a little bit about the funding experience in terms of the grant application, and where did your funding come from?
- Initially, it was all from the NIMH and there were ups and downs. During JE: the Vietnam War we had a grant from NIMH and about two months before funding was due to start we got a phone call that we should send in alternative budgets cut by a third or two thirds. If it was cut two thirds we would all three have to share an eight by eight office. Bob and I would interview the patients and Loretta would analyze the data. Luckily it was a small cut, not even a third. After that, it was primarily NIMH. Later, when I started doing some work with Wilma Harrison, on psychopharmacology trials in severe premenstrual mood changes, we began getting pharmaceutical company support. Over the past few years we developed instruments like the Quality of Life Enjoyment and Satisfaction Questionnaire, which is used widely now, the Daily Rating of Severity of Problems which is primarily used in menstrual cycle research, but has been slightly modified and is also used in some other studies with different conditions, and then the Work Productivity Scale. All these were sponsored by pharmaceutical company money with the condition that I could make them available to other investigators.
- DR: What specific drugs were you studying?
- JE: Up to that time, nothing had been shown better than placebo. In our first formal study, we did some pilot work with alprazolam. Wilma was working in the Depression Evaluation Service and had observed that some patients, with clinical symptoms that were similar to those seen premenstrually, seemed to respond to alprazolam. It's a mixture of anxiety, depression and irritability. So, we did a pilot study and got the funding. What we thought was extremely important was that most

studies of severe premenstrual problems either took all-comers selfdiagnosed or they didn't screen out premenstrual exacerbation of ongoing disorders. Who knew what condition they were studying? So we went through an elaborate procedure of screening the women and confirming their changes with daily ratings, then a placebo cycle followed by treatment. That was the first study that had ever shown anything was better than placebo. We got the lead article in the Archives on that. Our focus was on the methods; that if you carefully screened your patients and carefully described the type of patient, you could show a drug placebo difference. We did a series of studies with various SSRI antidepressants.

- DR: This was a major clinical focus you have had for some time?
- JE: A New York Times reporter asked how I became interested in this area? I said I had both a professional and personal interest. In doing a family study, you would ask members with depression, "Have you ever had a week when you had anxiety and irritability as well"? Some would say, "yes, every month".
- DR: Premenstrual episodes?
- JE: We started training raters to code that. About that time Uriel Halbreich started working with Ed Sacker. Uriel had done some work in Israel on premenstrual tension and he asked "How does the RDC handle premenstrual anxiety and depression"? I replied, "Badly, we just call it other". So, we started working on measurement techniques. In the meantime, Wilma was treating depressed women and running across premenstrual problems so she and I started talking about doing a treatment study. In many ways, the highlight of my career was when I had the opportunity to talk to FDA staff and the Psychopharmacology Advisory Committee on the evidence for premenstrual depression.
- DR: Dysphoric disorder!
- JE: Right. We went through the period of calling it Late Luteal Phase of Dysphoric Disorder. There was good evidence that it was a distinct clinical entity. It was primarily summarizing the evidence we learned since the source book was published.
- DR: The source book? Are we talking about DSM IV?
- JE: The APA source book.
- DR: Right.
- JE: In which the last reference was 1993. Since that time, once the criteria were available, there have been a fantastic number of studies.
- DR: Let me clarify for folks that are not familiar with the DSM IV which version had preliminary research diagnostic criteria.
- JE: That was DSM III R.
- DR: OK. Premenstrual Dysphoric Disorder (PMDD) was introduced as a supplementary diagnosis for further study in DSM IV. You were involved in the workgroup, as well?
- JE: I was.
- DR: Which was a controversial workgroup, so maybe you can say a little about that?
- JE: There had been a small informal workgroup for DSM III R, and we had come up with criteria a number of us had been using. When the workgroup for DSM IV was formed, it was apparent from the beginning when you read the names that we would probably disagree. I won't name any names, but it ranged from one extreme to the other. What was amazing was that we were able to work together and agree on criteria. Where we disagreed was, should it go into the main body of the nomenclature, be in the appendix or should there be something in between, an NOS, Not Otherwise Specified, code, with criteria in the appendix. Allen Francis, who was in charge of the process, kept trying to get us to agree. One day on a conference call I said, "Allen, we are not going to agree. Why don't you let us present our positions in writing to the nomenclature committee? Present our recommendation and rationale and let them make the decision"? They chose that middle NOS. We got our nose under the tent, but we didn't get inside. However, by having the full criteria in the DSM III R and DSM IV it has provided a real impetus to research on pathophysiology, genetics and treatment. Now there are four compounds approved by the FDA.
- DR: The publication of those criteria generated the kind of clinical trials for the four medications and I believe that fluoxetine was the first.
- JE: Fluoxetine was the first and then sertraline and paroxetine. And recently, a special formulation of a birth control pill, drospirenone and ethinyl estradiol which differs not only in hormonal content, but also timing. It is given twenty one days on and only four days off and that seems to make a big difference.
- DR: What is also of historical interest is that this was the first non-DSM diagnostic indication that the FDA has ever approved for a medication.
- JE: For a medication, yes, and there was concern. In other areas there is medication for pain; there is medication for fever, etc. But, as far as the psychiatric conditions were concerned, everything was in the DSM. We had a workgroup in Washington where we had invited FDA members to come. Out of that workgroup and all of the reports, we had written a paper; "Is premenstrual dysphoric disorder a distinct clinical entity"? They asked me to present that to the Psychopharmacological Advisory

Committee. If they didn't agree they were not going to consider fluoxetine. It was a no brainer, as they did agree.

- DR: It was a very important contribution. What would you say in your career was your most important contribution to the field?
- JE: I would say it's the RDC, because they really moved things along and led to better communication between clinicians and selection of samples. There are problems about the criteria; Joe Zubin used to say they should "cut nature at its joints", but at least they were an improvement. I think the work on changes in mood and behavior along the menstrual cycle was imporyant. It wasn't just at the level of the PMDD, but also improving the methods, so that if you were going to do pathophysiological studies, you had better documentation in terms of symptoms, particularly for lag time analysis and things like that.
- DR: Were there any honors, awards or distinctions that came along with any of this work?
- JE: I considered becoming a member of the ACNP one of the best.
- DR: What year was that?
- JE: 1975. There were some others, not a whole lot, but there were others. I became president of the American Psychosomatic Society and I think part of that grew out of some of my work. Always, through the years, I have had a tremendous amount of enjoyment working with other investigators and with PhD students. They were calling me and asking, do you suggest I use this or that?
- DR: Well, could you mention by name some of the people that you have trained over the years?
- JE: Wilma Harrison with the measurement part. She was the physician and knew the pharmacology part but she learned the method part and then went to Pfizer as a strong methodologist for their studies. I think that was important. There were so many people over the years, people in the Collaborative Depression Study that have gone on to do independent work elsewhere, like Nancy Andreasen. I just can't name them all.
- DR: That study continues to be almost like the Framingham study; it's a major resource for our field that has enabled us to draw on information generated from a longitudinal cohort of patients with major depression disorder that has been followed since 1978.
- JE: Right and we are still following sixty five percent of those that are not known to be dead.
- DR: It has both a clinical component and a biological component?
- JE: I was not directly involved in the biological component other than training some of the clinicians in the SADS in the RDC and conferring with

them about how to use those procedures in their analyses. We were in the clinical component.

- DR: That's the only one that has been sustained?
- JE: Yes.
- DR: Almost thirty years?
- JE: Thirty four years.
- DR: Okay.
- JE: Part of that was the development of SADS and the RDC?
- DR: Right, probably one of the longest running NIMH supported studies we have.
- JE: I think Myrna Weisman has one that has been going on a long time, too.
- DR: Could you tell us something about your family and how you managed to reconcile family and professional life?
- JE: I was very lucky. My husband went into medicine to do psychiatry and was into research also. We understood there would be periods when we were waving at each other as we were coming and going. We didn't have children, if we would that would have changed things considerably. He has always been very supportive and I am not a good cook! Assortative mating; you start to date and there are a lot of questions you don't ask. Then you find later you have shared interests and experiences that make you more understanding of the other person. I have been married for fifty-two years, so I guess it has worked.
- DR: Great. What is your husband's name?
- JE: Noble Endicott.
- DR: What other activities were you able to invest in outside of work?
- JE: We have collected tribal art for nearly thirty years and, prior to that, we collected ninetieth century American art. If we had unlimited funds, we would need a Hearst Castle. His brother asked about our stocks and bonds and we said we didn't have any. So he asked what we spend our money on and my husband replied, look around; it's on the walls and shelves. That has been marvelous, because it's not only fun, but you get to meet a lot of very interesting museum and gallery people, and other collectors. Early on neither of us had talked about any interest in art. When my husband was getting out of the Air Force we stopped in Georgetown and saw a picture in the window of a gallery and we went in and bought it. We tend to like and dislike the same things.
- DR: That's wonderful. I have known you for many years and had no idea about your interests. What current activities are you focusing on now?
- JE: I am helping analyze data on the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) from a number of studies. Like all instruments when we develop them, we are hoping they can be

used with a wide variety of patients with ADHD, ALS and in conditions with central pain from spinal cord injuries. I have also helped interpret data, of course, from patients with bipolar depression and different anxiety disorders. We are also involved in a registry of treatment resistant depressive patients. Some are getting Vagal Nerve Stimulation, (VNS), and others are getting treatment as usual. We do the independent interviews at baseline, three, six, nine, twelve eighteen and twenty four months. Several instruments I have developed are being used so I will be involved in the analyses. The Collaborative Depression Study is ongoing and we just put in a renewal request for another five years. We handle the data centrally and I am going to be working with several of the investigators to modify the treatment summary programs. We have gone to tables with outcome levels as opposed to equivalence. When we first started out in the seventies, there weren't many drugs used for Affective Disorder so we have made modifications. I am interviewing a lot of those patients. I have always done that. Anytime we are doing a study, I try to be one of the interviewers, as well as captain of the ship.

- DR: Who is the Principal Investigator (PI) now for the collaborative depression study?
- JE: Marty Keller. Bill Coryell is the co-chair in Iowa, Bill Shefner in Chicago, John Rice in Saint Louis and I in Columbia.
- DR: That's an amazing study and it continues to be productive.
- JE: Sometimes I get a call to say I am the collective memory; I have been here from the beginning. I reply yes, but that memory is wearing thin!
- DR: In a reflective mode, would you say your professional career turned out the way you expected?
- JE: I feel that I have been incredibly lucky, and have worked with a lot of very smart and generous people, willing to share. Being a psychologist in the medical field has made all the difference. From the beginning, I have been treated as a colleague and not as a helper; that has been better than I would have ever dreamed. People ask, when are you going to retire, and I just say never. If they enquire, what if you don't have funding, any staff or space? Then I say that I'll sit in the library, write papers and preach. It has been a marvelous career and I have been exceptionally lucky.
- DR: What do you see in the next five to ten years?
- JE: Maybe developing additional procedures. Bob Spitzer taught me early on that if a concept can be described clearly and you sit down with someone who wants to study something, a measurement procedure can be developed. Even with very vague concepts, maybe there will be problems with reliability and validity, but a stab can be made at it.

I like to do that. I work with other people who are developing things now. The way the quality of life form came up was Wilma Harrison asked. "What do you think about the available quality of life measures"? I replied that many of them were really symptom measures and not quality of life. I worked with cancer patients and at the Neurological Institute as a Research Fellow for a period of time and was impressed with how many patients had a good quality of life in certain areas. She asked if I was interested in developing a measure and I said I would want it to be from the point of view of the patient; if they are satisfied and get enjoyment out of something, then, fine. You can be the worst housekeeper in the world, but if you are satisfied, then, fine. I said think of the college student and his small messy room; but he is satisfied, okay? So she and I developed the Quality of Life and Enjoyment and Satisfaction Questionnaire. Later, I was asked to work on a pediatric version which is being used in some international studies. It is fun also working with the translators because the adult Q-LES-Q is available in seventy two languages or dialects. There are about ten Spanish and a number of French versions. Working with people doing the translations has been a real eye opener because I don't speak any other languages. I have been learning about concepts and how to convey concepts in a variety of languages and settings.

- DR: So the Q-LES-Q is being used in general medical as well as psychiatric settings?
- JE: It's been used with some general medical patients. Not so much in clinical settings, but in studies of patients who are HIV positive, have central pain, low gonadal hormones or arthritis. It was developed so that it was not tied to a particular diagnosis. Once a measure is out there people start using it; that motivates me. I have a fairly large division now, so a lot of my work is with junior people. I see that continuing among a variety of conditions. For example, what do psychiatrists know about the sexual interests and behavior of their bipolar patients, who are at high risk for risky behavior? One of the people in my department, Jennifer Downy, has worked in this area and we developed a form that has gone to a large number of therapists in one of the GAP groups. That's part of the fun!
- DR: One of the mantra's that has emerged in the last couple of years, particularly with the Star D study, is more measurement based care. It would seem that the kind of instruments you have been working on, whether its quality of life, functional or diagnostic assessment, are basic elements in measurement based care. What do you see as the limiting factor for getting more of these instruments into routine clinical care?

- Clinicians, these days, seem to be incredibly busy. One of the things JE: in treatment resistant depression that has impressed me is how little time patients have with clinicians. And it is relatively rare that nurse practitioners or social workers spend more time with them. You are lucky if you get fifteen minutes medication management. I see that as a real impediment to the use of measurement instruments. There have been some good programs with HMO's, where an assistant makes a telephone interview that is used as part of the feedback to the clinician. The Q-LES-Q and many other measures are available on IVR where the patient calls in, punches the buttons and makes self ratings. For many conditions, self ratings are what really count because, if the patient's quality of life doesn't improve, they are not going to be adherent to the medication. The clinician is focusing on side effects and on medication while the patient is saving. I am not enjoying life. Patient reports, either by telephone interview or by access to telephone self report measures should be used more. People are moving more to this in research, using a palm pilot report, or computers at home that have a reminder that pops up to make ratings. But that limits who can participate. I have found that patients are willing to fill out forms and take them to the doctors. The doctors don't have much time to look at them, so there needs to be a method to alert them that this patient has been on medication for six weeks and doesn't seem to be improving; maybe you should consider something else.
- DR: Having forms available for patients, either before they come in or in the waiting room or on a computer terminal or something that they could plug in, does seem to have potential particularly if our field moves into electronic health records and there is the ability to input information in an easy and time efficient manner.
- JE: John Greist did studies a long time ago demonstrating that patients often are more willing to tell the computer things than they are the clinician. He did some studies about suicidal ideation and found that patients would answer the questions positively with the computer but either wouldn't bring it up with the clinician or would down play it. Other people say nobody wants to use computers. Well, there are three year olds that use computers now and pretty soon that will not be a barrier at all except maybe with us old folks.
- DR: As I think about the contributions of your career, the whole issue of measurement has left the field with the RDC, which evolved into the DSM system. The functional assessment that measures the quality of life, all of these continue to make a tremendous impact and as we

get into more better information processing modes with computerized medical records and the like their use is just going to expand.

- JE: I agree, and it should. Even to get people to use them in studies. I am working on getting the FDA to recognize quality of life as a non-redundant secondary outcome. They say it's correlated with symptoms, but it is correlated at a level far below of what one would think of as redundant. So, right now, there is a resistance.
- DR: One of the biggest problems with adherence, as you have said, is that some of our available treatments have side effects that make patients choose to discontinue. Unless you are capturing that information, you are not able to follow them as clearly.
- JE: Right. Patients are not going to bring up a lot of things that are important if they are not asked.
- DR: I want to thank you, Jean. It has been a delight, to hear the history and the development of your contributions.
- JE: It has been fun to be able to tell it!
- DR: Thank you very much and thank you to the ACNP for providing the opportunity.
- JE: OK, thanks.

## **BARBARA FISH**

## Interviewed by Marcia Meldrum & Elizabeth Bromley Los Angeles, California, September 11, 2008

- MM: This is September the 11th, 2008, and we're starting our oral history interview with Dr. Barbara Fish\* here in her lovely home facing the sanitary landfill. Is this Brentwood or Encino?
- BF: No, it is just Los.Angeles.
- MM: I'm Marcia Meldrum, one of the interviewers. Could you tell me about where you grew up, who your parents were, how many kids there were in your family?
- BF: I was an only child. My father thought even one was too much. He was a mechanical engineer brought up in the ghetto of the East Bronx.
- MM: Dr. Beth Bromley, our second interviewer, has now joined us. You were saying you were an only child and your father was a mechanical engineer.
- BF: He couldn't even spell correctly in school and flunked, but somehow calculus was easy, so he became an engineer. He and I had a certain kind of relationship, all about science. I remember a total eclipse in 1925, when I was five. He explained the eclipse to me with a kitchen bulb, a grapefruit and an orange. We would walk together, looking at ants and bees, and then we'd read about them. So I was encouraged in nature study and science.
- MM: And you went to the Ethical Culture Fieldston School in New York?
- BF: It was a marvelous school. I had a scholarship all the way through high school.
- MM: Excellent. Did they promote your interest in science?
- BF: Oh, yes.
- MM: What was your favorite subject?
- BF: Science.
- MM: This was in the 1920s, and at some schools a girl who wanted to be a scientist would not have been much encouraged.
- BF: This was different. Whoever you were, you were encouraged.
- MM: In science, did you like the laboratory work, the experimental work?
- BF: Yes, everything.
- MM: Was there a particular class or experiment that you remember?
- BF: I remember dissecting a rat and putting the skeleton back together to make a model
- MM: What happened after high school?

<sup>\*</sup> Barbara Fish was born in New York, New York in 1920.

- BF: My mother didn't want me to go away to college. I could have won a scholarship anywhere. So I had to go to Barnard, which was very dull.
- MM: And your major at Barnard was?
- BF: Science.
- MM: Just science, it wasn't biology or chemistry?
- BF: I ended up with ninety-eight points of science and fourteen, or whatever was required, in each of the others.
- MM: But the teaching there was dull?
- BF: The ones in science were interesting. I was also on the National Youth Administration, part of the New Deal and it paid half my tuition, two hundred dollars
- MM: It was the Depression and a tough time for many people. What happened next?
- BF: I graduated at 20 and wanted to go to medical school, but I didn't think we could afford it, so I was planning to teach biology. But then the war came, so I was able to go to medical school at NYU.
- MM: You still needed to stay in New York?
- BF: Yes, but NYU was a good school.
- MM: Your family was able to afford the tuition?
- BF: I got a scholarship, but it was only a couple of hundred dollars. Then my dad was able to help. I also took a paid internship at Bellevue. You did all the scut work and took admissions until midnight, twenty-four hour shifts on alternate days. We worked hard.
- MM: You found that interesting, enjoyable?
- BF: Yes. You learned; you saw everything.
- MM: This was during the war?
- BF: Right, so we had to do the four years of medical school in three, so the men could join the army in Korea. After graduation there were plenty of jobs available for women so I went to Cornell to do medicine for a year. I really loved kids, so I decided to take pediatrics for two years. What I loved most was talking to mothers. So I decided to consider psychiatry. I knew Lauretta Bender, who was head of the child psychiatry at Bellevue.
- MM: Had you met her before?
- BF: In medical school I was kind of fascinated by her teaching about schizophrenic children. So after my pediatrics internship I wanted to have a year or two with her but I had to start at the beginning of residency, in the general psychiatry.
- MM: With the adults?
- BF: On the adult and adolescent wards before I was allowed to take a couple of years with her. She had a senior and a junior resident. I had one

year working under Al Freedman and the next year I was her senior resident. We split the three hundred and fifty admissions we got every year between the two services

- MM: Where did all these children come from?
- BF: From various agencies around the city. We took everybody that nobody else wanted, from the Bronx and Manhattan. You learned a lot. It was like cramming. We'd present our cases every week to Lauretta, and she would see much more than we had. It would be a teaching session, she would demonstrate everything.
- MM: She sounds like a very interesting person.
- BF: She was a fascinating person. She had been married to Paul Schilder and they were both geniuses. I knew their children growing up and visited their home on weekend.
- MM: What was it like on the children's service in those days?
- BF: The psychotic children got electric shock. We didn't have chlorpromazine. We had phenytoin which didn't do much of anything and diphenhydramine which was a little soothing. And that was it. We had play therapy and all kinds of activities. We had some wonderful aides who did recreational therapy of all kinds and we had a public school upstairs. It was a very good setup, basically.
- MM: Could you just talk about the way Lauretta Bender approached the children? Or anything that particularly impressed you about her?
- BF: She could sort of get inside them. It didn't seem mothering, and yet it was. She could ask very blunt questions and get right into the heart of what was troubling them. She started following kids in 1930. When I came in the early fifties she had five mothers who had kept baby books from the birth of their children with schizophrenia and she analyzed their development. She wanted me to do the same and I couldn't. If you're working up a hundred and fifty kids, you couldn't do it. So I said I'll start when I finish residency, and that's what I did. That's how my research started. Schizophrenia first fascinated me.
- MM: I can see that it would. How was schizophrenia understood at the time?
- BF: There was a whole spectrum. When I was running the service later we studied this in depth.
- MM: Go back to when you were working with Dr. Bender. What characterized a schizophrenic child? Weren't some of these kids what we would call autistic?
- BF: The most severe ones looked autistic. She would call a whole bunch of them just schizophrenic, but it was only later, when I came back, that we began dividing them up. They ranged from some very autistic retarded children to schizophrenic kids.

- MM: Today when you say schizophrenic, you're talking about kids whose thoughts are disordered. When did you finish your training with Dr. Bender?
- BF: In 1952.
- MM: Didn't you get analytic training as well?
- BF: Yes, at the same time. I avoided the New York Psychiatric Institute because it was very orthodox and instead went to the William Allinson White Institute where I had very good supervisors.
- MM: Did this help you understand about yourself?
- BF: Oh yes. But at the same time it didn't make scientific sense. Here I'd been doing pediatrics and worked with mothers and families and then with crazy kids; I knew there was a difference, there was something biological going on. There was no question about it. And by 1952 I was going to study their neurological development. That, to me, was going to be a clue to schizophrenia, and how it began.
- EB: At the time really you were dealing with very severely ill children and that stuck you as clearly biological
- BF: Right.
- EB: There's something off about the brain, their developmental trajectory. You put those kids in a different class in your mind then? Did some of the psychoanalytic ideas that made sense to you about your own life or about development in general, seem applicable to what you were seeing with the schizophrenic children?
- BF: No. That had to do with neurotic people, adults who had screwed-up parenting.
- EB: You saw these kids as different kinds of problems?
- BF: There was definitely something wrong in the brain in schizophrenia, there was just no question about it. The ones you saw later weren't as damaged as they were in the early onset kids. They had such difficulty in development that only a few of them with more language were able to go to special schools. With a later onset you could have a more normal development and some brilliant people, talented. Those were the ones whose parents formed the parents' group. They had these kids who before college, or maybe the first year, would just slide away from this brilliant development. It was heartrending to see.
- MM: We should start talking then about the well baby study. The first study you did, looking for early evidence of schizophrenia, was in a group of sixteen kids who came into the Well Baby Clinic at Bellevue.
- BF: Eventually there were just twelve of them that continued. A couple of them had moved and I saw them at ten years, but couldn't follow them after that.

MM: But you managed to follow quite a number of them.

- BF: Yes, I did.
- MM: For fifty years.
- BF: After they married.
- MM: How did you select them for the study? Was it a random selection?
- BF: It was a random Wednesday selection of early-comers and late-comers.
- MM: I like that.
- EB: I love that sampling strategy! I would tell them that I was interested in how babies grow up. All mothers, especially the new mothers, are so happy that someone's really interested and listening to them. Their feelings about the baby, their feelings about the husband, attitudes toward having babies, you know, the whole story.
- MM: You examined them numerous times during their first two years. Those were regular baby visits, or were they coming in especially for the study?
- BF: They more often came in at six weeks than twelve weeks, but I tried to get them close to monthly. When I had the state hospital babies, then I was able to schedule them because I went to their homes if I needed to.
- MM: What were your findings from these studies? There is a neurological disorder which they're essentially born with?
- BF: In the brain. It probably starts at about two-and-a-half months.
- MM: Either inherited or possibly some sort of genetic mutation?
- BF: Yes.
- MM: What you noticed was that it wasn't only just regression in development, but that there had to be a kind of pattern of acceleration and regression and then scattered development in different areas?
- BF: The cognitive defects were the highest, and then the neuromuscular stuff, and the brain development. And you could get abnormalities in the head circumference also.
- MM: By just measuring the head?
- BF: Yes. It was the neurological changes I analyzed first, but then was fascinated by the difficulty in language. Like the really psychotic boy who seemed bright as an infant and then regressed. I didn't see him after two, and he was fine but by the time he was ready to go school at six, he'd already regressed back to somewhere between two and six. And then there was the little girl I was able to follow. I saw her regress between two and four. She just lost language.
- MM: Really lost functions they have had before.
- BF: Yes.
- MM: Some of the early evidence you noticed was the difficulty in posture, in sitting, as a very young baby.

- BF: Well, they all had some early developmental regression, sometimes seen only on one exam and not on the other.
- MM: Not every time? Other times they would look perfectly normal?
- BF: Yes, or smart.
- MM: If a kid is suffering from this kind of difficulty, and they don't understand what's happening, and no one is able to connect with them this is going to make the kid less secure, more anxious, and more fearful.
- BF: Psychological factors come into it, too. You have mothering mothers and baffled mothers and mothers that aren't really prepared.
- MM: At the state hospital sample in 1959, you collected your sample of kids born to mothers who were schizophrenic.
- BF: Right.
- MM: So now you have two samples of children, and you've made a batch of observations on them. Was there anything that particularly surprised you? Was there anything that stood out?
- BF: I was looking for anything abnormal, regression as well as acceleration or irregular development of one part. I was analyzing all this in detail.
- MM: Anything abnormal?
- BF: In the neurological and psychological development. But the psychological development wasn't part of pan-dysmaturation. It was basically growth and brain development.
- MM: Was it surprising to you that they were showing motor difficulties sometimes at such an early age?
- BF: It's basically what I was looking for, because that was what Lauretta had picked up from the baby charts. I was looking for wide scatters, as well.
- MM: That's a good way of describing it.
- BF: Some kids are better at this than that. Some are better in motor function and others are better with thinking. Everybody's different. So you pick some of the personality stuff up, too.
- MM: During this time, you had been working in Cornell but when you started working at Bellevue again, were these mothers and children getting the same level of care as you were providing to your other patients? Were they getting kind of special care because they were in the study?
- BF: Oh, yes. I mean, they could call me any time.
- MM: So if a child who had come into the Bellevue program a couple years later and shown the same signs probably wouldn't have gotten that same level of attention?
- BF: By the time I came back there, I raised money so that there weren't just the two of us. We had a big fellowship and residency program. If you've got nine fellows in each of two years, they're really working with the children. And you have the social workers who work with the outside

agencies; we basically ran a clinic on the ward. If they wanted an emergency consult, they could come on the ward and would be examined by one of my two senior people. They'd get the parents' history and the child's development, everything they wanted. And I was there to consult with them. We were really running a clinic from the unit, as well as the outpatient department that was downstairs.

- MM: This was a new model of mental health care for children? Was anyone else doing this?
- BF: No, we ran a very special group. We had more residents and fellows in child psychiatry, two years with nine in each group, so that they had plenty of doctors and we had the parent group, and group therapy. We had everything that was available.
- MM: Where did the funding come from?
- BF: Harriett Ames.
- BF: She wanted the children to have real food, not just hospital food. So I had to take a third of my grant from her and have parties for the kids every Wednesday; we always had ice cream and goodies. They had special playthings outdoors in our big yard. She even had an architect make it look less like a hospital. The rest of the money I could use for research.
- MM: A number of the children in the state hospital sample were diagnosed with schizophrenia later in life, but according to the last report there were still a number who had various kinds of depressions or other difficulties.
- BF: Yes. This is when I got up-to-date modern diagnoses, when Ken Kendler began using DSM III. As an interviewer, he's fabulous.
- MM: Some of them are now in their forties and fifties. Overall the degree of defect noted in infancy was paralleled by their disorder as an adult. Do you think that's a true statement?
- BF: Pretty much.
- EB: Was it unusual to be doing longitudinal studies?
- BF: I wanted to follow them into adulthood to see how they turned out, but I lost some of them, especially the normal ones. The ones I was interested in I was able to follow and get them to come back. If families find you're interested, they become very cooperative.
- MM: By the time you had your unit working well the new psychotropic drugs began to appear. Talk about how it struck you that drug therapy had advantages or disadvantages over electroshock therapy.
- BF: There was just no comparison. To be able to give a pill that would help compared to what seemed to be so traumatic. Totally different!
- MM: Was it difficult finding the right drugs for the children?

- BF: The first drug study I did was chlorpromazine versus diphenhydramine versus placebo. I did that with Ted Shapiro during his fellowship before he became a professor at Cornell. He enjoyed that kind of comparative work. After the first big trial I worked mostly in the nursery with the two-to five-year-olds. We did trials of all the different drugs that looked good for psychosis.
- MM: In 1961, you were able to set up a pharmacology research unit at Bellevue, with a grant from the NIMH.
- BF: The Grant Foundation or one of the foundations gave me starter money before that.
- MM: That was to make a systematic study of the phenothiazines in children, because they had not been studied systematically in children?
- BF: They were just coming in.
- MM: They'd been around in Europe since 1954 hadn't they?
- BF: The very first studies were done in France.
- EB: But your studies were the first in children?
- BF: Yes.
- EB: With chlorpromazine?
- BF: Yes. There may have been some private practitioners doing work, but not official studies. In the ACNP, I was the only one working with children.
- MM: The model that you used was first the children were on placebo, so you could observe their normal behavior. Then you would put them on drug A, followed by a washout with placebo, and then drug B. So the children would serve as their own control. Why did you use that crossover model?
- BF: We knew the children very well and if you know the child, you can tell how the behavior has changed using them as their own control. So you could tell the differences between the medications. We stratified them into five groups by their language, comprehension, motor and social behavior. It was only the group with the most function that got better.
- MM: But some of the drugs worked better than others.
- BF: Oh, yes. Some of them stimulated the kids, even though they sedated adults. There were a lot of differences.
- MM: You compared notes with the adult psychiatrists?
- BF: Yes. We had a group of twelve or thirteen children that started off.
- MM: So there were just you with the children.
- BF: Yes, at Bellevue. We found that there were parallels. Some of the worst state hospital patients with schizophrenia would respond to the medication like my little ones did. But sometimes they would have different effects on the kids, more stimulating and less sedative.

- MM: So it's clear the children reacted individually.
- BF: Yes but we had to stratify them, according to social and language development. It was those that had basically no function at all, except motor function that failed to respond.
- MM: In order to assess toxicity, you would increase a dose until the child showed toxic effects and then cut it back?
- BF: Right
- MM: Some of the children were able to tolerate higher dosages than others?
- BF: Yes, the nursery kids apparently could tolerate higher dosage per body weight than the adults.
- MM: Did you have any concerns that multiple drug changes might affect them in some way? Or was it just that anything was better than nothing?
- BF: We didn't keep them in the hospital if they got well enough to move on, but we would keep them if they still needed hospital care, and then we would try different medications.
- MM: But if a child was doing well on a drug the next step was to put him on a placebo. Would you do that because you needed to do to complete the protocol?
- BF: If a child was well enough to be discharged, we wouldn't keep them in the hospital just to try medication.
- MM: So if the child improved markedly, they would be discharged?
- BF: Yes. The idea was to get them out if they could move up and some of them would be followed in the clinic as a research follow-up. But, only the top level ever got that good, the ones with some language.
- MM: Were you better able to work with them in any way?
- BF: If you could relieve the symptoms so that they could get along in a special group, you could find placements for many of them.
- MM: One of the ways you assessed the behavior was a non-blinded staff that knew what drugs the children were getting.
- BF: Yes but Ted didn't know.
- MM: Ted was the blinded psychiatrist who assessed them for specified periods of time, without knowing what drug they were on.
- BF: He didn't know when they were on and off drug. He would score them weekly or something like that.
- MM: Then you would look at the observations of both the blinded observer and the non-blinded observers. And they didn't necessarily always agree?
- BF: True, but we would take the blind rater.
- MM: Even though he had only seen them for a short period of time? His view would be determinant on whether or not the kids had improved?
- BF: Yes.

- MM: But not necessarily on toxicity.
- BF: We put all the data together, to describe the good and the bad effects.
- MM: One of the things you did with the drug studies is you developed a typology, which you just described. You had to stratify the children. Can you remember which came first? Were you doing drug studies and realized you needed a better way of grouping the children?
- BF: Yes.
- MM: Because the ways that people had been grouping them weren't working?
- BF: Yes, I still think our system was better than the current system. That's why I gave up when they started with DSM-III. It was too rigid.
- MM: You had four groups in your typology.
- BF: The four groups grew from our clinical material, but we had to subdivide the nursery kids because they had all ranges of language function.
- MM: So that broke that group down further?
- BF: Made it smaller by having subgroups within the type I psychotic kids that depended on language, comprehension and motor behavior.
- EB: I had a follow up on the study design questions. Who were you working with or collaborating with to develop that study design? Were there other groups doing similar things?
- BF: Ted and I worked on the typology together.
- EB: But there were other drug researchers working with adults?
- BF: Yes, but we were the only Early Clinical Drug Evaluation Unit for children, for along time. We started with just about twelve or fourteen and we used to meet regularly. I'd talked about the children and our typology and we'd visit each other's units.
- EB: Do you remember people in particular whose studies you admired and tried to emulate, or people who gave you good guidance about how to do your studies?
- BF: We were the only ones working with kids then, so the effects we were finding were often different than in the adults, because they were working with higher developmental functions. We would try and see what parallels there were or how the kids were different.
- EB: Was there concern about study design or methods?
- BF: There was a lot of talk about methodology. But I gave up that work when I left Bellevue. I'd learned what I wanted. I liked to see how drugs affected different kinds of kids and different functions. After that, it gets to be just one drug after another. They have to compare the old ones to the new ones to see if the new ones are better and study the toxic versus the positive effects. Now it's become just medicinal, and working with human beings is much less compensated.

- EB: Maybe you can tell us more about the origin of the ACNP. What brought you all together? What were you trying to do with the organization early on, would you say?
- BF: It was the beginning of the work on psychopharmacology and I was at Bellevue. In the ACNP as a whole there were a hundred men and five women. Lauretta Bender, Else Kris, who was also a state hospital person that Lauretta knew very well. I collaborated with her on some stuff, because she knew what I was doing with the babies. Then there was Eva Killam. It was a good comradeship. I just knew of those who were working in the field.
- EB: Would you say in the beginning you were meeting to work on trial design, to attract new trainees, to form a professional organization or to lobby in some way? What was the impetus for getting together and the mission?
- BF: We had not just the annual meetings, but those of us that were doing this early clinical work, the dozen of us, were also getting together. And then there was a larger group. We would meet with Heinz Lehmann from Canada and some of the big figures in the field. If you look at that first dinner picture of the ACNP, I'm sitting between the big state hospital guy, Henry Brill, and Heinz Lehmann. They were my buddies and they were brilliant guys. It was all very exciting; I was part of the gang.
- EB: Right.
- BF: In 1963 or 1964, the head of NIMH gave a speech there. Stanley Yolles stood up and said we were all going to solve schizophrenia in twenty years. We looked at each other, those of us at the ACNP, and knew he was just plain wrong. That was when they started to close the state hospitals. They were curing schizophrenia, and threw the patients out in the street.
- MM: You knew what he said wasn't true?
- BF: They couldn't possibly do this. It became a disaster. They threw the people out without any preparation. I remember because one of my classmates then, Al Miller, who was a very decent person, worked in the New York State system. I said, "Alan, you simply cannot do this. This is a terrible thing. There are no facilities ready for these people". He acted as though he was helpless and had to do whatever they told him to. He was a fine person but he gave in.
- EB: And you all had to rationalize this decision to close and reduce populations in state hospitals.
- BF: Well, we were against it. All of us at the ACNP certainly knew that schizophrenia wasn't going to disappear, and they weren't going to cure it in twenty years.

- EB: Yet in his position as NIMH director, he was perhaps saying, look, we've made such progress in drug research in the last nine, ten years, and the science is advancing fast.
- BF: This was in 1963; it was one of the first years of ACNP.
- EB: Twenty years from now, maybe we can find the right drugs that would help people manage the illness well. That didn't strike any of you as rational?
- BF: That the drugs were really going to cure schizophrenia? It was just expecting more than what was going to really happen.
- MM: Okay. So tell us a little bit about how you decided to make the move to Los Angeles. I mean, you've commented a little bit about how hard they were working you at Bellevue.
- BF: I was recruited by Jolly West.
- MM: How did he recruit you?
- BF: It was at a meeting that Dan Freedman organized. Dan was recruiting me at the same time for Chicago, and Jolly was trying to recruit me for UCLA.
- MM: So why did you decide to go to UCLA? They offered you a job, and they offered your husband a job, but you could have stayed in New York.
- BF: Yes, but that meant working till midnight. There was just not enough support at NYU, in those days.
- MM: Was that because they didn't value child psychiatry?
- BF: They didn't have the money; we had to raise our own. I don't know why.
- MM: So you came out to California. Aside from the fact that you didn't have the problem with having to work so many hours...
- BF: ...I could work with my longitudinal studies.
- MM: But how was it different otherwise? Did you find your colleagues less interesting, more interesting, and the working environment more interesting?
- BF: The Head of Child Psychiatry at UCLA was George Tarjan. He wanted me to work under Jim Simmons who was interested in learning and behavior modification in children. I was a good soldier and this was the setup; I had to take it. But it wasn't a comfortable situation. I was supposed to teach people from all different disciplines child psychiatry, and it was hopeless. They were disappointed in me, and I was disappointed in them. It was not a good fit.
- MM: What did you do about it?
- BF: Eventually I managed to get out of it. I took a cut and some money went with it. When men are in charge women don't make out very well. Once I put myself under Jim and George I was stuck. George and I

were friendly, but he held all the cards. Jim ran the outfit and had me under his thumb

- MM: So what were you able to do?
- BF: I was still doing my own studies, and had some good trainees to work with.
- MM: Were you still able to get funding?
- BF: When I was reviewed by the committee for a grant Don Guthrie, the statistician, eased me into starting to talk about the kids, and that was when the reviewers woke up. I knew the kids so well, their whole life histories from the beginning and they realized that this was a different study. There were larger studies, but I really knew these kids. So we got a grant for three years that I spread out for twice as long.
- MM: So you continued following the kids?
- BF: Yes, and going back to New York to see them.
- MM: How did you start working with Ken Kendler?
- BF: I met Ken when we were trying to recruit him, unsuccessfully, at UCLA. I took him to dinner, and we had a good long talk. He was interested in what I was doing and I was interested in what he was doing. So we made a tentative connection at that point. Of course, it was years after that that I was finally ready to have him look at my kids. But he remembered and agreed to do the blind diagnoses, which were amazing. He would spend an hour and a half, and made super diagnoses. It was quite unbelievable.
- EB: So how was care for children different in LA?
- BF: At Bellevue, we took all comers but UCLA was very selective. So it was a different mix. Everything was different; the whole atmosphere was less familiar and friendly. At Bellevue, the elevator man knew me, the porters knew me; they had seen me grow up. I was a student and eventually came back as a professor. At UCLA the doctors, talk to the doctors, the Hispanics talk to the Hispanics, and the blacks talk to the blacks; the class structure is so different.
- EB: That must have been strange.
- BF: It was not like Bellevue, where we all were part of a family, working for the kids. So it ended with my finding some of key women I enjoyed working with.
- EB: You found a group you could work with?
- BF: When I arrived I was the only woman. There were fifteen men. I had trouble keeping the men at Bellevue because they could make more money in private practice, so I would hire them part time, to keep a mix-ture of men and women working with the kids. At UCLA I was horrified

by the whole class structure. So I did my thing on the ward and recruited women. When Gaye Carlson was there we had a great time.

- EB: Was that just a result of the personalities at UCLA, or was it the profession?
- BF: Men are different. They're used to being in charge; they want to be in charge, even if they have no sense.
- EB: It wasn't that the profession was different on the West Coast than on the East Coast necessarily, it was that you had some unpleasant people who were making decisions that didn't work so well in that environment.
- BF: It was definitely not a warm atmosphere for women. I was the first woman in any senior position in the department. There were some women psychologists I recruited from pediatrics who I had worked with in Arthur Parmelee's group. Arthur was wonderful. I knew him from the child development group so I worked with the pediatricians and with him. I found the niches where I would be comfortable.
- EB: Did you notice improvements over the time you were at UCLA?
- BF: Not in psychiatry.
- EB: You managed to get good work done, nonetheless.
- BF: Yes, but I did it by cutting out the stuff I didn't want to do.
- EB: Salary as well?
- BF: I took a cut in pay, but it was worth it.
- EB: I have some questions about a different topic. You said earlier that after DSM-III, when Ken Kendler started to look at your subjects, a number of them were diagnosed with mood disorders in addition to psychosis. How did you think about mood in the kids you were seeing in the fifties and the sixties? Did you see kids as depressed?
- BF: We would see them and we would think of them as neurotic. We were not thinking of manic-depressive depressives. We didn't know it could occur so early. Gaye was very interested in that because she had worked with Fred Goodwin at NIH on depression and manic depressives. So she taught me.
- EB: Do you think it's helpful to think about mood more in kids?
- BF: It's very important.
- EB: What we do now is think about categories of children, and try to decide if a drug or an intervention might help these categories, those with manic depression, or those who are depressed, or those who have a certain kind of autism. We lose the picture of the individual child.
- BF: I know. I think that due in part to the restriction of time that's given to make a diagnosis.
- EB: We start to talk about drugs and whether a drug works, as opposed to really getting to know the child well.

- BF: It's very hard if they are only given twenty minutes. You can't do a thing in twenty minutes except titrate a drug.
- EB: There isn't any longer a child's ward at UCLA, and it is very uncommon to have children in the hospital for any length of time. That was so crucial.
- BF: I think it's a shame not to have a children's ward; a real loss for training. It was more of a cost decision, I am sure. It didn't bring in enough money.
- EB: Yes and it's not just a local trend. Across the country, there are fewer and fewer inpatient beds for children.
- BF: There are generally fewer and fewer inpatient beds, period. I suppose kids were cut out first. Boy, I'm glad I'm retired! What do they do with psychotic people?
- EB: Hospital stays are very short, and an effort is made to have people with schizophrenia come into the outpatient clinic. There are some teams that go out to where they live, but that's uncommon. There just aren't many services.
- BF: For the poor schizophrenic.
- EB: Right.
- BF: What a stinking system. It's the money! What are residents trained to do?
- EB: They get a lot of training in medication management and some training in therapy, but obviously it takes a long time to learn. You get a certain amount of training in some things, but then you have to go on in your career and gain other skills, depending upon the setting you're working in.
- BF: Depending on what's available.
- EB: Right, what kinds of settings you can work in. Some people would say that's because pharmaceutical companies have increased their influence and involvement in the profession.
- BF: Like the child psychiatrist at Harvard who's reaping in money; thousands of dollars from the pharmaceutical companies. That's stealing. That's really nauseating. I find it revolting. It's changing medicine. And the drugs aren't that great, they're limited. Even some of the old ones are as good as the new ones. Medicine has to change. I don't think this is a good system.
- EB: As you think back, even over the last couple of decades in your career, how did that happen?
- BF: Some people are just hungry for money. What do they go into medicine for? I guess I'm an archaic being, having enjoyed working in a hospital.

It's not where you make money if you want to really take care of sick people.

- EB: I wonder if you think there is more that the profession or professional organizations can or should do.
- BF: When the head of NIMH came to ACNP that was the beginning of a downward slope, when they threw people out of the hospitals. Some people need a hospital. Other healthcare systems, like the one in Sweden, are somewhat better than ours; socialized medicine, or whatever. They raise hell when we use that term, but we're supposed to be taking care of people, not just making money.
- MM: A lot of people fall through the cracks and don't get adequate care.
- BF: It's a lousy system.
- EB: One of the things that is important today and this process is to understand from you where the profession was, what was valuable about the environment that you trained in, about different work settings, the kinds of things that helped you think of new ideas and design innovative studies. What was it that helped you do that? Those are such important things to keep sight of, to not lose.
- BF: You're under many more constraints that I was.
- EB: I think so, as you describe it.
- MM: When you start applying concepts like cost-effectiveness to medicine, where are you? It doesn't work very well. Not with people who need long term care.
- BF: Right!
- EB: As you think back about the most important people in your career, the most influential figures, who are those people?
- BF: Well, Lauretta first, and my husband.
- EB: How about people today, maybe people in the ACNP?
- BF: A lot of my buddies are gone. Dan Freedman is dead; Heinz Lehmann's gone, I think. Henry Brill and Paul Hoch, none of them are around. They were outstanding people. The Killams, I guess, are around. But they worked at a more basic level in research. Our group kind of broke up. So I'm working with Tom McNeil, and he's working with Assen Jablensky in the Western Australia group. They're having a Barbara Fish Symposium at the International Conference on Schizophrenia Research.
- EB: That's quite an honor.
- BF: Before I die, a going away present! But going there is too much for me. Your gang will have to go.
- MM: We'll go and we'll do a videotape.
- EB: They're doing longitudinal studies? Is that why they named it for you?
- BF: Yes.

- MM: I wondered if you wanted to say a little bit about your husband, because he was very supportive of your career.
- BF: He was wonderful.
- MM: You met him when you were a resident, is that right?
- BF: Yes, I was in child psychiatry, in New York. When I was analyzing my data for the first time Loretta's response was that she knew it all, there was nothing new. Deflating a young research worker! But my husband Max said, "Listen, for her it's a theory. You've actually done the experiment. That's different scientifically than having a theory. Write it up"! He was the right guy for me. A career wife needs a Max!
- MM: On that note we're going to conclude. It's been a really good interview and a pleasure talking to you.
- BF: Like my analysis all over again!

## MARK S. GEORGE

## Interviewed by Robert M. Post Scottsdale, Arizona, December 9, 2008

- BP: I am Dr. Bob Post and I am interviewing Dr. Mark George.\* Tell us something about who you are, your credentials, and then we will go into some of the key issues about your career development.
- MG: I am a psychiatrist and a neurologist, born in Columbia, South Carolina and I went to medical school there after a philosophy undergraduate degree. In medical school, Dr. Jim Ballenger, one of your other students, grabbed me out of the masses and said, "I think that you have talent, so why don't you think about becoming a psychiatrist or neurologist or both"? I have been working in the field ever since.
- BP: That is great; you are one of few with credentials in both neurology and psychiatry. Where did you get your training?
- MG: Jim Ballenger had created a program at the Medical University of South Carolina (MUSC) in Charleston, which involved one year of each discipline over 5-6 years. I wish I could say it was a brilliant choice, but it was actually a compromise. I have always been fascinated with the brain and with behavior, so I looked at what kind of clinical training you could have. Neurology knows about diseases of the brain; they view it is an organ and look at brain tissue and circuits. But they ignore everything important: depression, emotions, hopes, and the impact of life events on diseases. Everything that was cool and interesting was just taboo in neurology, so it was insufficient. Psychiatry embraced all the interesting ideas but it was essentially 'brainless.' There were a few people like you who were talking about pharmacology and the brain but, by-and-large psychiatry was 'brainless' when I started. So I chose both, because neither was sufficient.
- BP: You got some early training from Mike Trimble. Would you tell us about that?
- MG: I got hooked on research during my residencies and became fascinated with brain imaging. I will never forget when I was a neurologist and MUSC received the first CT scan. There I was one night for the first time ever we had a patient that had a stroke and we could get a picture of the brain. I remember thinking we are going to be able to look at the brain and solve all our questions. The reason that psychiatry and neurology have been lagging behind other areas of medicine is because we haven't had access to our organ and this is going to do it! Interestingly enough, the patient had a stroke but we saw nothing on the scan.

<sup>\*</sup> Mark George was born in Columbia, South Carolina in 1958.

- BP: You didn't see the stroke.
- MG: When there is an acute ischemic stroke, conventional CT scans are not helpful. The patient was partially paralyzed and we had a revolutionary new tool that could image the brain but it was normal. It was a hint that things were not going to be as simple as we thought. I also remember seeing a paper in The Lancet on Magnetic Resonance Imaging (MRI) of the leg and realized we could non-invasively look at blood flow with this technology. So I decided after I finished clinical training that I wanted to do research with brain imaging. Jim Ballenger suggested I devote my career to schizophrenia but I didn't think that was the right choice for me. I was interested in mood disorders because there are no permanent sequelas. So he suggested I work at the NIH and helped set up my interviews with you. I also mentioned I would like to go to London and work with Mike Trimble who is a neurologist and psychiatrist. At that time brain imaging was only done, at maybe four or five places on the planet including NIH and Queen's Square. Queen's Square was a fertile location for a young researcher interested in brain imaging and I wanted to spend a year there before I came to work with you. You graciously said take a year and go over there; so that is what I did.
- BP: You came just at the right time because when I started out, there was no way to get into the brain and no way to see anything. What were some of the key things that you picked up, working with Mike Trimble?
- MG: Mike is basically a neurologist, unlike you, who is more of a psychiatrist. As you know, my whole career could be summed up with one basic neurological question, where is the lesion? While I was at Queens Square I did some SPECT and PET scanning and, serendipitously, I stumbled onto transcranial magnetic stimulation (TMS). They were doing it on a floor above where I was working and ran into a patient in the elevator who had been a subject in one of the TMS studies. He told me how they put this magnet on his head and they could stimulate his thumb to move. We rode down and then I punched the button back to the floor from which he came. I walked in and there was John Rothwell studying the motor cortex. I turned to John and said, "Professor Rothwell, what would happen if you move that thing forward over the frontal cortex"? And he looked at me and he said, "I don't know and why would you ever want to"? I replied "because all our brain imaging work implicates the prefrontal cortex and corticolimbic loops in emotion regulation. It would help augment the imaging work and establish the lesion in depression".
- BP: Yes.
- MG: The initial emotion imaging studies at that time were very crude, and we did some of the first studies of depressed versus non depressed patients.

We also did some of the first emotion inductions; we took healthy people and tried to manipulate mood inside the scanner. Compared to the elegance of the motor and visual systems, we couldn't show the precision of circuits in the same way that other parts of neuroscience could. But we had had identified certain regions as being important in normal sadness and pathological depression; the prefrontal cortex, cingulate, amygdala, insula, and hippocampus. These early studies I did with you and Terry Ketter contributed to an emerging literature with many others around the world. These studies, taken as a whole, identified specific regions that changed as a function of mood and were involved in depression. Those road maps were what led to brain stimulation techniques to test the theories, and hopefully evolve into therapies.

- BP: I remember your doing the mood induction studies at the NIMH, which were quite pioneering. We were fortunate to pull in the neurology connection with Mark Hallett and other neurology collaborators, so you must have felt right at home having neurology and psychiatry joined together in our little group.
- MG: Yes, Mark Hallett was very helpful. He had a Transcranial Magnetic Stimulation device at Bethesda and was using it to study the motor system and movement disorders. You helped arrange for me to meet him and we had the idea of using stimulation as maybe a treatment, but certainly as a research probe in depression. Mark Hallett had an open-minded but skeptical approach. He said come in, but don't hurt anybody, and you have to do your work before eight in the morning or after five.
- BP: That's right!
- MG: Because we have the real science going on in the middle of the day.
- BP: And he loaned us Eric Wasserman to help out.
- MG: Eric helped, but I think initially Eric was a security guard to make sure that we didn't hurt anybody.
- BP: Absolutely! So, tell us about some of the first clinical experiences with Repetitive TMS (RTMS). There were some notable patients that even I can remember.
- MG: Before we get into the anecdotes, I want to return to John Rothwell's question, why would we want to do that and my answer, where is the lesion? From the brain imaging studies we knew that there were these regions and right at that time, 1993, there was a seminal paper by Alexander, DeLong and Strick that described cortical and sub-cortical regulatory circuits and I thought that might be a way to use TMS to get in and change them. There was also data from Harold Sackeim, who has been very important in my career, with ECT, showing how

they were damping down the whole prefrontal circuit, which was linked with eventual clinical response. Our idea was that we could stimulate non-convulsively with TMS over prefrontal cortex which was a window into the regulatory circuit and that we could reset that circuit over time and cure depression. That is why we began and that is still the major theory about how TMS works, and I think we were right. It was a paradigm shift at the time, but not well-received by the administrators at the NIMH. You were open minded and so was Mark, but in the community at large, for a device to work, everybody had the model of ECT. They all assumed that you had to have a seizure and for us to come along and say you can use a device to change mood and it doesn't involve a seizure was anathema; it was almost taboo.

- BP: And, there are still a few people left who think that you have to have a seizure to change mood, right? So, you started doing 20 Hertz stimulation just over the left pre-frontal cortex at just below the motor threshold.
- MG: We had this new technology, but there were a gazillion guestions that we had to answer. Where do you stimulate; how frequently; what is the duty cycle; what is the dose; what do you have them do while you are stimulating them; all these things we had to make good first guesses at. You were extremely helpful from keeping me from having a panic. Faced with infinite possibilities, you said, do your best, so we took some reasonable first steps. The FDA was very concerned about the technology causing seizures, so they made us start quite conservatively and the IRB at the NIH would not let us do patients until we had shown safety and feasibility in healthy controls. So, we launched our first study in healthy controls. We did left, right and midline prefrontal, occipital and cerebellum TMS. We measured changes in subjective mood and peripheral measures, prolactin to make sure we were not causing seizures, and serum thyroid where we found changes prefrontally, which for me was an epiphany. This said that we can access circuits that interact with the hypothalamic pituitary axis (HPA). If we can do that there is a high likelihood that this intervention might be useful as a treatment. We did the controls first, and then we started with a few of the very treatment resistant patients on the ward. I think that some of the confusion down through the years has been that a lot of the patients were treatment resistant. We would often try something and it might work in some and not in others. What we were doing was trying a somewhat weak treatment in a very refractory group. We did the first open study and I remember the first patient. She was a pilot from New Hampshire, or Vermont, and she consistently responded to TMS. We

did PET scanning before and wrote up her case with a few others as an example to the world that intermittent daily stimulation can be useful.

- BP: I remember how excited you were one day when you pulled me aside and said, Bob, you have got to come up and see this! We climbed the stairs with the patient who could barely walk and was tired and then after the RTMS, all of a sudden she started smiling, talking with you, telling jokes, saying, I am not tired anymore, going up and down the stairs. It was a precursor of things to come! How did things evolve in the RTMS studies, and how did that lead to your getting involved in other brain stimulation techniques like Vagal Nerve Stimulation (VNS), deep brain stimulation and a whole program trying to become more and more refined, in terms of therapeutics and approaches to the brain?
- MG: Before we go into that I have a couple of stories to tell about early TMS.
- BP: Okay, go for it.
- MG: There are two things that happened that have reverberated through my career. One was when you advised me to take out a use patent. Do you remember?
- BP: Oh, yes!
- MG: I was reluctant to take your advice because the work was "outside the box" and people were skeptical. If we took out a patent it might stifle interest further and I would have to step aside to let someone else develop the procedure. So, I chose not to take out a patent; and, at the time I thought that was the smartest and best thing to do. But I have had to rethink whether that was a wise decision. Because there is no patent, there was no way for industry to protect itself while doing the studies needed to get approval. So the lack of a patent slowed things down, which is why it took fifteen years from that first paper until recently to obtain FDA approval. I ignored your advice and it slowed things but allowed me to continue to talk and work on the project. I had to leave the intramural program and went to Charleston where Jim Ballenger accepted me back. He didn't know about brain stimulation but was interested in my use of imaging, so I had to create an imaging group. I explained the brain stimulation work as a hobby and kind of side project and asked him to loan money to buy the equipment. He did; it cost thirty thousand dollars at that time and after I bought one I immediately applied for a National Alliance for Research on Schizophrenia and Depression (NARSAD) grant and paid Jim back. So I did a couple of TMS trials and there were some studies out of Europe where a non-psychiatrist, who didn't know about depression, started using it to treat the disorder. That paper came out in the Lancet and a lot of people around the world tried the treatment for just one week and

it failed. So, there was a negative opinion in the mid-1990s when people decided it didn't work. Because I had seen what I thought were small but legitimate effects I continued to plug away with systematic single site double blind studies. Most of the studies were funded by NARSAD and the Stanley Foundation. We continued to see a signal I thought was worth building on, but it would go nowhere without industry support for clinical trials. I remember an ACNP meeting in Hawaii where I spent an entire day talking to venture capital people who were thinking about buying or investing in a TMS device company. Some of them did and that was the basis of the company that eventually organized the multisite trial. I couldn't invest or be a part of those companies but I was their scientific advisor.

- BP: So, that was at the ACNP?
- MG: Yes.
- BP: Was that your first ACNP meeting or had you been coming before?
- MG: My first ACNP meeting was in 1989 or 1990 and I have been coming ever since.
- BP: Did the ACNP play any role in your career?
- MG: Oh absolutely, especially with trying to obtain legitimacy for brain stimulation and TMS. I remember the first workshop at ACNP. It was a study group at night where we had Bob Belmaker and a few other people who had been doing TMS around the world come together and share ideas. I remember coming to ACNP meetings and arranging to meet other scientists who were doing TMS. There were some groups in Israel who were publishing and I was looking for external verification of the signal I was getting. As a scientist, you are worried that you are putting your thumb on the scale and deceiving yourself, so it is nice when you see other groups replicate your findings. I used the ACNP meetings to hook up with people that I had read about in other places. I remember one meeting in Hawaii where I went dead set on meeting with Ehud Klein who had just published a very rigorous study which seemed to confirm what I was seeing. So, the ACNP has been really important as a community to fall back on.
- BP: Yes, a lot of interchange. I don't know if you know this, but about eight years after you left our program my boss at the NIH said he knew that TMS was not going to work.
- MG: There was resistance!
- BP: Yes, big time resistance! There were a lot of people that were very skeptical!
- MG: As you may remember, I was told not to talk with the media about TMS by the bosses and the intramural program at that time. It helped me

with my decision to move to Charleston, to be scientifically gagged, as well as getting kicked out of the Association for Convulsive Therapy (ACT) meeting by Max Fink. There was a lot of resistance to TMS and general brain stimulation for depression. The other thing that started at the NIMH was the idea to combine stimulation and scanning. We had done it with the PET scanning, but I was ambitious and wanted to do TMS inside the MRI scanner. I remember trying to talk to some of the people in charge of the MRI scanner at the NIH. They said that they would have absolutely nothing to do with that. So that was another reason why it was good to move to Charleston where I was in charge of the scanner and could carry out some of my ideas.

- BP: Let me switch topic. How did you get involved with vagus nerve stimulation?
- MG: You have a graphic you shared with me that you used to have in your office at the NIH. It showed a sagittal view of a person receiving light therapy, medications through veins, oral drugs, TMS and VNS. I followed that graphic, copying the people who had pioneered VNS for epilepsy.
- BP: That is another thing that we stole from neurology, their ECT seizures, the RTMS and VNS. The VNS epilepsy people said they didn't know how it worked for epilepsy, but their patients were feeling better; so that was a very early hint. So then you did work in South Carolina and brought that technique to a whole new level of clinical interest.
- MG: Well, I couldn't have done that all by myself. When they came to me, I said that it was a good idea. Imaging and clinical anecdotes supported it and I had met Paul MacLean when I was with you. I had lunch with him once a month and read all his work. Paul MacLean, in the fifties, had predicted that vagus stimulation would have neuropsychiatric effects.
- BP: He was a real genius!
- MG: No kidding, it's a shame that you couldn't recorded Paul.

We had the anecdotal positive reports of epilepsy patients becoming less depressed. VNS was a good idea, but I couldn't do it myself, so I called up Harold Sackeim and John Rush who were experts in the field with open minds and the three of us organized the initial clinical studies.

- BP: You ran into them at the ACNP too?
- MF: Absolutely, they were friendships brought about through this meeting.
- BP: That made a big difference.
- MF: Then we added Lauren Marangell, another of your children, as the fourth site and that was the group that did the initial pilot studies and organized the double blind studies.

- BP: Here's a tough question for you. VNS is now FDA approved for seizure disorders and mood disorders. Where do you think VNS is going? Almost no one is using it, because of reimbursement problems. Where will it be in ten to fifteen years?
- MF: The answer is yours; we need to understand the neurobiology of what VNS is doing in the brain. The company has ignored that core issue. If the neuroscience of the stimulation could be expanded it would likely have better clinical effects. Right now the VNS dosing parameters are just dumb. It's highly unlikely to be the best use parameter for depression. It might need to be individualized or depth adjusted and that should be driven by pre-clinical knowledge and the company has ignored that. VNS is FDA approved, but there's no first class evidence for its effect in depression. There is not a positive randomized controlled trial and we don't understand enough about the neurobiology. However, I'm an optimist; information is going to be developed and, ultimately, the randomized control trials will be done. We are now with VNS where we once were with TMS. There was initial excitement, ignoring it for awhile, and then it came back. So, I think VNS will come also back. It clearly has modulating activities that have a long term effect.
- BP: That is very interesting. So, what are your current most exciting concepts and where do you see things going for yourself in the next five years?
- MG: With Harold Sackheim's help, we've launched a new journal called Brain Stimulation. We've taken your idea, where we want people contributing, who are neuroscientists. We want bioengineers who understand what electrical currents do when they interact with neurons. We want neurologists, psychiatrists and cognitive neuroscientists to come together and see brain stimulation, not as ECT or TMS, these different devices, but to view the commonality of it all and try to understand the common rules. Because the techniques, I think will change, one hundred years from now, no one will be doing any of these things, ECT, TMS, and Deep Brain Stimulation (DBS). It will be considered quite crude, but they are all stepping stones toward this larger and more refined body of knowledge. So, this new journal is a lot of fun because so many people now get it. It's not one technology or another. Its understanding the underlining principles and then finding technology that will influence them. So, that's a lot of fun and I want to continue to grow that journal. But the main thing I want to do in the next ten years is to go back to your dream where we create a scanner that can be diagnostic. You could take, say a depressed patient, and put them in the scanner. You could do a series of scans to find the area of their brain or the circuits

that are pathologically involved. Then you could apply stimulation and scan again to look at the immediate effects and either do all the treatment and produce a cure or set the stage for follow up out of scanner treatments. I want to build that combination scanner/stimulator and use it like cardiac catheterization id used in heart work. How would cardiology work if they couldn't image a coronary artery, stimulate to unblock the clot, image again and then stimulate again if needed. I think in neuroscience we can create that technology, building on the two legs of my career with imaging and stimulation, and put them together in a real time feedback technique. I've been extremely blessed and, if I continue to be lucky, that's what I would like to do in the next ten years.

- BP: So, there's a thread all through your career of applying that initial question, where's the lesion; where are the pathways? But then asking, what can you do about it for therapeutic benefit to patients? What other brain stimulation approaches are you and your group thinking about?
- MG: Well, I'm an open-minded skeptic. Even things that look like hokey science will tell you if they are hokey or not if you are willing be openminded about it. Right now there is a non invasive technique called transcranial direct current stimulation (tDCS). We are starting to look at that for pain and, then, there are the more invasive techniques, deep brain stimulation and surface based cortical electrical stimulation, as well as new ways of doing ECT. We are doing ultra brief pulse right unilateral current which is a paradigm shift really in ECT. We are studying all of them with respect to mood disorders.
- BP: How promising does the frontal lobe stimulation look?
- MG: You were in Charleston a couple of weeks ago and you saw two of the star patients. We've treated five, and these are people who are as treatment resistant as you can get and still be alive. Two of them have their lives back now, at least temporarily. It's been only six months but it appears to be very powerful and promising. I don't know to what degree we will end up doing that in everybody, but if it works we might come up with other less invasive ways to do the same thing. Maybe this initial work with the most invasive techniques will inform us how to do it less invasively. For some people a small surgery isn't a big deal to get their lives back.
- BP: That's for sure.
- MG: As the editor of this journal and serving on study section I see so many fascinating ways of interacting with brain in terms of stimulation. Ultrasound, light, there are just so many different ways. It's so exciting to be alive, seeing this explosion of the potentially different techniques. We can do focal pharmacology in ways that will produce long term

change in circuits. That's what you taught me and that's the dream you gave me at the very beginning. So, it's very cool to be here today with you my mentor and friend, to talk about the progress we've made, but also dreaming about what's still left to do.

- BP: So, focal pharmacology...
- MG: That's the bread and butter of modern psychiatry, that's what I do with most of my patients in terms of managing medications. In drug therapies, some work and some don't. That's the background. What's new is that we are saying it's not soup; it's focal; it's in the circuit. You've said that all along in the work that you were doing with Susan, in terms of kindling interaction with drugs. You were doing focal pharmacology and modulation of circuits when I first got to NIMH and we are just now translating the basic idea there into clinical use.
- BP: It's an exciting time; that's for sure. You've told us about the collaborations you've built here at ACNP meetings, and the people you've got to know and some of the intramural aspects of trying to get rTMS going.
- MG: I love this meeting. The ACNP is a place where you can get away from everything else. I've said to my wife, who has sometimes been able to come, that I get more work done the week I'm here than the whole entire rest of the year. She doesn't understand that, but it is true. Conversations I had here, led to grants, and discussions in a poster session sparked ideas. The idea of a community of scientists, has been critical to me.
- BP: Same here, it's always been the most exciting meeting of the year for me too.
- MG: The other thing is that my family has grown up around these meetings and often we take a vacation. My son learned to swim at the sink hole in Hawaii before one of the meetings. I've a lot of fond memories of these meetings associated with family
- BP: Your work has recently been recognized with the most prestigious award that NARSAD gives out. Can you tell us something about that?
- MG: I've been very blessed and there have been a couple of awards that have recognized some of my work. One of them was the NARSAD Falcone award. I was fortunate to enter the field at a time when technologies were becoming available to look at brain circuits and to have the training and expertise to use them. I've been financially able to do all this. My wife has worked and supported our family so that I've been able to pursue science and not have to make a lot more money in other areas. But my greatest blessing has been in the people I've worked with and the mentors I've had who told me go for it, do the best science ad if it doesn't work, the worst that can happen is you fail, but other

treatments will emerge. I want to close with thanking the ACNP and you Bob for allowing me to do science.

- BP: What would you say to the young investigators now who were tempted not to go into the field because of concerns about tight funding, conflicts of interest in treatment and all the other adversities? Given your experience, what advice would you give to the youngsters now who might be interested in this amazing field of neuroscience?
- MG: Translational neuroscience is not for everybody and it's not easy. But if you are willing to make some sacrifices, if money is not a huge motivator, if you are able to work really hard, don't need a lot of sleep, and if you are motivated by helping patients, there's just no other choice of a career. I haven't put this up in my office, but I would love to have a huge saying "we produce smiles". That is really what you work for. You have a single patient whose life is ruined by treatment resistant depression but with a new and novel treatment that's come out of your head they get their lives back. And they thank you. Very few people have a job where that's what you can get. So, if that's what you want, then, you can make those other sacrifices. I'd absolutely say go for it. I don't know what funding will be like, but I think there will always be people who need treatment and the people who can do the science. I have no regrets about my life and for the right people it's certainly is a great career. Don't you?
- BP: Absolutely! Mark George it's wonderful to have you here at the ACNP. We look forward to your next iterations of these creative therapies. So many people have treatment refractory depression or bipolar disorder we really have to push the envelope. Most people aren't able to do it in the creative way that you have and a lot of people are going to need you to come up with the next generation of treatments. It's wonderful having you in our group, wonderful following your career down in South Carolina and I look forward to many splendid accomplishments. What you said about patients getting excited about that and having somebody, produce a smile, is just spectacular; so good luck with the rest of your career. A pleasure seeing you at this meeting all the time and thank the ACNP for creating a wonderful stimulating environment to push through scientific frontiers.
- MG: You're welcome Bob, thank you!
# ALEXANDER H. GLASSMAN

#### Interviewed by Thomas A. Ban San Juan, Puerto Rico, December 10, 2003

- TB: This will be an interview with Dr. Alexander Glassman\* for the archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College. It is December 10, 2003. I am Thomas Ban. Could you tell us where and when you were born, about your education and how you got involved in psychopharmacology?
- AG: I was born and went to school in Chicago and spent my early life in the Midwest. I went to undergraduate and medical school at the University of Illinois intending to go into orthopedics. I had an uncle who was quite successful, a high water mark for the family and very anxious that I join him. I never liked orthopedics, decided I cared more for psychiatry and wanted to be a psychoanalyst.
- TB: When did you graduate from medical school?
- AG: I graduated from medical school and was married in 1958. My wife had been attending Northwestern and was from the east coast. She wanted to return for one year to the east coast before we came back to Chicago. I interned at DC General Hospital in Washington, because to practice in the Midwest you needed a rotating internship that included both surgery and medicine. I went back to see my uncle and told him that I wasn't going to join him. He was guite distressed because he wanted to continue the family name in orthopedic surgery. It was unusual at that time for a Jewish person to be a surgeon and he was among the first orthopedic surgeons to practice sports medicine. He was a friend of George Halas who owned the Chicago football team and persuaded him to have an orthopedic surgeon as team doctor. Still, when I told him that I had decided not to go into orthopedics he was terrific. He put his arm around me, and said, "Sandy, I always wanted to be a psychiatrist". So that began my career in psychiatry. I was a resident at Jacobi Hospital in the Bronx and on the faculty of the Albert Einstein Medical School. I had a public health fellowship and it gave me a lot of latitude. It was really intended to increase the number of psychiatric teachers but in the fine print it said research was a good idea. So I thought it would probably be advantageous if I did research and applied for a grant particularly since I believed the attending I worked under was unpopular with the Chair of the Department and my position might be in jeopardy. I didn't think about research in biological psychiatry until I became interested in something that Alec Coppen was

<sup>\*</sup> Alexander H. Glassman was born in Chicago, Illinois in 1934. Glassman died in 2011.

doing in England with serotonin. It was very popular to study norepinephrine in the US, but instead I did a precursor study giving tryptophan to people on MAO inhibitors to see whether it altered response to the drug. I got a grant for a project that wouldn't be funded today because I had no credentials. My intention was to finish the project and go into analytic training. However I couldn't support my family, I had two children, and go into analytic training. I had almost finished the project when the Vietnam War intensified and I was drafted. I spent two years in San Francisco at Letterman General where I got increasingly involved in teaching about drugs and wrote a monograph for the army.

- TB: How did you get involved in teaching?
- AG: The reason was totally accidental and began before I was drafted. Jerry Jaffe, who did all the teaching about drugs, left Einstein to go to the University of Chicago when Danny Friedman became Chairman there. That left Einstein without anybody to teach about drugs. There was a meeting held by NIMH to foster psychopharmacology education and Milt Rosenbaum, the Chairman at Einstein, asked me to go. It was held at the University of North Carolina and I went, but I really felt insulted. I believed he picked me because he thought I was the least likely to succeed as an analyst in what was a very analytically oriented department. I already had some research funding for what he considered biological psychiatry, and he thought I would like this. I met a number of people there: Fred Goodwin, John Davis, and Biff Bunny, learned something about these new drugs, went back to Einstein and began to teach psychopharmacology, but it was still my intent to go into analytic training. When I was drafted, and the Army heard that I had been teaching psychopharmacology for several years, they were very eager for me to do so at either Walter Reed or Letterman. I had already been to Washington for internship so I chose Letterman. The Army was quite good to me. I was director of residency training for the first year and was having trouble financially. I was almost 34 years old and the Army salary was, I think, \$5,000. We were worried because we had one child in school and another one starting. So we put all the money we had saved into renting a house in a good school district, and then ate canned spaghetti. I got a second job consulting on patients who were problems for the California Mental Health System. I didn't know that much about schizophrenia, but I learned a lot by trying to teach it and developed more and more expertise about drugs. I also published the tryptophan study while I was in the military. The Army gave you a half day off every week and I worked with Bill Dement in his sleep lab at Stanford. He probably doesn't even remember, but I went

down there for about a year. By the time I got out, I knew a lot about drugs and had much more of an interest in research. I also felt if I went into analytic training, my children would graduate before I would. So, because of that Vietnam War enforced delay, I thought I would try my hand at research. I talked to the people at Einstein and at Columbia. The tryptophan grant I had started was finished by Stan Plattman who worked for Ron Fieve at Columbia with lithium. No one at Einstein had any experience with lithium so I spent some time with Stan to learn about it. I corresponded with him while I was in the Army and when I left the Army Ron Fieve offered me a job at Columbia.

- TB: When was that?
- AG: In 1969 I came back to New York, at Columbia, and I've been there ever since. It's now 34 years ago. At first I worked with Ron Fieve, but that didn't work out and I seriously thought about going back to Einstein. Then Kolb, who was Chair at Columbia, said that he needed someone to run the biological psychiatry program. Sid Malitz, one of the very early members of the ACNP, was the chief of Biological Psychiatry but didn't have time to run the department any more. It was located on an inpatient unit that studied depression and I took over as acting Director. There was a young physical chemist named Jim Perel who was very aifted and who developed a method for measuring imipramine. Until that time we did not have methods for measuring any psychotropic drugs, including the antidepressants. You could laugh when you think about how we had to do it. It was a fluorescent method that needed a dark room. Jim's interest had been in studying the effects of methylphenidate on impramine levels. I thought that the more interesting issue was not drug-drug interactions, but the question of whether blood levels make a difference in clinical outcome. The tricyclic antidepressants were very lipid-soluble compounds, with large differences in blood levels from one individual to another, but we didn't know if it made any difference. We got a grant in the early 1970s to look at this issue, and with Jim, did the first blood level study in the United States. There was a group in Sweden, Folke Sjoguist and Maria Asberg, that opted to study nortriptyline because it had no metabolite and seemed easier to study. We realized imipramine was a problem because we needed to measure both imipramine and desmethylimipramine and that was not easy, but it was the more widely used drug. Actually the most widely used antidepressant at the time was amitriptyline, but we couldn't get it to fluoresce, and it was seven or eight years before anybody developed a stable method to measure it. So we did the imipramine blood level study, and the results were really guite striking. There was a very real

relationship between blood levels and therapeutic effects with the tricyclic drugs. Originally our interest was entirely in people who were rapid metabolizers, who burned the drug up, had low levels, and didn't get better. Gradually it dawned on me that there were people at the other extreme who were poor metabolizers, had high levels, and I became interested whether being a poor metabolizer had any consequence. We had a patient who developed heart block and we published that paper in, I believe, 1977. It was interesting because that was a cardiovascular side effect that was directly related to the rate of metabolism. The patient was taking ordinary doses of imipramine but had very high blood levels. As the blood level dropped, the heart block went away. That was the first case of a tricyclic-induced cardiac adverse effect at usual oral doses. It's something you usually see only in overdose. Those kinds of reactions, in truth, turned out to be rare, but it got us interested in the cardiac effects. We looked first at the cardiac effects in normal people, and they were very modest. The drug would prolong the QT interval on the EKG, but not in a way that produced serious problems. There were issues with orthostatic hypotension and I wanted to follow that up in a second grant, but one of the site reviewers, a cardiologist from Yale said, you shouldn't keep studying people who are healthy. We know that's safe. The question is how much danger is this in people who have heart disease. That comment got me involved in heart disease and so we did the first trial of an antidepressant in patients with overt heart disease.

- TB: What about blood levels and therapeutic response?
- AG: The other thing that happened in the blood level study was that patients that were delusional were doing very poorly. Also in 1977 we published a paper before we had any blood level data, saying that delusional patients don't do as well as non-delusional patients. Non-delusional patients got better about 60 to 70% of the time. In the old days, the tricyclic drugs were very effective in inpatient populations but they had side effects that killed people in overdose. With a good blood level, we were getting 75 to 80% of the patients that were in hospital better. But the delusional cases did very poorly. I published the paper in the American Journal of Psychiatry, presented it at the national American Psychiatric Association (APA) meeting, and thought everybody would believe me and accept it. I was just naïve; I didn't know for a long time that you have to advertise your findings. And one paper doesn't do it. You have to write half a dozen. We wrote a few papers about delusional depression and over the years it has come to be accepted. Nowadays you are taught to use combined treatments, but it took a

decade before that was accepted. That began as a clinical observation in a group of people in a blood level study. A lot of our time in the 1980s was spent with cardiovascular studies because the tricyclic compounds were problematic drugs in people with overt heart disease and in overdose. I thought by the mid 1980s I had exhausted the area because we knew everything there was to know. I became interested in stimulants because some patient told me that his amphetamine was much better than my imipramine and that he didn't want to have anything to do with tricycle antidepressants. I began study amphetamine in people with major depression to see whether they were useful or would augment antidepressants. As soon as I got seriously involved, it occurred to me that the stimulant that depressed people used most often was nicotine.

- TB: So that is how you got involved in smoking.
- AG: That got us into a whole series of studies with smoking. We got the idea that maybe clonidine would suppress nicotine withdrawal symptoms. We did a study which was published in Science in the late 1980s, and showed that clonidine had an effect on nicotine withdrawal. That seemed like a sidetrack. I wasn't sure I wanted to pursue it, because my experience for 15 years, had been working with depression, and I didn't know much about smoking. But we published it because it was a novel observation. No one had ever shown a non-nicotine drug could affect withdrawal from nicotine. The truth of the matter is we got a patent on it, which never turned out to be very valuable. It took a lot of time. We did a study with normal subjects because it seemed hard enough to stop smoking without being schizophrenic or depressed. Being a psychiatrist, it was easy for me to do a psychiatric interview, so everybody at the smoking clinic had a standardized psychiatric exam before they entered the study. We made a startling observation; an astounding number of smokers had a history of depression. Once we saw that we looked to see whether it affected their guitting smoking, and people with a history of depression were much more likely to fail. It was a small study. I think there were 88 patients. Clonidine turned out to be a very mediocre smoking cessation drug. It worked, but it wasn't as effective as the nicotine patches or gum. But I got interested in the relationship between depression and smoking, and thought that maybe an antidepressant drug would be useful in smoking cessation. We suggested that at an APA meeting. We did some pilot studies, and looked at a number of antidepressants, including bupropion. Linda Ferry in California saw our paper in the Journal of the American Medical Association linking depression with smoking cessation failure and did

a double-blind trial at the Veteran's Administration hospital She had, I think, 42 smokers, half on placebo and half on bupropion. There was an impressive quit rate on bupropion. The drug manufacturer, Burroughs-Wellcome, pooh-poohed the idea so she called us and asked how we measured depression. We gave her scales and taught her how to use them. Her mother, recently retired from the California school-system, administered them. Linda studied 192 smokers, all free of depression, and bupropion still worked. That led to Zyban, buproprion in a new formulation for smoking. There were headlines about depression and smoking and I was invited to give presentations to non psychiatric audiences.

- TB: By now you must have been pretty pleased with your findings.
- AG: Yes, but there was also a part of me that was concerned or unhappy. I don't know exactly how to put it. I had always had in my mind not just the cardiovascular effects of antidepressant drugs, but the cardiac effects of depression itself. I had a strong bias that depression was causing heart disease. The literature was controversial about whether increased mortality was from depression or just the drugs used to treat it. There was clearly an increase in cardiovascular mortality in depressed people, but all the patients came from clinics or hospitals, and were all medicated. So you couldn't disentangle the medication from the diagnosis. Jane Murphy did a community epidemiological study in 1988. I honestly thought that once she went into the community, the relation between depression and death would disappear, because the cases would be much milder. I thought you'd need a really severe major depression to produce heart disease. That's not what happened. She showed a relationship, and a couple of years later the Yale group replicated that. In the late 1980s, when we started on our smoking work, I thought the depression and heart disease relationship was nailed. But I began to realize it could simply be that depressed people are more likely to smoke, and smoking causes heart disease, and no one had ever controlled for that. At a meeting of the American Medical Association in Chicago (AMA) I met a cardiovascular epidemiologist by the name of Anda. He had replicated our observation about smoking and depression, and its ability to interfere with cessation. When I asked about his data set, Anda had one that prospectively recorded deaths. He not only knew whether someone was a smoker and if they'd quit, he also knew if they died. We could look at the relationship between depression and death, controlling for smoking. He convinced me you have to control for all the cardiovascular risk factors, not just smoking. We published a paper in 1993 showing that even controlling for all cardiovascular

risk factors the relationship between depression and cardiac death persisted. That got me more and more into this issue of depression itself affecting heart disease. When I had gone into smoking, I thought it was unrelated to depression. It turned out to be very much related; so much for planned research.

- TB: You got also involved in mortality studies with depression. How did this happen?
- AG: In the early 1990s, a Canadian, Nancy Frazier Smith, did a psychiatric exam on 222 post MI patients in cardiac intensive care and followed them for six months. People with major depression were almost four times more likely to die. Even controlling for risk factors and severity, this has been a very consistent finding. But hers' was really the land mark study. Even though there were a very limited number of patients, I felt we needed to do a clinical trial to see if treating depression would reduce mortality and that was really the beginning of the sertraline antidepressant heart attack randomized trial (SADHART). That study had a very rough beginning, nobody wanted to do it. Wilma Harrison attended the ACNP for a number of years as a representative of Pfizer. She eventually ran the CNS division and she was somebody special. Most of the company people did not want to do the study but Wilma insisted it was crucial. After about two years of in-fighting they eventually agreed to do a pilot study. But we demonstrated that we could collect the patients and do the measurements and we had some pilot safety data so they didn't have to worry that anything terrible would happen. The definitive study did not start until 1997 and wasn't published until 2002. The results were beyond our wildest dreams. I thought I was doing the world's largest pilot study. It was really a stepping stone. I wanted to do a mortality study but because there was no safety data and we needed that first, the design did not have the power to show if treating depression reduced mortality. That would need 3,000 to 4,000 patients if there was a 20% reduction in mortality, and I didn't think it would reduce it by that much. A 10% reduction would still save 1,000 lives a year. But there is another aspect in addition. It would change the stigma attached to depression, both in the patients themselves and in physicians. Many physicians still don't accept that depression is an important condition. If you could show that treating that condition would reduce mortality, then they would pay attention to it. So I'm still working to get that definitive trial. The SADHART results suggested that there was at least a 23% reduction in life-threatening events. It just missed being a trend. But the study and sample size was nowhere near adequate to look at mortality. It did prove safety, and that makes a larger study much more

doable. And then the NHLBI study, encouraging recovery in coronary heart disease (ENRICHD) showed that psychological treatment reduced depression, but it didn't change mortality. The ethics committees said, if you had a patient with a Hamilton Depression score of more than 24 you have to give them an antidepressant. It turned out that about 20% of patients, for one reason or another, were already on an anti-depressant drug, usually an SSRI. But in ENRICHD drug use was not randomized nor was it controlled. Some people started it early, some started it late. Nevertheless, there was a 42% reduction in mortality in the drug group compared to the non-drug group. You would expect a higher death rate in the more severely depressed, but there was a 42% reduction in mortality. So it looks very much as if antidepressants reduce mortality. There are things to be done, but so far that's the story.

- TB: There are things to be done you said. What should be done?
- AG: What would I like? The most important thing is to do a simple definitive trial; to take 4,000 patients and randomize them to an SSRI or placebo. I'm a consultant for the American Heart Association on their standards of care committee, and they look at our data and say, it's very suggestive, but it's not definitive. It can't be made a standard of care on the evidence we presently have. If it isn't a standard of care, some people will do it, some people won't. The drug companies can't really advertise it because there is not evidence that the FDA would accept. If we did a definitive trial, and showed a reduction in death, that would have such an impact on how other physicians look at depression and how the patients looked at themselves. I honestly think that depression is a disease of the whole body. The same story exists with stroke. There is not as much evidence, but it looks very much like it. And there's very good evidence that bone metabolism is affected by depression. Once you prove that treating depression reduces mortality, than there will be a whole slew of studies looking at why. As a group that studies psychopharmacology, we put up fences between other disciplines that limit our understanding. We may have one of the best cardiac drugs. This may be beneficial in anyone with bad heart disease, not just in depressed people. If we reduce death in depressed people with an SSRI, people will look and see if it works in all cardiac patients.
- TB: Is there anything else you would like to talk about or add?
- AG: No, I don't want to add anything. That's fine.
- TB: Well, then, I think we should conclude this interview with Dr. Alexander Glassman. Thank you very much
- AG: It's a pleasure.

# URIEL M. HALBREICH

### Interviewed by Daniel P. Van Kammen Waikoloa, Hawaii, December 12, 1997

- DV: We're here to interview Dr. Uriel Halbreich,\* next to me sits Brian Leonard my co-interviewer from Galway, Ireland and I'm Dan Van Kammen from Pittsburgh. Uriel, what sort of training did you have?
- UH: I started my psychiatric training, after my Navy service in Israel.
- DV: When was that?
- UH: This was between 1969 and 1972, during which I was a Vice Chief medical officer of the Israeli Navy. From being a big shot in the Navy, I became a first year resident in one of the hospitals affiliated with the Hebrew University at Hadassah Medical School, which were guite conservative, psychoanalytically oriented hospitals. So my first training was in psychoanalysis and, then, I became an odd ball and started doing psychoendocrinology studies. When I completed my residency I also got a post graduate diploma in psychotherapy from Sackler School of Medicine in Tel Aviv. Then I came to Columbia University in New York to work with Ed Sachar, who was the Director of the New York State Psychiatric Institute of Columbia University. He got a grant for exactly what I was doing in Israel which was much more convenient. During my residency, we did twenty-four hour studies of psychoendocrine rhythms in depression, mostly of cortisol. Doing it in a psychoanalytically nonresearch oriented hospital meant that for twenty-four hours at a time I was doing lots of blood drawing every twenty minutes and running to the laboratory to get the plasma samples, two nights or three nights a week. This was not exactly convenient. At that time I involved Leon Greenhouse, who is now doing well in his psychopharmacology and psychoendocrinology career. The main reason for courting him was that I needed somebody to share the blood drawings with me during the nights.
- DV: Why, in a psychoanalytic environment, did you decide to do something crazy like going into psychopharmacology?
- UH: When I needed to decide about my career, there were three options, and I had interest in all three, which were neurology, psychiatry and Ob/ Gyn. I chose to start residency in psychiatry because I had not been able to enroll in neurology. But from the beginning I had a very good relationship with the people in neurology, with Sol Friedman, who was Chair of the department and Dean of the medical school, and with Lavi who was there before I did my dissertation. In Israel we needed to do a

<sup>\*</sup> Uriel M. Halbreich was born in Jerusalem, Israel in 1943.

dissertation for an MD and mine was in neurology using very primitive imaging that became available at that time. I was already as a student, interested in the interface between neurology and psychiatry, with an emphasis on women's hormones. So I followed my own path from the very beginning.

- DV: Did you focus on neuroendocrinology?
- UH: During my time in Israel, I worked with junior people. We didn't have mentors but we published good papers in the *Archives of General Psychiatry* and the *Lancet*. It was quite a unique beginning of a career with no mentor whatsoever, mostly on psychotic and subtypes of depression. I also became interested at this time in dysphoric disorders in women and affective disorders, in general. We had several studies on aspects of Pre-Menstrual Syndrome (PMS).
- DV: You say that you started out without a mentor, so there's nobody there that you can blame your career on?
- UH: Well someone who was close to a mentor was Herman van Praag, who came as a visiting professor to Hadassah. We had some plans to do things together, but he was just a visiting professor for a year. He was supposed to stay as the Chair, it didn't work out but for a while there was a lot of moral support. It was very important, because the designated future Chair supported the junior people doing research. It helped to stabilize our schedules, and improved our work with the psychoanalysts and the social workers in the department. But it didn't have any impact in any other way and so I was very glad when Ed Sachar proposed that I come to work with him. This was shortly after he came to Columbia University and he needed fellows and assistants.
- DV: Which year was that?
- UH: This was in 1978.
- DV: What projects did you become involved in?
- UH: It was, more or less, psychoendocrinology, in which we used medications as challenges to study the physiology of depression. We did a lot of studies with amphetamine, with methylphenidate and with insulin hypoglycemia. The medication was only a vehicle to a study people before and after treatment, not for the purpose of clinical trials. In 1980, after I finished my fellowship, I went to Albert Einstein with a recommendation from Ed Sachar, because before he became Chairman at Columbia, he was the Director of the Division of Psychoendocrinology at Albert Einstein College of Medicine (AECOM). We continued collaboration with people at Columbia University and eventually this became the Division of Biological Psychiatry, which included endocrinology and psychopharmacology. That's when we started studies of selective

serotonin uptake inhibitors, (SSRIs). We also studied the influence of hormones on women's behavior.

- DV: Any particular hypotheses that you studied?
- UH: There were two hypotheses. One was that in major depressive disorder, there is an abnormality of diurnal rhythm that is reflected in plasma in prolactin or cortisol levels. We also studied monoamines and receptors in platelets and plasma to check this hypothesis. This was my first independent project and a continuation of what we did at Columbia. First of all, we developed a new cortisol test to have a more accurate discrimination between depressives and normals. What eventually came out of these studies were the findings that rhythms are not only abnormal but are different in major depression. We found an early surge of cortisol in depressives with discrimination between different functions of the hypothalamic pituitary axis (HPA). Not just an abnormal HPA system in depression, but there are different abnormalities distinguishable from each other. This was the beginning of the notion of sub-groups of depressives instead a global "depression" that didn't catch on until now, unfortunately. We had several papers, in which we tried to push the idea that in major depression, as in DSM-III and beyond, you have to look at people who are abnormal within the syndrome, compared to those who are normal. Fortunately, this is something that now seems to have caught on.
- DV: Would you say that, as a result of your studies, there are differences between female and male patients with depression which are hormonally linked?
- UH: This is something we found towards the middle of our studies. It is very apparent there's a gender difference from the prevalence in which women are more depressed in a ratio of almost two to one compared to men. A consistent line of research was to take a closer look at what might lead to a major depressive disorder in women. This was my first interest in PMS. You can study the same woman, when she is depressed and when she's not, and that's something we did at Columbia, together with Jean Endicott. We developed diagnostic tools to evaluate and assess PMS and then did a series of studies. This included the disassociation between PMS and major depressive disorder, the pathology and pathophysiology of PMS, and associations between pathophysiology of major depressive disorder and pathophysiology of PMS. Other people followed very similar lines of research with postpartum depression and with the peri-menopausal side effects of medications and hormones. We were very instrumental in showing that there is an association with other hormones and life cycle related disorders. Dysphoric disorders

are related to major depressive disorder and to each other. They are also related to changes in gonadal hormones which might increase vulnerability of women to develop an affective disorder. This is a line we are pursuing more and more, because currently the emphasis is on the hypothalamic pituitary adrenal (HPA) system and looking at major depression as a homogenous group, which it isn't. We believe that very shortly we will move to a more interactive model of associations between the HPA system, gonadal hormones, thyroid and several other systems to look at equilibrium. The studies have moved to changes over time and vulnerability to affective disorders, in which women are very good models to study.

- DV: You talk about PMS; isn't there a lot of controversy about whether it exists or not, or has that been resolved? Where do you fit in that controversy?
- UH: Part of my contribution to the field, with all modesty, was to show that it does exist from our first studies in 1978 -1980. We had to show it's not just a male chauvinist plot to discriminate against woman, which was more difficult for me, as a man. We looked at the statistical association between PMS and depressive disorder to convince the scientific community. This is something that is not just minor, but is worthwhile studying. We also wanted to look at situations of the menstrual cycle and association between PMS and other situations in which there's depression, and then get into the biological aspects, which we never actually studied. Then we looked at the association between biology, cognitive functioning, mood and changes over time.
- DV: So, we're talking about conceptual areas of interest.
- UH: Conceptually, that's something I struggled with. What is the definition, what is the focus? It's well known that if you want to get funded or get grants, you need to study details and specifics from the very beginning of a project. I believe that that's not the way to go, so my first or second grant application was to look at the interrelationship between noradrenergic and serotonergic function with endorphins and connect them to other multidimensional systems. This idea was published in the *Psychopharmaclogy Bulletin*, and looked at the consequence of an imbalance between two or more functions or systems, operating at different levels, starting from the pre-synaptic, synaptic and then interneuronal activity. This was criticized as silly and was not funded. Even now, seventeen years later it's not easy to get funded for this. By the way, I was not the only one who was rejected. The review didn't say stupid, but something very close. It was unfocused because we described multidimensional processes operating for PMS. At this

time, in 1980, part of the hypothesis was that if we wanted to look at the endorphins in women with PMS, we needed to study more then one endorphin receptor. We had to give two different dosages of naltrexone, which were calculated based on some studies with animals. This was also rejected on the grounds it didn't make sense that there was more than one endorphin receptor. There is a negative correlation between the grants that I got funded and how innovative they were. The most mundane grants were well funded, because I learned my lesson very quickly, but the ones I thought were more interesting were not.

- DV: That's not just an America problem. It's an international problem.
- UH: It's a very big problem because most grants are funded for very small incremental steps based on past findings and not what might be a conceptual leap. Yes, "safe" funding.
- DV: The visionary research is much harder to get across. So how did you manage to stay in the field?
- UH: I was very lucky, because, since I came to the United States in 1978, I have been constantly funded with hard money. I didn't have to fight for my financial survival. I got mostly federal funds in 1978, because I won the National Service Award. This financed part of my salary. I got more money from industry and chose trials I was interested in that supported biological studies.

For example a Federal grant to study another hormone in women of a productive age called for pre-treatment and post-treatment. The compound we studied, RU 486 (mifepristone), came from industry and when we did hormonal replacement therapies studies, they were also funded by industry. The serotonergic, noradrenergic or other parameters were supported by different grants, including parts that I have to support myself because the results might not be favorable to industry. One of the first examples was tamoxiphen, which I predicted might have a positive effect on the central nervous system. The company that produces tamoxiphen didn't want to support the study because they felt that they would get negative results even though, eventually, we came out with the finding that it was a very positive monamine inhibitor. It has the same influence as estrogen on key proteins, blood flow and pH2. The industry missed the boat and other companies are now developing better drugs. This was one example where industry didn't want to support a study based on preconceived formed interests. We tried all the time towards a balance between federal and industry grants as well as others that were not funded by anybody.

DV: So called unfunded research?

- UH: It's research that is funded by money that was designated for some other project, which you manage to conduct in a cost effective way, creating financial flexibility.
- DV: What was the general impact of your work, looking at psychoendocrine aspects, changes in female sex hormones, linking in with depression? How unique was your position? Were other groups at the time working in similar areas that you could interact with and exchange ideas, or were you the front runner?
- UH: In the beginning I was the front runner in the psychoendocrinology of PMS from my residency in Israel in the mid 1970's and then in the U.S from 1978 until the mid eighties. Even now some of these areas are not in the mainstream of psychiatry. But they became more mainstream in the early eighties. Other people got into the field, like David Rubinow and Peter Schmidt at the NIMH, Barbara Perry, first at NIMH and then at San Diego, Ellen Freeman in Philadelphia, and several others who were a bit younger in the field. Meir Steiner was doing studies very similar to mine at the same time as well as Roger Haskett and many others. We interacted guite well with Bruce McEwen and Hoffer from the basic science aspect. We introduced the concepts of diversity among syndromes, hormonal imbalance or disturbed homeostasis as well as the importance of rate of change over time. The dimensions of the field and the topics that that people work on, are changing now. Part of the change is because of political clout from women, the influence of the pharmaceutical industry and politicians and policymakers shifting the focus to studies of women away from men.
- DV: Your original focus has been on depression and how it translates in women, particularly the interaction with hormones. Are there any other major psychiatric disorders that may vary due to gender?
- UH: My emphasis is on depressions especially, during the recent years. We know that about sixty five percent of people treated with any antidepressant respond but we do not know how they differ from the forty percent who do not. Conceptually we look for differences based on symptoms and nosology but I believe the emphasis needs to be on biological variability, whether or not this is related to gender.
- DV: Biological subtyping has not led to any clear differentiation at this point has it?
- UH: Biological subtyping is not working because the departure point is still based on syndromal typing which might not have anything to do with biology. In every textbook you see forty, fifty or sixty different pathways to get depressed. Some of them are central nervous system disorders, some of them are peripheral. We didn't make the conceptual shift to

look at these pathways to see if one medication or another was good for a specific pathway. We have a book coming out now that takes the departure point as biology, not the phenomenology. This has been the way in other specialites. Hypertension, when I was a student, was a diagnosis. Now it's the beginning of differential diagnosis. The question is not how to treat hypertension; the question is do we have a specific medication for a specific type of physiology that might lead to high blood pressure. The same is true with diabetes and with abdominal pain. There was a time when abdominal pain was a diagnosis. Now the best treatment is to see what is causing that pain and treat it. This is a conceptual shift but, unfortunately, psychiatry has yet to accomplish it.

- DV: Is there a role for molecular genetics in this?
- UH: That's also an important concept. We are working together with about a dozen collaborators to prepare a grant that looks at the vulnerability of women to develop affective disorders. This is based first on genetics, then on environment and hormonal load or instability, which might be positive or negative influences or create a kindling effect. The assumption is that there is not one depression and one gene, but multiple genes interacting with each other, which might cause initial vulnerability, and which might be expressed or not. It's a complicated field, but the departure point is not exclusively gender which I believe would not be productive. Public agencies are still not funding most of these projects but I believe this will be one of the first to be funded, because it includes policymakers and it's working together with the federal government and drug companies.
- DV: The antidepressant market is interesting because when we find new drugs, it seems to expand. It appears that there should be room for that kind of genetic or biological differentiation.

Is this leading to an education as far as the industry is concerned, in terms of future drug development by showing the role of genetics, hormones, neurotransmitter systems and their interactions?

- UH: Yes. This is a very fortunate time, because we have convergence of two processes. Hormones are playing a major role in many patients and some abnormalities are detectable. There's a lot of interest in the industry in developing medications that are very specifically targeting hormonal changes. Not just looking at hormones as a window into the brain, but, actually, using hormones or hormonal like compounds, for treatment of affective disorders.
- DV: In other words hormones which we always thought targeted organs outside the brain, have a role in the brain itself that affects behavior. I would say that your major contribution to psychopharmacology was

showing interrelationships between sex hormones, general endocrine processing, and mental state. This could be very important for the future development of specific and effective treatments. In summary, would you say that's been your major contribution?

- UH: That's a good summary of it. I also saw the educational need, because it's important. You can have knowledge, but if this knowledge is not transferred to others, it's really not seving what it should. Part of what we're doing now is trying to extend the information from just psychopharmacologists to clinicians, primary care physicians and families about better ways to treat patients. That's what we are doing with the International Institute for Education and Mental Health (IEE). That's one of the contributions Brian Leonard and other colleagues, including Dan Van Kammen and myself are making. We`are spreading the word beyond the ivory towers, where it's produced, to actual applications in places where it can be used.
- DV: It's not just taking it beyond the ivory towers, within Europe and North America. Even more important is the focus on developing countries, the training of psychiatrists, neurologists and pharmacologists about the application and use of drugs in the community. This is an area which has been neglected by us in the past. This is where the CINP has been important and the IIE is coming in from the practical point of view. But the other issue is that scientific improvements are taking fifteen or twenty years before they get applied in the field.
- UH: I think that's a very important point that we've raised. There is a world beyond the universities; there's a world beyond the United States and Western Europe. We are at the point where industry realizes there's a large market made up of real people in need so we have to educate professionals at every level, because in most places they don't have psychiatrists.
- DV: There are two important aspects that relate to membership in the ACNP. Do you see your future as one of the grand old men carrying on in research, or is your future more as a mentor and educator?
- UH: That's a very good question and a good place to finish. As a relatively young investigator, when I came to Columbia and met the big names, Ed Sachar, Don Klein, Sid Malitz, Sandy Glassman and Joe Zubin and others, I was able to interact with them. The main impact was to see that these giants, were actual human beings, and my reaction was, if they can do it I can do it, too. At this point, even though this interview is for a history of the ACNP, I don't see myself as history. I think it's important that younger investigators interact with more experienced mentors like you and me, on a continuous personal level. We need to keep active

not just locally but bring in more people not only from the United States, or from the ivory towers, but from places in which young scientists lack immediate mentors as in South America. That's a very important educational challenge for the future. We have to show younger people that they can actually do research and provide them tools to do it on their own.

- DV: Any views on the future beyond the educational point? New illnesses, new drugs, and the way the field is moving, from your viewpoint?
- UH: I hope my main contribution to the field will be the definition of a focus for research. The focus of research should not be just the serotonergic system or a specific post synaptic receptor within the serotonergic system or norepinephrine or glutamate or inositol. What I'm hoping for the future is that there will be financing that support studies with a multidimensional focus. The idea is that a multidimensional balance is more important than a specific single end point. I hope the field will be moving to find treatment modalities and medications for imbalance of impaired immunostasis. I believe that is the bottom line in affective disorders and it calls for a conceptual shift to convince researchers and industry to try this particular, but not so safe, avenue to develop compounds.
- DV: Right! To move towards a more complex, but much more dynamic, and probably much more exciting approach in research. Is there anything else that you would like to leave with us?
- UH: I thank you very much and the ACNP for providing this opportunity to chat with friends.

# **KATHERINE A. HALMI**

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

- TB: We are at the Annual Meeting of the American College of Neuropsychopharmacology in Waikoloa, Hawaii. It is December 10, 2001, and we are going to do an interview for the Archives of the College with Dr. Katherine Halmi.\* It is December 10, 2001. I am Thomas Ban. Let us start from the very beginning. When and where were you born? If you could tell us something about your early interests, education and how you got into the area of eating disorders.
- KH: I was born on October 23, 1939. Most women don't like to give the date when they were born, but I'm over that at this point in my life. There is something satisfying to admitting I am the grandmother of the eating disorder field. I was born in St. Paul, Minnesota and from there I received my education in the Midwest with a General Motor's scholar-ship to the University of Iowa for my BA. and MD degrees. My medical interests were in endocrinology. I initially completed pediatric training and began working with Professor Zellweger, who was one of the first pediatricians to do genetic research. When I was a medical student I learned how to do chromosome counts in Professor Zellweger's laboratory, and that was my spur to interest in research.
- TB: So, Dr. Zellweger had an important impact on your life?
- KH: Dr. Zellweger had an important influence in developing my research interest. Then I was coached by my first husband, Nicholas Halmi, a well known basic endocrine researcher and the editor of *Endocrinology*. He taught me how to think very precisely and how to respect scientific quality. I think that is a very important thing in developing your research career. He was a severe critic in the best Hungarian-Jewish tradition. So, I quickly learned how to think clearly and defend myself.
- TB: Where did you move from Iowa?
- KH: I became board certified in pediatrics and joined the faculty at the University of Iowa, studying cortisol metabolism.
- TB: Was this your first research project?
- KH: My initial research was with Dr. Zellweger.
- TB: When did you have your first publication and what was it on?
- KH: My first publication was on identifying Trisomy 18 in Dr. Zellweger's lab.
- TB: When was that?
- KH: In 1968.
- TB: It was your first publication and your first research project?

<sup>\*</sup> Katherine Halmi was born in St. Paul, Minnesota in 1939.

### KH: Right.

- TB: And you were a resident at the time?
- KH: I was a pediatric resident, in the process of completing my residency. I became more and more interested in behavior and did a fellowship in child development. From there I decided I was ignorant in understanding behavior and went into psychiatry.
- TB: So, you moved from pediatrics to psychiatry in the early 1970's?
- KH: Right. At that time, George Winokur became the Chairman of the lowa Department of Psychiatry. He was just a wonderful supporter of research and an excellent investigator himself. That was a good opportunity and he taught me the methodology and principles of clinical research. He also provided the environment, opportunity and time to do the research.
- TB: After your residency in pediatrics you did a residency in psychiatry?
- KH: I completed a residency in both. When I was a psychiatric resident I got into eating disorders. Dr. Winokur came to me one day and said, "I have this young lady on the unit that I believe has anorexia nervosa. I want you to investigate and take care of her. There are very few publications on anorexia and nobody knows much about it so I would like you to look into it". I carefully went over the literature and he was right. There were very few publications. I examined the young lady carefully and decided she did not have anorexia nervosa. She really suffered from schizophrenia because her delusion was that different colors of food would erode her gut. That is not the kind of delusion present in anorexia nervosa. The problem patients with anorexia have is denial of their illness and the refusal to recognize that starvation may cause death. It is not the same quality as a psychotic delusion. Having learned how to argue aggressively in my training I presented that to Dr. Winokur. To his credit, he acknowledged it. Then he went on to say that the University of Iowa Psychopathic Hospital had an unusual collection of records because it was one of the four original psychopathic hospitals. They had a wonderful record system, which Dr. Winokur was using for his schizophrenia studies. Starting when I was a first year psych. resident, I spent every lunch hour down in the medical records room. After I devised various criteria, I went through about 3,000 records. Nobody had classified anorexia nervosa in those days and it was often coded as a psychophysiological gastrointestinal disturbance. Among the almost 3,000 records I was able to find 96 young women and 4 men who met the Feighner criteria for anorexia.
- TB: Was this before or after 1974?
- KH: This was before.

- TB: About the time the Feighner criteria was published in 1972?
- KH: Yes. My first publication in the field of eating disorders was in the *Journal* of *Psychosomatic Medicine* on the group of patients from the chart research. Then, I decided to follow them up and was able to locate 79 patients, which was fairly good for record research. I admitted them to the clinical research center and conducted a series of endocrine investigations and standardized interviews. That resulted in a longitudinal follow up publication and propelled me into becoming more interested in eating disorders.
- TB: You read through those famous records. Can you tell us how they were structured?
- KH: The ones at the psychopathic hospital were structured, but those in the medical school were not. I had to go through many records in internal medicine as well because people were not identified as having a psychiatric illness at that time. Those in the psychiatric hospital had very long descriptions of family history and of the patient's personal development as a child. It was excellent descriptive writing which we often don't see today. That was an invaluable collection. From that I went on with my Chairman, who was eager to support me and who now stated I was an expert in the treatment of eating disorders, which of course, I wasn't. Nevertheless, I soon began receiving referrals because Dr. Winokur announced my expertise to the State Psychiatric Association. So I had to quickly set up a program. That is how medicine was practiced in those days. At that time, the only book on anorexia nervosa was by Bliss and Branch, which emphasized their hypothesis that a hypothalamic disturbance was present with deficient pituitary secretion of follicle stimulating hormone, (FSH), luteinizing hormone, (LH) and so forth. But they didn't have any recommendation for treatment. Then, there was a group from London, England, Professors Russell and Crisp, who were using gross behavior methods at the time, putting people in bed until they reached their target weight. Since those early days, cognitive behavioral therapy has developed and is much more sophisticated. Along with that, psychopharmacology evolved. Many patients were treated with chlorpromazine which reduced their exercising as well as ruminations about food and being thin. It was exceedingly helpful, but there has never been a double blind, randomly assigned, controlled study with chlorpromazine. In the European, especially the German literature, there are many cumulative case reports in anorexia nervosa treated with the drug, but no one has ever done a double blind study. We wanted to do that, but it was impossible to get funding. As a pediatrician, I used chlorpromazine with effective results in agitated patients.

I still use it in many cases for severely emaciated patients, starting with 10 mg half an hour before meals in liquid form, then, gradually increasing the dose while monitoring lying and standing blood pressure. In studying the medication management of anorexia nervosa we have a huge problem because it is almost impossible to complete an adequate sample.

- TB: So, you had problems in recruiting patients?
- KH: Right.
- TB: Did you work at a clinic?
- KH: Well, I developed my own clinic.
- TB: Did you have an eating disorder clinic?
- KH: You have to remember, the population of Iowa City was only 40,000 and it probably still is. We had a very good socialized medicine system, whereby cars went out from the University of Iowa Medical Center all over the state, bringing in medically ill patients. An outpatient clinic wasn't feasible, so I had an inpatient operation in the clinical research center. I needed to establish my independence in treating these people the way I wanted and avoid the administrative structure of the psychopathic hospital. So, I developed research protocols and every patient was on one or the other. It was fortunate for me that the clinical research center needed to have their beds filled so I could work out a contract with them.
- TB: Where did your patients come from?
- KH: From the entire state of Iowa, because the state cars would bring them in. As I began publishing and became known in the field, I would get them from out of state, as well.
- TB: Am I correct that most of your patients had anorexia nervosa?
- KH: Predominantly. Bulimia nervosa was not really recognized as a separate entity until about 1979. All of us doing research in the area recognized the clinical and even physiological differences that existed between the anorexia nervosa restricting patient and the anorexia nervosa bingepurge patient. My studies were some of the first to differentiate these. The binge-purge patient has much higher co-morbidity with alcohol abuse, drug abuse and Axis II personality disturbances especially cluster B, the impulsive type. They also have differences in response to serotonergic challenge tests. Those who binge and purge have a decreased response of prolactin to fenfluramine challenge; whereas the restrictors, if they are not severely emaciated, have little diminished response. We began to differentiate the subtypes, but then Russell identified a group of patients who had normal weight and were bingeing and vomiting. Once a group of patients has been identified people start

finding the cases. That happened all over our country. Cases were publicized and bulimia nervosa became an independent diagnosis.

- TB: So, physiological differences in patients were associated with differences in pharmacological responsiveness?
- KH: That was determined later, but in the 1970's there were several different approaches. One was the development of cognitive behavioral therapy, and Stewart Agras at Stanford University was highly instrumental in that. Stewart was one of the first, along with me later, to develop controlled treatment studies, examining the efficacy of various medications and cognitive behavior therapy in treating anorexia first, and then bulimia. Agras developed some more sophisticated forms of cognitive behavior therapy (CBT). Professor Russell in London had done mainly endocrine research, while Crisp, also in London, had a very psychodynamic approach, even though he also used strong behavioral contingencies and chlorpromazine. In the United States, at that time, there wasn't any eating disorder controlled treatment research other than Agras, myself and collaborators. There were psychoanalysts, Hilda Bruch, and Minuchen who developed a family therapy for anorexia nervosa. The first international meeting was at the National Institute of Mental Health, sponsored by Vigersky who was an endocrinologist. At that meeting, a small group of eating disorder experts included Stewart Agras, Hilda Bruch, Crisp, Russell and me. Then, there were some invited people that sat around on the outside. The meeting was especially amusing because Crisp and Russell did not believe Minuchen's exaggerated results that family therapy cured these patients, and they questioned him intensively. He got very angry, banged his fist on the table and walked out.
- TB: Did he come back?
- KH: No, he did not. But, one has to give him credit for developing and emphasizing family therapy. This led to a series of studies that developed, predominantly in London, examining what type of family therapy and for whom it was effective. Today, there are controlled studies to show that family counseling of some sort is essential for children under the age of 18.
- TB: When did this first meeting take place?
- KH: In 1976.
- TB: Did people working in the field come from all around the world?
- KH: Right. At that meeting, much attention was paid to endocrine research. I did some of those early studies at the University of Iowa.
- TB: What proportion of the participants were psychiatrists and what proportion endocrinologists?

- KH: I would say only about a quarter were endocrinologists and the others psychiatrists.
- TB: So, the meeting was held before some of the pharmacological research was done with bulimia nervosa?
- KH: Yes. Since then, many controlled pharmacological studies have been conducted for bulimia nervosa, because our challenge tests indicated that there was a definite deficiency of serotonin regulation in normal weight bulimia nervosa patients.
- TB: When did the challenge tests come about?
- KH: They came about in the 1980's. Those were done with m-chlorophenylpiperazine (MCPP) and, then, of course, serotonin turnover was studied with CSF samples at the NIH by Walter Kaye. Since the 1980's Walter Kaye has been a pre-eminent researcher, both in the endocrinology and neuroendocrinology of eating disorders.
- TB: When, were the biochemical studies on CSF, conducted?
- KH: In the 1980's. That was also developed with Walter Kaye at the National Institute of Health. Because it is so difficult to get patients with anorexia nervosa to cooperate, the area is riddled with the problem of adequate sample size. Most of Walter Kaye's CSF studies have never been replicated because we cannot get enough patients. What is unique about those studies is that he was able to get continuity of patients when they were acutely ill and after weight restoration.
- TB: When did you move from Iowa to New York?
- KH: In 1979.
- TB: What was the status of your studies when you moved?
- KH: I had already completed the first multicenter study examining the efficacy of cyproheptadine and cognitive behavioral therapy in anorexia nervosa. That was my first NIH grant. It was actually a multi-site treatment grant.
- TB: How many other sites?
- KH: There was the University of Minnesota and the Illinois State Psychiatric Institute. We were interested in cyproheptadine because it was a serotonergic antagonist, and serotonin produces fullness and satiety. We thought if we could decrease the action of serotonin it might facilitate weight gain in patients with anorexia. It turned out this hypothesis was probably wrong because anorectics are hungry unless they are extremely emaciated. The reason why serotonin facilitated weight gain to a very modest degree was probably due to its antihistaminic effects. We then placed activity monitors on patients' wrists and ankles, and were able to show that high doses of cyproheptadine, up to 24 mg a day, significantly reduced physical activity. That was probably the

mechanism whereby they were gaining weight and why it was so modest.

- TB: In how many centers was the research conducted?
- KH: We had three centers.
- TB: In Chicago, Minnesota, and Iowa City?
- KH: Right, for the treatment study. The activity study was at Cornell, after I moved.
- TB: How many patients did you have, altogether?
- KH: In the treatment study, about 96 patients.
- TB: That was quite a good sample size.
- KH: It was a very good sample size.
- TB: You had cognitive therapy in that study?
- KH: The cognitive therapy was a strong behavioral component. We learned it was very difficult to study CB in anorexia nervosa inpatients. Back when we didn't have managed care, it was possible to treat them in an inpatient setting until they got to their target weight. We learned another important principle; you can't randomly assign anorexia nervosa patients, who are near death, to a therapy. We had several other problems. The nursing staff became convinced that cognitive behavioral therapy was absolutely essential because it helped them in managing the patients. Behind our backs, they were instituting various cognitive behavioral principles surreptitiously. So, when we analyzed the data there was no statistical difference between cyproheptadine and cognitive behavioral therapy since all the patients were indirectly receiving CBT. You can't compare psychotherapy with another treatment on the same unit
- TB: Where did you publish the findings?
- KH: That was published in the *British Journal of Psychiatry.* It was in a series of five publications in that journal.
- TB: What year?
- KH: In 1979.
- TB: Was your study the first in a series of multi-center studies in that area of research?
- KH: It was the very first multi-center study in the treatment of eating disorders, examining the efficacy of a pharmacological treatment by comparing cyproheptadine with cognitive behavior therapy.
- TB: Didn't you carry out some research with chlorpromazine?
- KH: Not systematically, because I was never able to get that funded, which shows that the whims of research committees sometimes dictate the direction of research.
- TB: Did you work with any of the other neuroleptics?

- KH: I used only chlorpromazine and cyproheptadine. With bulimia nervosa, it soon became evident that any antidepressant was effective in reducing binge-purge behavior. Bulimics are very willing to participate in trials; they are motivated to get over their illness and, thus, there are about 40 controlled, randomly assigned antidepressant-placebo trials for bulimia nervosa worldwide.
- TB: So they are very different, in that respect, from the patients with anorexia nervosa. Are patients with bulimia very anxious?
- KH: They are anxious to get over their illness. That is a huge difference. So, we became involved in those studies, which initially included the tricyclic antidepressants and the SSRI's when they are available.
- TB: Which ones?
- KH: Everything was studied. All antidepressant medications, irrespective of structure had about the same efficacy. Only 20 to 30% of patients had a complete cessation of bingeing and vomiting and about 40% had a 50% reduction. The drugs produce some relief, but aren't curative. We are still at that stage today, but we have also done studies with cognitive behavioral therapy and comparison studies with medications. Today, cognitive behavioral therapy, which is now highly sophisticated with organized special treatment manuals, is the state of the art treatment. It results in about 40-50% complete cessation of bingeing and vomiting with about 70% of the patients reducing their bingeing and purging by 50%.
- TB: Was this research done already in New York?
- KH: Right.
- TB: It was in your new setting. In Iowa, you had an eating disorder unit. By the way, was your eating disorder unit in Iowa the first eating disorder unit in the country?
- KH: Not specifically, because it was in the context of the clinical research center in internal medicine. There were other units in those years being set up, but nothing was exclusively eating disorders. Arnie Anderson at John Hopkins set up an eating disorder unit; the NIMH did, and, so, they were beginning to develop. The problem was, I couldn't forever depend on the clinical research center. I had this wonderful opportunity at Cornell Medical College in the Westchester division, which had a 300 bed psychiatric hospital, known in the past as Bloomingdale's, to have a 20 bed unit and run my own operation with the independence I needed. Then, I moved to New York. It was easier getting patients because of the huge Metropolitan population.
- TB: Did you have a free hand in setting things up in New York as you wished?

- KH: Pretty much so. The thing that was missing there was lack of proximity to the main hospital. It was 35 miles away. That was a drawback.
- TB: You had grants to carry out your first studies of cognitive therapy and cyproheptadine. Were you able to get funding in New York?
- KH: I have had funding my entire career. When I got to New York, I also obtained a grant to study the comparison of amitriptyline and cyproheptadine in treating anorexia nervosa. That was a collaborative study with the University of Minnesota. We completed that and then I had a grant to do a longitudinal follow-up.
- TB: What did you find?
- KH: We found that neither drug was dramatically effective in increasing weight gain. Both were equally effective, but to a modest degree, in reducing the length of time for patients to get to their target weight. The average time was 14 days. There were far fewer side effects with cyproheptadine than with amitriptyline.
- TB: Fewer anticholinergic effects?
- KH: Yes. Cyproheptadine was effective in reducing weight gain exclusively in the anorectic restricting types and not in the anorectic bulimia types. This was exciting information that made good sense in terms of what we were finding in our physiological studies because the bulimics had a deficiency of serotonin whereas the restricting anorectics did not, unless they were severely emaciated. That went along nicely with the studies Walter Kaye was conducting at the National Institute of Health. He was very excited about our treatment findings because his CSF studies showed that the bulimia nervosa patients had a significantly decreased serotonin turnover, compared with the restricting type. So, we, essentially, had information from two different types of studies to indicate that the serotonin dysregulation occurred in both subtypes, but to a different degree. Then I conducted, with the University of Minnesota, a long term follow-up study on those original patients we treated in Iowa, including endocrine studies.
- TB: On how many of the patients could you get follow up information?
- KH: We actually got follow up information on 100% of this set from Iowa and Minnesota and Chicago were not part of the study. This was published in the Archives of General Psychiatry. Our follow-up studies had rather grim results. At the 10 year follow-up 7% had died; only a fourth of them were completely cured; and about a fourth of them were still very chronically ill. The other 50% were in various stages of illness. That brought to light that anorexia, in a very systemically studied follow-up, is a serious and chronic disorder. That study has been the most complete follow-up with a large sample size that has ever been conducted.

One of the reasons for the 100% follow-up was that many of those patients were from the Midwest where people tend not to move as frequently, compared to New York. They also tend to be more compliant with follow up in treatment protocols and studies. In New York people are very mobile; they are far less cooperative, and it is a much greater challenge to do any kind of study, even though you have a huge population base.

- TB: Was your first study in New York the cyproheptadine and amitriptyline comparison?
- KH: That is right.
- TB: What did you do after that study?
- KH: Well, we conducted the follow up study from New York, because we had funding to set up an office back in Iowa City, and I had a research assistant who moved there and flew all over the country.
- TB: Did you do any other research at the time?
- KH: I became involved in pharmacological treatment studies with bulimia nervosa using the serotonin reuptake inhibitors.
- TB: Was this research done in the mid '80's?
- KH: Yes, and then, I did some work with Peter Stokes on endocrine studies and anorexia. Previously, at Iowa and New York, we found that the deficiency of LH and FSH was not a pituitary deficiency, but rather a deficiency of the hypothalamic secretion of gonadotropin releasing hormone. We did a study injecting luteinizing hormone- releasing hormone (LHRH) into anorectic patients and found that their response was adequate, even though they were emaciated. So it stimulated the pituitary to release these hormones. That was published in the Archives of General Psychiatry. The results surprised us. We didn't think it was going to be that effective, but it definitely proved that the problem of amenorrhea was at the hypothalamic level and that it was not producing gonadotropin releasing hormone. Then Stokes and I were interested in examining the function of the dopaminergic system. We did challenge tests with apomorphine and chlorpromazine, measuring prolactin response. In that study we were able to show that there was a probable defect at the dopamine postsynaptic receptor in anorexia nervosa patients. The reason we came to that conclusion was that our studies showed the deficiency when these patients were emaciated and after weight recovery. It has become so fashionable to just focus on the serotonergic system that it is difficult to get funding to study the dopaminergic system. Now, I am involved in a five nation study on the genetics of these patients and we are getting some exciting prelimi-

nary findings to indicate that the dopaminergic system is also involved significantly in anorexia nervosa.

- TB: Isn't the dopaminergic system involved in self-stimulating behavior?
- KH: Animal studies show dopamine function is complex because in the paraventricular nucleus it has different functions, depending on the stimulation. Low amounts can stimulate appetite and high amounts can definitely decrease it. So it has a complex function. What was so appealing about serotonin was it was less complex. If you destroy the serotonergic pathways in the paraventricular nucleus the animal has no satiety and will eat and become obese. Most of the hypotheses concerning dopamine are reward reinforcement hypotheses. Bulimia, especially the binge and purging behavior, has characteristics in common with addictive behaviors. We use many of the same cognitive behavioral principles also used in treating addictive disorders, because bulimia nervosa has a high reinforcing aspect to it. We know that animals will reinforce the dopaminergic system for food.
- TB: The dopamine system seems to be involved in both increasing and decreasing eating behavior.
- KH: Avoidance of eating in anorexia alleviates anxiety in patients and can be a self-stimulating behavior. They become very anxious if they have to eat, because that means gaining weight. If you are a normal weight healthy person you have to face the responsibilities of an adult person. That is the core psychological dynamic. Anorectic patients do not want to face the responsibilities of interpersonal relationships in dealing with their environment. Maintaining the illness is a strong secondary reinforcement. They are absolutely terrified to give up their illness and totally unmotivated to enter treatment. No anorectic wants to be treated, because abstinence from eating provides a reward.
- TB: You mentioned a five centers multinational study. Which are the five countries?
- KH: This is a study that began about almost 10 years ago, funded by the Price Foundation.
- TB: Did it start in the early 1990s?
- KH: Right. Walter Kaye in Pittsburg is the overall organizer, but it involves Wade Berrittini, whose laboratory is responsible for doing the genetic linkage analyses and a group from the NIH that began the research for dopamine and serotonin polymorphisms. It also involves UCLA, my center at Cornell, the University of Pittsburgh, a private clinic associated with the University of Munich in Germany and the University of Toronto. Originally, it involved a center in London that is no longer involved.

- TB: So, in some of the countries there are several centers?
- KH: There also was a center in Italy for the original pilot investigation. Now the study involves only Germany and Canada. We have added some other areas that can collect patients in the Untied States, but not university centers.
- TB: What is the size of the study population?
- KH: The Price Foundation sample size is very large. We probably have a unique and precious sample, something like 100 anorexia nervosa sibling pairs in two categories, anorexia nervosa restricting type with a sibling who has the same disorder and anorexia nervosa restricting proband with an anorectic-bulimic sibling. I can't remember the exact numbers of those two types, but I believe we have 104 sibling pairs. In our bulimia study, there are well over 200 sibling pairs. We have blood for DNA on all these patients and a very thorough systematic interview. This includes the Structured Clinical Interview for DSM diagnoses (SCIDS), measuring personality traits with the Temperament and Character Inventory (TCI), depression with Hamilton ratings and other specific eating disorder psychopathological characteristics with validated instruments. All of our interviewers and raters have established an acceptable score. It is a very special sample.
- TB: Can you say something about the findings?
- KH: I am under pressure not to reveal these until they are published.
- TB: That is fine.
- KH: What I am allowed to say is that there is strong linkage on Chromosome I for the anorexia nervosa restricting type. This area of Chromosome I is interesting because it also involves a significant serotonin receptor site and an opioid receptor site, both of which we are interested in. All these papers have been submitted for publication. So that's what I am allowed to say at this time.
- TB: Thank you for this information.
- KH: This is the direction of research for anorexia nervosa at this time. It means probably another 10-20 years of very painstaking research, because once you identify a cluster of genes you have to determine what proteins they produce and what the proteins do. That is the way to go, because every time a new peptide has been identified, like Orexin that affects the appetite, everybody jumps on the bandwagon to measure it in anorectic patients. They think this is going to be the cure for anorexia nervosa, developing antagonists or an agonist to the peptide. That is simply not where it lies. This disorder is very complex. There are going to be multiple factors that contribute to the biological vulnerability. It is not going to be one single peptide.

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- TB: Is there any other research project you would like to mention?
- KH: We continue to try to refine treatment techniques. With the issue of managed care and the unavailability of good, well-trained therapists in state of the art treatment. I am in the process of doing a cost effectiveness study. This examines both efficacy and efficiency in a collaborative study with the Universities of Stanford, Minnesota and North Dakota, four centers in which we are examining cost effectiveness and treatment efficacy in two arms of treatment for bulimia nervosa. Over the years, bulimia nervosa has been identified and has become far more prevalent than anorexia. About 3% of women in America will have bulimia nervosa at some time in their life. So, one arm of treatment starts out with a guided self-help manual, which is based on the principles of cognitive behavioral therapy. An untrained social worker can read the manual and guide the patient through it, seeing her briefly once a week for 8-10 sessions. If, at the end of that period, the patient hasn't reduced her bingeing and vomiting, she will be assigned fluoxetine, which has been proven to have some effect. That is less costly than state of the art psychotherapy. She is evaluated after eight weeks, and if she is not responding she will begin CBT. In previous studies we have done with Stanford, we were able to predict after only six sessions of CBT what the outcome would be for the standard course of 20 treatment sessions. Because of this finding, in our new grant we analyze every patient after six sessions, and if they haven't reduced their bingeing and purging by 70%, we begin fluoxetine. We carry on the CBT for the full 20 sessions, along with fluoxetine. We are following all these patients for a year. It has been wonderful collaborating with Helena Kramer, because she has been able to use signal detection analyses, which allow us to identify and predict what set of patient variables predict outcome.
- TB: Could you elaborate on signal detection?
- KH: It is a complex analysis taking all sorts of variables every week during the course of treatment and assessing where the patient is at that point in time.
- TB: You said that you are using fluoxetine because there is some evidence of efficacy?
- KH: Right.
- TB: What about other SSRI's? Are they used?
- KH: Efficacy of fluoxetine has been shown in a double blind controlled study for reducing binge-purge behavior. In my clinic and on the inpatient unit, we use other SSRI's and so does everybody in private practice. Other pharmaceutical companies have been riding the coattails of the

company who did the first study because the mechanisms of these drugs are very similar. In clinical practice, for example, if we want more anti-anxiety or sedating effect, we use paroxetine; although, there has been no double blind controlled study.

- TB: So, efficacy has only been demonstrated with fluoxetine.
- KH: Right.
- TB: Is there any comparative study of a tricyclic and fluoxetine?
- KH: No, there is not. Tricyclics aren't used because of the side effects. There are patients who do not respond well to fluoxetine and, for those, we use desipramine. There have been a couple of studies, including ours, in which we added desipramine after fluoxetine and the response was not impressive.
- TB: Was this done on the basis of theoretical considerations?
- KH: Yes.
- TB: Because desipramine is more selective for norepinephrine?
- KH: Right. Bulimia nervosa patients have high co-morbidities with depression and anxiety disorders. Some patients who have severe depression concurrent with a lot of anxiety don't respond to SSRI's. We may also use venlafaxine because that affects the norepinephrine reuptake system as well, and some patients respond to that.
- TB: What doses are you using for anorexia?
- KH: The same doses one uses for depression. We only use venlafaxine after SSRI's have failed. The problem is if you increase the dose very much then you start getting the anticholinergic side effects.
- TB: So, the primary treatment has remained cognitive behavior therapy?
- KH: In bulimia. In anorexia, after the atypical antipsychotics came out, I now use olanzapine instead of chlorpromazine for patients who are extremely emaciated. Many anorectic patients have read about how that drug induces weight gain. I have to promise I will stop the medication as soon as they get close to their target weight.
- TB: Are they very concerned and reluctant to take the medication?
- KH: That is right, but with olanzapine there are just case reports and no published double blind study.
- TB: Am I correct, that none of the antipsychotics were studied properly, as yet, in this group of patients?
- KH: Way back in the early 1980's, there was a small study with pimozide and one of the other antipsychotics, and it didn't show dramatic effects.
- TB: Was pimozide chosen because of its selectiveness for dopaminergic structures?
- KH: Yes.
- TB: So, it had some effects?

- KH: It had a very modest effect.
- TB: Is pimozide available today in the US?
- KH: It is, but we don't use it because it is not very effective. We use olanzapine or chlorpromazine in very small doses.
- TB: Is olanzapine the only one among the new drugs that is used?
- KH: Others may be used, but there are no double blind studies.
- TB: Let me go back in history. At the time you started, people hardly knew of anorexia nervosa and the field expanded rapidly.
- KH: It certainly did.
- TB: When did the change start?
- KH: Well, at first, the media was a tremendous help in increasing our business. They somehow caught onto this and started presenting beautiful movie stars, such as Jane Fonda and Princess Dianna, as having bulimia nervosa. Then it had the opposite effect. The young teenage patients would say, "Well, you know, Jane Fonda hasn't had such a bad life. Despite her bingeing and vomiting, she still is very attractive and she has married multimillionaires". The same with Princess Diana; it didn't help at all. The media always meant to dramatize these illnesses.
- TB: When did the media get involved?
- KH: In the late 1980's. They were totally attracted, as you can imagine, to the dramatic aspects of eating disorders. When they interviewed me, they wanted to see patients and the dramatic aspect. They never wanted to listen to the rather grim outcomes and criticism of the different kinds of therapy, or the fact that treatment centers were springing up all over that had no qualifications whatsoever. Our country has no restrictions on psychotherapy. If you are a physician you have to be licensed. If you are a clinical psychologist you have to be licensed, but anybody can set up a shingle as a psychotherapist. That is what has happened in the field of eating disorders. All sorts of crazy things are going on that are totally unregulated. The media loves it. They go to the most infamous center in Vancouver, Canada where a lady bought a Charles Adams type house and, with her family, started treating anorexia nervosa patients.
- TB: What did she do?
- KH: She did what she called love therapy, but word came out that it wasn't completely love therapy and there were problems. Eventually, the Canadian government investigated her, but ABC television thought it was wonderful.
- TB: What does it mean, love therapy?
- KH: Spending a lot of time with the patients, establishing what she considered a love that their mothers hadn't given them, a kind of passionate

understanding that they hadn't received in their lives. Patients flocked from all over Europe and the US, but it was only wealthy clientele, because the costs were enormous. I have found, in my experience, that extremely wealthy people dictate their treatment. If you don't allow that, they are not interested. They go to totally unqualified people. This woman in Canada did not even have a BA degree. We have a person like that in New York City that was promoted by the media. He had no degree in anything. The media loved that. They promote these people because they have charisma. It's very exciting, but the rest of us who have done research tend to be rather boring.

- TB: At a certain point in time, eating disorders entered the universities. At Vanderbilt, our chairman, Mike Ebert, is an eating disorder specialist. There are a steadily increasing number of eating disorder specialists. Is that just in North America, or do you see the same thing all around the world?
- KH: That has happened in all industrialized countries. An interesting comparison is the island of Taiwan, with mainland China. In Taiwan, the prevalence and incidence of eating disorders is the same as Western Europe and the United States. In mainland China, in the 1980's, when I was there, they could only identify three cases of bulimia nervosa in all of the psychiatric clinics in Beijing. Now that mainland China is becoming more industrialized there are interesting changes occurring. There are health clubs set up in which women keep themselves in shape, but actually they are dieting and trying to stay slimmer because, now that people are not starving, they are gaining weight and this is upsetting a large population of females. We are now seeing the incidence and prevalence of eating disorders increasing in mainland China. So it seems to be associated with industrialization.
- TB: What would happen if the film industry changed the image of women to create a different kind of heroine?
- KH: I think if the entire value system of beauty changed throughout western civilization it would have an effect. Most of us who have done clinical work and research in this area for years understand that the provoking stress in developing both bulimia nervosa and anorexia nervosa is dieting. Even though you may have the genes and biological vulnerability to develop these illnesses, you won't develop them unless you start dieting. So, dieting is the major stress event for vulnerable people.
- TB: So, vulnerability is influenced by dieting behavior?
- KH: Exactly, because if you can stop the dieting behavior and return to normal healthy eating, then they get over it and stay over it. But, if they become concerned again about their appearance in complex ways

connected to their competency to deal with life, they resume dieting. If you can get them to stop dealing with stress by dieting, they will stay healthy.

- TB: Thirty years ago there was a significant difference with the upper and upper middle classes having a higher prevalence. That has changed. Today, the difference is not even present in some countries. In the New York area, for an example, twenty years ago we never had a Hispanic in our program with anorexia or bulimia. Now there has been an enormous increase of both anorexia and bulimia in the Hispanic population.
- TB: So, at this point, it is widespread?
- KH: It is across all social groups.
- TB: During these thirty years, you trained many people. Would you like to mention just a few of them?
- KH: I wish I could say I had many famous researchers. That has not been the case. Most of the people I have trained have gone into clinical practice all over the Metropolitan area and throughout the country.
- TB: So, they are mainly practitioners. I have trained two young men who went to pharmaceutical companies, and they are both doing very well, making about 5 to 10 times my university salary. One is very nice to me and we sometimes collaborate. He was with Lilly and he is now with Pfizer. With Lilly, Steve Romano and I set up a huge multicenter site studying fluoxetine in bulimia.
- TB: So, Steve Romano was working with you in the fluoxetine study?
- KH: Right. That was a one year study, one of several studies.
- TB: You talked about your finding with fluoxetine. What about findings in the other studies?
- KH: Our first study and many of the other studies were NIH funded. Most of my studies have been from NIMH or Foundations. Pharmaceutical companies provided the medications. We have just finished a multisite study on sibutramine for the treatment of binge eating disorder, but those results haven't been completely analyzed, so I can't tell you the results. Binge eating disorder is similar to bulimia. The big difference is that in binge eating disorders patients don't compensate the calorie intake by severe dieting or vomiting or laxative abuse. So, about 90% of that population is obese. The trial with sibutramine was to see if we could institute control of the binge eating episodes, which might then regulate their weight.
- TB: Have you been involved in developing guidelines for the treatment in these disorders?
- KH: Yes, I have been. As you know, the guidelines are produced by the American Psychiatric Association. That is a complex phenomenon,
because in my field there is a large contingent of psychoanalysts and psychodynamic family therapists. I have been rather outspoken about the fact that we need to look at the evidence from controlled studies. I was disinvited from the last guidelines committee because I wasn't empathetic enough to allow guidelines recommendations that had no proven efficacy, not even single case studies analyzed in a structured way. I think this is a very good question, because I can't believe it is unique to my field.

- TB: So, people who are psychodynamic are still involved in your field of work?
- KH: Yes, in my field. I can't speak for other fields, but I think it is important for us to examine who is producing guidelines. Maybe the American College of Neuropsychopharmacology ought to produce their own guidelines, because the American Psychiatric Association is highly political. Those guidelines often include suggestions that are not always supported by evidence based trials.
- TB: That is very important to know. When did you get involved with ACNP?
- KH: I got involved with ACNP in the early 1980s with the first multi-site collaborative study.
- TB: Have you been attending the meetings regularly?
- KH: Since the early 1980s. I was admitted as a member, in 1984 or 1986, about that time.
- TB: Have you served on any of the committees?
- KH: I have served on the Education Committee and on the Program Committee. Right now I have been having a very exciting time on the Credentials Committee.
- TB: Have you been involved in writing or editing books?
- KH: I have edited two books. One was on a meeting that was conducted by the New York Academy of Science that was published in the late 1980s. The other book I edited was the Proceedings of the American Psychopathological Association meeting when I was president and the topic was the psychobiology and treatment of the eating disorders. It was published in the mid 1990s.
- TB: Is there anything that you would like to add?
- KH: You were very thorough in questioning me. I think the future direction of research in the field of eating disorders now lies in the genetic research aspect.
- TB: Didn't you start your career in genetic research?
- KH: I started with Zellweger in genetics and, now, I am not going to say at the end of my career, I am back to genetics. When I first had the invitation to be interviewed my response was, "Oh dear, I am one of the over

the hill people now, the grandmother of my field". I was a little bit jarred by the invitation.

- TB: I'm glad you came. How much of your time are you spending in clinical practice and how much in research?
- KH: It is pretty much 50-50. I manage a huge clinical operation, which is profitable to the New York Presbyterian Hospital, or I wouldn't be here. That is my big task. To see that operate effectively I need to have hands on control. There are very few of us across Europe and the US who have been trained to do this effectively. We need to oversee the direct operation.
- TB: However fast the eating disorder field is growing you probably still know most of the people involved?
- KH: I know everybody who has federal grants in the research programs. I certainly don't know everybody who is treating patients.
- TB: You are fully active and it seems that you intend to continue with your research.
- KH: I am fully active and I intend to stay fully active for a long time. My Chairmen should take note of that!
- TB: You still would like to see evidence based guidelines in your field. Thank you very much for sharing all this with us.
- KH: Thank you.

## DILIP V. JESTE

#### Interviewed by Thomas A. Ban Waikoloa, Hawaii, December 13, 2001

- TB: This will be an interview with Dr. Dilip Jeste\* for the archives of the American College of Neuropsychopharmacology. We are in Hawaii at the 40th anniversary of the college. It is December 13, 2001. I am Thomas Ban. Could just tell us where and when you were born and something about your early interests, education, and training?
- DJ: First of all, I want to thank you for this interview. I come from India where I was born in a place named Pimpalgaon, a small town in the state of Bombay, now called Maharashtra. I was brought up in Poona, which is about 100 miles from the city of Bombay. My father was a judge, and my mother was a housewife. I was the fourth out of five siblings. I also went to medical school in Poona. As a teenager I enjoyed reading Freud who I found inspiring, especially *The Interpretation of Dreams, Everyday Errors of Life, and Psychology of Neuroses*. Before going to medical school I had decided that I wanted to go into psychiatry. So I never saw myself primarily becoming a physician other than a psychiatrist. After I graduated from medical school I moved to Bombay, which is a much larger city with more academic psychiatry. I was fortunate to work with Dr. Vahia, one of the pioneers of psychiatry in India. He spent a couple of years of his early professional life in the USA and had a strong interest in research.
- TB: Who was your professor of psychiatry in medical school?
- DJ: Dr. Roshan Master was the head of psychiatry. At that time, the psychiatry rotation was six weeks at the B. J. Medical College and Sassoon Hospital in Poona. I found it interesting but not exactly to my liking. Clinical psychiatry was not what I wanted to do. It was not academic.
- TB: What kind of psychiatry was it?
- DJ: It was essentially pharmacologic and other somatic treatments, especially ECT. The patients were often from villages; they came to the city for treatment when they had psychotic episodes, and did not have money for medications. They would get some ECT to control them and then would go back to their villages.
- TB: But you still wanted to become a psychiatrist?
- DJ: Correct, but because of the clinical psychiatry I saw in medical school I wanted exposure to academic psychiatry.
- TB: So, you were ready to do a residency in psychiatry?

<sup>\*</sup> Dilip Jeste was born in Pimpalgaon, India in 1944.

- DJ: Yes, I went to Bombay, and met Dr. Vahia at GS Medical College and King Edward Memorial (KEM) Hospital. It was the best hospital and medical school in Bombay. Of course I am biased. My wife went to another medical school in Bombay, Grant Medical College, and she maintains that was the best medical school! What I found really exciting was the research perspective. Dr. Vahia was a famous person in India and patients flocked to see him. Yet, he always made it a point to go to the library every day. As residents we had to read whatever was being published. Whenever we discussed a patient, we had to look for articles on the topic, and this was really unusual for a country like India. There were so many patients to be seen in a short time and not enough psychiatrists. Yet Dr. Vahia emphasized research and I felt that was what I wanted to do.
- TB: What year was that?
- DJ: I was in KEM hospital from 1968 to 1974. From 1968 to1971 I was a resident and then I was on the faculty. Interestingly, Dr. Vahia's interest was in yoga therapy, but not in the yoga we practice in the United States. It wasn't yoga exercise or relaxation, but personality integration. What he called psychophysiological therapy, which was used for people with psychosomatic disorders such as hypertension. The treatment was based on the concepts of an old Indian sage named Patanjali. Dr. Vahia showed that it had significant physiologic effects such as lowering blood pressure. The result, were published in the *American Journal of Psychotherapy*.
- TB: What year?
- DJ: In 1973.
- TB: Wasn't this your first paper?
- DJ: This was one of my first papers.
- TB: What was your first paper?
- DJ: It was a review on *Hysteria and its Management,* published in 1969 in the *Indian Journal of Medical Sciences.* I was the second of two authors. I also worked with Drs. Doongaji, Bagadia and Shah. They were quite sophisticated investigators, and we conducted epidemiologic and treatment studies of schizophrenia, depression, and epilepsy. In India you could easily study 400 or more patients with a given disorder in a short time because we saw over 50 patients a day in our outpatient clinic. Those studies were mostly descriptive, as all we could do was collect demographic and clinical data. Anything more than that, for example biological data or longitudinal follow up, was very difficult. We also did treatment studies. For instance we compared unilateral with bilateral ECT in patients with schizophrenia; that paper was published

in the *British Journal of Psychiatry*. We also conducted research on educational measures such as testing with multiple-choice questions which was unheard of at that time. In India you could not be a full time researcher. There were only part time jobs in the university; so faculty had to be in private practice too. I did well in private practice, but that was not what I wanted. I only wanted to be a researcher and that was not possible due to lack of financial support.

- TB: The doctors had their office somewhere in the city outside of the hospital?
- DJ: Right.
- TB: So, during the mornings you were at KEM, and during the afternoon you practiced in your office?
- DJ: Yes.
- TB: Alone, or in a group?
- DJ: It was a solo practice. I remember the first time I saw a patient and the patient paid me money, I just could not bring myself to accept it. I did not feel that I deserved to be paid. I felt guilty asking for money. Before long I was getting more patients than I could handle, and I was happy I could do something clinically, but my heart was in research, and I found I couldn't do both. For a country like India, it doesn't make sense to spend money on research when there are more pressing needs. I realized I needed to go somewhere I could do research. At that time, and even now, the US is the country for conducting full-time research. I knew something about American culture. We read American, British and Canadian textbooks and, of course, movies, novels, and magazines like Time and Reader's Digest. My brother was in the US and he sponsored me for my green card. I was accepted for residency by applying without going for interviews after I got my ECFMG. I completed the first year of my psychiatry residency at the New Jersey Medical College of Medicine and Dentistry. It was a very interesting experience. I thought I knew the culture, and yet it was a shock. A culture shock in terms of psychiatry too. I was amazed at the dosages of medications compared to those we used in India. For example, if you gave 2 mg of haloperidol to an Indian patient, the Indian patient would be stiff as a board and have marked sedation. In America I found that we could give 20-30 or even 50 mg of haloperidol and see practically no side effects. Of course, there is a difference between Americans and Indians in average body weight, but it did not fully account for the difference in dosages. I believe that there is a differential pharmacogenetic response to medications and I found that interesting. At the same time, the New Jersey Medical School was very clinically oriented with little research.

- TB: Who was the chairman of the department?
- DJ: Dr. Thomas. He had done some important work in minority training. One of the nice things that happened in New Jersey was that I met George Alexopoulos, and we became close friends. I also did a small study of tardive dyskinesia in New Jersey.
- TB: So almost immediately after you arrived you became involved in research?
- DJ: Yes.
- TB: Was this in the mid-1970s?
- DJ: July 1974. It was a very simple study. We compared three times daily with once daily administration of antipsychotics in patients with tardive dyskinesia and found that the movements were better suppressed with multiple daily administration. This was nothing great, but useful and interesting. And it did get published. I also studied the evolution of psychiatric treatments and the role of serendipity in biological psychiatry although I did not complete that work in New Jersey. I realized I needed to find some place else to conduct research, so I spent my second and third years of residency at Cornell, Westchester Division. Bob Michaels was the Chair of psychiatry, and Lomy Feder was the Medical Director at the New York Hospital in White Plains. That was a wonderful experience.
- TB: In which journal was your first paper in the US published?
- DJ: The first paper was published in *Diseases of the Nervous System*. It was based on the work I did in the first year of my training in New Jersey. I think it came out in 1977.
- TB: You continued your research at Cornell?
- Right. I was always interested in biological psychiatry, particularly neu-DJ: ropsychopharmacology, but Cornell at that time was very psychotherapy oriented. I found it enlightening although I knew it was not something that I was going to practice later. I think it made me a better psychiatrist when I learned the principles of psychoanalysis and psychodynamics. In my last year of residency, I did something very different and worked with Jerry Smith, who was the Director of the Bourne Research Lab. I became involved for the first time in animal research. We conducted studies of a stereotactic infusion into the cerebral ventricles, looking at the effects of catecholaminergic activity on behavior in rats. It taught me a lot and made me a better researcher although I knew that was not something I was going to do for the rest of my life. I have always liked history so I worked some more on the serendipity paper. Cornell had a great department of History of Behavioral Sciences. I also wrote a paper there on the history of schizophrenia. That paper challenged an

existing notion of schizophrenia. It is usually taught that schizophrenia is a disease of civilization which appeared 100 to 200 years ago. What we found was that schizophrenia is probably as old as mankind. There is something called the Poem of a Righteous Sufferer which may be the first description of a paranoid person, maybe paranoid schizophrenia, on the cuneiform tablets from the Mesopotamian culture representing the oldest human writings. Of course, we cannot diagnose schizophrenia in ancient writings using DSM criteria. But going through that as well as some descriptions from medieval times, and a number of later writings, we provided examples of what looked like schizophrenia throughout human history.

- TB: Did you try to differentiate schizophrenia from delusional psychosis and manic depressive psychosis?
- DJ: The differential diagnosis of people in old literature can be very difficult. At the same time, there are some features that seem to be strongly suggestive of schizophrenia. There was a description in Indian Rigveda, written a couple of thousand years before Christ, of a young person with "insanity". It looked like there were people who had psychotic symptoms without obvious evidence of bipolar disorder. I believe that schizophrenia is not a disease of civilization but a biological disorder present from the beginning of human history. I think the incidence and prevalence have varied depending on environmental factors.
- TB: So you did some work on the history of psychiatry.
- DJ: In addition to a great Department of History of Behavioral Sciences, Cornell owned several ancient books which were a dream. I always liked reading. Even as a kid going to the library and getting books was my passion. The history research at Cornell was exciting because I found some fascinating old literature and was able to interpret it in a new way. It was intellectually challenging.
- TB: Did you publish your research on the pre-history of schizophrenia?
- DJ: Yes.
- TB: Where was it published?
- DJ: In *Comprehensive Psychiatry*. But the study I mentioned earlier on tardive dyskinesiainfluenced my career the most because it challenged the conventional wisdom of the time and was published in the *Archives of General Psychiatry* after I moved to the NIMH. The ACNP Task Force report in 1972 had suggested that tardive dyskinesia was the result of long term neuroleptic treatment and that stopping treatment from time to time, so called "drug holidays", might prevent its occurrence. We found that stopping treatment not only increased the risk of relapse in schizophrenia but intermittent treatment also seemed more likely to be

associated with tardive dyskinesia. It was a cross sectional study, so we could not establish causality, but the findings led to a long discussion in the field and over the years people began to accept our conclusion. Years later, John Kane, in a longitudinal study, confirmed the finding. This was one of two papers that were published in the Archives at nearly the same time. The other was on serendipity in the discovery of psychiatric treatments.

- TB: So you published on serendipity in the discovery of psychiatric treatments?
- DJ: That research was done at the Cornell History of Behavioral Sciences Department. The word serendipity relates to ancient Ceylon or Sri Lanka (Serendip) where the anti-malarial properties of quinine were accidentally discovered. But we found that most discoveries in biological psychiatry were not really serendipitous. The discoverers did not know what they were going to find, but they were looking for something. Let's take the example of malaria therapy. Wagner von Jauregg got the Nobel Prize for malaria therapy in cerebral syphilis. He found that people with syphilis who had malaria were less likely to have psychosis. This led to the idea that if you induced malaria it could improve or prevent psychosis due to schizophrenia. At that time this made sense because there was no other effective therapy for schizophrenia. Let's take one of the more recent discoveries of antidepressant effects of antituberculosis medications such as iproniazid.
- TB: Nathan Kline's discovery?
- DJ: Right. He and others found that patients with tuberculosis treated with drugs like iproniazid showed improvement in depression, so they tried the drug in depressed people without tuberculosis. At the time they did not know about monoamine oxidase. However, they were smart enough to put two and two together and come to the correct conclusion.
- TB: And they discovered the antidepressant effect of iproniazid.
- DJ: Correct. Another example would be the neuroleptics. These drugs were used by anesthesiologists and surgeons who found that sedative and antihistaminic "lytic cocktails" calmed patients before surgery. The thinking then was that you could use these drugs to calm psychotic patients. You could argue that it was not a scientific or logical discovery because they did not know the drugs blocked dopamine receptors. There is also the discovery of lithium which is often given as an example of basic science research leading to clinical discovery. Cade, a practicing Australian physician with a basic science laboratory, found that lithium had a sedating effect on animals.
- TB: You are implying that serendipity is not enough.

- DJ: The point is that scientific discoveries are not usually a pure accident. There is some luck, but luck alone does not help unless you have the potential and ability to use it. Only Newton came to the conclusion that gravity caused an apple to fall from a tree. Others saw apples fall from trees but did not discover gravity. I believe that science involves lots of work and that you need to be looking for something relevant. Of course if you knew exactly what you were looking for it would not be a discovery. I remember there was a book on *Discoveries in Biological Psychiatry*. I thought you contributed to it.
- TB: I didn't. Frank Ayd and Barry Blackwell published that book.
- DJ: Anyway, I had those two papers, on tardive dyskinesia and on serendipity published at about the same time in the *Archives of General Psychiatry*. Those are still two of my favorite papers. At Cornell, I applied for and was selected for a research fellowship at NIMH. This had been my dream when I was in India. I wanted to go to NIMH because everybody knew it was the place to learn and conduct research. I was dreaming about something I had never seen.
- TB: So you went to the NIMH?
- DJ: Yes. At Cornell I found that learning new things really turned me on. I was doing dynamically oriented psychotherapy with borderline patients, going through the history books, working with animals or conducting clinical research. Cognitively it comes to the same thing the excitement of learning something new. That is what turns me on.
- TB: When did you go to NIMH?
- DJ: 1977. I was there for nine years and worked with Richard Wyatt in the neuropsychiatry branch at St. Elizabeths' Hospital along with Floyd Bloom, Ermino Costa, the basic scientist, and Chris Gillin.
- TB: It had to be very stimulating.
- DJ: It was. I could not believe that people were paying me to learn and conduct research. I thought I should pay them! The National Library of Medicine at NIH was the largest in the world. I felt like a kid in Toys 'R' Us. That is the fascination of NIH; there is an expert in every area and so many topics to explore.
- TB: That must have been a great experience for you given your interests and expectations.
- DJ: Yes, Richard Wyatt was my supervisor, and he was very good. He let me do a lot of different things. I conducted clinical research, did some animal research and worked in neurochemistry labs. I found it helpful to explore different things and find out what suited me most. One of the first things I did was to write a book on tardive dyskinesia. It was during the fellowship and I spent about a year doing it. This was not an edited

book and it was about 250 pages long so I had to teach myself neurochemistry and neuroanatomy in order to write it. It was the first book I published and I still think it is the best book on tardive dyskinesia. Richard Wyatt was the second author. Ross Baldessarini reviewed the book, and did a great job helping me take the subject further. I found it a tremendous experience. I also worked on the neurochemistry of schizophrenia, especially paranoid schizophrenia. I performed some neuropathology studies and did some collaborative research with people in India. I am proud to be an American citizen but also proud to have come from India. On one trip I went back to India and collected spinal fluid from a group of hospitalized patients with tardive dyskinesia to take back to NIMH and look at the levels of norepinephrine. I felt that the dopamine receptor supersensitivity theory of tardive dyskinesia had been overblown, and that it was not the explanation for tardive dyskinesia. I thought there were other mechanisms with increased catecholaminergic activity that were critical. In this study we found that was the case; there was an increased level of norepinephrine metabolites in patients with tardive dyskinesia compared to controls. We published that in the British Journal of Psychiatry. An interesting aspect of that study was that the Indian customs would not allow people to take biological fluids out of India. They did not want blood to be sold or misused. Even a tiny amount of cerebrospinal fluid could not be transported, so we did something which we might not have been allowed to. But I feel it was the only way to study the biology of tardive dyskinesia in India using American technology and expertise. Tardive dyskinesia is less common in India, but the neuroleptic dosages are also much lower. One of the fringe benefits of being at NIMH was that I completed the two remaining years of my residency while I was conducting research in the evenings and on weekends. That was also the time my wife, who is a child psychiatrist, had our second daughter. So, it was a really busy period, but I found that it was helpful being a neurologist. It made me much more knowledgeable about medicine. I published almost a hundred papers while at NIMH.

- TB: Did you publish exclusively on your findings in schizophrenia?
- DJ: Not exclusively, but a number of the papers were on schizophrenia. One paper I should mention, which I worked on with several of my colleagues, won the A. E. Bennett Award from the Society of Biological Psychiatry. It was on heterogeneity in schizophrenia from a biological viewpoint. We noted hat schizophrenia is usually classified on the basis of clinical symptoms as paranoid, hebephrenic or catatonic. It did not make much sense because, except for the paranoid type, the others

are not biologically distinct. So, we looked at different dimensions for grouping people with schizophrenia. One dimension was tardive dyskinesia. One was size of the ventricles on CT, large versus small. Another was neurochemical, and so on. That was what we called "ex uno multi", which means many out of one. It is the opposite of "e pluribus unum", which means one out of many. It is not that there are different types of schizophrenia, but there are dimensions. These are not distinct sub-types that you can divide patients into, rather they are dimensions.

- TB: So, agan, what are the different dimensions?
- DJ: Ventricle size, tardive dyskinesia, paranoid schizophrenia, neurochemical and cognitive changes.
- TB: Negative symptoms?
- DJ: There could be a dimension of negative symptoms. An individual patient could be categorized according to all of those dimensions.
- TB: One of the dimensions you mentioned was tardive dyskinesia. Some patients develop tardive dyskinesia, others don't.
- DJ: Right.
- TB: Is there any way of predicting who will not develop it?
- DJ: I think there are people who would not develop dyskinesia even if you treated them for 100 years. We saw patients in St. Elizabeths' Hospital who were being treated with high dosages for 30 years but did not have one symptom of dyskinesia. On the other hand, there were patients treated for six months who developed severe dyskinesia. So susceptibility to tardive dyskinesia is an important dimension.
- TB: And you have the other dimensions.
- DJ: It is a multidimensional concept. For example, somebody with schizophrenia who has large ventricles and severe negative symptoms would be susceptible to tardive dyskinesia but that might not solely explain the risk. There might be something else that we do not yet know about dyskinesia. So, while our results were interesting, more important was the approach. We should not divide people into specific subtypes such as type I and type II, but look at them in terms of different dimensions and how much of each dimension a person has. That was the approach we took to understanding the heterogeneity of schizophrenia. A patient could be rated on each dimension, say 30% susceptible to tardive dyskinesia, 40% in terms of ventricles, etc. Saying that schizophrenia has multiple dimensions is better than saying that there are fixed subtypes, which is usually how schizophrenia is conceptualized.
- TB: Do you think that schizophrenia is a valid diagnostic concept or it should be broken up?

- DJ: My view is that chronic psychosis is the syndrome. In maybe a decade or more chronic psychosis will be identified as a syndrome when we find something unique biologically about it. I do not think schizophrenia is necessarily a unique disorder and that schizophrenia, psychotic mood disorders, delusional disorder and psychosis not otherwise specified, are all probably more similar than different biologically. Right now we differentiate all these disorders on the basis of clinical symptoms. I think that is not going to stand the test of biology. I expect we will identify genes for mood disorders, and genes for psychotic disorders. Within psychotic disorders, we will have subgroups which may be more dimensional than categorical. For example, if you have an equal number of genes for schizophrenia and for depression, you will have a psychotic mood disorder. If you have multiple genes for schizophrenia and only one or two for mood disorder, you may have schizophrenia with mild depression. Something like that. Right now we are focusing so much on dividing schizophrenia into clinical subtypes, and then separating schizophrenia from psychotic mood disorders, and so on. I do not think that will stand the test of time. We will have chronic psychotic disorder as a syndrome that includes schizophrenia as well as psychosis with depression or other disorders.
- TB: What are the symptoms of chronic psychotic disorder?
- DJ: The symptoms could be delusions, hallucinations, and thought disorder. Actually cognitive impairment would be present in all of these patients, not the type of cognitive impairment we see in dementia, but cognitive impairment in terms of learning and executive function. Many patients will also have some negative symptoms.
- TB: Such as?
- DJ: Negative symptoms such as flattening or blunting of affect, social isolation, social withdrawal, alogia. So, the patients would have some positive symptoms such as delusions and hallucinations and some negative symptoms plus cognitive impairment. There would be differential response to antipsychotics. Only the positive symptoms would show significant improvement.
- TB: Are these patients distinctly different from patients with mood disorders?
- DJ: Yes. One important differentiating factor would be the usual age of onset of illness, something I became interested in when I left NIMH.
- TB: Where did you move?
- DJ: After I was at NIMH for a number of years, I decided that I needed to move on and do something on my own, so I looked at different places. At the University of California in San Diego (UCSD), I found exactly the

type of place I wanted and so I moved there. It was partly by serendipity, though not entirely so, that I got into geriatric psychiatry; UCSD had an opening in geriatric psychiatry. They were just starting a program and wanted me to be its Director although I did not see myself as a geriatric psychiatrist at that time. However, I had a wonderful fellow by the name of Jackelyn Harris. Once I decided I was going to run a geriatric psychiatry program with my research background being in schizophrenia it seemed to make sense to focus on schizophrenia in older people. Again, it was exciting, something new that very few people had studied before. I found out how little was known in this area, especially in the United States. There was a long tradition of geriatric psychiatry in Europe, and a lot of work on paraphrenia for example. Canada also had a number of excellent studies done on paraphrenia and late-onset schizophrenia. In the United States, on the other hand, there was very little published on the topic. DSM-III, which came out in 1980, said that you could not diagnose schizophrenia when the onset of psychotic symptoms was after age 45. So, I wanted to study people whose illness looked like schizophrenia but with an onset after 45.

- TB: So your interest turned to late onset shizophrena?
- DJ: I found that challenging so I started with a literature review; there was very little and yet people had strong biases. Then we collected a sample of patients who had what looked like schizophrenia but with an onset after age 45. Most researchers did not believe there was such a thing as late-onset schizophrenia. We studied those patients with a grant from NIMH, the first I received. We performed extensive clinical evaluations and conducted comprehensive neuropsychological studies.
- TB: In what year did you get the grant?
- DJ: In 1987. It became a ten-year grant after I received the NIMH merit award. That was a wonderful experience. As I got more and more into it the whole field became fascinating. Now I identify myself first as a geriatric psychiatrist, something which I never would have thought of until I moved to San Diego.
- TB: But didn't you still continue your research in schizophrenia?
- DJ: Yes. My work is still primarily on schizophrenia and aging. I find that there are two exciting parts to this; one is late onset schizophrenia and the second is what happens to early onset patients as they get older. I find the concept of dementia praecox wrong; schizophrenia in older people is neither dementia nor is it necessarily "praecox"; it can have late onset.
- TB: Didn't Kraepelin adopt the terms from Morel via Kahlbaum?

- DJ: Yes, that is true. He described paraphrenia in later life. However, he still believed that paraphrenia was a different illness from dementia praecox and that these were people whose course was more benian than dementia praecox. On the other hand, Kraepelin's students who followed his patients found that the course of paraphrenia was generally similar to that of dementia praecox. Still, if you talk to most researchers in schizophrenia, they think it is dementia praecox, although they don't use that term. When DSM-III changed to DSM-III-R it removed the restriction on age of onset. But there remains a fair amount of skepticism about onset of schizophrenia after 45, and similar doubt about possible remission of schizophrenia. The concept of schizophrenia as dementia persists - not Alzheimer-type dementia, but a neurodegenerative disease. The concept of schizophrenia is a life-long illness; once you have schizophrenia you will always have schizophrenia. I find that a fallacy. In many cases schizophrenia is a life-long illness, but there is a proportion of patients who I believe have a true remission. I find that in late-onset schizophrenia remission is not common. Nonetheless our understanding of these conditions has the potential of revolutionizing treatment in two ways. I see late-onset schizophrenia as nature's experiment for delaying onset of the condition. While most people who have schizophrenia develop the illness between 15 and 25 years of age, some people are protected from developing it until age of 50 to 55. If you could identify factors that lead to delay in the development of illness, modify them, and slow the onset of schizophrenia from early life to the 50s, the improved quality of life would be tremendous. That is something I believe we need to do.
- TB: On what basis do you imply that it's schizophrenia?
- DJ: Good question. How would you know somebody has schizophrenia? You can't look at the brain and make the diagnosis. So, what we call late-onset schizophrenia are patients who meet all of the usual criteria for schizophrenia and would not meet criteria for any other major DSM disorder. We have followed these patients longitudinally, some for over ten years. These patients are evaluated every year and continue to meet the criteria for schizophrenia. They are treated just like other patients with schizophrenia except for lower dosages of antipsychotics. The concept of late-onset schizophrenia is well accepted in other countries. Last year we published a paper in the American Journal of Psychiatry on the International Consensus Statement on Late-onset Schizophrenia. There were people from a dozen different countries, including Robert Howard, Mary Seeman from Canada, Peter Rabins, and myself.

- TB: So, Mary Seeman was also involved in this area of research?
- DJ: Mary has done some great work in older people with schizophrenia and estrogen especially. Anyway, we published the consensus paper in which we said we believe in late-onset schizophrenia, and that it is different from early-onset illness in some ways. Gender is a big difference. It is much more common in women while early-onset schizophrenia is much more common in men. That may give us some clue about estrogen or something related to it as a possible protective factor; I think it is simplistic to say that it is only estrogen. But to answer your question, I do think it is schizophrenia, but schizophrenia is a broad, heterogeneous entity. Obviously, not all people with schizophrenia are similar. There are different subgroups. Patients with early-onset and late-onset schizophrenia are different in some ways. However, they are also similar in many ways. What we need to do is find out what protects some people from developing schizophrenia until later in life. Most Alzheimer's patients develop dementia at 65, but some people get it at the age of 40. These are not only people with Down syndrome, but also people homozygous for the APO-E4, gene. I think we will find genetic and other markers that could be associated with late-onset schizophrenia. It could be some neurochemical abnormality or a unique psychosocial factor. We need to find those to help us delay the onset. and even, in the long term, prevent schizophrenia. The other side of the coin is remission of schizophrenia in old age; that too is a controversial concept. Most researchers think that there is no such thing as remission of schizophrenia. If you read the older studies of Manfred Bleuler, he described patients with schizophrenia who after decades of institutionalization, began to improve and function well. That is one area that we have been looking at. We published a case of a patient we had been following longitudinally, who had schizophrenia and subsequently went into a persistent remission. The point is that there is a small minority of people who seem to have a true remission of schizophrenia. We need to study those patients well, and find what causes remission because if we identify those factors and modify them, a cure of schizophrenia would be possible. Right now to talk about prevention or cure of schizophrenia is heretical.
- TB: As you know, it has been proposed by some to split schizophrenia into two classes of disease. What are your thoughts about that?
- DJ: I personally do not think you can split them into two groups, however, I think a very important dimension I would use is age of onset.
- TB: In terms of age of onset doesn't paranoid schizophrenia have a later onset than the other forms?

- DJ: Are you talking about paranoid schizophrenia or paraphrenia.
- TB: Paranoid schizophrenia.
- DJ: Paranoid schizophrenia does tend to have a later age of onset than non-paranoid schizophenia. In terms of paraphrenia Kraepelin did not use age of onset as a differentiating criterion. The distinction was only made later when Sir Martin Roth, one of the pioneers in geriatric psychiatry, reported on paraphrenia and late paraphrenia, the latter being after age 65.
- TB: But you do separate that late-onset group from the others?
- DJ: Yes. Late and early onset schizophrenia are different. However, I personally do not think there is any fixed age cut off that one should use rigidly to differentiate. This is not just true for schizophrenia but also applies to other disorders in the chronic psychotic syndrome including psychotic mood disorders, psychosis not otherwise specified, etc. All of them have different dimensions on which they can be subtyped, and one of the really important dimensions would be age of onset of the psychotic syndrome. However it wouldn't be a fixed age cut off. Kraepelin was right about differentiating mood disorder and schizophrenia, but the differentiation would not be so much in terms of the course, which he used for this purpose. I believe that schizophrenia is not necessarily a continuous life-long illness, and, at the same time, mood disorders are not necessarily episodic. Recent work on minor depression shows that it can be very common in between episodes of major depression.
- TB: It seems that you are in agreement with Leonhard's classification.
- DJ: Was he the one who called it process schizophrenia versus reactive schizophrenia?
- TB: No, he was the one who separated unsystematic from systematic sczophrenia. Unsystematic schizophrenia is episodic, whereas systematic schizophrenia is continuous. Are you doing any research in this direction?
- DJ: What we are now focusing on are mainly middle aged and elderly people with psychotic disorders. We have an NIMH funded Center to look at that. We study schizophrenia, delusional disorders and psychotic mood disorder.
- TB: Just late-onset psychotic disorder?
- DJ: No, not just late-onset. These are people who are currently middle aged or elderly; the majority, had onset in early life but are getting older. We take anybody over 40 and there is no upper age limit. In my next few years I want to focus on the geriatric patient population, over age 65, because that is the population that has been understudied over the

years, the elderly psychotic patients. Yet that population is going to increase tremendously.

- TB: Could you elaborate on this project?
- DJ: We do longitudinal studies of psychopathology, neuropsychological performance and motor function, but in the last few years we have moved into intervention research. We are doing studies of not just pharmacologic treatments, but also psychosocial interventions like combined cognitive behavior therapy and social skills training.
- TB: Are you comparing the effects of different treatments?
- DJ: Almost everybody needs antipsychotics in this group, so what we do is study the effects of antipsychotics plus cognitive behavioral and social skills training. Antipsychotics alone would not necessarily improve patients' functioning. In the last few years the focus has been more and more on psychosocial treatments and much less on neurochemistry because I don't have the right type of neurochemical markers to look at. I am at the stage in my life where I want to do something to help patients directly. While understanding the illness is important, how can we really help them? We assess the patients at baseline, and there are different treatment protocols. Just about all of these are federally funded research studies, but some are long term treatments for nine months. Let me give one example. We are comparing three different atypical antipsychotics, risperidone, olanzapine, and guetiapine in middle aged and older patients with psychotic disorders, looking at the therapeutic and side effects, not just dyskinesia. Tardive dyskinesia is much less common with this new class of drugs than with the older drugs, but we have new tardive disorders. In other words it is not tardive dyskinesia, but new long-term side effects, like diabetes, weight gain, and who knows what others. It took 10 years after neuroleptics were introduced into psychiatry before tardive dyskinesia was reported, five years actually to be perfectly correct, but 10 years before people really became aware of it. Most of the newer drugs have not been out that long. So, we may still see something in the years to come. Another study is headed by a young faculty member, Laurie Lindamer. She is looking at the effects of estrogen in postmenopausal women with schizophrenia. A couple of psychologists in our group have studies of combined cognitive behavioral therapy and social skills training in older people with schizophrenia. One study we have not started yet, but I am excited about, will look at work rehabilitation in older people with schizophrenia. A number of studies have shown that in a younger population it works very well, though not in everybody. In the case of older patients there is rampant ageism so it is important to show that

older patients can work too if they are provided with appropriate help and training.

- TB: What would you consider your most important contributions to the field of neuropsychopharmacology?
- DJ: Only time can tell, but what I find most exciting is the work on aging and schizophrenia both in terms of age of onset and remission. It has the potential for markedly improving our understanding of schizophrenia in general.
- TB: What about your early work on tardive dyskinesia?
- DJ: It was a really useful experience in terms of learning research and helpful in showing that there is something called tardive dyskinesia. When I started working in that area many people did not accept its existence. In the late 1970's there was a paper in the *Journal of Clinical Psychiatry* titled, *Tardive Dyskinesia: A Myth*? Even in the 1980s there were papers in journals like the Archives that said there was no such thing as tardive dyskinesia in patients with schizophrenia.
- TB: What would you consider your most important publication?
- DJ: The papers on tardive dyskinesia were important because they brought attention to tardive dyskinesia and also showed how it was different from what many people thought. Another is the paper on late-onset schizophrenia. I think my best paper is yet to be written. One paper I want to write would crystallize my thinking on schizophrenia and aging. I am considering a new book in the next few years on aging and mental illness.
- TB: What was your last publication?
- DJ: The very last paper that I published was on psychosis in Alzheimer disease. If you are asking about a database paper, there are several that came out around the same time.
- TB: Just the one you think is the most important.
- DJ: Not necessarily a paper that I am the first author on?
- TB: Not necessarily.
- DJ: Two such papers came out recently. One, in the *Archives of General Psychiatry* was a longitudinal study of schizophrenic patients with cognitive assessments on an annual basis. That was one of the most comprehensive papers on stability of cognitive deficits in older people with schizophrenia.
- TB: When did you become a member of ACNP?
- DJ: A long time back. I do not remember the year; it was the early 1980s, maybe 1983 or so. I was very fortunate to be selected a member the first time I applied. The ACNP is a wonderful organization. It makes you very humble because you see how smart other ACNP members are.

- TB: Am I correct that you are the president of a new organization?
- DJ: Yes. I wanted something that was like ACNP but international, and focusing on Geriatric Psychiatry. So, we founded the International College of Geriatric Psychoneuropharmacology, (ICGP).
- TB: Aren't you also the editor of a journal?
- DJ: Yes. This is The American Journal of Geriatric Psychiatry.
- TB: Is there anything we left out and you would like to mention?
- DJ: I find the field of geriatric psychiatry extremely fascinating and important. In the next 30 years growth of the elderly population is going to be tremendous. I hope that I can do something to help them.
- TB: On this note we should conclude this interview with Dr. Jeste. Thank you for sharing this information with us.
- DJ: Thank you.

### SEYMOUR KAUFMAN

#### Interviewed by Thomas A. Ban San Juan, Puerto Rico, December 11, 2002

- TB: This will be an interview with Dr. Seymour Kaufman\* 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 11, 2002. I am Thomas Ban. Let us start from the very beginning.
- SK: I was born in Brooklyn, New York, in 1924, and during the early part of my life I was sure I was going to be an artist. I had talent, enough so I got into a noteworthy high school in New York City called the High School of Music and Art, with a competitive entrance exam. It was during high school days I became exposed to science and faced a conflict. I was very interested in chemistry. Being at the music and art high school, I was exposed to kids with real talent, and guickly realized I would never earn a living as an artist. So I decided to switch to science. That was a very wise decision, because my wife and I have a daughter who is a professional sculptress; she is really very good but is having a terrible time supporting herself. I started my advanced education at Brooklyn College and stayed for two years, and then decided that living at home I was missing something I expected college to do. So I made one of the very important decisions in my life. I decided to leave Brooklyn College and transfer to the University of Illinois at Champaign-Urbana. I selected Illinois because it had a reputation for an excellent chemistry department, and that is what I was interested in. I stayed there for my bachelors training and then got a masters degree. I would have stayed for my PhD but they had a very sensible rule; they did not allow anyone to stay for all their degrees in one place. At that point, Dr. Hans Neurath, at Duke University in Durham, wrote to the chemistry department and asked if they had any graduate students who were strong in chemistry. He needed a chemist for his research program. So they recommended me and I went there to work on my PhD. That proved to be a good choice for several reasons. Neurath was an excellent teacher so I learned a lot about protein chemistry and kinetics. Not only that, but I met my future wife who was getting her PhD at the same time. In retrospect, I'm firmly convinced that one of the important factors in success in research is the kind of training one has and I got excellent training with Hans Neurath. After that I did a post-doc with Severo Ochoa at New York University before he won his Nobel Prize. I was there only one year when he offered me a position on the staff at

<sup>\*</sup> Seymour Kaufman was born in Brooklyn, New York in 1924. Kaufman died in 2010.

NYU medical school. I ultimately stayed for five years. With Severo I learned a lot about enzymology that complemented what I had learned with Hans Neurath. After five years I was offered a job at the National Institute of Mental Health in Giulio Cantoní's department. I think it was called General and Cellular Pharmacology. I had got to know Cantoni while he was a post-doc with Dr. Ochoa during the time I was there. Around this time, Cantoni moved to NIMH to start a new laboratory, and Giulio offered me a position to join him. I went to the National Institute of Health in 1954, and I am still there. In 1970, I was offered an independent laboratory of neurochemistry at NIMH. NIH proved to be a very fine place to do research in those days.

- TB: Could you say something about your different activities before you went to NIMH
- SK: During the time I was with Severo Ochoa, his great interest was enzymes in the citric acid cycle involved in the metabolism of carbohydrates.
- TB: Was that your first research project?
- SK: No, I had done a masters thesis at Illinois that dealt with fatty acid oxidation in leukemia. There was an observation that leukemic mice had fatty livers, and my thesis advisor, Dr Carl Vestling, said if they have fatty livers maybe they have a defect in fatty acid oxidation. My goal was to either prove or disprove that thesis. And we found a significant defect in fatty acid oxidation.
- TB: This was your master's thesis. Was it published?
- SK: It was my first publication in The Journal of Biological Chemistry. Unfortunately, in those days, not much was known about fatty acid oxidation, so we couldn't continue the analysis to pinpoint what was wrong. But it was a very good introduction to research and culminated in a publication. At Duke, Neurath's great interest was proteolytic enzymes; we had three graduate students and each was assigned one of the proteolytic enzymes to work on. The enzyme I was assigned to was contripsin and my wife's was capoxy peptidase. The enzyme I was on was known to require an aromatic amino acid. So I prepared amino acid ethyl estrins to test them as inhibitors because they were supposedly good candidates for being inhibitors. To my great surprise, we found that they were excellent substrates for the proteases. Each one of us in turn demonstrated the same phenomenon with respect to proteases. In those days, enzymes were thought to be much more specific than they are now so this was guite a startling finding. In retrospect, it doesn't seem astonishing, but it was at that time. It's fair to say it gave Neurath's career a push. It gave my career a big push too. Then I moved to NIH. At NIH I had a bit of good luck. It started out as bad luck

because the laboratories we were supposed to occupy were not finished. So for about six months, I didn't have any place to do research. I thought that was a tragedy but it turned out to be a blessing because I spent the time in a library thinking, a rare commodity, trying to decide what kind of project I would work on. I knew I wanted to work in some aspect of enzymology and decided I would select an enzyme reaction where you couldn't easily write the equation. I figured that if the reaction was so mysterious you couldn't write a simple equation, there might be something unknown, something interesting. The reaction I chose to study was the conversion of phenylalanine to tyrosine because if you write that down on paper, the only way to have a balanced equation is phenylalanine plus half an oxygen molecule. That's fine, except there is no such thing as half an oxygen molecule in nature, so there was clearly something mysterious. In addition, I wanted a project that had some elements of a double acrostic puzzle. I don't know if you're familiar with them but they come out in the New York Times periodically wherein you solve the puzzle in one dimension and the first letter of words in the vertical dimension spell out the author's name while in the horizontal dimension the quotation is spelled out. If you solve the horizontal direction, the solution to the vertical problem comes automatically. It seemed to me that phenylalanine hydroxylase had some of the elements of a double acrostic puzzle, because I was aware of a genetic disease called phenylketonuria, and it was known that there was something wrong with phenylalanine metabolism in the patients. Not a whole lot more than that was known and I had a feeling that if I could advance our understanding of the way phenylalanine was hydroxylated, out of that might come some new information about phenylketonuria. So that was a double reason for selecting the project. Using the methodology I learned in Ochoa's laboratory, specifically how to separate a complex system into its individual parts, I started to work on the phenylalanine hydroxylating system in rat liver and very guickly broke it down into different components, two enzymes and a nonprotein cofactor. You asked me to point out what I thought was my biggest accomplishment. Working on the structure of this nonprotein factor and proving its structure was certainly one of the biggest accomplishments in my life. It took me a couple of years to work out the structure and it turned out to be a compound whose derivative was present as a natural component in human urine. No one had ever detected in liver the parent of that component in urine. So I isolated the natural cofactor from rat liver and proved that it is tetrahydrobiopterin. Biopterin is a pteridine and another compound in nature which is a pteridine is folic acid. There is a slight

resemblance between biopterin and folic acid. But biopterin itself is not a vitamin, because we can synthesize it, whereas folic acid, being a vitamin, we cannot synthesize. So we slowly tried to unravel what the role of the three components was, two enzymes and the cofactor. It turned out that the role of one of the enzymes, which we named dihydropteridine reductase, was to regenerate tetrahydrobiopterin which during the course of hydroxylation gets oxidized to dihydrobiopterin. In order for it to work in the body it has to function catalytically. The role of the second enzyme was to reduce the biopterin back to the tetrahydro level. Then we quickly realized there might be at least three different forms of phenylketonuria. One caused by a lack of each of the essential components. In fact it was already suspected that the cause of phenylketonuria (PKU) at the enzyme level was a lack of phenylalanine hydroxylase. Jervis had shown that. But Jervis didn't know about the multi-component nature of the hydroxylating system. Jervis had pinned down which was the missing component. It could have been any one of the three components. I managed to get biopsy samples from two PKU patients and showed they had normal amounts of tetrahydrobiopterin and that the only missing component of the hydroxylating system was phenylalanine hydroxylase. The other two components were present in adequate amounts. Having done that, we realized there might be variant forms of PKU caused by a lack of reductase and biopterin. So we were primed to expect to read about that. Not being a clinician, I didn't do the initial work on that. About ten years went by and there were no reports of the expected variant forms and then I remember the day I received a call from a pediatrician, Tony Holzman, at Hopkins. I had met him at a scientific conference. He said they had a PKU patient who was a couple weeks old who was on the accepted treatment for the disease; a low-phenylalanine diet. In order to be effective, the diet had to be instituted very early in life, within the first couple of weeks. Holzman said the child had what pediatricians describe as a failure to thrive. He just didn't look right. And he wanted to know if he could supply us with a biopsy sample of the liver that we could analyze for the three components. He suspected that there was something funny about this particular child. So I said, send us a piece of liver, which he promptly did. In one afternoon we assayed for all three components and showed that there was not a trace of the reductase in this child's liver. He had adequate amount of the cofactor and adequate amounts of hydroxylase. So this was the first established case of a variant form of PKU due to the lack of reductase. In contrast to classical PKU, which is caused by a lack of the hydroxylate, this variant cannot be

treated with a low-phenylalanine diet. And the reason why is that we, and others, had shown that tetrahydrobiopterin and the reductase were essential components of tyrosine hydroxylase and tryptophan hydroxylase. Just withholding phenylalanine would cure only one part of the disease these children suffered from. They had three metabolic lesions, and you had to treat all three. We suggested in our first publication they had to be treated with the neurotransmitter compound beyond the block in their metabolism; with 5-hydroxytryptophan for the block in tryptophane hydroxylase, and dopa, for the block in norepinephrine synthesis, in addition to a low-phenylalanine diet. Unfortunately, this treatment was started too late and the child died. So these variant forms of the disease used to be called malignant or lethal forms of PKU. Subsequently we were contacted about other children who looked like good candidates for reductase deficiency. And they were adequately treated with neurotransmitter precursors. A couple of years after that publication, I was contacted by another pediatrician, Dr. Stan Burlow, from the University of Wisconsin, and he also had a child who was not doing well and wondered whether there was still a different variant of the disease. He sent us a liver biopsy from his patient, and we showed that the child was deficient in tetrahydrobiopterin, with adequate amounts of reductase of hydroxylates. So this was the second variant form of PKU that we have described, PKU caused by a lack of an enzyme involving tetrahydrobiopterin synthesis. These were very rewarding studies, the discovery of two new diseases and their treatment. I should say that treatment, for the lack of tetrahydrobiopterin, is not very satisfactory yet. You would think the natural way to treat them would be to just give them tetrahydrobiopterin, what they are missing. But tetrahydrobiopterin does not cross the blood brain barrier readily. Nonetheless, it is used. It will cross the barrier to some extent. But, the treatment is not ideal; a better treatment is required. What I regard as my most important findings were the isolation of tetrahydrobiopterin from the liver, and the discovery of the variants of phenylketonuria.

- TB: What is the time frame of the research?
- SK: From the time I first went to NIH, from 1954, until I retired about two years ago.
- TB: It was one major continuous research effort?
- SK: Yes. The other important contribution was when I found that tetrahydrobiopterin was the cofactor for phenylalanine hydroxylates; I had no idea how general a role tetrahydrobiopterin played. It was clear from its involvement with both tryptophan and tyrosine hydroxylates and phenylalanine hydroxylates that it was a cofactor for aromatic

hydroxylations of various kinds, and I wondered whether it was also involved in what is called a side-chain hydroxylation. In the pathway for norepinephrine synthesis is an enzyme that catalyzes the conversion of dopamine to norepinephrine that involves the side chain hydroxylation of norepinephrine. So we were interested in whether tetrahydrobiopterin was a cofactor for that hydroxylation. We worked on the enzyme that ultimately went by the name of dopamine- $\beta$ -hydroxylase. In fact we showed that tetrahydrobiopterin was not the cofactor for that enzyme, but instead ascorbic acid is the cofactor. In the course of answering this question we dicovered one of the few well-demonstrated metabolic roles for vitamin C. Just as tetrahydrobiopterin is oxidized during the course of phenylalanine hydroxylation, ascorbic acid is oxidized during the conversion of dopamine to norepinephrine. That was the first insight as to how metabolically vitamin C can work in the body.

- TB: When was this shown?
- SK: In the mid 1960s. That work is not as appreciated as it should be. If you read a nutrition book about vitamin C, they often don't mention that this is one of its important roles in metabolism. It needs to be publicized more. This about summarizes my scientific career.
- TB: These were major contributions.
- SK: There is still a lot of room for improvement in the treatment of these variant diseases.
- TB: You said that you retired two years ago. Does this mean that you stopped going to the Institute?
- SK: I go in once or twice a week. I was granted emeritus status and still retain part of an office. I have access to secretarial help, but I no longer have any post-doctorate fellows.
- TB: Are you involved in any research?
- SK: Very indirectly. I get asked to review a lot of scientific papers, but I'm less interested in reviewing papers than I was when I did research.
- TB: Are you on the editorial board of any journals?
- SK: No. I feel I put in my time as an editor of *The Journal of Biological Chemistry* (JBC) and *Archives of Biochemistry*. I worked ten years for the JBC. I mentioned I started out early in life thinking I would become an artist and, after retirement, I tried to pick up that interest, to take some art courses.
- TB: What kind of courses are you taking?
- SK: Hand-eye coordination is very important in art, so the first way to get back into art was to take a life-drawing class. My daughter agreed with me. And so I took several life-drawing classes, drawing the nude figure. I took those at the Corcoran Museum School. Most recently I took

a course on etching at Montgomery College. Those were both very enjoyable. And I did write a book on tetrahydrobiopterin along the way.

- TB: When was it published?
- SK: In the mid '90s by Johns Hopkins University Press.
- TB: Was that the only book you wrote?
- SK: Yes. I also edited several books of research.
- TB: Can you mention just a few?
- SK: I edited one volume in a series called *Methods in Enzymology* that was started by Sidney Colowick and Nathan Kaplan and published by Academic Press. They asked me to edit their book on aromatic amino acid methodology. And I was the editor of several different symposia dealing with amino acid metabolism. That's about it.
- TB: Is there anything we left out and you would like to mention?
- SK: I am thoroughly enjoying my retirement. It's very important to have structure to your life. Some of my retired friends seem to be at a loss as to how to spend their time. But if you plan ahead I think it can be a very enjoyable part of life.
- TB: You seem to be quite a sportsman.
- SK: I was. Now I'm less so.
- TB: What were your sports?
- SK: Mainly tennis. One of the bad effects my heart surgery had, for some reason, it interfered with my ability to walk. I had a lot of physical rehabilitation and it has improved a good deal, but not enough to play tennis. I do miss that.
- TB: When did you become a member of ACNP?
- SK: Maybe 15 years ago.
- TB: Have you participated in the activities of the College?
- SK: I regret to say I have not.
- TB: Did you attend the annual meetings?
- SK: Yes, I attend the meetings religiously.
- TB: Did you present at the annual meetings?
- SK: I was invited several times. I presented a few years ago at the symposium on tyrosine hydroxylates. Steve Paul organized it and I gave a lecture.
- TB: You talked about your mentors at the universities.
- SK: Hans Neurath and Severo Ochoa.
- TB: Can you say something more about Neurath?
- SK: Neurath was very demanding of his students. He transmitted that attitude to me, and I tried to transmit it to my post-docs. But he was a man of great integrity. He never cut any corners when it came to doing the ethical thing. Both my wife and I were very fond of Hans.

- TB: During your career you trained many people. Would you like to mention a few?
- SK: Most of them went into enzymology. One of my best post-docs was Daniel Fisher. He was one of my earliest ones. Unfortunately, he left biochemistry and went into psychiatry. Michael Davis did important work in my lab. Unfortunately, he left and became a lawyer. And then there is a young fellow by the name of Bruce Citron. He was important in the evolution of my laboratory because he was well trained as a molecular biologist. It was very hard to find someone willing to be the only molecular biologist in an environment of enzymologists. Bruce was daring enough to do it and he spent five years with us. He helped us a lot.
- TB: What was your last publication?
- It turned out that there was still another surprise about the phenyla-SK: lanine hydroxylating system. I was working with purified enzymes of the system, assaying the phenylalanine hydroxylating reaction under conditions away from what we call ideal, slightly more alkaline conditions, and found there was a factor in liver that could stimulate the reaction. It came as a great surprise. We thought that we had identified all the components required for hydroxylation. Well, it turned out there was still one more component at least. We purified that component from the liver, using an assay based on the stimulation I observed. That discovery proved to take a very surprising turn which ties in with the fact that our lab had got into molecular biology at that point. We purified that protein to homogeneity with no idea what it was doing. One of the first things we wanted to know was whether or not it was a known protein. With the tools of molecular biology, you can do partial DNA sequencing, and see if it's any enzyme or protein already described has a sequence in common. To our great surprise, there was a protein already described that had the same sequence as the protein we isolated. That protein went under the name of DCoH, and had a well-established role in gene transcription in the liver. A man by the name of Crabtree at Stanford University had found that. So I called Dr. Crabtree, and said we've isolated a protein from liver that has the identical sequence to your DCoH protein, only our protein has a role in phenylalanine hydroxylation. He was as astounded as I was and agreed we would exchange proteins. I sent him a sample of our pure protein, he sent us his. His protein had as high an activity in the phenylalanine hydroxylating system as ours did in the gene transcription system, purified by a totally different procedure. We went on to prove that the protein had a role to play in hydroxylation and catalyzed the regeneration of tetrahydrobiopterin

from the dihydro form. That was a step that normally would take place non-enzymatically, one wasn't aware of it, the reaction just occurred. But under the funny assay conditions I had accidentally set up, the nonenzymatic reaction was rate-limiting, and required the presence of this other enzyme to catalyze it. Immediately, we realized there was a possibility for still another variant form of PKU, one caused by the lack of this enzyme. We called it a dehydratase. We did manage to get a liver biopsy and show that there was a patient with a very rare form of PKU that lacked dehydrotase. A few other centers in Europe made similar findings. The children that have been described so far are not really sick. They have hyperphenylalaninemia, but it is fairly mild, which is not surprising because this reaction also occurs non-enzymatically. Even if they lack the enzyme, they can survive pretty well without it. I'm looking forward to seeing the next phase of PKU research, which will probably deal with gene supplementation.

- TB: Is this what you would like to see?
- SK: I would say we are a couple of decades away from that.
- TB: Is there anything else you would like to see happen? How do you see the future?
- SK: There is an adequate dietary treatment for phenylketonuria, but it is a pretty awesome burden for the family and the patient. They can't eat any natural foods and subsist on an artificial mixture of amino acids, from which phenylalanine is removed. There is a lot of room for a better treatment. I can only imagine that gene therapy would be the wave of the future for the disease. That's what I hope, will happen within the decade, but I'm not terribly optimistic.
- TB: Anything else you would like to add?
- SK: No, I think that's about it.
- TB: On that note we conclude this interview with Dr. Seymour Kaufman. Thank you very much.
- SK: I enjoyed it. Thank you.

# RACHEL G. KLEIN

#### Interviewed by David Healy Las Croabas, Puerto Rico, December 14, 1998

- DH: I am David Healy and interviewing Rachel Gittelman Klein\* on behalf of the ACNP at the 1988 ACNP annual meeting in Puerto Rico. Could we begin with where you were born?
- RK: I was born in Paris, France and lived there until I was 15 when my family immigrated to the United States.
- DH: Any particular reason they moved?
- RK: My father and mother, who were Russian born, decided to leave France immediately after the war in 1945, because of the great hardship they had experienced. A paternal uncle of mine lived in the US, making their plan possible. The common wisdom then was that there would be a world war between the Soviet Union and the United States, and Western Europe would be squeezed between the two. However, because of the McCarran Act, which imposed quotas on immigration based on country of birth, it took four years for them to obtain visas.
- DH: So you had to move schools and learn a new language. How did you cope?
- RK: I worked extremely hard until I became fluent in English. I went to Midwood High School in Brooklyn for two years, and on to City College in New York City. I worked for a few years and then enrolled for a PhD in Clinical Psychology.
- DH: Why did you go into Clinical Psychology? How did the field look, what was your interest, what was your motivation?
- RK: My motivation was to work with normal children. During college I worked in an after-school program in a community centre located in a New York City ghetto. I had been resoundingly successful. The kids loved me, I loved them. I was determined to show them that there was a world outside the ghetto. We did all sorts of things together in the city. It was terrific. I thought I would continue that sort of work but on a higher level and I needed a degree. Also, at the age of 18, I married someone who became a psychologist and that also influenced me.
- DH: What was your PhD thesis about?
- RK: On the prognosis of schizophrenia. It seems inconsistent with my original goals, but many events altered my trajectory. First, I decided to work toward a degree in clinical rather than developmental psychology. At the time, clinical training was the most prestigious psychology track. Second, probably the key event which was to play a major role in my

<sup>\*</sup> Rachel Gittelman Klein was born in Paris, France in 1935.

professional life is that I got a job for the summer at Hillside Hospital, where Max Pollack, Max Fink and Don Klein were conducting some of the first systematic psychopharmacology research. Getting the job was pure serendipity. I met Max Pollack at a resort, we became friendly and he offered me a job to evaluate patients in their ongoing studies. I was a graduate student in clinical psychology and the whole idea of using medications in psychiatric patients seemed rather distasteful.

- DH: Can you explain that for me?
- RK: I wasn't as passionate against medication as many people then were. But I believed that if it worked, it did so only during the active phase of the illness and that there had to be treatments with greater promise. I viewed medication as a temporizing treatment strategy, and therefore devalued it. At the same time I was extremely critical of my training. Even though I had chosen to study clinical psychology, I was appalled by the content of my graduate training. You see, I had not studied psychology as an undergraduate student. I had studied literature, and assumed that clinical practice was rooted in empirical data. I was amazed at how little was known, and at the fact that we were being taught without any basis in fact. I felt that clinical psychology practices were questionable, and that the same was probably true of psychopharmacology. Through my experience at Hillside Hospital with the research team, I developed immense respect for the scientists conducting the trials. They were intelligent, serious, caring and were not trying to prove an ideology. Their goal was to get very sick patients better, and to understand the therapeutic process. You have no idea how refreshing and exciting that was. My job was to evaluate patients at the initiation and the end of a six week study that compared chlorpromazine, imipramine and placebo. Chlorpromazine was already on the market, but imipramine was not. These were patients whom I will never forget; severely depressed individuals with retarded or agitated depressions. People I wanted to run from because they were in such pain, causing me pain. Yet, six weeks after the initial evaluation, when they had been on medication, they walked into my office and they were well; I get chills even now thinking about them. They talked with me the way you and I are talking now. One could not dismiss that sort of event. It seemed miraculous. At that point I thought that the objections, obviously there were problems, did not vitiate benefits that occurred in six weeks. This experience, combined with a lack of respect for other unfounded therapeutic practices for which wild claims were made, tilted me toward the direction of empirical approaches to treatment.

- DH: Did this begin to put you at odds with the other people training with you?
- RK: Yes, I had joined the enemy, but I never saw it that way. To this day, I've never been invited to give a talk at Columbia University Teachers College, my graduate school. There is still a great deal of territorial distance between those who study psychopharmacology and others. I think we are still viewed as superficial, doing uninteresting things, etc. However, I cannot say that I felt hostility per se. The one related exception was the reception my PhD dissertation when I defended it. As I told you, it dealt with prognosis in schizophrenia. I chose the topic because the research department was conducting a large follow-up study of hospitalized patients. I needed a PhD dissertation, and saw an opportunity. At the same time, I wanted to do something that was interesting. At that point my job had evolved. I now had a permanent position as a research assistant, and was involved in many aspects of the research. I had to rate the charts of all patients who were being followed-up for childhood adjustment, because both Max Pollack and Don Klein held developmental views of psychopathology. They felt that there might be patterns of childhood behavior that would be predictive of adult psychopathological outcome, and would foster study of different causal mechanisms. During my reading of hundreds of charts. I became struck by differences in the reported childhood histories of various types of adult patients. Depressed patients reported fearfulness, anxiety etc., whereas schizophrenic patients reported behavior and social problems. I began to explore the literature on the topic. At the time, we had the great luxury of having a library at Columbia that contained old psychiatry texts directly available in stacks. I spent literally weeks going through a broad range of writings. This led me to Kraepelin and others from the 19<sup>th</sup> and early 20<sup>th</sup> century. I found that Kraepelin had observed that hospitalized patients who had a poor chronic course or deteriorated tended to have had a childhood history of social withdrawal and isolation. That premorbid function predicted outcome had already been reported by Phillips and others. But these investigators had focused mostly on interpersonal sexual adjustment in adolescence, did not restrict their studies to function that was antecedent to the onset of active illness, and never focused on asocial behavior. I decided to do so. As an aside, by then, I had worked with Don Klein who was giving a great deal of thought to the nature of psychopathology. I remember announcing to him that he was a Kraepelinian, to his considerable surprise. Up till then, he had not read Kraepelin. That's how I became interested in the prognosis of schizophrenia. Findings

strongly showed that over a three year interval, the course of young schizophrenic patients was curvilinear as a function of their premorbid adjustment in childhood. All those with withdrawn social adjustment had poor outcomes, and none had been able to function independently. In contrast, outcome was variable among schizophrenic patients who had a history of unremarkable social functioning in childhood. My dissertation committee was highly critical of the research, and raised two issues, both of which I found offensive. One, there was concern that the references consisted mostly of papers written by psychiatrists and not psychologists; two, that I failed to indicate in my discussion the causal role that families played in the development of schizophrenia. Approval of my dissertation was delayed, but the content was not altered to address the criticisms. This was the only instance where I felt strong hostility toward an approach that did not conform to the views in the field of psychology. It was a very difficult experience.

- DH: You got your PhD in 1966. What did you do after that?
- RK: I left Hillside Hospital to work at Downstate Medical Center with David Engelhardt. He was one of the first to conduct long term studies of schizophrenic patients on medication. I had been impressed with the clarity of his writing. So much in psychiatry then seemed vague, not quantitative and not crisp. I thought that his writings stood out.
- DH: What was his background?
- RK: He was a psychiatrist who ran the psychopharmacology branch at the Downstate Medical School, a New York medical center. He had one of the first grants on outpatient antipsychotic treatment of schizophrenic patients. Then, most clinical research in schizophrenia was with inpatients. He was looking for someone to conduct a study with schizophrenic and autistic children. He himself had an autistic child. I think that may have been why, in part, he became interested in doing work with these youngsters. At the time there were very few people who even knew how to conceptualize a psychopharmacology study. He hired me to assist in preparing a grant submission and run the study. We compared chlorpromazine to diphenhydramine, a compound that was not expected to have clinical efficacy, but would have similar side effects to chlorpromazine, and placebo, in very young children with autism and other severe developmental disorders, what we now call pervasive developmental disorders. This work was never published, which is too bad. We found that chlorpromazine was markedly superior to placebo and diphenhydramine in reducing disruptive, hyperactive and uncontrollable behavior.
- DH: At that point in time there was controversy about schizophrenia being caused by the parents; the "schizophrenogenic" mother or the cold

kind of family that causes autism. Did you run into problems trying to treat this kind of condition with pills?

- RK: I never thought we were treating autism. I believed that perhaps we could make the children more manageable and the family could avoid institutionalizing the child. These were not trivial goals since many autistic children ended up in chronic residential settings, and preventing institutional care would be a major step forward. I never found the concept of the "schizophrenogenic" mother convincing. Perhaps that is related to my own personal background, since by all standards I had a traumatic childhood due to living in a Nazi occupied country during WWII, but I developed normally. Parenthetically, I know that in retrospect you can explain anything. I felt that parents could not be so powerful as to cause such devastation in a human being, since there were so many other influences in a child's development. Essentially, I believed that development could be perturbed, but not completely reversed, except perhaps with severe malnutrition or other brain damaging events, but not by subtle interactional processes. Moreover, I felt that blaming parents was extremely destructive, and I was hostile to this theory of infantile autism which I viewed as cruel, especially in view of the total lack of evidence. The parents were desperate. They had virtually no objections to using medication since they were grasping at anything that could possibly help their child. The use of medication was an issue for the field, but not for parents.
- DH: Was this the point at which you began to focus more clearly on childhood disorders or did you go back to adults?
- RK: That experience pushed me into child psychiatry. Essentially, we do what we know how to do, and I'd become quite expert at assessing children and interviewing parents. At that point, in the late 1960's, Don Klein had a grant to study children who had separation anxiety. He needed someone who could develop the protocol, run the study, etc. and my experience conducting a psychopharmacological trial with children made me a rather rare commodity. I was hired to do the study at Hillside Hospital. I originally had left Hillside for Downstate because Don and I had developed a personal relationship that had become rocky. By the time I returned to Hillside to conduct the study with anxious children, our difficulties had been resolved. I mention this aspect of my personal life because were it not for it, I very likely would have continued working with adults, and would not have gone on to work with children. So much for careful career planning!
- DH: So you went back to work with children with separation anxiety to treat them with pills, with what?
- RK: With imipramine. I think this was 1969. Don had already done important work with inpatients that had what he labeled panic disorder, noting that a great many presented with a childhood history of severe separation anxiety. He posited that childhood separation anxiety and panic attacks were variants of the same psychopathology. Over time, as a result of numerous studies he has conducted, he has modified his views on this point. In any case, there was enough shared psychopathology to postulate that perhaps we were dealing with similar pathophysiological processes. As a result, Don predicted that imipramine, which he had shown to be effective in adults with panic attacks, would have beneficial effects in separation anxious children.
- DH: So this would involve giving imipramine to children of what age?
- RK: They were 6 to 15.
- DH: The climate in the US at that time wasn't very favorable to treating anxiety with pills was it?
- RK: That's correct, it was not. In contrast to our experience with autistic children, it was difficult to recruit children. However, because we wanted to ensure that change could be documented by very objective behaviors, we accepted only children whose separation anxiety interfered with school attendance, and thus posed major problems for families and schools. Consequently, parents were extremely distressed, and were more likely to try medication than if their child had been less impaired.
- DH: But would the emphasis still not have been to use a behavioral or psychodynamic approach?
- RK: Yes, very much so. In fact, some of these children or their parents had been involved in other treatments since the two most influential views at the time placed responsibility on the mother. Either she had engendered a neurosis, à la Anna Freud, or transferred her own anxiety to the child, as claimed by Leon Eisenberg, of all people. However, behavioral interventions were not widely applied then, and the bulk of treatment consisted of non-specific psychotherapy. Our research design facilitated parental acceptance because we treated the children very vigorously with behavior therapy. The medication study was offered only to those who failed to respond to a behavioral program which involved the family and the child's school; about half the children responded to this initial effort. Moreover, psychotherapy continued during the experimental drug trial. Therefore, parents knew that we were not treating the children exclusively with pills. Parents were told that we were going to make an all out effort to treat the child without medication, and if we failed, there would be the option of medication. There were some

who refused, and others who would not even consider the possibility of medication and were never referred. But most of those who accepted the use of medication did so because we were sincere in our attempt to help them before we suggested it was time to try medication. By the time we did so, we usually had developed an alliance with the families who were confident that our effort to help was genuine.

- DH: When you talk about looking at the outcomes, this was really in an era before rating scales had begun to be used widely, before they'd become the sine qua non that they now are. What kind of outcome measures were you looking at; people being able to actually get back to school, real life outcomes?
- RK: The Rutter scales had been published, and we used them. In addition, we made up our own rating scales. I had experience with the systematic assessment of adult patients for whom there were already quite a few scales. These were not necessarily all that satisfactory, but at least there were established methodologies to assess symptomatology, clinical progress and improvement. We followed the model of generating measures that reflected the particular psychopathology under study. By the time we started the study we had a good understanding of separation anxiety disorder, and could target its main components. That this is the case is indirectly documented by the fact the diagnosis of separation anxiety disorder was introduced in DSM-III, based on the children we evaluated in our study. Remarkably, the disorder stands out for having undergone the fewest modifications over the ensuing two versions of the DSM. It has stood the test of time, and has remained virtually unchanged over 16 years.
- DH: And imipramine helped?
- RK: It helped enormously. In fact, I felt that the statistical results did not do justice to the clinical impact of the medication. It transformed the children. By the way, the very first child we treated with imipramine was my own four year old daughter who had severe separation anxiety. She responded marvelously. That was not the reason why I studied children with separation anxiety, but that is probably why I understood them so well and was comfortable doing the study. I must tell you I was extremely nervous when I gave my child her first pill. But this was a four year old little girl, who could not get out of bed in the morning unless I went into her room; who could not go to sleep at night, who could not be in a room by herself in her own apartment. There was this darling little girl who could not enjoy life, and who would literally panic if I stepped away from her. But she did not have panic attacks per se. She was fine if I was with her and she never panicked spontaneously.

After being on imipramine, she would play by herself in her room in the morning. It was truly uncanny; could it just have been coincidence? Perhaps, but I was encouraged by that experience, all the more so that she did not know she was taking medication. It's of some interest that she's now a thriving young woman who shows no sign of anxiety. The disorder is not invariably a life sentence. I thought our study results were phenomenal, and that the tests of significance did not reflect the quality of change. But one study doesn't make a finding. We wanted somebody else to do the study again but nobody has.

- DH: Why not?
- RK: I don't know. There were small studies that yielded inconclusive results. These clinical treatment studies are not easy to do. It's very difficult to recruit cases, it's expensive and you need trained staff. I kept puzzling about the same question. Why doesn't anybody try it? They shouldn't believe only one study. So we decided we would have to do another. Many years later we got a minimal grant to repeat the study, but this time the children did not have to have school phobia as part of the separation anxiety disorder. Unfortunately we were able to recruit only 20 children and the study was negative. We obtained no imipramine versus placebo difference, and I must say the statistical results reflected reality this time. As impressed as I had been about imipramine efficacy the first time, I was completely unimpressed the second time. I understand that there's a new study that finds significant efficacy for imipramine in children with separation anxiety. However, I have not seen the data. Maybe that's the reality of clinical research; results are not positive in every instance even if one is dealing with effective compounds.
- DH: Could it have had to do with the first trial having a more severely ill group of subjects?
- RK: It may be that children in our first study were more severely ill. Also, the practice of child psychiatry may have changed so much in the interval between the two studies that different patients with separation anxiety were referred for treatment, and these differences were not obvious from a clinical exam.
- DH: When you say things changed so much in child psychiatry. What had changed? What was happening?
- RK: By the time we conducted our second study, many more child psychiatrists were using medications and perhaps children treated successfully in the community were not referred to us. No child in our first study had received medication except for a few who had been given Compazine (prochlorperazine) by pediatricians because of complaints of stomach aches and nausea when separation was attempted, such as when they

tried to go to school. By the time we did the second study, I think our work and others' work had become known, and medication was much more commonly used in anxious children. In addition, there were many more child psychiatrists so that treatment availability had greatly increased. These factors may have affected the clinical populations we studied at the two time periods.

- DH: Were there any key people in the field whose work or public attitude helped to change things? People like Leon Eisenberg for instance.
- RK: Early on, Leon Eisenberg was critical. He was one of the very first to conduct psychopharmacological studies in children with behavior disorders, although my impression is that the work he did had very little impact on clinical practice. The Montreal group with John Werry and Gabrielle Weiss was more influential through their systematic trials of stimulant and phenothiazine treatment of hyperactive children. It's difficult to pinpoint any one person as being key or having a major influence. I think perhaps the greatest influence was the meteoric change taking place in adult psychiatry. As hard as people tried, they could not escape the tremendous progress in psychopharmacology and the ensuing payoff. Adult psychiatry really had more influence on child psychiatry than the few child psychiatrists who were doing unusual things. A case in point is our imipramine study of separation anxiety which emanated from adult psychopharmacology. This work did not only have treatment implications, it also represented a major diagnostic shift. For the first time, a childhood anxiety state was singled out as deserving specific attention, and as having specific distinguishing pathological features. This approach was very unusual in child psychiatry, where descriptive diagnosis in general was not a hot topic, much less diagnostic refinements within the anxiety disorders. This development was entirely initiated by the clinical observations made in adult patients by Don Klein. The study of separation anxiety in children had further scientific ramifications. Since we had gained experience in studying medication in children, our interest widened. We eventually conducted large pharmacotherapy studies of children with ADHD, and have gone on to do similar studies in children and adolescents with other disorders such as major depression and conduct disorders. Directly and indirectly, child psychiatry has been altered from without, by adult psychiatry, rather than from within. Fortunately that has changed, but not as much as one would wish.
- DH: That's curious and that may help to explain why things didn't change in the same way in the UK; adult psychiatry didn't change the same way it changed in the US. We haven't had this big watershed around 1980

where things changed from one mode of being to a completely different one.

- RK: I think the other change that took place in the States, which also distinguishes it from Great Britain, is the shift to DSM-III, and the great influence that had. In contrast, DSM-III was resisted and viewed with hostility in Great Britain.
- DH: Another of these things from the United States that we are going to resist if at all possible!
- RK: Something like that. In the US, diagnosis became important in child psychiatry, just as it had become important in adult psychiatry. It also influenced practice in terms of leaning towards psychopharmacology.
- DH: You say you were asked to write the criteria for DSM-III for separation anxiety. Who asked you and what does it mean to have to write criteria? How above board was it?
- RK: It was very above board. A committee on childhood disorders was put together by Robert Spitzer, who was in charge of the DSM-III. Initially, it consisted of a small group whose members had conducted systematic clinical research in child psychiatry. The key was to avoid unsubstantiated etiological theory and to develop specific inclusion and exclusion criteria. As the process became increasingly more political within the American Psychiatric Association, working groups were enlarged to meet various constituencies. There was tremendous hostility toward the DSM from a large part of the psychiatric community convinced of the importance of "dynamic" rather than descriptive diagnosis. We were each assigned different jobs. Because of my clinical experience with children and separation anxiety, I suggested that the disorder, which did not exist in the nomenclature, be included. I offered to write the text describing the condition. It was reviewed by the committee, questions were raised, and suggestions were made. The criteria came later. That was a much more collaborative process. I don't recall how decisions were made regarding inclusion and exclusion criteria. Those issues, though arbitrary since we had little to guide us except our clinical experience, followed general principles. For example, there should be enough opportunity to diagnose individuals with a specific disorder but varying clinical presentations. We knew that reliability was likely to be improved if relatively more criteria were included. Consequently, whenever possible, we avoided having very skimpy criteria sets. Also, we tried to make sure that diagnoses had high enough thresholds to avoid large rates of false positives; at the same time the diagnostic threshold could not be set so high that false negatives would be common. For the most part, back in the 1970s, when DSM-III was formulated, we

had to rely on our clinical fund of knowledge. It is remarkable how well we did in many instances; not in all, of course. I'm not sure things are much better now.

- DH: By this time you had also begun to move into the ADHD field. Can you tell me when you began to do that and how the field looked at that point in time?
- RK: By the time I went back to Hillside Hospital to work with separation anxiety in children the work by Eisenberg and Keith Conners on the efficacy of stimulant treatment in hyperactive children had been published, but there was very little else. I thought the findings were extremely curious, and took them with a grain of salt. I'm not an easy believer and don't join bandwagons easily; that's probably why I went into research. Don and I discussed it and he also found it very interesting and curious. We started treating a few children clinically and were impressed. But we didn't quite buy it, so we went on to design a controlled study.
- DH: Why not? Was it a problem that you would give a stimulant to kids who were over stimulated to begin with?
- RK: Exactly. And how could one make sense of this? Traditionally, child psychopharmacology was a straightforward translation from adults to children. Even the work I did with pervasive developmental disorders extended the use of chlorpromazine in adult schizophrenia to children, the reasoning being that these children had something akin to schizophrenia. Although I did not believe that was the case. Child psychopharmacology essentially consisted of transposing practice down to younger individuals rather than positing new ways of looking at children. Don was the first one to propose a different approach to the treatment of a childhood disorder in that the use of imipramine in separation anxiety derived from a specific theoretical model of child psychopathology. He posited a relationship between separation anxiety in children and adult panic disorder that led to the drug study in children. With the hyperactive children, the observation of stimulant efficacy was completely accidental, just as with the rest of psychopharmacology, but it had been so long since the early reports by Bradley, which I had not found that compelling.
- DH: This goes back to 1936. Did you ever meet the man?
- RK: No. I didn't know him at all.
- DH: The other person who was doing work with kids who may have been using methylphenidate was Lauretta Bender. Did you have any contact with her at the time?
- RK: I met but never knew her. Barbara Fish, her student, conducted controlled psychopharmacology trials with schizophrenic children or various

sorts of developmentally impaired children. I certainly was familiar with Barbara Fish's work, but was most impressed with the work of John Werry, Keith Conners and Leon Eisenberg. However, I had to see for myself. In a way we started doing that work out of disbelief. That's why there is so much research on the treatment of hyperactive children. Many psychologists have found the notion that medication is effective distasteful, and have gone into the field with the expectation that they will disprove drug efficacy, improve on it or find a competitor. Every time they have tried, they've failed. We were not trying to find fault with the treatment, but were sufficiently intrigued to see for ourselves.

- DH: During the 1960s, how did the disorder look? What did people think it was? There are a whole load of theories that it was food allergy. Was this the minimal brain dysfunction period?
- RK: Yes. There was the minimal brain dysfunction view of Paul Wender and others which was held by the more "organically" minded, but it was a vague concept that explained perhaps too much. There was also the family theory that argued that parents had failed in the socialization of the child. Those were two major trends, but there were also other family theories that posited that the child expressed the family's pathology, the systems view of patients. That also explains everything. The most influential academic theory was the learning theory of maladaptive behavior, which advocated that the child had received positive reinforcement for negative rather than appropriate behavior. It was expected this could be rectified through behavior therapy that was designed to reward the child for behaving appropriately, and to provide negative consequences for misbehaviors. The drug studies were atheoretical. We were not making any assumptions about the nature of antecedents. We never assumed that medication efficacy proved a disorder had a biological origin. You could treat psychological reactions with medication, and you could treat biological phenomena with environmental manipulation. Etiology was not troublesome to us in terms of justifying treatment.
- DH: This is the mid to late 1960s; you've begun to treat the first few kids. The whole field then begins to take off and you get things like food allergy syndromes beginning to come into play. How did you see it going? Who were the key players, why did things go the way they went?
- RK: You raised the issue of resistance, consumer resistance or professional resistance to using medication; that attitude was most influential in the treatment of hyperactive children. It had been relatively easier to offer medication to parents of children with separation anxiety, autism or schizophrenia. But here we encountered enormous social opprobrium. In the States, the issue had racial as well as political overtones. Many of

the children being treated for hyperactivity were minorities. It was argued that medication was a form of pharmacological genocide, interfering with children's free will and controlling their behavior. It was argued that the behaviors of hyperactive children could be interpreted as resisting the irrational demands of an authoritarian world. Essentially these lively rambunctious children were being turned into passive pawns. These views were not limited to minority children, but to all hyperactive children. The diagnosis was viewed as representing parents' and teachers' inability to tolerate children's expansive, enthusiastic style.

- DH: Who was actually saying this kind of thing and when did it reach the Church of Scientology level. When did it become a public issue?
- RK: Thomas Szasz, a psychiatrist, was a major figure in the anti psychiatry movement. By the early 70s, treatment was much politicized. The Church of Scientology came on the scene a little later. Remember that this was pre-DSM-III; there were no diagnostic criteria, or objective quantitative standards for quantifying hyperactivity. We faced the dilemma of how to diagnose ADHD. Initially, strong resistance came from the psychiatric profession and other care providers. There was immense hostility to the notion of giving medication to hyperactive children. In addition, the few who used stimulants justified it on the basis that they used them only in children whose hyperactive behavior had an "organic" cause, and not if the disorder was "emotionally" based, whatever this distinction meant. Therefore, some expressed a need for neurological examination prior to medication. No studies had been done to show differential stimulant effects based on these distinctions which, of course, had no validity. The controversy was expressed in schools, in the mass media, but was not as nasty as it subsequently became. Although there was early hostility towards a psychiatric establishment viewed as controlling children's behavior, later on the attacks became more systematic. At the same time a constituency on the other side developed, such as parent groups. When we started, there was no promedication constituency. Because of the negative climate concerning the diagnosis and treatment of hyperactive children, we decided that we would diagnose only children whose parents agreed with the school regarding the child's comportment, and who had a history of hyperactivity. The reasoning was that, if children had signs of the condition in two important functional settings, home and school, one could not challenge the notion that the children deserved professional attention, or claim that the teacher was the problem.
- DH: Can you remember any early meetings or occasions where you realized there was this hostile point of view and that it was going to be an issue?

- RK: I cannot recall a point at which the situation changed. It always was a problematic issue among those who argued that the disorder did not exist, those who argued that it was due to improper conditioning and that medications were undesirable, and those who felt that the disorder represented impaired function independent of specific environmental factors. Perhaps I'm missing the gist of what you're trying to get at.
- DH: You were getting very good clinical responses, better than with other conditions, yet you had to face the hostile public reaction that ADHD triggered. I'm trying to understand the point when you realized this wasn't just minor hostility but really serious.
- RK: That's the feeling we're experiencing now. We did not then. Although there were real objections, there was not this fervor to attack psychiatric practice. The first book attacking the notion of diagnosing children with hyperactivity was published in 1975 by Schrag & Divoky, *The Myth of the Hyperactive Child*. It received a great deal of attention in the mass media, and was followed by similar attacks. Thus, as early as the early 1970s, there were passionate criticisms of medicating children, but it was not as systematic as it is now.
- DH: When did the contributions of Paul Wender and Judith Rapoport begin to play a part?
- RK: Paul was a major influence from the beginning with his book, *Minimal* Brain Dysfunction in Children. He was not the first to express the view that these children had a biological disorder, but he did it in a very articulate fashion. There was a dearth of literature and his book filled a vacuum. His way of describing the children was wonderful, and the book gave compelling examples. An additional appeal of the book was Paul's theories of the neurochemical and psychological abnormalities in hyperactive children. He suggested that the children were resistant to reinforcement and therefore to corrective experiences, because of abnormal dopamine regulation. These theories gave the field a scientific cloak that made sense. Paul was very influential through his compelling observations and theoretical formulations. I thought the work suffered from not having enough empirical support; there wasn't a lot of evidence for the theory. There were no abnormalities on EEGs, etc, or if there were, it was only in a small sub-group, and dopaminergic compounds were not the only effective medications. For example, phenothiazines, contrary to the stimulants, block dopamine activity. Yet, they also worked. It was difficult to document the minimal brain dysfunction model. Things may be changing, but then the theory was based strictly on the fact that stimulants had dopaminergic properties. It's rather simplistic; stimulants affect the dopamine system therefore that system

must be deranged. Nevertheless, I think that Paul was extremely important in making people think differently about this syndrome. Judith came on the scene in the 1970s. Her first study compared imipramine and methylphenidate. She became very productive and thoughtful in her attempts to pursue issues of associated CNS development, such as minor physical anomalies, and other neurobiological models that could distinguish hyperactive children.

- DH: I understand she gave stimulants to either her own children or of other staff at the NIMH, showing that even kids who weren't hyperactive showed a particular effect. Did that influence things?
- RK: She tested the notion of a paradoxical response in hyperactive children. However this was a single dose study and one cannot generalize about the effect of chronic medication from a single dose. The fact that stimulants enhance attention in non-hyperactive individuals is not surprising. In fact, their effect was discovered through such observations in normals. The more relevant issue is whether, when given chronically, they reduce activity in normals as they do in hyperactive children. We don't know whether the reduction in activity level would be sustained in normals over extended periods of exposure. It's a complex issue; the stimulants are excellent "energizers", or anti-fatigue medications. For example, it is well known that during World War II the Japanese army made extensive use of methamphetamine, and that this enabled the troops to undertake extraordinary feats of endurance. These effects are not really compatible with a model that stimulants lower motor activity or have so-called calming effects. But Judy's study is widely guoted as putting to rest the notion that stimulants have a paradoxical effect on these children, and that therefore the children have a distinct physiology. That's important insofar as improvement on medication cannot be used as unambiguous confirmation of the diagnosis.
- DH: You've raised an extremely important point which is that if we give stimulants to you or me we wouldn't be able to eat or sleep but when you give these drugs to hyperactive kids they are able to eat and sleep when they weren't able to before. Did that play a part in legitimizing the condition?
- RK: Yes and Judith's work made this view less tenable. Until then people were claiming that these medications had specific effects in hyperactive children. There was some argument that you could use response to stimulants to confirm the diagnosis in ambiguous cases. Now people said, "everybody gets better, so there's nothing specific about this diagnosis, and we are not dealing with a pathological entity". Judith's work did not lead to this conclusion, but the notion that there was no

paradoxical effect of the medication was viewed as very important. The question of "paradoxical stimulant effects" led us to conduct a study, in the early 1970's, aimed at determining whether the attentional effects of stimulant treatment were specific to hyperactive children. Given this goal, the issue was who could one treat ethically with stimulants for any length of time? You can give one dose to normals but it would be difficult to justify extended exposure. We felt we could justify treating children with learning disorders, such as reading disorders, who had no behavior problems. Based on systematic assessments, we documented that over 12 weeks of stimulant treatment attention was improved, but behavior did not change. Subjects did not become less active, unlike the normal kids who had received one stimulant dose. If, in fact, there is no effect on non-hyperactive children's behavior over time, then there is indeed a specific stimulant effect in hyperactive children. I do not think that we can assume that activity level is generally reduced by stimulants, even when attention is enhanced.

- DH: When did you get to the point of doing long-term trials?
- RK: Obviously, long-term studies had to come after short-term studies. We have conducted two types of long-term trials. One is simply giving medication over long periods of time, and two is doing longitudinal follow-ups. As we have discussed, the treatment of hyperactivity has been extremely contentious. It is clear and dramatic that medication works only as long as it is administered. If it is discontinued, the effects are not sustained. This phenomenon led to devaluing stimulant treatment, no matter how broad and effective. There has always been the argument that "medication is not enough". I do not know of any treatment that is enough for all patients. That is the sad part of psychiatry I guess; we don't have cures. In this case, medication was indicted for not taking care of all that ailed the children. It was conceded that children were better behaviorally, which is what they are being treated for, but not academically, which is not what they were being treated for. People were always upping the ante while claiming that non-medical techniques were less deficient than stimulants. So, with Howard Abikoff, we devised trials that attempted to address aspects of function other than primary symptoms of the disorder. At the time, the view was very vigorously promoted that hyperactive children suffered from metacognitive deficits, that they could not process problem situations appropriately, whether these were social or academic. We tested therapeutic interventions aimed at addressing these deficits. At the same time, we were convinced that you could not control children with hyperactivity without medication. Therefore, we compared adding ancillary treatments

to ongoing stimulant treatment, since many stimulant treated children have residual problems; at the same time, many do not. We did one trial in which we added cognitive training to stimulant treatment. It was a demanding program in which children were seen several times a week for four months, and included training for parents to implement the programs at home. Surprisingly, there was zero advantage of this ambitious program over stimulants alone. These results were most disappointing. We reasoned that perhaps we had taken the wrong tack in that we hadn't been strict enough in identifying children with clear cut residual problems. So we undertook a second study which was rigorous in selecting hyperactive children who, though they had benefited significantly from stimulant treatment, had quantifiable residual academic and other problems. Even in this instance, the introduction of intensive cognitive training added nothing to the medication effect. It's important to understand that we did these studies with a great hope of finding effective interventions. Earlier on we had studied the effect of behavior therapy compared to medication, as well as combined with medication in hyperactive children. We did not find any advantage from adding behavior therapy to stimulant treatment, except in a few instances. I think behavior therapy has something to offer in addition to medication in difficult situations, but cognitive training does not. Yet, if you saw it in action, you would be impressed and seduced into thinking it was doing something important. In the meantime, follow-up studies by Gabrielle Weiss and Lilly Hechtman in Montreal, and later by ourselves in New York, had revealed that hyperactive children have difficulty over time, and the field moved toward looking at whether one could modify their course early on to improve long-term outcome. The next step, with Lilly Hechtman in Montreal and Howard Abikoff at Hillside Hospital, was to develop a much more ambitious intervention for young hyperactive children to supplement medication. We implemented a two year intervention, in which family therapy, parent training, social skills training, individual psychotherapy and academic tutoring were administered. The treatment was individualized and efforts made to address each child's difficulties. Treatment was very active for one year, and continued in maintenance fashion for another year. There were two expectations. One was that, compared to children who received only medication, those treated with medication combined with the enriched treatment package would be better at the end of treatment; second was that these children could go off medication more easily after a year of treatment because parental behavior had changed, and the children had learnt all these wonderful social skills, etc. We found that there was

no advantage to the combination of medication with the treatment program over medication alone, and when children were switched to placebo at the end of the first treatment year, every one of them had to go back on the medication within a month regardless of the treatment they had received. The same outcome ensued after two years. The results are not published yet. So, none of our attempts to modify hyperactive children's difficulties with enormously costly psychosocial treatments paid off. What we find is that we're on a slippery slope. It's a bit like psychoanalysis; it must work, and if it doesn't, it's because you didn't do it right. Others claimed that we did not do it right, but they can. The multi-site study sponsored by NIMH began where we left off. It tested a 14 months treatment program which was extremely ambitious; it included placing a paraprofessional in the school with each child for 3 months, a costly summer camp, parent training and other interventions such as behavior therapy. The study had the advantage of examining the impact of the psychosocial treatment alone, medication alone and the combination. There was no significant difference between medication alone and the combination, in spite of the enormous effort that went into the latter. Medication alone was far superior to the psychosocial intervention. The study had a very nice twist in that a group of children were randomly sent back in their own community for treatment. and those children did as well as children in the ambitious psychosocial treatment. The data have not been published, but presentations indicate that the community children, many of whom received medication. did not do nearly as well as the children on medication alone in the study. That raises the question as to what happens to study findings when they're exported into the community. Medication management is not done as well in the real world as in research protocols. That raises an important problem of how to educate care providers to optimize children's care. My guess is that, compared to the study, the dose level used in the community was lower and compliance was likely worse, and therefore outcomes differed in favor of the study children.

- DH: Let me take you back to DSM-III. The process of trying to draw up the criteria for ADHD must have been an interesting one?
- RK: That was very interesting. However, I was not prepared for the controversy that the DSM-III triggered in the profession. The animosity, the hostility, the pejorative attitude we encountered in the psychiatric profession was really remarkable.
- DH: What were the issues?
- RK: They varied; in general it was felt that classification without inferences as to causality was missing the boat. Most child psychiatrists had been

trained in the psychoanalytic tradition, and were completely committed to it. The critics' opinion was that they knew what caused children's problems that they were getting to the root of the difficulties through play therapy. Removing these etiological concepts from the nomenclature was very threatening. If we had their wisdom and their vast experience, we would not be doing these terrible things! We were attacked right and left. I remember going to a meeting of child psychiatrists in St. Louis in 1976 or 1977 with Dennis Cantwell and Judy Rapoport to present the childhood disorders of DSM-III. We were nearly lynched. As we walked out, I turned to Judy and Dennis and jokingly said to them, "You two have a lot to answer for. How did you ever get into this field"? They proceeded to answer me in all seriousness, as if this was a legitimate question, giving all sorts of excuses for being child psychiatrists, given how dismal the field was. There was no rigor at all; even worse, there was no desire for it. If one asked, "what's the evidence" it became clear that the question had never occurred to the clinicians who criticized us. Moreover, they viewed the guestion with consternation and contempt. I found that very surprising. Perhaps I was naive. These clinicians felt that they had a way of doing things that was perfectly satisfactory. If you said, there's no reliability in what you do, and as a result the field has no credibility, it meant nothing. They did not care. There was no rational argument possible. There were also family therapists who felt, perhaps rightly so, that the DSM-III would change the field forever by averring that individuals might be ill. It was felt that if diagnoses retained vague, with imprecise descriptive standards, one could incorporate the diagnoses into any theoretical framework, and the proposed DSM blocked that opportunity. From their point of view, social systems and not individuals were ill. The DSM-III would shape people's way of looking at psychopathology and take away from focusing on the family system. I think that it is in part true; the DSM does shape people's thinking. There were many arguments. Bob Spitzer took a lot of heat, the brunt of it. Eventually, compromises were made. If the document had been as originally intended it would have been much thinner, and much more rigorous. The process became very political and various constituencies had to be accommodated. In the end, after what appeared to be hopelessly mired negotiations, accommodations were largely minor, such as including the term neurosis in parentheses after anxiety disorders. Initially it had been dropped since it was defined by exclusion of psychosis, and had no specific descriptive content.

DH: You mentioned Dennis Cantwell. What role did he play? My impression was that behind the scenes he was involved in the politics?

- RK: Dennis was actively involved in the DSM-III process, but I think you're pointing to something real. Dennis will be remembered as someone who fostered the field through his intense involvement and active training of young psychiatrists. He had great respect for research and for establishing practice from systematic studies. He was scholarly, and had an uncanny knowledge of the literature. Denny was then part of one of the largest child psychiatry departments in the US at UCLA at a time when there were no research departments in child psychiatry. He had a lot of charisma and became very well known in child psychiatry, to which he was completely dedicated. There are people who commit themselves in a way that's so convincing that you pay attention to what they say. He was a very popular, wonderful speaker and this appeal contributed to his influence. He had been trained in St. Louis, which at the time was the pace-setting center for diagnosis, with Eli Robins, as head of psychiatry, and Sam Guze and George Winokur in the department.
- DH: Which is where, in essence, DSM-III came from?
- RK: The St. Louis impact on the childhood section of the DSM was both direct and indirect. The indirect impact was through their contributions to the field. St. Louis was where the Feighner criteria had been developed and Bob Spitzer had been greatly influenced by them. We also all felt that Guze and Robins were on the right track. The direct impact came through Lee Robins who was a key contributor to the diagnosis of conduct disorder. But they were not actually involved in launching the DSM, and by the time Dennis joined the DSM team he was already in California.
- DH: As regards DSM-III, did Bob Spitzer figure that the same thing could be done for the child field as was being done for the adult field or was he a bit unsure about how all that was going to work out?
- RK: I don't think that the child section of the DSM was given the same importance as the adult section.
- DH: While we're doing all the rest we may as well do them too?
- RK: Right. However, once it was explained that it was important, he never resisted and he gave it the same kind of attention and care that he did to the adult section, but perhaps with less passion.
- DH: As regards ADHD itself were there any issues in particular when it came to clinical criteria for that?
- RK: Yes, not so much when it came to the criteria, but to what it should be called. Paul Wender won and I lost. Paul held the theory that the underlying, as well as the manifest disturbance, was in the attentional domain, and that it should be called Attention Deficit Disorder. Other

influential figures in research also held the view that impaired attention was the central dysfunction. I felt that was a mistake, that we did not know enough to assume that a specific function was central and that the name should be exclusively descriptive. The salient dysfunctions were impulsivity and hyperactivity. I felt that the syndrome should reflect this clinical presentation and that we should not make any assumption about the nature of the pathology. The diagnosis of Attention Deficit Disorder was adopted, and was qualified as being "with" or "without hyperactivity".

- DH: You would have called it what?
- RK: I would have called it Hyperactive Impulse Disorder. There was a strong sentiment to change the name in the DSM-III-R. Interestingly, the name ADHD was retained because of petitioning by pediatricians.
- DH: So in a sense what Paul Wender achieved went against the grain of DSM-III which was to leave any theoretical preconceptions out?
- RK: Right, but at a different level. In terms of the neuroses, the preconceptions involved intrapsychic conflictual and defensive processes, whereas here they evoked one aspect of the disorder as underlying all its other manifestations, much like Bleuler's notions in schizophrenia.
- DH: Paul Wender also introduced the idea that kids don't always grow out of this. That there may be a reasonably large proportion who, when they become adults, will still have some features of the condition. When did the idea that it's not just a childhood disorder come into play?
- RK: Paul is responsible for introducing the notion of adult ADHD. He was the first to bring the adult condition to the field's attention. He did not do follow-up studies of the children, and I'm not sure of the origin of his observations. It was probably in his clinical work. Having been sensitized to the childhood disorder, he could recognize it in adults.
- DH: Roughly when did the issue of adults having the condition begin to come into focus?
- RK: In the early 1990s. Articles appeared in the literature, and clinicians gave talks about their personal experiences. In addition, research grants were awarded for studies on the adult disorder. Paul Wender published psychopharmacological studies in adults. In one instance, he found that stimulant efficacy was evident in adults whose parents reported childhood hyperactivity, but not in those whose reports of childhood hyperactivity were negative.
- DH: After the DSM-III criteria were put in place, things were reasonably settled for a time. You had a real entity which you could research and treat but as you say in recent years it has become a big public issue. What's driving this?

- RK: The mass media have a tremendous influence, both good and bad. Not long ago, it would have been unheard of to have parents come into your office asking for, demanding, medication for their child. Now it happens often; at times you have to talk them out of it and suggest that we try something else first. The term "chemical imbalance" has gained wide currency among parents. TV shows, articles, books; parents are great consumers of these "how to help your child" materials and welcomed the notion that they were not the bad ones. They've lived in a world in which they were guilty until proven innocent. In fact they never could prove themselves innocent, no matter how compelling their case was, even in infantile autism, a condition that is so blatantly neurobiological. I think that's a great relief. I don't see parents abusing the new views. They are still willing to examine how they themselves can contribute to their children's progress. On the other hand, the attitude that parents are entirely responsible for children's difficulties is still very common. I have not done a survey, but I would bet that it is still the most commonly held viewpoint in child psychopathology, at least by the public, and by many in the profession.
- DH: How do you explain the fact that in the United States more kids are being treated for ADHD, there is more research, but also the controversy has been much larger than in Europe?
- The reason for the relatively elevated prevalence of treatment and diag-RK: nosis in the US may be akin to the situation that had previously existed for manic depressive illness, which was diagnosed much more frequently in the UK than in the States. In the US, schizophrenia was the rule. There was a vogue for seeing it under every rock. We even had the diagnosis of pseudo-neurotic schizophrenia for patients who had no history of psychosis. In the UK, this was not the case. Schizophrenia was clearly distinguished from bipolar disorder, and psychiatrists used lithium in bipolar disorder, whereas they did not in the US. The US psychiatrists, simply put, were off the mark. Having an effective treatment for bipolar disorder, such as lithium, eventually called attention to the diagnosis. It paid off to recognize manic depressive illness, to make differential diagnoses, and easier to abandon the view that psychosis and personality disorganization were invariably linked to schizophrenia. Not every very disturbed, psychotic patient was schizophrenic. I think the same situation has occurred in ADHD. In the US, we have a wonderful treatment for it, so it makes sense to try and recognize the disorder. But it's a treatment the UK has never accepted. As a result, there is no specific intervention for the disorder. If there is no specific intervention for an illness, one is not likely to attempt to ferret it out. If treatment is

the same for all behavior problems, there is little point in trying to sort them out. Until the treatment situation changes in the UK, it is likely that the diagnosis will continue to be ignored. Now why has it caught on here? It's because the work was done here. That's a real issue. You know the expression NIH: "Not Invented Here"? Unfortunately I'm afraid there are still some territorial attitudes. The work has "Made in the USA" stamped all over it. If there had been a body of work done in the UK, the situation might be quite different. Historically there has been very little treatment research in child psychiatry in the UK.

- DH: Absolutely. Why?
- RK: I think the Maudsley has been a major influence in child psychiatry, and a wonderful one. It has made major contributions, certainly in diagnosis, in identifying relevant social factors through seminal epidemiological and longitudinal studies, in debunking much myth. I could go on and on about the incredibly important work done at the Maudsley, and elsewhere in the UK as well. But treatment seems to have been devalued. I do not know why. I think you would have to ask the leaders at the Maudsley who have shaped child psychiatry research. Somehow, treatment research is low on the status totem pole.
- DH: Why is that?
- RK: I have no idea. Psychopharmacology has a major influence in shaping views in the past 30 years in adult psychiatry. Theories of neurobiology have all emanated from psychopharmacology. And yet, in the UK, treatment in child psychiatry largely has been ignored. When it is done, it seems to be reluctantly. How do you explain it?
- DH: I think you're right about the Maudsley. For whatever reason and it isn't only in child psychiatry, they have not been enthusiastic about advocating the use of any kind of treatment. Their influence in this regard in the child field has been even more pervasive. It's curious. So how do you see the field going from here? Is it generally accepted now that it's okay to treat children with pills in the US or are there wars that still need to be fought?
- RK: I don't want to represent American child psychiatry because I live in a special world, in a psychiatry department that is dedicated to research, and where the influence of biological psychiatry is enormous. Perhaps I have an over optimistic view of where the field is going.
- DH: Where is it going?
- RK: I think the effect of biology is enormous. Genetic studies are taking off and there's very serious attention paid to the possibility of genetic transmission of various childhood disorders. Whether that will pay off or not in terms of practical consequences, I don't know. But there's the

conviction that it has to. The numerous psychosocial treatments for hyperactivity that have been studied have been so disappointing, that I cannot imagine further research in this area, unless someone comes up with a very innovative plan. But I have been wrong before, and I may be wrong again. We need longer acting medications for hyperactive children. We know very little about proper psychopharmacology of most childhood disorders. The studies are minute, there's very little on anxiety disorders and depression. Here, I hope there will be changes in the field. I view adolescent depression as a heterogeneous diagnosis; that's not a generally shared view and there has been very little attempt to distinguish clinical entities within the class of adolescent depression. I also hope that the next DSM will bring greater precision to clinical terminology. Child psychiatry has become embroiled in controversies that seem due, in part, to the varied usage of diagnostic terms. Clinical features, such as grandiosity, mean different things to different people. A case in point is a current debate about the diagnosis of bipolar or manic-depressive disorder, in children. Some claim that it's highly prevalent and that it is misdiagnosed as ADHD. Others, including ourselves, believe that the clinical concepts such as grandiosity are being applied in idiosyncratic ways, leading to diagnostic confusion. The future DSM will, I hope, minimize interpretational variance. We have limited knowledge in child psychopharmacology. We will of course expand that body of knowledge. The movement is towards multisite studies. Right now almost everything that is done has many participating sites, each contributing a few cases or a proportion of the study. I think that is fine for testing a treatment hypothesis, but it has limited value fostering astute observations and hypotheses that lead to further discovery. There is something missing from these trials; the principal investigator does not have much input and often such trials do not attract top clinicians to assume hands on care of patients. That's a huge problem for the whole field. Increasingly, very few leading people run trials and get a good feel for what is happening clinically.

- DH: It's probably worthwhile to point out that one of the good things in the child field is that drug trials to date have not been linked to industry, whereas the adult field is largely controlled by industry. Perhaps the findings look more unbiased and independent than work in the adult field.
- RK: I agree. That's true. Until recently, industry has not been particularly interested in children. It's probably due to the fact that, in the United States, liability issues with children take on enormous proportions. However, there are now pressures from regulatory agencies to study

children; another thing that does not hurt is that it has become good business, whereas it was not in the past. Childhood is a transient state with a relatively small temporal window for treatment, and medication in children was very unpopular. As a result, the market value of a psychotropic product in children was not very favorable. That has changed with the recognition that there are very large numbers of children with psychiatric disorders. The challenge for child psychiatry is to develop a cadre of experts who can train young people. How do you initiate that process? That's a major issue; these medications are used widely but poorly.

- DH: What's going to happen to the opposition? Outside each APA meeting these days, you have the Church of Scientology and they always have their posters about the use of methylphenidate for hyperactivity. Is it going to fade away or are these forces going to be with us for some time?
- RK: I do not know what they have in mind or what their plans are. I do not know how important it is to their integrity or finances to keep picking on psychiatry. It is not clear to me why they have opted to do so. It seems obvious that methylphenidate is an easy target because it is used so widely. There is no point in rallying support to attack a practice that's relatively esoteric or unusual; the methylphenidate issue is understood by everybody. Will that change? I doubt it. Right now in the States we're going through a difficult period; it has become more difficult to do studies with children. It's not easy to identify what fuels these media hyped fluctuations. Our society is extremely polarized and it is not likely that these controversies will end until we can demonstrate objectively that we are dealing with diseases. Short of that, I think there will always be those who have unreasoned, passionate objections to rational medical treatment. My hope for the future is not too different from anybody else's. We still have a long way to go for diagnosis to have the precision necessary to optimize treatment. Practice is vastly superior to the time when I started in the field, though it is hardly terrific, but the changes are almost unbelievable. Better knowledge of the longitudinal course of various childhood disorders is needed; that is very poorly mapped out. The burgeoning of brain scans demonstrating abnormalities in many psychiatric conditions has been ideologically helpful in supporting the view that the brain has something to do with psychopathology, and in weakening the position that disorders are in the eyes of the beholder. However, the treatment payoff is not imminent. At the same time, with growing specificity, child psychiatry will be more similar to general medicine diagnostically. That should translate itself into better treatments,

and better understanding of the pathological mechanisms that are corrected with treatment. Much of what we do is still empirical. It's certainly better than it was, but it's a far cry from the precision we hope for.

- DH: Is there any particular area you would like to discuss further?
- RK: I don't think so, David. I don't think there is anything major that has been left unsaid.
- DH: Great. OK
- RK: Thank you very much.

## DAVID J. KUPFER

## Interviewed by Alan F. Schatzberg San Juan, Puerto Rico, December, 1996

- AS: I'm Alan Schatzberg and with me is Doctor David Kupfer.\* David, how long have you been a member of the ACNP?
- DK: I became a member back in 1975. The first meeting I attended, which I was very struck with, was in 1970. We are talking about almost twenty six years ago and there was a lot of discussion about good old fashioned neurotransmitters. It was the era when drugs were relatively new and we were seeing fascinating things happening to patients.
- AS: What were the hot topics in the early seventies?
- DK: Before I moved to the National Institute of Mental Health for a clinical associate position around 1967 through 1969 I was involved in a biological training program; there were weekly lectures by Daniel X. Freedman, George Aghajanian and Floyd Bloom and a lot of the issues brought up were with norepinephrine, epinephrine, and serotonin. All of us were beginning to feel comfortable using the antidepressants.
- AS: The tricyclics?
- DK: The tricyclic antidepressants, and lithium. We wanted to find out why these drugs were working and that began the long trek into biological psychiatry, examining what tools we could use to find this out, although there was very little available relatively speaking.
- AS: Urinary MHPG and platelet MAO were the big ones and your studies about sleep physiology.
- DK: That was pretty much it. We were able to do the first lumbar punctures at NIMH to look at cerebrospinal fluid. And in those days we were looking at some of the metabolites of our favorite transmitters.
- AS: In the early days, when you first started coming, were there presentations on clinical trials or was that from the start more at meetings like NCDEU?
- DK: There were some because I was involved in a few of those presentations. It was more of a balanced meeting of the kind we have recently to get back to. Part of that had to do with the fact that we didn't have all the neuroimaging tools, the neuroscience breakthroughs in genetics and the other exciting things that are going on today.
- AS: Mostly about antidepressants?
- DK: Yes, but the balance was contributed by the fact we were still learning so much about how these drugs worked in clinical trials and the extent to which they worked. I remember, in the 1980s, we started talking

<sup>\*</sup> David J. Kupfer was born in New York, New York in 1941.

about maintenance treatment and that was a brand new thing. Outside of lithium there had been nothing very much around maintenance until we began to get all the trials in schizophrenia. That led to recognizing not just rapid changes in neurotransmitters, but more slowly acting changes. That then began to inform some of the basic neuroscience research.

- AS: Thinking back I remember a conversation with Gerry Klerman in 1975. I was a young instructor and we had been studying depressed people with Joe Schildkraut in drug free studies, looking at catecholamine turnover. The thing that struck me was the number of patients who seemed to meet criteria for endogenous depression, who had been depressed for a long time. I remember talking to Gerry about chronic depression. Gerry seemed startled when I pointed out that when you ran a clinic like ours you saw a lot of patients with either recurring episodes or more chronically ill than we learned of in text books. The whole field has changed to a very different concept about these major diseases.
- DK: You are absolutely right; when we began our careers we thought of schizophrenia as being chronic but everything related to either manic depressive disease or depressive illness was episodic with nothing in between. Obviously there was a lot in between and our neurochemical or biological theories began to change as we realized that through treatment studies and longitudinal follow up. There had been follow up studies before drug treatments were available, but now we began them with drug treatments. That changed what we saw clinically and helped redefine the science; ultimately it extended more broadly because we began thinking about anxiety disorders, obsessive compulsive disorders, diseases of aging and childhood disorders. When I was fortunate to win the Efron Prize in 1979 most of the concentration was still in the mid-adult period. We were still operating under the sense that even though things looked complicated we were very hopeful they would have simple solutions with relatively simple tools. As we entered 1980 and the decade after, we began realizing that the issues were much more complex. There was more heterogeneity than we had previously thought and the treatments were not as effective as we believed they were in the sixties and seventies. That began a tremendous set of developments we are beginning to see in the nineties with new generations of drugs and a whole host of neuroscience tools.
- AS: When you think back to the treatment of depression before 1988, before the first selective serotonin reuptake inhibitor (SSRI) came on the market, do you now view that as a period of tremendous limitations in terms in our ability to treat patients?

- DK: We were fortunate enough to begin working with the SSRIs before then, in about 1982. I was very interested in the effects of these drugs on sleep, both in terms of normal subjects and depressed patients. We used fluvoxamine and found it to be a very effective clinical drug and that the effects on sleep were not different from the tricyclics. So we assumed, somewhat naively, that these drugs would work in inpatients and outpatients. We were less concerned about the side effect profile or adherence issues although that has had a lot to do with the relative success of the new generation of SSRIs. I have always felt that the efficacy would not be better than the older drugs, but that they would all be about the same. I mean, they all had the same effects on REM sleep. Perhaps, their effects on sleep continuity were a little different, as we found out much later. But, I was prepared even in the early eighties that this would, perhaps, change the way we thought about depression. At the same time, this was still the era when we hadn't even had the report of the first collaborative study of maintenance tricyclics in long term treatment. The NIMH collaborative study was finished in 1982, but there was no report until 1984. We presented a lot of the material at the ACNP and that validated using tricyclics for long term treatment, certainly in the United States. But, that didn't tell us anything more about dosages, the use of combined treatment or of other modalities for maintenance.
- AS: What thoughts do you have about the notion of dose? We have gone from low dose under prescribing in the late sixties to realizing these are serious illnesses and need more aggressive management.
- DK: This is the kind of topic where an organization like the ACNP can be a terrific forum to present clinical information and also basic neuroscience findings. We were all taught you could be aggressive in acute depression but, once things were under control, you did your best to find the minimum dose. This is what we were taught and what we practiced. The only problem was that it was wrong and, later on, we began to find out that the dose that got you better would keep you better, a notion we didn't embrace until the late eighties. A full dose strategy for long term was not only applicable but gave you a much better outcome. You then put more of a burden on convincing the physician, patient and family that it was good to stay on a high dose. So you had to have the family clear about what side effect profile was acceptable so it would not interfere with adherence or the therapeutic alliance. When that is the case we see a positive attitude to long term treatment. To this date, we don't have a total handle on why these drugs work in the long run and what risks we incur. Some of the exciting newer tools with receptors and neuroimaging may help us. A whole new generation of researchers

in pharmacology is beginning to explain, from a metabolic and genetic point of view, why individuals are different and what kinds of metabolic changes may be genetically determined. This is the kind of information we need clinically that is going to be derived from basic science.

- AS: What about the ACNP's influence on clinical practice? You raise these issues about the presentations; that this is a somewhat elite professional group. Do you think the materials that get generated or presented here have an influence on the field?
- DK: That's an interesting and not a simple question. There have been times we have not taken our responsibility to heart. Clinicians can have a very robust effect on dissemination of knowledge which has implications for clinical practice. We have sometimes not been conscious of our need to do that and other organizations have assumed that responsibility. Right now we are in a cycle where we have more clinicians on the ACNP council than in a long time; hence there is a great deal of emphasis on dissemination through education. The positive influence of the pharmaceutical industry for the College has been to present much more information than can be readily comprehended by the broader public or even a young basic scientist or clinician investigator.
- AS: What about the role of the ACNP in professional identity? What has the college meant to you as an investigator, as a chair, as a professor?
- This may go back to the feeling I had in 1975 when elected to a very DK: prestigious organization to which all of my intellectual heroes belonged; people who have mentored me, both close and afar. That never really has changed. I have felt that way through the early eighties. Translational science is something departments of psychiatry should be all about. They should be, at one level, departments of clinical neuroscience and behavior. Sometimes, there are appropriate criticisms we don't take into account enough of the behavioral sciences in what goes on at ACNP. That is always the kind of dialectic that is in play. But, if one were to ask where is the society that most fits the academic mission of a department of psychiatry, certainly that would not be the ACNP. But, in many ways, it does embrace a lot of that academic mission. It has retained a prestigious value that is well justified and, with respect to other societies, it has been a jewel. I have had some wonderful experiences with other organizations, some of which I have been privileged to be an officer and even president of. But, I must say that being a fellow of the ACNP, having served on the council for three years in the eighties and, then, having the honor of becoming the President of the organization is a fabulous experience. I don't know of a single organization that has had as much impact on my thinking about the linkages that a

department of psychiatry should have with other scientific enterprises. That has certainly had an impact on the intellectual development of Western Psychiatric Institute and an influence on what clinical research centers funded by NIMH need to do. It has influenced my own research career, both in terms of the sleep and biological rhythm side, as well as the treatment and long term understanding of mood disorders.

- AS: I have the same impression. The ACNP, of all professional organization's I belong to, has had the greatest impact on my sense of belonging and of professional identity, in terms of both investigation and administration. Do you think the society is too small and a little too elitist? The young people coming up and the young faculty really enjoy the meeting. They all strive to become members and it's something they think is going to be important. As you said, it's a small jewel, but are there downsides to that?
- DK: I don't think so. If we got much bigger we would lose our ability to invite people to present and to make sure fresh ideas come in; we might also lose the specialists. We probably range between eleven to fourteen hundred people at the meeting. If we get much larger we become akin to a small American Psychiatric Association meeting. We would lose any opportunity of giving traveling fellowships for young people or any sense that young people can come to a meeting and find somebody they have read and would like to talk to. We are at a threshold where, if we increase the number of members, I believe we would have to decrease, in proportion, the number that can attend the meeting. Once you go much above one thousand people, you have a very different meeting and, since it is almost a week long, something would be lost. Having said that we come to something else we have grappled with; is the society simply a meeting that happens annually or an organization that operates throughout the year? This is something the whole college has wrestled with on an up and down basis, depending on whether the issue had to do with advocacy or with what we think scientifically, needs to happen locally. Or what is our obligation with respect to education throughout the year as much as the annual meeting, and would that come through CME activities, which, is something we all work with? Even the origin and the development of a journal was a response to how does one keep the identity of the college and disseminate information.
- AS: What about the journal; do you think it has been a success and is it doing what you wanted it to do?
- DK: One of the issues is what is going to be the newer forms of communication. Are they going to replace, not only the telephone, but all the books we have on our shelves, let alone all the journals? The founding

of our Journal was based on our expectation it would allow interaction between clinical and basic activity in the fields of pharmacology and neuropsychopharmacology. That would represent what the annual meeting was all about as well as drawing ideas from the field. The jury is still out as to whether we have achieved what we were hoping. Over time, and it may be relatively soon, some kind of connection may develop between the Journal and our other educational activities such as the CD-ROM and web pages we are setting up. One of the things we haven't talked about is the Generation of Progress series.

- AS: I was going to segue into that.
- These began in the 1970s and we have now gone through four genera-SK: tions of progress in multi-author volumes. It is impressive how many advances there have been in the last forty years. They reflect a kaleidoscope of change in both clinical and basic science areas. I have been a contributor to these volumes and now, at the request of the ACNP Council, have edited the fourth generation volume with Floyd Bloom who represents basic science. This has been a tremendous education for me in terms of working with people who are both members and non-members of the College. One of the most interesting things has been how receptive the majority of the people were, whether they were members or not, to contribute their time and energy. It turned out to be a superb volume and has been one of the high points of my involvement with the College, only exceeded by the honor of being President. And we have been able to get a CD ROM version which means you don't have to go to the gym in order to carry a two thousand page book. This allows you to have a lot more flexibility in making slides from the material and getting all the references. The information in the book will look fairly primitive in twenty four months to thirty six months which says something about the excitement I was, eluding to earlier, concerning more advanced, sophisticated communication and ways to educate. It is going to put an increasing burden on the College to assume that responsibility, particularly in the area of integrating clinical and basic science.
- AS: The fourth generation has over two hundred chapters?
- DK: I think it was one hundred and seventy seven or something like that.
- AS: That's a mammoth book and some of us have been involved with trying to get updates for the new CD ROM version. It has become an encyclopedia of the interface between clinical and basic neuropsychopharmacology. There are books that are more clinical or basic but nothing that works in a comprehensive way like the new generation books. You and Floyd did a remarkable job getting out the materials in a relatively quick

period given the number of contributors. Obviously, people felt invested in it or scared dealing with the editors.

- DK: We did use threats and it was effective!
- AS: I was at another editorial board meeting where they had the so called "impact" factors, and I was struck by the fact that *Neuropsychopharmacology* was fifth in the ranking. *Archives of General Psychiatry* was first and, then, the *American Journal of Psychiatry*. I think it has moved up and we are getting more basic papers. It is starting to have the impact you and a number of people hoped for originally.
- DK: We had the wisdom to recognize that the clinical and basic fields were growing separately and the Journal would benefit from having an editor in each area who was also knowledgeable about the other. We took two wonderful people, who were very much involved in the College, Herb Meltzer on the clinical side and Roland Ciaranello on the basic side. After Ronald's death Chris Fibiger took over and has done a terrific job. The increase in the impact factor suggests this integration under two co-editors is successful. I sometimes feel that we need to do something more on the clinical side. Don Robinson, Bob Prien and Jerry Levine recently edited a book that raised issues around clinical trials and those questions remain to be resolved. That is going to be an interesting debate that will continue for the next five to ten years. Another area worth chatting about is advocacy. When I was first on the council we met guarterly and at least two of those meetings were in Washington. Part because one of the councilor's responsibilies was to find out what was going on in Congress and do some diplomacy with respect to a science agenda. I remember very vividly that the expectations for council members was to go meet with the White House staff, as well as representatives or staffers of representatives who controlled the appropriations, both in the House and in the Senate. That was a strong activity. We don't do that anymore; however we do other things. One is that the College recognized we had some natural liaisons, including with patient and family advocacy groups. In the last couple of years we have had plenary sessions involving them; these interactions have been good for the College and we now have a strong advocacy committee. The other activity that I should mention was that the council would have fifty to a hundred members of ACNP involved what I call science politics both locally as well as nationally. That meant we needed to get information and even some modeling to others about what we do as an organization and at the annual meeting. I remember several years ago conducting a kind of lobbying one-on-one for about thirty to thirty five college

members. Other organizations, such as the Society of Neuroscience, are working in conjunction with the American Psychiatric Association.

- AS: Right, the so-called academic consortium.
- DK: The academic consortium advocacy groups are working with us to soften the fact that the ACNP once had to be the only elite scientific voice. I don't think we have that single role anymore. I feel that historically, when one looks at what we were doing in the mid nineteen eighties, what we are doing now is much better. On the other hand, I feel sometimes we get complacent and think other organizations will take care of it with their hotlines, will get in touch with representatives and not make use of the unique characteristics of the scientists that belong to this organization. We need to be public advocates, not just private advocates for the kind of science we stand for.
- AS: Earlier, you mentioned some mentors within the college and thinking back, which members had the greatest impact in terms of your career development?
- DK: It's hard to separate out members of ACNP who also wore other hats. As I look back a lot of my formative experience was at Yale. My first residency supervisor was Gerry Klerman who was one of the first people who get interested me in the fact that there was a world that could come together between psychotherapy or psychosocial research and psychopharmacology. Tom Detre has been a mentor all along. He actually joined the College a few years after I did, and represented, not so much a practicing scientist, but somebody who was able to link what we were doing in the clinical world with health policy to provide a broader view of where psychiatry and the ACNP fit in the whole array of medicine. We very briefly had a Pittsburgh monopoly on the Presidency, when I succeeded him.
- AS: Back to back!
- DK: Everybody was worried we were establishing a dynasty! But, there were other people who were very influential. I would have to say that Floyd Bloom in terms of his impact on what I began learning about biological psychiatry in the late nineteen sixties. Later on, the ACNP allowed me to develop a relationship with him, where he was the more basic scientist so we had a fair trade that led to a number of foundation activities that continue to this date. There have been other individuals within the ACNP, certainly my relationship to Dan Freedman, another president of the organization.
- AS: Another Yale graduate.
- DK: And somebody I met in medical school who put a real stamp on the way the ACNP has been shaped over the years and not just in terms of his

role as editor of the *Archives of General Psychiatry.* Some of the think pieces in the Archives were generated by the annual meetings and I had the opportunity to write a couple of things with Dan that stimulated symposia or panels at the ACNP. The ACNP has also been a place where a number of colleagues from abroad have become corresponding foreign members who had a significant impact on my thinking. Arvid Carlsson is somebody that comes to mind and there were a number of other distinguished colleagues able to come here almost every year. I have missed very few meetings. What's interesting about mentors is that when we enter middle age our mentors become members of the College.

- AS: Yes!
- DK: I am excited as they become participants of the ACNP. That's why I feel, as you can jera from my voice as positive about the intellectual fervor that continues to take place. That comes back to our earlier discussion which is that ACNP can't get too big or we will lose that intimacy.
- AS: Let's talk about the social aspects of the ACNP. What kinds of things come to mind, either here, in Hawaii, or occasionally in Washington?
- DK: We were in Washington, I guess, ten years ago?
- AS: Right.
- DK: We were there for the twenty fifth anniversary and this is the thirty fifth anniversary so we shouldn't forget it's been ten years already since Washington. When I first came to an ACNP meeting, I am almost positive it was 1970; I was told this was a good meeting because it was a sunny meeting that took place in winter. The allure of being able to be outside for five to seven days has a lot to do with not simply social events but the exchange of intellectual ideas. If one were to walk along the sand and record the conversations they are often about science. Young and promising faculty members can interact with senior people, giving them a sense of what it would be like to work with some of them and vice versa. There is no question that the ACNP always was, and continues to be, a job market as long as there continue to be jobs.

One of the issues the ACNP hasn't tackled yet is the future of the academic departments of psychiatry, neurology and clinical neuroscience. That is something for us to put on the agenda over the next couple of years. I don't think we should interfere with the activities going on now. Young people are coming to meetings looking for jobs that do exist, involving advanced fellowships, whether they be psychiatrists or post docs. That is one of the positive sides of having this kind of social environment. The meetings are also a place for old friends to get together, and I don't want to underestimate that, but it's not the only place where that happens. What is special about this meeting is more interaction between young and older individuals.

- DK: Something we haven't talked about is the poster session, which becomes another way of having a social and science interaction. You may or may not remember there was considerable debate about what would happen if we had a poster session. Well, here we are with probably a total of three hundred and eighty posters; the session is going to be taking place on Monday, Tuesday, and Wednesday.
- AS: I think the poster session has become the most exciting part of the meeting in some ways.
- DK: It's exciting in the sense of new and fresh data from young people who are not going to get on the panels. The one thing I am concerned about remains making sure the panels and the poster sessions remain places where we put forth our newest ideas. There has always been a great deal of pressure to have symposia for a day or two before or after the meeting. That has been resisted, by and large. There are some in terms of other scientific societies, or small groups that plan clinical trials together. There has been no real discussion about whether this has gone overboard. There are probably four or five journal board meetings down here, certainly more than anywhere else except the American Psychiatric Association, as well as other societies doing their business. That may very well come up for discussion but is a little harder to legislate. Our plates can be easily filled with things that have nothing to do with the science program. If we don't have time for science, free time to discuss intellectual matters and fun things that come out of these we will become too much like other meetings and that is a concern. If it's not already under the review of the program committee, it is a concern for the whole College.
- AS: What about the influence of pharmaceutical companies on the College? What kinds of thoughts do you have in 1996 and moving forward?
- DK: I think the College has struck a wonderful balance at this point; there is no question the pharmaceutical industry has been extremely generous in helping us with unrestricted educational grants. I think of the teaching day, I think of the president's lecture, and I think of other advantages we have to bring people in for special lectures and other events that have been extremely helpful. I think some of the things like newsletters and some of the CME work has been very helpful. They recognize, just as we do, that this exposure to a more high class way of thinking about neuropsychopharmacology can help create a better educated public and a set of policy makers regarding the positive aspects of what is going on in the field. Are there risks? There are certainly risks, but

these can be minimized as long as we control the educational content and avoid special sessions that are auctioned off, the way it sometimes happens in other societies. That is the best defense, not only for ourselves, but for the pharmaceutical industry. They gain much more if this partnership is a very open one and the scientific content is left to the College to determine. There are going to be not easy times ahead and unless these partnerships continue to be present between the pharmaceutical industry and the college, the various advocacy groups and the college and with other organizations there will be financial trouble. Many of us favor putting our other hats on, which is, it would be nice to balance the budget. On the other hand, the closer you come to balancing the budget the less discretionary income will be present for science. And that will begin to impact on what the college can do intellectually.

- AS: Final thoughts about the future of neuropsychopharmacology, psychopharmacology and the ACNP?
- DK: The future of all three is tied together. When Floyd and I were putting together what would be the new developments there were five or six chapters at the end of the book. Not surprisingly, there were chapters that ranged from ethical treatment issues when we know more about the genetics of disorders, to what will happen in terms of designer drug strategies as we take advantage of new insights and the techniques. Those are the kind of issues that are going to drive the College over the next five or ten years. We need to have people join the college, who have expertise in those areas, and we have to be aware that it is not going to be a straight shot. Some of the things that have come up in the last couple of years that the College and I have wrestled with, in my time as president, is this whole issue about informed consent, the use of placebo and what will we be able to do in future clinical trials. We will have to face what to do in the area of neuropsychopharmacology and genetic testing. What will be the coupling between the genetic origins of diseases and the design of certain interventions? How will we deal with that and what will be the interdisciplinary expertise necessary? These issues may influence not only the kind of membership, but what kind of training and what kind of educational responsibilities the college needs to undertake in the next five to ten years. We won't be able to hide our head in the sand and I don't think we should, but it's exciting.
- AS: Do you think the College in fifteen or twenty years will be doing more with gene therapy and those kinds of things?
- DK: I think so. The toolbox will be quite full. One of the things the college will have to deal with is what tools and how those tools are being used. When the College was founded in the early 1960s people said,

my God look at these drugs and how they change behavior. Now we are entering a whole new revolution or evolution, which is going to influence dramatically what we will do over the next fifteen to twenty years. One only has to look at what is going on in some of the medical diseases like breast cancer. We will be dealing with the whole neuropsychiatric spectrum of diseases and that will influence both ethical issues and behavioral issues. We will be much more represented in childhood and adolescent areas around issues of high risk and prevention. These areas I see as a College, and a field, we are going to be grappling with. But, it should be fun!

- AS: Any other thoughts as we come down to the end of this tape?
- DK: As we have chatted, I have felt fortunate to have been part of what's happened in neuropsychopharmacology in the last twenty years. My membership in the ACNP is not only symbolic but a real treat to be so actively involved with the life of the College. All I would hope for in the next twenty years is that all of us be lucky enough to remain healthy and intellectually pushed by our young colleagues to be a part of a similar chain of events.
- AS: Speaking as a member of the College and a member of the council, we appreciate all that you have done for the college and for psychiatry. Thank you.
- DK: Well, thank you very much.
- AS: Thank you.

## SARAH HOLLINGSWORTH LISANBY\*

## Interviewed by Andrea Tone Paris, France, July 5. 2004

- AT: Thank you for agreeing to the interview. Why don't you start by telling us how you got interested in psychiatry, what your background is, and why you chose this specific field?
- SL: I first got interested in the field of brain science in high school. I went to a private girls' school and we had fairly advanced psychology classes. One class included field-trips to pre-schools which brought the theories of child development we were reading about to life by having us make direct observations of child behavior. During high school, growing up in the Washington, DC area, I was always working in labs at the National Institute of Health and at military research facilities, because my father was in the Navy. One lab at Maryland University worked on the anatomy of the human brain. I remember coming home in the summer, after I had actually held a human brain in my hand and how exciting that was. So, from early on, I was interested in the brain and the mind and the relationships between the two. When I went to college, I majored in Psychology and Math, because I also had very strong quantitative skills. It was during that time I began to learn the differences between psychology and psychiatry. I started to volunteer in hospital settings to learn about serious mental illness and the different ways to help people if I were a medical doctor as opposed to taking the PhD route.
- AT: What kind of problems did you encounter in serious mental illness when you were working in the hospital at the time?
- SL: I was volunteering at John Umstead's hospital in Butner, North Carolina. That's a state hospital, and I was assisting on one of those classic backwards where the patients were from sixty to eighty years old or even older and had been there for decades, most with chronic schizophrenia. As a college student, to read in a textbook about schizophrenia is one thing, but, to actually meet patients, interact with them, including catatonic patients with schizophrenia is another. I became aware of how seriously the thought process became disordered and I was awfully disturbed by the lack of a cure. I became aware that mental illness can be really serious and can destroy your life and your family members' lives. I realized there was a great need for scientific research to find better treatments and ways to manage them. That's what got me hooked. Now, professionally, I have specialized in depression, not schizophrenia, but these were my earliest encounters that taught me that mental

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illness was a serious medical disorder and got me interested in applying science to develop better treatments.

- AT: I'm fascinated by the fact that you went to an all girls' high school. I taught for many years at Georgia Tech, which is devoted to math and engineering. One of the ongoing questions was why don't we have more women in math and in engineering. Do you think there's anything to be said for all girls' schools to encourage women intellectually?
- SL: Absolutely. I'm a very strong believer in single sex education as an alternative option for people. It's not for everyone, but, for me it really was formative. In high school my role models were the female teachers and the Dean of the school. I came out of that process with the idea that I could study anything. I never encountered the concept of sexism until I went to college and, then, medical school. It was a very sheltered environment but I felt that shelter, during those formative years, was crucial. Also my parents always encouraged me to study whatever I was good at; I seemed to be good at math from an early age and they always encouraged that. They didn't give me that Barbie which, when you pull the cord, says "I hate math".
- AT: Tell about your experience in medical school.
- SL: I went to Duke Medical School, which was a wonderful experience. One of the nice things was you had the entire third year for research. To be able to devote a whole year to research as a medical student was just fantastic. I credit that with the path I've taken in psychiatry to go into academic psychiatry and research full time. That early experience got me really excited about designing experiments and using them to test concepts that might ultimately be used for clinical treatment. During that year I worked in the laboratory of Jay Weiss, studying how stress can provide a nice illustration of the mind-body interaction. That really got me excited about research. I entered medical school knowing that I wanted to be a psychiatrist but during the clinical rotations I toyed with going into something like surgery or urology. I like doing things with my hands and it turned out I happened to be good at tying one handed knots with sutures, but I always ended up coming back to my first passion, psychiatry.
- AT: How unusual was it for people who enter medical school knowing what specialty they'd embrace and how unusual was it for someone to embrace psychiatry, early on?
- SL: Typically, people who go into psychiatry know that from the beginning. I think psychiatry and surgery are the two specialties that people pretty much decide before they get into medical school; they might see something that would deter them or attract them more, and they might

change, but most of my colleagues that I've asked about this knew early on that they wanted to go into psychiatry. I think that there is a pressure in some schools not to declare your major if it's psychiatry, because of a fear that it would be looked down on. That sentiment was present at Duke to some degree at the time I was doing my training. In my surgery rotation I was warned that on the first day the Chair goes around and asks each student what they want to go into. The myth was that those that say psychiatry got low grades, so, typical of my personality, I said, "I want to be a psychiatrist". I just wanted to put it on the table because I wasn't ashamed by it. I thought it would even be more challenging than surgery and I would be happy to explain to anyone who was interested to know why. I ended up getting honors in surgery, proving that you could still do well in that rotation without pretending you wanted to be a surgeon.

- AT: I didn't realize there was that kind of pecking order within the medical system.
- SL: Oh, yes. I was in medical school from 1987 to 1991. During that time, some people doubted psychiatry and there was an attitude that you go into it because you're not smart enough to go into other fields. In fact, one of my medical attending physicians gave me a backhanded compliment. He wanted me to go into medicine, and said, "Why are you going into psychiatry? You don't have to do that".
- AT: So, you committed to psychiatry. Was it already clear that you would devote yourself to research and what made you gravitate to the kind of research you currently do?
- SL: While I was in residency at Duke, there were wonderful academic psychiatrists and researchers, who served as role models. One of those was Ranga Krishnan, who is now the Chair at Duke. I started when I was a medical student and continued as a resident, doing imaging research in depression with him. But probably the most influence I can trace it back to during that period is working with convulsive therapy (ECT) and devising new ways to do treatment. I remember vividly some of the first patients. One of them had catatonia, so she was mute, had stopped eating, was just wasting away and was going to die from her depression, it was so severe. She got ECT and the afternoon of her first treatment, she started talking, and I thought this is a miracle. It took one more treatment, but the improvement was so rapid I thought, this is a fantastic treatment, I've got to learn about this. So, I got really interested in ECT, reading about how it works and trying to learn about different aspects of the procedure. My teachers at that time were Rich Weiner and Andy Krystal, both ECT researchers at Duke. When I was
finishing my residency, looking for what to do afterwards, I was, also, this might seem strange, interested in psychotherapy and psychoanalysis. I had won a Fellowship from the Psychoanalytic Institute to go to the winter meetings in New York, at the Waldorf Astoria. I went to that in December of my final year of residency and while in New York, decided to see what other Fellowships were available. So, I interviewed for a Fellowship at Columbia, where Harold Sackeim was and still is. He's a very well known researcher in the field of ECT, so I interviewed for a Fellowship at Columbia and I became connected to him; as a mentor and he was fantastic. And, so, the opportunity to do the Fellowship with him was just fantastic. When I interviewed for the Fellowship, he said, "There's this new procedure called transcranial magnetic stimulation; we aren't doing it here, but we need to and I want you to look into it and set up a transcranial magnetic stimulation program so we can see if this could be an alternative to ECT".

- AT: You said that you developed an interest in ECT at the same time that you had advanced training in analysis and it does seem odd. I have done interviews with dozens of people who say they are doing biological psychiatry out of the critique of analysis. You found a way to reconcile the two positions.
- Just to clarify, I'm not an analyst but, during my residency, I did receive SL: training in psychodynamically oriented psychotherapy and I had a lot of psychotherapy patients. My supervisors on these cases were analysts. I was considering analytic training after residency. Some people do choose biological psychiatry because they don't believe in the therapy approaches. But I believe in both approaches. I'm kind of an optimist. I believe in what works and I think that we should stay with what works, because it's going to teach us something. Psychoanalysis and psychotherapy are very important tools for certain conditions. To be specific, for the severely schizophrenic patients, I had my first encounters with early in my training, psychoanalysis was not the right treatment but the neuroleptics are. Certain psychotherapies are helpful in major depression and data has shown that therapy combined with medication is synergistic; it's more effective than either treatment by itself. Data has also shown that certain psychotherapies, just like medication, induce similar changes in the brain, as visualized by functional brain imaging. Whether you are treating a disorder by medication circulating in the blood stream and being deposited in the brain, or whether you are treating the brain using behavioral approaches, the substrate is still in the brain. So, I don't feel that it's "either/or". The final common pathway, the site of action, is biological but using psychotherapeutic tools, I think, is

very elegant. If that works, isn't it fantastic? We shouldn't be surprised that certain behavioral experiences help disorders, because we know they also cause disorders. Take for example post traumatic stress disorder, which occurs because something happens to you, behaviorally. You experience the trauma and that's a psychological experience that changes your brain and causes a significant psychiatric illness. That can be treated with medication or therapy, or both. This gives you some sense of my conceptual framework. I believe in the biopsychosocial model, in which biological, psychological and sociological factors are all important. But, if you're going to do research, you need to specialize and I made the decision that, even though I was doing therapy, I needed to specialize in biological research in order to have a handle on the techniques and to make a contribution. I also believe that when we treat our patients we should use whatever tool is appropriate for the patient, not just the tool we're the fondest of. The bottom line is what's in the patients' best interest, whether it fits with your theory or not.

- AT: You mentioned that your mentor encouraged you to develop an alternative to ECT?
- SL: Yes, I was looking for an alternative. While ECT is the most effective treatment for major depression and for some other serious disorders, it does have drawbacks and these include the side effects, in particular amnesia, which is of most concern to our patients. The application of electricity and the induction of a seizure change the brain and many of those changes are essential to a response, but may contribute to side effects. There was an old theory that ECT worked because it caused patients to forgot why they were depressed, but it turns out not to be the case. If you look at whether memory loss correlates with an anti-depressant response, it doesn't. So, there is an opportunity to improve convulsive therapy by trying to figure out what is the essential component, enhance that, and reduce the non-essential component, which may be a way of retaining the efficacy of ECT without the side effects.
- AT: So, is it the electricity that causes the effect or what is it?
- SH: Everyone who has ECT has some degree of memory loss. It varies as to how extensive that is. For example I do ECTs and even though I've seen that person for about a half hour, three times a week over a period of a month, it's not uncommon for them to not know who I am when they're being discharged. They've met and interacted with me during the few minutes before and after the seizure but that time period can be permanently lost. That could be a small price to pay if your depression recovers. But, in some people, the memory loss is more extensive, so that they might not remember, for example, that their family member

visited them the day before they had a treatment, or that they went on a family trip the week or even the month before. The extent of losing past memories, retrograde amnesia, can extend, in some cases, for several months or even longer, and is highly variable. It does depend on the way we do the treatment, whether we treat one side or both sides of the brain or how much electricity is used can influence how extensive the memory loss is. The leading edge of ECT is to improve the treatment parameters so we can minimize the memory loss. The fact that the electricity and the seizure spread to areas of the brain that are important for memory, for example the hippocampus, may cause some of these memory effects. What we're trying to do with this new treatment, magnetic seizure therapy, is to focus the seizure in the very front of the brain and cause it to not spread to deeper brain structures like the hippocampus. We're trying to direct the treatment where it needs to go and protect areas of the brain that do not need to be exposed to the electricity and the seizure.

- AT: Can you explain exactly what this new treatment entails in layperson's terms? A lot of people reading this transcript may have an image of ECT that comes out of "One Flew over the Cuckoo's Nest". I have no idea what magnetic seizure is or how it works and how different it is from other treatments.
- SL: Suppose you were considering receiving magnetic seizure therapy as part of a research study. Here's what it would involve. The procedure of magnetic seizure therapy (MST) is, in almost every respect, identical to ECT, electroconvulsive therapy. I will describe ECT first and then MST. First of all, it's done in a medical setting by a psychiatrist and an anesthesiologist. It's done in a treatment room, which is like a small recovery room. You enter the room, lie down on a stretcher and a catheter is placed in your vein. Monitoring is done throughout the treatment to measure heart rate and your vital signs. After the catheter is placed in your vein, the anesthesiologist will give you a short acting anesthetic agent that will put you to sleep for five minutes and will also relax your muscles. During the time you are asleep, the anesthesiologist will help you breathe by applying oxygen through a mask. Once your muscles are fully relaxed we would put metal electrodes two inches in diameter on either side of your temples. In bilateral ECT electricity would be passed between these two electrodes for a matter of two to five seconds which would cause your brain to have a seizure, which we monitor by using the electroencephalogram (EEG). We also place a blood pressure cuff on one foot so that we can see the motor convulsion. By keeping the muscles relaxed with medication, the rest of the body does not shake

at all. The seizure could last for about one minute or less and, then, you would gradually wake up. After ECT, people tend to be confused when they're waking up and it can take up to an hour or more for that to clear. In the case of magnetic seizure therapy, I'll take you back to the part where you've been given the anesthetic agent and the muscle relaxant and you're asleep with an oxygen mask helping you breathe. Instead of putting metal electrodes on your head, we would put the magnetic stimulator on your head, which is a magnetic coil about the size of a ping pong paddle. Inside that coil are loops of wire, to which we pulse electricity. So, the electricity is not being directly applied to your skin, like the ECT, instead, it is circuited through coil wire that is held over your head. This induces a magnetic field. The magnetic field enters vour brain and is being turned on and off very rapidly. It's fluctuating, and that induces a small amount of electricity or electrical spark in your brain. So, instead of applying electricity through the skin and skull into your brain directly with ECT, we use this magnetic field which can be focused more precisely. That small amount of electricity will induce a seizure that is primarily focused at the spot where we were holding the coil. This will last less than a minute and, then, you'll gradually wake up. With magnetic seizure therapy what we have found in research, is people have less confusion, wake up more quickly, develop less amnesia, and have better retention of memory around the period of the treatment. We're trying to reduce the side effects and although it's still in the research phase our tests have been very encouraging. At the same time we're modifying ECT to make it safer and when ECT is safer, my prediction is that it will leave people less afraid and more willing to use the treatment. It's not like what you see in the movies and the more people understand the facts about ECT and the more we improve it, the less they will be afraid. Our colleagues in psychiatry and other medical disciplines will also become more willing to refer their patients.

- AT: That's a very good point. Some people that aren't in the field of ECT take the approach that the best way to fight stigma is to communicate that ECT is safe.
- SL: That's an important message; however, we can't say that it's one hundred percent safe, because it does have side effects. My personal approach to fighting stigma is with the facts and to say it does cause memory loss. But we've studied this, we can modify the memory loss and we're working on experimental new forms of the treatment to make that memory loss less and less. That's a better way to fight stigma, not to be defensive, not to conceal the facts. If you say it doesn't have any problems, your patients who've had it are going to instantly not believe

you, because they know the truth. Also, the doctors who've had their patients get it know that they do have some side effects.

- AT: You said that the treatment is in the experimental stage. How many patients actually received it and you said that it reduced memory loss? It doesn't eliminate it, so how valuable is that?
- Magnetic seizure therapy is brand new. I did the first treatment in the SL: year 2000. We started with animal research and I did the first treatment in an animal in 1998. Magnetic seizure therapy is not totally devoid of side effects. If a person has had a seizure, there will be some side effects. However, patients who had MST and previously had ECT told me that it was like night and day. After magnetic seizure therapy, the period of disorientation lasts two minutes compared to thirty or sixty minutes after ECT. People in the study told me that they were happy they were not so confused after the treatment; it was a less frightening experience for them. It is helping them overcome the obstacles to getting treatment; they don't dread it and are not scared. One point I would like to make is that sometimes when others in the field of psychiatry look at my work with transcranial magnetic stimulation or magnetic seizure therapy they think I must be anti-ECT, because I'm working on improving or replacing it, but I'm not anti-ECT; I'm pro what works. ECT is a fantastic treatment, but I don't think our patients should have to settle for its current level of side effects. We can do better and we should apply all these great new developments to figuring out how it works, how to make it better and how to reduce the side effects. ECT can save lives but if we don't improve our techniques it's not going to be around. There are already significant pressures to eliminate or ban ECT; below a certain age, it is unlawful to use ECT in Texas. In California, New York and Vermont there are some restrictions on the use of ECT. Many states have had legislation put forward by the anti-psychiatry movement, funded by the Church of Scientology. In these state legislature studies, they find people who say, "ECT fried my brain" or "I lost all my memory". I don't think they are lying, by the way. There are some people who report more severe side effects. The only way to win the argument is to admit ECT does have side effects and that we're trying to understand why they happen so we can reduce them. This can be a life saving treatment and we are pushing the field forward to make it even better.
- AT: I am struck by how much emphasis is placed at meetings like this on, biological psychiatry, where psychiatrists promote drugs. There is no space devoted to the kind of research you're doing. What is it like being

a psychiatrist in the so called age of biological psychiatry devoted to drug therapy?

SL: That's a good question. It's about money. Drug companies make money from selling their products; they have enough money to buy big exhibits at meetings and to advertise their drugs to persuade more people to prescribe them. I'm not saying that's all bad; these big companies also have money for new drug development, because NIMH does not fund all the research that's involved. Most of that is done by drug companies. The companies that make ECT equipment are different. They don't have money on the scale of the pharmaceutical industry. There are only two companies that manufacture ECT devices and they only get your purchase price once. They're small companies with less money and they don't invest in advertising to a significant degree. So you don't see them having a large presence at these meetings. For transmagnetic stimulation, there are several companies that make about four devices but they are not yet approved by the FDA, so they cannot be promoted. You cannot advertise an indication that is not approved by the FDA. Multi center trials are under way to look at whether magnetic stimulation, at a level below that which causes a seizure, may be effective in treating depression. I'm very involved in that multi center trial and we just received a National Institute of Mental Health grant to study that. as well. Within a few years, transcranial magnetic stimulation might be approved for depression if these studies turn out well. If it is, then you will begin to see the presence of companies that make the device at meetings like this. What is it like for me personally, to be at meetings where what I do is not represented at all? It means, for one thing, that I don't have companies beating down our door offering me money to run trials, like people who work with medications experience. So, we have to go to other agencies like the National Institute on Health or to the private Foundations, which fund the bulk of this work. I do wish that device-based treatments were more represented on the program. Whenever I go to a meeting I do a quick search of the program to find out what's new about ECT or TMS and it's always a very small proportion. It still surprises me because, ECT is so effective, people need to be taught about it; but it's always the smallest topic on any program; sometimes it's not even on the program. That motivates me in a strange sort of way. I feel that next year I've got to propose something. We have this technique that's as good as or better than other treatments. We need to get this on the program.

Let me tell you about the organization for people that do ECT. I'm immediate past President of the association and I've been an officer

for eight years and I love that meeting. It's small, but you find people who participate. There are a lot of clinicians, and researchers, but everyone there cares about ECT and the people they treat. If you care about that segment of the population, you might be motivated to say, we've got to improve ECT; we've got to go get the leading researchers in the world working on the technique, because our patients need that. At the Association for Convulsive Therapy meeting, there's a wonderful opportunity to pull together everyone who does ECT research internationally, and so we've broadened our membership to include the magnetic devices that are on the horizon. This past year was a good beginning when we held a joint meeting between the ECT and magnetic stimulation organizations. We are keeping ECT alive, but also looking toward the future, understanding that we should not cling to a particular tool, just because we love it, but we should be trying to improve the overall outlook for our patients.

- AT: With the kind of research you're doing and the techniques you're pioneering and improving, what kind of appeal have they for a patient population that is inundated, especially in the United States, with drugs that are advertised with ad after ad which say, "take this drug, no big deal, depression's gone". How can the device industry overcome that?
- SL: I don't know. To subject the patient to advertising, I find highly disturbing. But, if you wanted to design an alternative public information campaign for people with severe mental illness, I would design one that taught people what depression is. These are the symptoms and how you recognize them and these are the different treatments available for you. There is something you can do about it. So see your doctor or a therapist.
- AT: Whose responsibility is this and where would the money come from?
- SL: I think it's an example where psychiatry has fallen down. We are not doing a good enough job of educating the public about what we are doing and what it means to have a mental illness. Look at the stigma of mental illness, in general, not just ECT. Why are we sitting back and not doing anything when so many movies that come out misrepresent the field? Advertising magnetic therapy would be easier than ECT, because magnetic stimulation is less scary to the public. I've never seen a commercial for ECT.
- AT: Neither have I.
- SL: Go to any doctor's office and open a magazine or look at all the drug company trinkets on his or her desk. To popularize mental illness and treatment in the public mind and counter the prevailing drug culture is a great challenge and we need to do a better job of educating future

clinicians and researchers. We have to teach them not to prescribe reflexively what's in the commercials and what they see at drug fairs and meetings. We need to teach them practice guidelines; to prescribe what is a medically appropriate treatment, not what is advertised.

- AT: I have a final question and I would invite you to add anything to this interview that you feel that I haven't covered. Thinking about you as a math major and a woman and as someone who, early on, elected psychiatry at a time when that wasn't considered the hip thing to do, going into convulsive therapy at a time when drug therapy reigned supreme, there is a sense in which your professional development and intellectual trajectory has been bracketed by a minority ethos. You're swimming against the tide and it raises the question, what is it like to be a woman doing all these things? You're experiencing the added, I wouldn't call it a burden necessarily, but the added variable of being female in a male dominated field. How has being a female influenced your experiences or changed your outlook?
- SL: It is something I've paid a lot of attention to throughout my career. I want to encourage other women to not be threatened by technological fields or by medicine and they are worth trying. My philosophy is, I haven't hit the glass ceiling yet and when I do I'm carrying a great big hammer. It's getting better for women every year. Psychiatry has a higher involvement of women than other medical specialties. I don't think I've had as great a challenge as women who came generations before me when just being a doctor was unusual and women in general experienced more blatant discrimination than I have. Even in my own short career so far I have seen some changes. When I was in medical school I did see some pretty blatant discrimination and harassment; some of the surgeons were pretty awful in their sexual jokes and one delighted in making the female medical students do hernia exams on rounds to embarrass us. I chose not to go into surgery at that time based on my exposure to it as a medical student. I don't think that's the case any more, but at the time it seemed to be hostile to women, and I'm not a masochist. I teamed up with other women and told myself that things were better than when my father went to the Naval Academy and their motto at that time was, "we'll make a man out of you", even if you were a woman.
- AT: Terrible.
- SL: I didn't want to be made a man and I felt I could do well, academically. I'm glad I had the desire to go into psychiatry rather than surgery, because it would have been more unpleasant to have to face open discrimination. Within psychiatry, interestingly, ECT is mostly done

by men. I don't know why but I would like to see that change. I think that I was the first woman president of the Association for Convulsive Tharapy; the membership has very few women. I was very aware of that and wanted to encourage women to get involved. I did not experience hostility toward me as a woman in that organization, but when there are only a few women role models, I think fewer women choose to join. That's something I'd like to change by showing other women that this is a great field and we can excel. One answer to why there are such a few women in ECT is that it does, perhaps unfairly, have a reputation for being a violent, aggressive kind of intervention. I wonder if, in a certain mind set, that is more attractive to men. It is an intervention; more active than passively writing prescriptions. The way ECT was practiced twenty years ago, before anesthesia, muscle relaxants and other modern innovations it might have been more violent. A person would have a full body motor seizure and that might look violent. But now, with modern ECT, I don't see that as violent. As a woman I like to do something active in psychiatry and ECT treats serious disorders and is the most effective and rapidly active treatment. Why wouldn't you want to learn that? I don't know whether this is because I'm a woman or just my personality, but I tend to specialize in people who are afraid of ECT, by trying to make the experience more tolerable for them. When I see patients and explain to them that I do ECT and if you need it, I can admit you, they're always blown away by that. I don't know why. Some patients are very nervous and I explain we can play music, or you can have a family member with you. In a way I'm trying to create a kinder, gentler ECT by making the environment more inviting, by improving the treatment and reducing the side effects.

- AT: I am struck by the way you have achieved so much. Do you think there's something unique about your constitution or is there an outlook you can share with others that would help to democratize the field?
- SL: I've been very fortunate. I have taken chances, by taking advantage of opportunities. I learned that early on. No one is going to just give it to you. You need to go out and get it.
- AT: That's true.
- SL: I would encourage everyone to go out and pursue what really excites them and not be deterred by the fact that only a few women are doing that. A part of that might have been my educational experience or my parents, who always encouraged me and felt I could do as well as any boy.
- AT: Is there anything you wanted to add at this time?

- SL: I'm grateful to the CINP for giving me the Max Hamilton award. It's a tremendous honor that I appreciate and which recognizes the combination of groups that, as a team, I've had the good fortune to lead. I appreciate that.
- AT: Thank you.

## WILLIAM T. McKINNEY

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

- TB: This is an interview with Dr. William McKinney\* for the archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Tell us where and when you were born, about your early interests, education and how you got involved in neuropsychopharmacology.
- WM: I was born September 20, 1937, in Rome, a small town in Georgia, where I grew up and attended high school. I was an only child, my father was the town fire chief and my mother was a housewife. Not many people in my family had gone beyond high school but my parents had wanted me to and saved money for it. They were of modest means; my father built houses as an investment and then sold them to raise the money for me to attend college. I went to Baylor University in Waco, Texas. I think the reason I chose Baylor is that I was reared in a fairly religious background in the Southern Baptist Church and it was the largest Baptist College that existed at that time, and may still be the largest. The idea of going to Texas appealed to me. My undergraduate major was in Psychology and English. Baylor had a very strong English department and I got very interested in writing. I had no idea that I might go to Medical school when I started college; my family probably expected me to be a minister. But, when I got to college, my interests broadened quite a bit. I also loved psychology from day one. In the Abnormal Psychology course my teacher brought in a psychiatrist as a visiting professor. I don't remember the man's name but what he had to say was exciting. He talked about the brain and, even though this was in the 1950's, how behavior could be related to biological factors. I began to think I might want to be a psychiatrist but to become one I would have to go to medical school. I had no science courses in my junior year, so I had to catch up in order to meet the medical school entrance requirements. The last part of my junior year, the following summer and all my senior year was biological science. I took a year's worth of chemistry that Harvard put on in the summer. I don't think I could have abided it for a whole year. I completed all the requirements in my senior year and applied to medical school so that I could become a psychiatrist.
- TB: It seems the psychiatrist your teacher brought in as visiting professor had a great impact on your future even though you don't remember his name?

<sup>\*</sup> William McKinney was born in Rome, Georgia in 1937.

WM: I don't. But I do recall he was from a private practice setting in the area.

- TB: So he was a practicing psychiatrist?
- WM: He talked to us about the patients he saw and what his work was like. I was totally taken by it. At the time I applied to medical school I had completed very few biological science courses and was still in the middle of catching up. I didn't want to wait another whole year, so I took the Medical College Admissions Test, and my scores were widely split, not surprisingly. They were very high in the verbal part and low in biological science. Some medical schools wanted to know more about me and others would look at the numbers and decide "No way". I was accepted and turned down by some very good medical schools but ended up deciding to go to Vanderbilt, which is only a few hours from my home town. There were just fifty-two students in our entering class.
- TB: What year was that?
- WM: I graduated from college in 1959, and started medical school that fall and graduated in 1963. During medical school, I changed my mind a few times about what I wanted to do, but I think there was a guiding stream throughout. I found myself migrating to psychiatric journals in the library when I had spare time. I enjoyed a lof other things and came very close to going into neurology. There was a superb neurology teacher at the time, Charles Wells. He was head of neurology when I was a medical student and we wrote a paper together.
- TB: What was it on?
- WM: It was a historical paper about the Civil War, Weir Mitchell and neurasthenia.
- TB: So, you did your first paper with Charles Wells on neurasthenia?
- WM: I did my residency from 1964 to 1966 in Chapel Hill and, during that time, Charles decided to go into psychiatry himself and moved to do his psychiatry residency to Duke.
- TB: At the time you did your paper with Charles, who was the chairman of psychiatry at Vanderbilt?
- WM: William Orr. He was very influential and a wonderful teacher who taught the first two year courses although, in the second year, we also had small groups in which we started to learn psychopathology and the different syndromes, taught by Frank Luton.
- TB: Frank Luton, a great man.
- WM: A wonderful teacher. I had great teachers in psychiatry and neurology, throughout my medical student time. Frank Luton, William Orr and Charles Wells, were on the front lines in terms of teaching and available to talk to us as students.
- TB: Did you stay in contact with Charles Wells?

- WM: We kept in touch.
- TB: Are you still in contact with him?
- WM: Not now, it's been awhile. But we've kept in touch over the years.
- TB: What about Frank Luton?
- WM: My memories of Frank are of sitting around a table with him in the conference room, going through the different syndromes and interviewing patients. We'd see people with different types of disorders and he was a very wise, wonderful man. It was a very positive experience to be exposed to him and to Bill Orr. Later, it was a real privilege to be asked by Mike Ebert to come back to Vanderbilt to give the first William Orr memorial lecture. I don't know how he got anything done in administration because he was always there for us and always very warm and interested. He was just a fascinating man.
- TB: So you were taught psychodynamic psychiatry. Bill Orr was a psychodynamically oriented psychiatrist. Frank Luton was trained at Hopkins by Adolf Meyer. .
- WM: Yes, and we learned Adolph Meyer's way of thinking about psychopathology, early on. Charting life events and integrating those with temperament and genetic traits. Some of the things we now think of as new, Frank Luton was teaching me when I was a medical student. I'll never forget the first patient in my clinical psychiatry rotation. I was out at Central State Hospital near Nashville. He had catatonic schizophrenia of the kind where the patient didn't move, didn't talk and was mute. Frank and Bill Orr taught us to respect the patient's need for distance and predictability. You're respectful, not too demanding, but just there. They've got their space and you don't encroach on it. I would ask him if he wanted to talk or say anything but I wouldn't push too hard. I would just show my interest and might be there ten minutes or go away and come back another day. Weeks passed and he didn't say a thing. Finally, toward the end, the patient started to talk. I'll never forget that.
- TB: That was a great experience.
- WM: And, internal medicine was taught well too. Grant Willow was my endocrinology teacher. He was a great lecturer, very clear and a cutting edge clinician. I graduated there in 1963 and had made the decision to go into psychiatry, but in1963, one had to do a twelve months internship in something else. So, I did a full twelve months in internal medicine, a specialty I liked as a student. I did that at Bowman Gray Medical School in Winston Salem, and that was a good year. It was my first experience having front line responsibility for patient care. It was just about the time time that they were stopping to do insulin therapy.
- TB: Were they using modified insulin?

- WM: No, the deep coma. They were doing it when I was an intern. We looked after also some of the patients when they were given sub-coma insulin.
- TB: Was this in the mid sixties?
- WM: July of 1963 through June of 1964.
- TB: For what indication did they you use it?
- WM: For some forms of anxiety, and some forms of schizophrenia.
- TB: Insulin coma therapy for schizophrenia was lingering on.
- WM: In July of 1964, I started my psychiatry residency at the University of North Carolina in Chapel Hill. During my senior year in medical school, I had some elective time, and I spent it with Art Prange at Chapel Hill. I did my first research project with Art. Morey Lipton was still there.
- TB: What did you study with them?
- WM: We published a paper called *The Achilles Reflex in an Unselected Psychiatric Population*.
- TB: That's interesting.
- WM: Art was getting interested in the thyroid and one measure of thyroid function was the Achilles Reflex. You tapped a person's ankle and it had break, a beam of light. The reflex was recorded on paper which measured the time it took. We found that in a non-selected group of inpatients, those who were suffering from depression tended to have slower ankle reflexes, as a group.
- TB: So, you found that depressed patients had slower ankle reflexes?
- WM: Yes. There was another experience I had as a medical student that was relevant to my subsequent career. I spent a summer, between my sophomore and junior year, working in the Preventive Medicine Public Health Department as an apprentice with a bio-statistician. He was doing consultations with faculty members on the design of their projects. When the study was done, they would do the data analysis. That was wonderful training in design and methodology issues.
- TB: Both these research experiences as a medical student provided a groundwork for your residency.
- WM: Yes. In 1964 Chapel Hill was a very active place with a lot of good faculty and residents whose names you'd probably recognize, in the field.
- TB: Can you name some of them?
- WM: In my class were, Fred Goodwin, Bruce Green, Peter Whybrow, Lynn Dailey, David Markot and Ali Jahre, who was from Saudi Arabia. I'm leaving two or three out, but I can picture them.
- TB: That's fine.
- WM: And a year ahead of us, were Wyatt McCurdy, Albert Allen Wood and Joe Mandels, all I think, active in psychopharmacology.

#### TB: Was Morey Lipton the Chairman of the department?

- WM: Morey was a senior research faculty member; the Chairma was George Hamm. George Hamm had come from Chicago to start the department at Chapel Hill. George was a psychoanalyst, and brought some other people with him. They had a series of acting Chairs during the time I was a resident. Morey was running and helping the research programs in the department. He was very important in my development, as a good advisor and senior mentor, as was Art. As a resident I knew early on I wanted to do combined clinical and animal research and they really helped me do both for two years before I transferred to Stanford for my third year because I wanted to see a different part of the country while I was single. I didn't leave out of dissatisfaction but for personal reasons. Stanford was very good, David Hamburg was Chair, and a lot was going on there. In 1966-1967 I did my third year of residency and met my wife. We were married in 1967 and have been married ever since. That was a good year. California was like a whole new world for me and I remember a number of things about that year. A lot of people associated Stanford with research at that time, and that was true. They had good clinicians and researchers. I was able to arrange a consultation with David Hamburg about career development. He seemed very glad to meet and talk with me and advised me about a variety of issues. I finished my residency and, up to this moment, I had not done any primate research.
- TB: What did you do after your residency?
- WM: That's when I went to NIH for two years and from 1967 to 1969 I was at the National Institute of Health, and worked part-time with William Bunney who was branch chief. It was a very exciting time, because they started to use the new rating scales on their inpatients on the ward. This whole concept of doing clinical research and the way they were doing it, in a control setting was very exciting. Biff Bunney put me on to the path of depression research, but I didn't guite know what aspect until he suggested the animal models of depression. He had not published in that area and was too busy with other things to tackle it. There were a number of things in the literature that had never been brought to bear in an explicit way on this topic. One of the people whose work I was very interested in was Harry Harlow. I had known about his work as an undergraduate psychology student so I wrote and asked if I could have some of his time. He was president of the American Psychological Association, with a long series of honors, but he wrote me a very thoughtful letter about the directions I might think about, including primate work. I began thinking that's the direction I want to go

into and learn how to do animal research. Meanwhile, at Bethesda I ran into Doug Bowden, who was in the Institute of Neurological Diseases, and had a primate laboratory. So he and I started to do my first real primate project at NIH in the intramural program. That was a study in which we looked at the separation responses of rhesus monkeys with different types of frontal lobe lesions compared to intact animals and found that they were much more sensitive to the separation with more dramatic effects that lingered longer. It was an interesting project. In the Public Health Service, during those two years in Washington, I was also working in a psychiatry training branch at Bethesda involved in NIMH training grant review committees.

- TB: When did you move to Wisconsin?
- WM: I went to Wisconsin to work in the Primate Center and joined the faculty in July 1969. I could have gone to a couple of other places that had primate centers, but I found the psychiatry department in Wiscosin very different and interesting. The Chair was Milton Miller. I like Milt a lot. He's a very caring person and thoughtful administrator. It's a nice combination. It was also a very strong clinical psychiatry department at that time. All of all that, with the primate center and Harry Harlow being there, was what attracted me. I also liked Madison, the town, so I wound up there. When I started, the primate center lab didn't have an office for a psychiatrist, so Harry, this world famous psychologist, invited this brand new faculty member to share his big office. I shared it for maybe a year or so. Harry was always prey to people, coming in to talk to him, but it was very rarely that he asked me to leave. That was a real growth experience.
- TB: So your interest in primate work started while working with Biff Bunney looking for animal models of depression?
- WM: Yes, absolutely. I knew I was interested in some type of depression research. When I got to NIH, after finishing my residency, Biff challenged and stimulated me to look for animal models and to think about opening that up as a research area. He deserves full credit for that. He and I wrote one of the first papers called Animal Models of Depression in which we charted out some of the criteria and how to go about developing models and criteria for evaluating them. He and I wrote that article around 1969 and I think it was published in the Archives. Biff stimulated me in the general area of animal models and Harry provided me an infrastructure and a setting in which I could learn to do primate research and think about behavior in a developmental sense. Harry was interested in building on the work he had done over many years, starting first with learning, based on the cognitive work developed with the

Wisconsin General Testing Apparatus. From there we went to the relevant social attachment systems, to disruption of attachment systems and then to separation studies. He was interested in extending it into biological areas, but it wasn't quite his thing to link it up with psychopathology. So, the timing was good, because I was able to help him with that and he certainly helped me in providing an infrastructure in terms of learning how to do primate research. There was a lot going on there at the time and it was a very exciting place to be.

- TB: Are we now in the mid-1970s?
- WM: I arrived at Wisconsin in 1969 and over the first five or six years we got my primate research program going.
- TB: Could you say something about the primate research you did?
- WM: I had to learn the techniques of doing primate research, how to develop and utilize different types of rating scales, how to work with the animals and what kind of biological and drug studies one could do in primates. I also had to think through where primates fit in the spectrum of different approaches. I'd been intrigued early on by the literature that was starting to emerge about the role of early experience in shaping behavior and influencing neurobiological development, across the life span. It was in Harlow's group that some of the findings in this area of research came from. There are four or five other people who have documented effects of early isolation on biological and behavioral development. I was interested in that, so that's an area I started with. We worked with animals who had been socially deprived and then tried to find ways to reverse it. We tried chlorpromazine in some monkeys and it reduced the large array of abnormal behaviors they displayed. When we stopped the medication abnormal behaviors came back. We didn't have a variety of different neuroleptic agents as we have now to study. Later on we tried antidepressants in some of the separation paradigms, too.
- TB: Which paradigm did you work with?
- WM: I was working with the isolation and the separation paradigm.
- TB: So, you worked with both paradigms?
- WM: Yes. In the isolation paradigm, we were involved in studies showing that a neuroleptic was effective in reversing all the abnormal behaviors; benzodiazepines were not.
- TB: So the reversal worked with chlorpromazine?
- WM: It did.
- TB: Could you see the effects of separation on individual monkeys?
- WM: Not individually. If you make social isolation severe enough you start to minimize the variation although you don't do away with it. The more

severe you make it the less individual variation there will be. Just like an extremely traumatic event.

- TB: What would chlorpromazine actually do?
- WM: It would reduce a lot of the abnormal behaviors that the animals would show as a result of the early experience. We also found, in collaboration with Harlow, that you could treat these animals by providing them social experience with younger peers. We did more recent work through the MacArthur Foundation showing how early experience got effects in a lot of domains, including neuroanatomical changes. We did this later work in collaboration with a group in New York at Mount Sinai involving John Morrison and Steve Siegel. We demonstrated for the first time that early isolation experiences could have significant cytoarchitectural effects in the hippocampus. I don't think many people knew guite what to make of that but the finding was solid and clear. Subsequent work in a variety of early stress paradigms has replicated and expanded this initial finding. In collaboration with Gary Kramer, a student in my group, we demonstrated that if you took socially isolated animals and rehabilitated them so they looked normal, and then you challenged them with a low dose amphetamine, they were hypersensitive to it, as opposed to animals that had not been in social isolation. They became hyperaggressive; even lethally hyper-aggressive. So the early experience was only seemingly reversed. They were carrying scars of vulnerability, based on their early experience, and if you challenged it, you could bring it out. Finally, maybe I'll talk about the separation paradigm. Harlow and two or three other labs had already shown that by separating rhesus monkeys from their mother, you get a biphasic protest-despair response, which show significant similarities to descriptions of human infants. I did a series of studies focusing on the pharmacological aspects. I studied imipramine first and it worked. If it doesn't work right away, you had to take them through a couple of cycles, but imipramine can block the separation response. We've recently shown that fluoxetine does the same thing. Antianxiety drugs can influence the initial response but don't block the total depressive responses that occur after separation.
- TB: Did you try desipramine?
- WM: We did do desipramine.
- TB: What about MAOIs?
- WM: That's a good question .we don't know whether an MAOI would do it or not.
- TB: What about meprobamate?
- WM: Meprobamate has not been tried, to my knowledge.
- TB: What about diazepam?

- WM: It doesn't work. The studies take a while to do, they're not so simple.
- TB: You started to work with the separation model in the 1970's and are still using it?
- WM: Yes. In 1993, I moved to Northwestern to start a research and treatment center. I wasn't really looking to move, but this was a good opportunity.
- TB: Before moving onto that, am I correct that you were at a certain point Chairman of the Department of Psychiatry at the University of Wisconsin. When was that?
- WM: I was department Chair from 1975 to 1980.
- TB: But, even while you were chairman, you continued your research?
- WM: Yes. I liked being Chair anddid not dislike the administration. I didn't leave it for that reason, but realized I couldn't do everything and decided to focus on research, teaching and clinical work. I had accepted a Dow Chair at Northwestern to start this Center. It was a new challenge.
- TB: Could you say something about the Center?
- WM: The overall charge is to be multidisciplinary, dedicated to understanding the diagnosis and treatment of depressive disorders. We have a basic division and a clinical division and the basic division is heavily oriented toward, behavioral neurosciences. We have four or five basic neuroscientists in the basic science division and a clinical mood disorder program with five psychiatrists involved and an administrative person. We have a small primate operation focused on circadian biology issues. I'm collaborating with a neuropharmacologist, Dr. Dubocovich, and there's also a strong circadian biology group on the Evanston Campus, looking at melatonin receptors.
- TB: So you are looking at melatonin receptors?
- WM: Collaborating with the neuropharmacologist, looking at melatonin receptor subtypes she has characterized in other species. She's looking at different agonists and antagonists through the different melatonin receptor subtypes, and characterizing the effects they have on circadian biology disturbances in primates. Three or four people at the basic science level are looking at different types of gene expression and working at the molecular neuroscience level. The Center ranges from scientists working at the molecular neuroscience level to clinicians doing clinical trials.
- TB: Do you have an outpatient clinic to treat patients?
- WM: Primarily outpatients, although people in the program will work on the inpatient service, if patients need to be hospitalized.
- TB: Do you have a certain number of hospital beds?
- WM: The department has its own service and we can admit someone as long as they're beds available.

- TB: Are you having both unipolar and bipolar patients?
- WM: It not designated bipolar and unipolar; it's defined as mood disorders.
- TB: Mood disorders?
- WM: We see bipolar and unipolar patients and people with major comorbidities. We are not an anxiety disorders program but anxiety disorders comorbid with depressive disorders are fine. We also see people with substance abuse problems and mood disorders.
- TB: Could you say something about the ongoing clinical research in the center?
- WM: I'd have to add them up. We're one of the regional centers for the Star D study. We're also a regional center for the KD schizophrenia and KD Alzheimer's studies. We're involved in the TADS, adolescent depression project, with a psychologist named Mark Reineke, who is the Principal Investigator (PI). We are one of the sites for ancillary studies from STAR D to Child STAR D.
- TB: Can you tell us what STAR D means and something about the study?
- WM: STAR D means Sequence Treatment Alternatives to Relieve Depression and this is an NIH funded, multi-site study, with John Rush and Madhukar Trivedi, a PI at the University of Texas. There are fourteen regional centers around the country and we're one of those. One of the ancillary studies to that is a Child STAR D and there are five or six centers in that study.
- TB: So you are very active.
- WM: Very active. It's been a good move; a new challenge at this phase of my life and I'm glad I did it.
- TB: How much of your time is spent in clinical, how much in teaching and how much in research?
- WM: Probably a ten-hour day, seeing patients during a week. And then, of course, there are add-ons to that.
- TB: So you spend at least one fifth of your time seeing patients?
- WM: At lease one fifth of my time seeing my own patients and I see other patients in the context of some of the studies and trials.
- TB: How much teaching?
- WM: Teaching varies. I teach a journal club to our residents and organize the neurobiology seminar series. I teach in that series, organize it and get other neuroscientists from around the place to help teach the residents.
- TB: How much time does that mean?
- WM: Probably about half-time and about half-time. I've always felt strongly about maintaining my own patients.
- TB: What would you consider your most important contribution?

- WM: From a research standpoint, I think developing the concepts of animal models in the field of psychiatry and laying out the groundwork and framework for a series of studies that have since been expanded by others in a variety of different directions. It was really a major move in terms of opening up that whole area for the field. I've trained people over the years and I feel good about that.
- TB: Would you like to name some of the people you trained?
- WM: Hagop Akiskal was a resident of mine. Nick Kalen came to Wisconsin when I was on the faculty and did his first primate work with me. Akiskal came to me as a third year resident and transferred into our program to think through ways to approach research in depression. Akiskal has, obviously, blossomed. He's editor of the Journal of Affective Disorders; he just got the NARSAD Award this year in the Affective Disorders area. There's a number of clinicians I've been involved in training. They're in various practice settings, some academic and some private settings around Wisconsin and I've watched the leadership roles they've taken over the years. I feel very good about that. Gary Kramer, a graduate student of mine, is now a tenured faculty member at Wisconsin. We trained a half dozen or so people who have gone on to various kinds of careers in the field. I feel good about one of our chief residents in Wisconsin, Randy Thompson, who is now down in Chicago heading up one of the major hospitals. I, also, feel good about the fact I have not stayed in the lab all the time. I've done other things. For example, I've been Director on the American Board of Psychiatry and Neurology for eight years and just finished up my rotation. That was a very time consuming job, but I felt strongly about staying active in the field of psychiatry. I, also, tried to keep a personal life through all this.
- TB: Would you like to talk about that?
- WM: I have other interest besides my work. There's absolutely no way I could have achieved what I have without the support of my wife Carolyn and my children, who tolerated a lot. The things I've described take a lot of time, in travel. My family has been very supportive, so I feel really good about that. My son, Scott, who is twenty-nine, is married to Kristin and I have a daughter, Julia, she's twenty-five, who lives and works in Houston. I've tried to keep my priorities straight over the years. I've got interested in running and I've become a runner.
- TB: A runner?
- WM: Yes, not racing, just jogging and running. I've been running all my life. I think I've done eleven marathons now. I started that when I was fiftyish.
- TB: That's great! What was your last paper?

- WM: Gary Tucker called and asked me if I would edit a special issue of the journal that he's the overall editor in *Seminars in Neuropsychiatry*. He wanted to do a special issue on Stress and Affective Disorders and asked me if I would be the guest editor and write an article for it. I did the editing, rounding up everyone to write the papers, wrote an introduction and an article myself on *Stress, Animal Models and Depression*.
- TB: You have been involved with ACNP for approximately twenty years.
- WM: A little bit more than that now.
- TB: Have you served on any of the committees?
- WM: I've been on committees. I've been active. The meetings are at a difficult time of the year, in terms of family life and the things we value as a family. I've tried to come to meetings but I've missed some. I'm on the education and training committee now; I've been on the committee that deals with advocacy groups and I'm joining the animal committee, starting in 2002.
- TB: Have you written any books?
- WM: I've written two.
- TB: What are they?
- WM: One called *Animal Models in Mood Disorders* that I wrote myself and the other called, *Mood Disorders: Towards A New Psychobiology*, is written by me, Peter Whybrow and Hagop Akiskal.
- TB: When were they published?
- WM: In the late eighties.
- TB: Is there anything important we did not cover?
- WM: As a junior faculty member when I had a research career at NIMH I was able to put together a sabbatical with Robert Hind in Cambridge, so that was really important. And, then, in the mid eighties, I was a Fellow up at the Center for Advanced Behavioral Sciences at Stanford for a year and that was also a very good, important year.
- TB: Is there anything else you would like to add?
- WM: I think this is a very exciting time for the field right now. So many new developments are going on. I would like to see basic and clinical developments, to see these domains stay in touch with each other. The areas are getting so specialized that to do it on an individual basis can be awfully hard. One person can no longer bridge this any more. We've got to think through new ways for it to happen, for the interaction to occur. This is where I think the College has played an increasingly important role, because you've got in the same organization, clinician researchers and highly skilled basic neuroscience researchers. Things have changed so much that we've got to find other structures to help to do this.

TB: On this note we should conclude this interview. Thank you very much. WM: Thank you.

# JUDITH L. RAPOPORT

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

- DH: This is the 15<sup>th</sup> of December 1998. My name is David Healy and I'm interviewing Judith Rapoport\* on behalf of ACNP. Judith, could we begin with where you were born, why you went into medicine?
- JR: I was born and grew up in New York City and come from three generations of Midtown Manhattanites. Perhaps most relevant was that my grandfather produced Second Avenue Yiddish theatricals. I mention this because I think some fraction of research involves enjoyment of presentations. Interest in medicine came during my senior year in high school. A friend's mother was a physician, named Dr. Ruth Fox, a psychiatrist. She had realized that psychotherapy wasn't very helpful in alcoholism and pioneered the use of Antabuse (disulfiram), which over about a ten or fifteen-year period probably was the most novel and, possibly, one of the more useful treatments.
- DH: Sure.
- JR: Watching the quality of her life, making a difference and not passively going along with treatments which clearly weren't working impressed me. The variety of the research life also made an enormous impression on me, particularly when they invited me along on a summer "vacation" to Mexico. I was to be a companion for the daughter, but Dr. Fox was also lecturing to Alcoholics Anonymous of Mexico City, largely expatriots from other countries, and I was fascinated.
- DH: That's awfully interesting.
- JR: Dr. Fox was having a very stimulating and interesting life.
- DH: I know.
- JR: Her husband had died of alcoholism but she moved on in a positive way.
- DH: This then led you into medicine?
- JR: Only partially. As an undergraduate at Swarthmore College the potent teachers of the time were in the experimental psychology department, dominated by the Gestaltists. Exposure to this field proved relevant to a career in psychiatric research. Professor Wolfgang Kohler tried to teach us, through cognitive and perceptual studies, that large "molar" units of behavior were researchable. In contrast to the rat-in maze learning-model dominating psychology it dealt with how people, and monkeys actually, perceived the design to solve a problem. The most useful message I got out of that experience was that you could

<sup>\*</sup> Judith Rapoport was born in New York, New York in 1933.

do reliable research on complex behaviors. Solomon Asch, for example, was studying the influence of perceptual judgment. My classmates who continued in experimental psychology went on working with perception and learning in graduate school. But, I preferred research on more complex behaviors. So, I was a natural for medical school, thinking about psychiatric disorders. Harvard psychiatry was dominated by analysts. Greta Bebrane was the best-known along with Elvin Semrad. More interesting were people like the pediatric neurologist, Phil Dodge, who was carrying out research that I followed on from my undergraduate experimental psychology training. In fact, the neurology teaching in phenomenology was remarkable and time I spent on a student elective at Queen's Square Hospital in London was unforgettable. Between Dr. Ian McCulloch and MacDonald Critchley there was amazing work going on. Those three months were formative. Some of their studies were exotic. For example, Critchley had five people on his ward, who had congenital sensory neuropathy. They'd never felt any pain or temperature on the surface of their bodies and he wanted to know, "could you feel tragedy watching Shakespeare if you'd never stubbed your toe". It was a strange but wonderful way to start thinking about phenomenology. I knew then why I had gone to medical school. They also had two pairs of Siamese twins from India and he wanted to know if one was asleep, could the other one be awake. Critchley was seeking the answer to circulating hormones controlling sleep. The notion of naturalistic experiments and how much you could get out of systematic observations made an impression that never left me.

- DH: Why on earth did you do psychiatry, given what you just described?
- I was never sure. Morris Bender was the dominant figure at Mount Sinai JR: where I interned and I thought he was truly remarkable, not just his knowledge of neuroanatomy, but he thought deeply about phenomenology. They were using double simultaneous stimulation to infer cortical lesions and were interested in neglect phenomena and so on. I was accepted to the neurology residency at Mount Sinai. But I had also been a student at the Mass Mental Health Center and started out my residency there instead. They had a mixture of psychoanalysts and the seminars were a wonderful mix of psychoanalysis and new research. Ives Hendricks, one of our psychoanalyst mentors, used to talk about the most astonishingly personal and bizarre matters. It didn't quite hold me though. I married a medical school classmate, who was in Washington at the NIH. I went to complete my training at St. Elizabeths' where I was immediately given a building of three hundred patients to attend. As the only MD, I found Kraepelin more useful than Freud.

- DH: You had to look after three hundred patients?
- JR: That's right. That was my building.
- DH: Any supervision?
- JR: This was 1961. There was somebody who would appear occasionally. I don't remember her name, a very elderly German woman. She mostly objected to my changing any medication and many of these patients were on seven. Moving to St. Elizabeths' was a shock. At Harvard, there was an hour of supervision at least, for every hour of patient care. At St. Elizabeths' I had a few hours a month. It was very hot, the building wasn't air conditioned and I signed a lot of death certificates because many patients were elderly. One woman spent her days curled up in a fireplace for thirty years. There was another Ophelia-like creature floating around. So I started to read Kraepelin and learned all I could.
- DH: All these people were there, even though we had had chlorpromazine for five or six years?
- JR: There's this focus, currently, about how many years going without treatment may affirm chronicity. I don't think that case is proven but medications weren't doing very much for the patients I saw that summer. We have to think about selection as well and I suppose that anyone that had a good response would have not been in that building.
- DH: When you saw all these people, who weren't responding all that well, did you want to leave?
- JR: Well, there were good things. I had about thirteen supervisors in the year at Harvard and seminars all the time and there was something liberating about having to make my own observations and come to my own conclusions. So it wasn't all as bad. Secondly, this was not a career job. My husband had decided that instead of the electrophysiology lab at NIH, he would go to Sweden where Professor Teorrell was a biophysicist. My husband's, Stanley's background made him fascinated by the line between physics and biology. So, I knew that we were going to Sweden and I managed to find a mentor there. We were able to each get postdoctoral research grants for this. So, after I'd been about fifteen months at St. Elizabeths', we went to Sweden.
- DH: What did you do there?
- JR: We spent our two and a half years in Uppsala. My first mentor was Dr. Ingmar Dreman one of the first people doing systematic studies of amphetamines' effects on humans. He was interested in some rather "Gestalt" measures, which attracted me, such as perception of motion and whether this satiates if the wheels start changing direction. This work combined my psychology from Swarthmore and added amphetamines, which made it more medical. The second year, in 1962, I moved

to the Karolinska hospital and spent my time with Professors Borje Cronholm and Dr. Daisy Schalling, who was a wonderful physiological psychologist. She was interested in physiologic arousal in relation to psychopathy. They told me he was very good.

- DH: What was it like in Sweden?
- JR: Swedish psychiatry was more like MacDonald Critchley neurology.
- DH: Very biological?
- JR: Yes, even the phenomenology. Borje had written his thesis on phantom limb; he was one of the unrecognized but enormously creative people in psychiatry. If he hadn't died at 55 of a brain tumor he would be much better known today. His other monograph was on two Swedish famous artists, who had been intermittently psychotic; he wrote on the difference in their art between their psychosis and well periods. The kind of phenomenology he did was like the best of Queen's Square, quite inspiring. Anyway, a couple of interesting projects were chosen for me. This was in the day when Sweden was being overwhelmed with people seeking abortions. Time Magazine had done a rather misleading story about a woman named Sherri Finkbine, who had taken thalidomide and had obtained an abortion in Sweden where the laws were actually rather restrictive. She gave an interview for Time saying Sweden performed abortions on anyone who didn't want to have a child. You couldn't even discuss the topic publically in the United States at the time. My project was to study the women who were coming from the US. I published in the Archives several years later, probably the first really open paper on American women seeking abortions. I had some outcome data also. My other project was on memory deficits after electroshock, one of Professor Cronholm's interests. The project was successful but I found the measures unrelated to outcome. My mentors in Sweden were wonderful people who guided the next several years of my life. When we returned to the US, the NIH had just recognized there was a drastic shortage of child psychiatrists. I'd become semi-interested in this because of the abortion study and it turned out that the Fellowships were well funded; they paid almost the same as an entrylevel job. So, I took a child psychiatry Fellowship and spent part of my time with pediatric neurologists at Children's Hospital in Washington.
- DH: When it came to Child Psychiatry as you entered the NIMH, what did things look like? It was not an awfully pill oriented field. Only a few people, like Leon Eisenberg, had begun to use medication.
- JR: I had a job before I went to work at the NIH, working in a city clinic where they had so few hospital beds you had to treat almost everyone as outpatients. The city monitored how many patients you saw each

afternoon to determine clinic support so the drug clinics were the best way to maintain the clinic staff. We saw a few patients more intensely, but everyone also ran medication clinics. You treated the mothers with antidepressants and it would help the parent/child relationship. It was there I learned how much antipsychotics could do. The job was a kind of domestic Peace Corp experience. This was part of the 1960s liberal movement where there were a large number of white psychiatrists working in inner city settings. This was a very deprived population and what they wanted was to have their child better so that grandma could look after it. I probably made one of the more useful observations at that job. Many of my patients shared bathrooms and, so medicines were kept in their refrigerator. On two or three occasions, I saw a perfectly nonhyperactive ordinary child, who had taken some of their ADHD sibling's amphetamine or Ritalin. The mother would bring the child concerned about bad effects. These calm children just got calmer on stimulants! One of the first studies I did at the NIH was giving amphetamine to normal children, which proved this impression correct!

- DH: Who were the normal children? The myth is that you used your own children and those of the staff? Is that the case?
- JR: Yes. There was nothing like the debates going on today about the ethics of research. Even though it was just one single dose of amphetamine, plus a no drug and a placebo day, I took enormous care. We were worried about informed consent because the parents were doctors, lawyers, and, in one case, a president of the local ACLU. My own sons were the first two subjects. I was surprised how much normal children improved on our test battery. It wasn't particularly useful, but that made a very big splash because it showed stimulant drug effects in children to be non-paradoxical.
- DH: It did. I guess one thing that Rachel Gittelman-Klein would say is that this was only one dose and we can't know for sure that normal children on chronic dosing would have the same response as ADHD children.
- JR: Absolutely. But there were some replications of longer term administration. John Werry studied children with no psychiatric diagnosis but with mild bedwetting. He found several weeks of stimulants medication benefited cognition and behavior in these normal children. He also measured bedwetting and the stimulants didn't help although he had a rationale that it might lighten sleep.
- DH: The other angle on all this was the notion that normal children would be hyped up by stimulants and hyperactive children calmed down.
- JR: People cited my normal child stimulant paper for many purposes. The "anti-drug" people said, you see, this isn't a diagnostic test and you're

just drugging children; the "pro-drug" people said this means stimulants are not "thermostat" drugs. Many of the basic physiologists thought this might be regression to the mean. What was most interesting was that stimulant drug effect was not paradoxical with respect to age. Our study included a group of young adults. It was their first exposure to amphetamine and they had very similar pattern of responses to the younger normal children.

- DH: As you were saying, it's not just a pediatric response.
- JR: That's right and it's not paradoxical with respect to age and diagnosis.
- DH: Thiis was just about the time that ADHD was introduced. What were the theories about what this condition was? Did people generally accept it was real or were there concerns, as there are now?
- JR: Well, the study addressed a more sophisticated question than the field held at the time. "Minimal Brain Dysfunction" was still a new concept. Science was coming to child psychiatry through psychopharmacology and epidemiology. Remember also that the first controlled trial methodology was only established in 1948. Insisting that the people I worked with get inter-rater reliability and make observations blind, was a dramatic step.
- DH: Tell me more about that. Are you able to recall the conversations of people in the argument or debate?
- JR: Absolutely. Although Yale now has a very active and excellent research program the senior staff at the time objected strongly to our initial use of structured interviews They were not considered to be clinically ethical!.
- DH: What was the problem?
- JR: That an interview with a younger child was best done with less structured interactions. They focused on fantasies. Now one couldn't get a grant without structured interviews.
- DH: Right. Let me hop to DSM-III, because I know you were involved in trying to draw up the criteria. How did the DSM-III process go down with the average child psychiatrist or child mental health worker?
- JR: Very badly. There was a psychodynamic diagnostic system based on complex observations, and a great deal of interpretation of behavior. This is no longer a major issue in this country. It still is in South America and some parts of Europe though.
- DH: Even in the UK there are people who boast that they haven't given a pill in their life.
- JR: A second exciting area at the NIH related to obsessive compulsive disorder. Before I started at NIH, I went back to visit Sweden. Börje Cronholm introduced me to their new research fellow, Marie Åsberg, who became a close friend. She was interested in serotonin and

suicidality in depression. As a contrast group, she was studying adults with obsessive compulsive disorder (OCD). They were starting to do a small study on very ill adult obsessive-compulsive patients, whom they'd collected from institutions all over Sweden and transferred to the research ward at the Karolinska. I was starting as a research child psychiatrist at the NIH and on rounds with Marie, in my still good Swedish, interviewed the patients on the ward asking for their age of onset. Remarkably, eight out of eight of their patients had their onset in childhood. That inspired a parallel study at NIH. I was happy for an excuse to keep in close touch with that extraordinary group of colleagues. We started a control trial of clomipramine in obsessive-compulsive children. Everyone said there weren't any or that it was terribly rare. So we started advertising all through the United States and Canada. They were trickling in until one of our patients went on the local radio with me and this early teenage boy simply described his experience. After that the phone never stopped ringing. This was about 1978 and after a local television story we never needed to recruit outside the Baltimore/ Washington area again. Drug treatment of OCD seemed counterintuitive as OCD appeared so "psychological". We switched to a study design comparing desipramine to clomipramine. That became a "formula" we used over a series of cases: it was truly double blind as the side effects were the same.

- DH: When you say at that point in time the condition looked so psychological, what do you mean? What were the theories?
- JR: If we go back to Kraepelin's original reports he noted that patients with OCD didn't deteriorate and could be normal much of the time. He used this as a contrast with schizophrenia, which he was sure, was a brain disease. Many OCD symptoms do seem fraught with psychological issues. For example, a boy who couldn't sit in the chair if a girl had sat in it would suggest a psychological formulation.
- DH: Oh, obviously.
- JR: What was astonishing how dramatically the drug worked for about half our cases; when we did a clomipramine (CMI)-desipramine (DMI) cross-over, the responders on desipramine then deteriorated.
- DH: What you found wasn't it considered first antidepressant effect?
- JR: Oh yes. Isaac Marks had been quite vocal about that. He had Marie's data to show, unlike her own analysis, that depression was the true target. One reason we switched to the CMI-DMI methodology was because they were similarly effective antidepressants. Studying children was a lucky choice. We saw that young children would often have motor compulsions without any notion of why they were doing that. Occasionally

a child would come up with a theory. One had been at a science fiction movie and thought, maybe, people from Mars were "making him do that". It was a happy movie and he was a happy kid. The point was that OCD was not driven by psychological conflict. Secondly, we were finding that almost forty percent of our kids had motor tics. We were the first to show that first-degree relatives were more likely to have either OCD or Tourette's. Since children are "therapeutic orphans" the study also kept the child OCD population up with the adults. The other piece of this was that we went on to show that clomipramine was effective for trichotillomania. Most colorfully we treated dogs that licked their paws excessively, referred to as Canine Acral Lick and that responded only to serotonergic drugs.

- DH: You also wrote the book, *The Boy Who Couldn t Stop Washing*, an absolute classic. When did you begin to write it?
- JR: Over about 13 years of these studies, we had collected amazing stories that weren't quite right for scientific journals. There were broader notions that went beyond child psychiatry. For example, the relationship between religious ritual and art or whether certain religious groups were more likely to have OCD. OCD raises the question of "hardwired" modules of behavior. Other issues about compulsive personality and about famous figures who had OCD were covered. I learned a lot from writing a popular book, having to discuss one's work with the public from "Oprah" and "Donahue" to National Public Radio or "Larry King Live". I was amazed at how stimulating that proved to be for research. You don't usually think about television talk shows as a source for research ideas, but I can think of at least three studies that came from that.
- DH: It had to be an interesting experience trying to take this to the public, having the feedback.
- JR: It had a dramatic effect on me. It stopped my inverse snobbery. And it also had a large impact on public awareness. The Obsessive Compulsive (OC) Foundation was just starting and I insisted they get all of the calls from the one hundred TV and many more radio programs I went on after the book became a best seller.
- DH: Public awareness accelerated.
- JR: The OC Foundation, about five years later, gave a fund raiser dinner in my honor at The Four Seasons hotel in Philadelphia. The membership, who felt their lives changed because they read *The Boy Who Couldn t Stop Washing*, each wrote a page or two. So it was a giant scrapbook and a testimonial to the power of the book and of TV. The book was translated into twenty-two different languages. Over a million copies sold worldwide.

- DH: That's extraordinary, isn't it?
- JR: Amazing.
- DH: You obviously brought OCD in from the cold but do you think the public went too far?
- JR: It was certainly clear from the absolute beginning that this was a danger; there wasn't a celebrity interviewer or camera crew member that didn't call me over afterwards to discuss their "OCD symptoms" such as "I count steps every day when I go out of my house" There was a danger that trivial everyday routines could become "medicalized".
- DH: When you mentioned the Canine Acral Lick model you used all of the 5HT drugs. Didn't this open up the whole idea of serotinergic spectrum disorder?
- JR: Well, this happened at the same time that plausible arguments were made for treating body dysmorphic and somatizing disorders like OCD.
- DH: What's your opinion about how the drugs are working, if it's not by lifting mood?
- JR: We don't know what the distal action is. I think some kind of motoric and cognitive ordering and re-arranging of a hardwired system is involved. Dr. Susan Swedo, a pediatrician and branch chief at the NIH, is working on OCD and infection. It has long been known that seventy percent of cases of Sydenham's chorea have OCD. And Sydenham's chorea occurs in twenty percent of rheumatic heart disease patients as an autoimmune response to streptococcus Dr. Swedo's has identified a group of children, who don't have rheumatic fever or Sydenham's chorea but may have tics due to post streptococcal OCD. You could argue that some basic ritualistic behavior is an artifact of the immunological interplay between the host and streptococcus infection.
- DH: That's absolutely fascinating. Your work has given OCD legitimacy by taking it out of the purely psychological realm.
- JR: Right, the academic psychoanalysts always felt that they couldn't really touch it.
- DH: So it was reasonable, in a sense, to use pills. At the same time there's this huge area of controversy, especially in the US over the use of stimulants for hyperactivity and antidepressants for childhood depression. But there isn't controversy about the use of pills for OCD.
- JR: I think you're right. The antidepressant controversy is based on lack of efficacy in children. With the hyperactive children, it's more a question of whether there is long-term benefit. That is also not clear.
- DH: You've also moved that into the area of childhood psychosis. Can you tell us how?

JR: That came from a number of things. I work in the intramural program at NIH and we are supposed to do things that would be hard to do on the outside. We should not compete with our extramural colleagues. For example, when we started to work on obsessive compulsive disorder, we would never have obtained a grant for this on the outside. Can you imagine telling your granting agency that you need personnel and beds on a ward, but you don't know how many years it will take you to get a sample?

Now that the rest of the country has started doing OCD research we began looking at normal brain development with MRIs taken prospectively and studying childhood onset schizophrenia. In the intramural program there were collaborators who could help us show clinical and biological continuity with adult patients. Are the children drugged or are they simply normalized? The study started in 1991, and unlike OCD, which we thought was rare but turned out to be common, we felt psychosis was rare and it stayed very rare. We have shown abnormal brain development and a high rate of genetic risk. It looks like genetic factors of several kinds are much more active. The drug trial that we were able to do was one of the first showing how much superior clozapine is to haloperidol although we didn't have enough subjects to show that, for these kids, it's also better than olanzapine.

- DH: Do you have any feel for why it's so much better?
- JR: The entire industry is still puzzled.
- DH: Extraordinary, isn't it?
- JR: Absolutely. We're in a unique position because we have a couple of children who were virtually cured on clozapine. If I ever write another popular book, as opposed to the professional one, it would be stories of these children.
- DH: That's extraordinary if it's produced those kinds of changes.
- JR: Yes, but it's a small minority.
- DH: Isn't it a mystery? We've had the drug for ten years and people have been working hard on just this issue and haven't got a good lead. It must be doing something radically different. It's not just the balance between serotonin and D2 receptors but something more serious.
- JR: This is probably one of these cases where you want a massive screen of gene expressions, for example. There you could compare clozapine with olanzapine, risperidone, haloperidol and so on.
- DH: Can I bring you back to overview the field again? In the UK, more than you see in the US, there is resistance to giving pills to children. Why?
- JR: There are a number of issues. One is the accurate and important notion that children need to see their lives as developing a sense of

responsibility under their own control. The dominant theoretical structure in social psychology, to this day, has been "focus on control". This is a very strong public model; can you do things yourself, without a drug? But sometimes a drug is necessary to establish control when psychological measures fail. Behavior modification has not been successful for attention deficit disorder. ADHD children are really out of control but, with the aid of medication, they can then put on the brakes. At the same time, there's a growing sense in this country, part of the enormous concern about avoiding drugs during pregnancy, that children may be harmed. So, we're working very hard to select ADHD children on and off stimulants for our prospective brain studies to look at drug effects on brain development. Finally, I think journalists feel that success has to do with uncovering wrongs and they adopt a much more investigational, conspiratorial model of reporting than ever before.

- DH: That's interesting. I haven't heard anyone put it quite like that. At the same time you did suggest there is an awful lot of our most precious cultural rituals might derive from a disease origin. That has to look attractive to some people.
- JR: Yes, but I don't think that the Federal Government would ask us to study this.
- DH: No! Although, in the UK, I see a number of child psychiatrists who prided themselves on never using pills who have become neuropsychiatrists. Do you think things have changed completely in child psychiatry in this way?
- It's so complicated. I think we don't realize how our experience interlocks JR: with everything that impinges on the system we work in. Eric Taylor in the UK and I did a cross national study about the use of drugs in hyperactivity. We trained twenty clinicians in the US on the use of DSM- III. DSM-IIIR and the ICD-9 and, they did the same at the Maudsley. We taped twenty cases in each country, and we had both groups doing the diagnoses in both systems. There were dramatic effects, both in the types of cases being referred, the diagnostic systems and where the raters trained. The nature of the cases differed because if the psychiatrists didn't use stimulants, no one referred a case where hyperactivity was the main problem. So they were seeing conduct problems, which do respond to behavioral management. When they saw the type of child we were seeing in the US, who were referred for stimulants, they had no trouble saying this is a hyperactive child. So, systems feed on themselves.
- DH: True, but back when you tried to draw up the criteria for DSM-III, you met a group of people who said what we do is far too complex to put into operational criteria. Has that changed?
- JR: No, I don't think it has at all. In every new edition of DSM, most of the criteria probably are premature. There's the general public. There are the psychotherapists. There are the psychologists, who prefer a dimensional to a categorical approach. Thirty percent of patients do not fit into any one of the categories. On the other hand managed care is promoting this categorization because without a diagnosis, you're not going to be reimbursed. People are forced to document in order to provide a care. One of my more recent consulting jobs is for a company that develops pediatric algorithms in psychiatry and I am helping them write the algorithms bought by the majority of managed care companies in the United States. I've been doing this now for about three years, so I'm starting to get feedback as to which ones are problems and which aren't. It may be a beneficial influence because people are really paying attention to who they're calling an adjustment disorder five years later.
- DH: So, you're one of the people that the average clinical person on the street would think is trying to curtail their freedom?
- JR: Probably, although the people writing the algorithms aren't the managed care companies, who don't have the time or the expertise. But there's a lot of slippage between the algorithms and what managed care does with them. They may buy them, but they're not obligated to use them.
- DH: From an organizational point of view, have you had much time left over to get involved in kind of the organizational end of things with the APA and ACNP?
- JR: I've always been fairly active in the ACNP. I was on the Program Committee for several years and Chair of the Committee. I've been on Council twice. Right now, I'm on the Credentials Committee. I've been active in Research Groups for the APA and chaired various Prize Committees. I've been President of a clinical group, called the American Psychopathological Association, which represents both psychologists and psychiatrists doing patient oriented research. That's a small group with a long tradition and it's been a very gratifying experience. The last meeting was on Research Benefits and Very Early Presentation of Psychiatric Diseases, of which, in my own work, OCD and schizophrenia are an example.
- DH: When you were in ACNP, did you advocate for a workshop on child issues or some kind of study group that might inform the adult scientists and researchers?

- JR: I've been in the organization since 1976, and in the beginning, people were perhaps too uncritical about work in child. There are people interested in very specific models on how to translate the bench to bedside findings. Right now there's a lot of interest in developmental neurobiology.
- DH: You can feel that beginning to come through.
- JR: Yes, it's mostly basic researchers talking about what could be candidate systems in schizophrenia, what could go wrong and neurogenetics. I think Sue Swedo's work with the immunological model has struck a chord with people looking at immunological models across other disorders. There's Michael Meaney's work on maternal simulation in rats. The program is turning away from patient oriented issues. Clinical trials are being run by people who are not members of the ACNP.
- DH: Quite disastrous to see nobody doing clinical trials.
- JR: Absolutely. The drug companies want somebody who'll make sure that all the FDA forms are filled out correctly.
- DH: Sure, but you need people who are clinically skilled to do the observations, to recognize the new things that are happening.
- JR: Exactly. ACNP would be a place to preserve this approach. In our trials of childhood onset schizophrenia, half of the children have subsyndromal autistic symptoms that go away when they're about four; what might this mean is that it is related to the fragile X types of behavior? You won't get that level of observation in a clinical research organization doing routine drug studies for the pharmaceutical industry.
- DH: Of course not.
- JR: All these genetic studies are finding new diseases within clinically homogeneous groups but the intellectual excitement is not going to be maintained with the way clinical trials are being done.
- DH: Just to round things out, who have been the other key people in the last thirty or forty years who have helped shape the field?
- JR: With the respect to hyperactivity, one of the early people, not so much known for sophisticated research, was Magda Campbell, who is a member here, worked with Barbara Fish and pioneered studies in psychotic and autistic children.
- DH: Are they both working at Mount Sinai?
- JR: Bellevue, I think it was, or maybe even Creedmoor. I haven't actually worked as a physician in New York, but Loretta Bender was there. So, that would be one group. Certainly, Keith Conners has had an influence on me, who's a member of this organization. Leon Eisenberg, very briefly, because his work moved from psychopharmacology, but he's a leader who is very eloquent and he has been an inspiration.

- DH: He's always been in the middle, saying, hold on a bit with the drugs, but he's not hostile.
- JR: A person, who's influenced me and stayed a good friend but not having anything to do with drug treatment, is Mike Rutter. His epidemiologic study gave a rational overview of child psychiatry. Mike would say that he had a lot of treatment studies; they just were non-pharmacological. He would talk about recognition and early diagnosis in terms of what diseases and situations were at high risk I think he'd say his studies of children of psychiatrically disturbed parents would have identified populations for preventive intervention. All of these have social treatment implications. His current studies on the orphans in Romania and what became of them are interesting scientifically and have practical applications. Mike also studied the lighting in the doorways of different housing projects in relation to delinguency rates. It depends on what you mean by treatment. He would say, very possibly, if there are preventative implications it is social treatment. The most exciting thing about the OCD Phase 2 trials of streptococcus vaccination is that if there are two hundred thousand children one may have prevented that many cases of OCD in a few years.
- DH: It would be extraordinary if we could eliminate a condition like OCD in the way we took out general paralysis of the insane with penicillin wouldn't it?
- JR: Yes.
- DH: How we view the history of psychiatry would be changed.
- JR: You're interviewing many clinicians as part of this process. This organization has played a golden leadership role and the ACNP has had a wonderful influence on me, but I hope that they work very hard to encourage the kind of clinical research that couldn't be done within a CRO, but would be beneficial to the scientific field.
- DH: That seems like a good note on which to end our interview. Thank you.
- JR: And thanks to you!

# BARRY REISBERG

### Interviewed by Elizabeth Bromley Waikoloa, Hawaii, December 11, 2005

- EB: This will be an interview with Dr. Barry Reisberg\* for the archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College in 2005. I'm Elizabeth Bromley. Please tell me where you were born.
- BR: I was born in Brooklyn, New York.
- EB: Can you tell me something about your family?
- BR: My father worked in an office, as an accountant for a Wall Street firm. My mother was a housewife and, together, they had about a year of college.
- EB: Do you have siblings?
- BR: I had a brother.
- EB: And, was anyone else in the house when you were growing up?
- BR: No, just the four of us.
- EB: Were your parents from Brooklyn?
- BR: All of my grandparents came from Europe. My father was born in Manhattan, but lived for almost his entire life in Brooklyn and my mother was born in Brooklyn.
- EB: Was there a reason your father's family came from Manhattan?
- BR: It was a Jewish family. Many Jewish people arrived as immigrants in the lower east side of Manhattan and then made it across the river to Williamsburg, in Brooklyn. That's what happened to my father; it was a very common migration pattern. His father had a pretzel factory that I visited when I was young in Williamsburg. They called it a factory but it was the sort of thing I saw, later on, in Afghanistan; a small basement where they had a kiln and all the equipment that was necessary to make pretzels. That was my grandfather, my father's father, and my mother's father was a tailor.
- EB: Can you tell me about junior and high school?
- BR: I went to public schools. I was interested in science and I knew, very early on, I wanted to be a scientist, although I had no real role models.
  I knew medicine was one way of going into science, but I had decided that I was going to be a biologist because I knew no doctors.
- EB: What did you like about science?
- BR: Even at a very young age, I thought I could make a contribution. The meaningful thing to do in life was to discover new things and, for what-

<sup>\*</sup> Barry Reisberg was born in Brooklyn, New York in 1947.

ever reason, I thought I could do that. So, I would go to the local library in Brooklyn and I would read all these children's science books.

- EB: Did you have teachers or someone that encouraged you?
- BR: My mother. She once took me to the Museum of Natural History and got me to meet a man who had some relationship to people I knew from the books I was reading. That was as far as I ever got as a young child. At age 11, while I was in my first year of Junior High School, I travelled on Saturdays from Brooklyn to New York University (NYU), on Washington Square in Greenwich Village, in Manhattan, to meetings of the Junior Astronomy Club. There were lectures from astronomy and physics professors, visits to observatories in the neighboring states, at Swarthmore, Princeton and Yale, and seminars from brilliant students from Stuyvesant High School. Subsequently, at age fifteen, I won a National Science Foundation Fellowship at the end of my second year of high school. I had taken a special New York City competitive examination and I succeeded in winning admission to a specialized science and mathematics high school, Stuyvesant High School. Beginning at age 13, I traveled from central Brooklyn, East New York, Flatbush, to be precise, to attend Stuyvesant High School in Manhattan. Stuyvesant was a very good school. Even at that time, they had Nobel Prize winners who had been prior graduates, whom I sought to emulate. Even now, at the present time, people who win the Nobel Prize sometimes come from Stuyvesant.
- EB: The NSF scholarship, was that at Stuyvesant?
- BR: In junior high school, before high school, I had "skipped" the 8<sup>th</sup> grade of school through New York City's Special Progress (SP) Program for excellent students. It was possible to take a special examination and be accelerated one year through the school system. Therefore, I graduated high school at sixteen, a year younger than most students. While I was in high school, when I was fifteen, I did a National Science Foundation Fellowship over the summer. It was at a small college, Nasson College in Springvale, Maine, and it was fantastic. There were science student awardees from many regions of the United States. I chose to do a project on the comparative histology of the vertebrate kidney. I had to collect snakes, find turtles and do comparative histology. We had an island in Portland Harbor, in Maine, where we saw sea urchins and ate lobsters. It was a very unusual, special experience.
- EB: What year was that?
- BR: I graduated from high school in 1964, so it was in the summer of 1963.
- EB: How did you decide on college?

- BR: Well, Stuyvesant High School was extremely competitive. All the students had passed the competitive entrance examination. If I recall correctly, only one of seven students who took the exam was admitted to Stuyvesant. There were over seven hundred students in my class. If you were not in the top one hundred you were not going to an Ivy League school. I was in the top third of this extremely competitive school comprised entirely of very bright students interested in science and mathematics. I was a year younger than most of the students. I had a New York State Regent's scholarship, which provided me with a small stipend to go to college. So, I decided to go to Brooklyn College, part of the City University of New York, which was free of charge, plus I got paid through the scholarship, and it was within walking distance of my home.
- EB: And, you majored in?
- BR: I majored in biology, my minor was in chemistry.
- EB: What were you thinking your contribution would be? Did you have an idea?
- BR: Like any biology student, I certainly thought about uncovering the secrets, that is to say, the mechanisms, of aging. However, much more practically, I wanted to get into medical school, but I also wanted to broaden my life. Between college and medical school, I won a Council on International Educational Exchange and Japan Society Fellowship. On this Fellowship, I went to Japan with a group of anthropologists to attend a Jesuit school in central Tokyo, near the Imperial Palace. The name of the college I attended is Sophia University, in Japanese, Jochi Daigaku. While I was there, I studied Japanese art, language and Chinese history. It was a very rich cultural experience and, while there, I lived for a week, with a family in Hiroshima and traveled around Japan.
- EB: How long were you in Japan?
- BR: Just a few months. It was the summer after I graduated college and before I started medical school. I came home from Japan, and the next day I started medical school. I was twenty years old starting medical school, which was young. I went to New York Medical College, which was affiliated with Flower Fifth Avenue Hospital and Metropolitan Hospital, basically, in East Harlem. I lived across the street from Central Park in northern Manhattan, in a Hispanic area. Medical school did not seem very meaningful. Not having role models made a difference in terms of my reaction to the whole thing. It seemed meaningless to memorize all those muscles, bones and ligaments. I reacted psychologically against the whole thing and almost destroyed myself.
- EB: By leaving?

- BR: Well, I didn't do well in the first semester at all, but I did what I had to do. The first chance I got in my second summer of medical school, I travelled across Asia. I backpacked from Istanbul to Bombay through Turkey, Iran, Afghanistan, Pakistan, India and Nepal. That was very enriching and after the first two years, medical school also became more enriching.
- EB: So you were looking for the human element in medicine?
- BR: I was. In the third year of medical school, we started to see people and it became more of a human enterprise. That had a lot to do with my choice of psychiatry; the idea that one could be a doctor and still have the human element was very appealing to me.
- EB: To understand people and connect with them?
- BR: Yes, definitely. Along the same lines I traveled a lot in medical school; I believe I went to twenty countries. For my medical school elective, I found a preceptorship position in a small village, Irua, in the interior region, specifically, the Midwest State, in Nigeria, West Africa, for three months. I worked in a single physician hospital. It was interesting how one person, a surgeon, Christopher Okoge, was able to manage a hospital with a lot of help from many nurses. While I was in Nigeria, I traveled to a leprosy village and a leprosy hospital, visited a psychiatric hospital in Abeokuta, near the city of Ibadan, and a psychiatric clinic, in Benin, the capital of what was then, the Midwest State of Nigeria. I became friends with an Italian missionary doctor in one of the nearby villages. I also befriended a Dutch nurse in another village near Irua. I was befriended by the local Irish priests and missionaries. I also became friends with an American Peace Corps volunteer. I visited local indigenous healers and I visited a sewage treatment plant. I went up to Kano, in the northern, Islamic part of Nigeria, where I visited a veterinary hospital. It was an extraordinarily enriching experience.
- EB: Was this in the early 1970s?
- BR: I graduated in 1972, so this was my elective time, 1971 to 1972. I knew that I was going to go into psychiatry. I had already decided that and I did my psychiatry residency in East Harlem in Manhattan, New York City. Once I went into psychiatry, I was able to connect with people the way I wanted to, but I also decided there wasn't enough substance.
- EB: Was the department very psychoanalytically oriented?
- BR: It was. Even though this was a good department of psychiatry, there were really only two people who did research. I was a resident of one of them and I was very intrigued by what this person did.
- EB: Who was it?

- BR: Michael Allen Taylor. He was studying the phenomenology of mania and schizophrenia. He was writing articles, frequently for the *Archives of General Psychiatry*, on the similarities and differences between bipolar disorder and schizophrenia and, also, to some extent, on psychopharmacology.
- EB: You mentioned two people?
- BR: Mickey Taylor worked with Richard Abrams, who was an ECT (electroconvulsive therapy) investigator, in addition to being interested in the issues Mickey Taylor was addressing. I wanted to publish and to go into research so in my final, third year of psychiatry residency, I did a fellowship in behavior therapy, which is the psychological discipline closest to research. I did this fellowship in London, at the Middlesex Hospital Medical School, part of the University of London, in central London, near Oxford Street and the British Museum. I didn't prescribe medicine in London, but I treated patients with phobias and related conditions with psychotherapy. It was enlightening, but it still wasn't research. I finished the residency knowing I wanted to get my psychiatry board certification, take a faculty job and start research. I also wanted the experience of being a regular junior faculty psychiatrist, running an acute psychiatric inpatient unit, etc.
- EB: Did you have people around doing brain research?
- BR: No.
- EB: You didn't get exposed to psychopharmacological research either at the time?
- BR: No, it wasn't possible. After the Behavior Therapy Fellowship, I took two months off to write a book on *Pragmatic Psychotherapy*. In retrospect, I don't think it was really very distinctive, and I wasn't able to get it published. Eventually, a few months after completing my residency, I took a job at a Veterans Administration hospital in Westchester, in Montrose, New York, about 25 miles north of the New York City border. The hospital was affiliated with my former medical school, New York Medical College, the same medical school where I also did my residency training. I was promised a teaching unit with fifteen acute inpatients, however, I was assigned to 30 acute inpatients. I wrote a protocol on lithium treatment on my own, without instruction or help, and got it approved by the hospital research committee. I also worked with Turan Itil, a psychopharmacologist, and a member of of the American College of Neuropsychopharmacology, on his research. I had interviewed with Turan prior to taking the VA position. The promise of being able to do research with Turan was a major reason for my taking the job. Together, the medical school teaching, the extensive clinical patient

experience, and the research, made this an excellent opportunity. Turan would give me books and papers of materials and I wrote a half dozen publications. My first research paper was titled *Use of Psychotropics in the World.* It turned out that there was more variability in psychopharmacologic prescribing practices in New York City than there was in the worldwide data, which is not so surprising for New York City!

- EB: Where did you get that kind of data?
- BR: Turan had it. He gave me a large pile of papers and materials, and I wrote a journal article based on the material. I also applied for a grant for my work with Turan from the Veterans Administration research funding agency, but the grant came back with a review something like, "fools rush in where angels fear to tread".
- EB: You wanted to do, what in your grant?
- BR: I don't think it was such a brilliant idea, but I wanted to try different medications with the patients available to me. The patients at our VA hospital who were available to Turan and myself were chronic, treatment resistant patients, who were said to have chronic schizophrenia. These reviews often tell the truth and it's important to get the message. I ended up at the VA for two and a half years, teaching the medical students from New York Medical College, doing administration, running the ward and doing research. But if I had stayed any longer, my life would have become repetitive. So, I knew I had to leave. I had passed my boards and was going to international conferences. I started to interview with ACNP members like George Simpson and Samuel Gershon. Sam Gershon was exactly the person I was looking for and I accepted a position with him. Sam directed the Neuropsychopharmacology Research Unit at Bellevue Hospital which was part of the New York University School of Medicine's Department of Psychiatry. Sam had twelve junior faculty members in similar positions to the one I accepted. These junior faculty included psychiatrists, pharmacologists and biochemists, all trying to find their way, more or less at the same level as myself.
- EB: When was this? What was the most important work that you did there?
- BR: This was February, 1978. This is where I really started. Sam didn't exactly tell me what to do but there were two topics I was gently guided to. One was working on lithium, the other was geriatric psychopharmacology. Sam had written one of the early books on lithium, and he had conducted pioneering research on the usage of lithium in mania and related conditions. I was asked to review the side effects of lithium therapy. So I wrote an article on the side effects of lithium therapy which was published in the Archives of General Psychiatry. The

other area which Sam guided me to in research was termed "geriatric psychopharmacology". There was a research unit devoted to geriatric psychopharmacology at the Millhausen Laboratories, located at the NYU Medical Center, across the street from Bellevue Hospital. This unit, working under Sam's direction, had a National Institute of Mental Health (NIMH) grant, and several ongoing pharmacologic trials in the area. The Principal Investigator on the NIMH grant was a psychiatrist, Gregory Sathananthan, who apparently also was the nominal director of the unit. However, Gregory, for some reason, had become unable to fulfill his role, and apparently, I was hired, in part, to replace him. Steve Ferris, a research psychologist, had been working on the unit, with Gregory, under Sam's direction. I began to work with Steve. I quickly realized, within a matter of months, that geriatric psychopharmacology, was a neglected area. I then focused in this area, and I devoted my full time and energies to geriatric psychopharmacology, and related issues.

- EB: Did you have diagnostic categories that you used in practice?
- BR: There weren't any formal published categories. However, very importantly in retrospect, our laboratory, did have an unpublished schema, consisting of seven levels, with the words, "no deficit; very mild deficit; mild deficit; moderate deficit; moderately severe deficit; and severe deficit". There were psychometric test performance criteria, which went with these phrases. Over the subsequent years, I succeeded in adding accurate clinical, behavioral) descriptions to these otherwise meaningless qualitative terminologic labels.
- EB: Were there some colloquial descriptors of symptoms in dementia?
- BR: There were also measures developed by the NIMH. I used a measure called the Inventory for Psychic and Somatic Complaints of the Elderly (IPSC-E), for my pharmacologic treatment trial assessments. However, the scales which I utilized at that time didn't have anchor points. I realized that I had this neglected illness, now termed, "Alzheimer's disease", and this condition had been virtually undescribed. I also recognized the enormous dimensions of the problem I was studying. I became totally involved at this point, using my anthropologic background and interest in describing the stages and in developing appropriate rating instruments. When my first book, brain failure, was published in 1981, I had three phases of the illness process. However, by 1982, I had clinical classifications of seven major stages from normality to most severe dementia, for the condition now called Alzheimer's disease. From February of 1978 until today, we've been following those patients for twenty-seven years. Very soon after I began my work at NYU, I wrote a grant and I was awarded funding in

the first round of grants, from the newly created US National Institute on Aging, in 1979. This was termed a "Special Initiative Award for Research on Aging." The book, Brain Failure, was a hit. Brain Failure was reviewed in JAMA, The New England Journal of Medicine, and other medical and scientific journals. Many of the reviews were very favorable. For example, the Journal of the American Geriatrics Society, stated that brain failure, "...should be on the bookshelf of every clinician interested in geriatric medicine..." and that the book was "...a good reference source for families seeking additional information regarding current concepts in brain failure". In 1982, I published the seven clinical stages of brain aging and what is now termed, progressive Alzheimer's disease, in the Global Deterioration Scale (GDS) in the American Journal of Psychiatry. The GDS was published together with validating psychometric test concomitants, FDG positron emission tomographic (PET) data on brain glucose utilization, and computerized tomographic brain scan neuroimaging data. That paper is as revolutionary now as when it came out and remains a guidepost for understanding the progressive brain changes of subjective cognitive impairment, mild cognitive impairment, and the subsequent, clinically manifest stages of Alzheimer's disease.

- EB: Can I ask you how the imaging got in there?
- BR: Because of the research which our group was conducted the beginning of 1978 on CT brain imaging and beginning in 1979, on fluro-deoxy-D-glucose labeled, positron emission tomographic studies of brain glucose utilization. As a result of our group's collaboration, in 1979, I obtained an appointment at the Brookhaven National Laboratory in Upton New York as a member of the Medical Staff and as a Research Collaborator. Because of this collaboration, I accompanied the first Alzheimer's disease patient ever to receive a PET scan from New York City to the Brookhaven National Laboratory in Long Island, about 70 miles east of Manhattan. Monte Buchsbaum, then at the NIMH, flew up from Maryland to watch the procedure that day. I didn't do the imaging analysis, but I tried to integrate my clinical descriptive work with the other modalities. Subsequently, in 1980, our group published the first results demonstrating a decrease in brain metabolism, in various brain regions, using the then new positron emission tomographic scanning technique. In the twenty-seven year longitudinal data we are able to predict who becomes worse and who doesn't deteriorate on the basis of the quantitative, computer analyzed electroencephalogram at baseline, with ninety percent accuracy. I continue to utilize various imaging techniques in my investigations until the present time. I also continued

my clinical descriptive work subsequent to the publication of the Global Deterioration Scale.

In 1983, I came out with an edited textbook entitled, *Alzheimer s Disease*, which was much larger than the single authored book I wrote and published in 1981. That larger textbook was also very well received. At that time, in 1983, I was very enthusiastic. I was young and maybe, too enthusiastic. We had done a drug trial that seemed to be working and I published a letter in the *New England Journal* that attracted enormous attention. We got boxes of mail from all over the world asking for assistance. However, I was wrong. The medication was eventually shown to be ineffective. It hurt. Perhaps I was moving too fast. But I continued to move forward.

- EB: Did you want to say more about that letter and being wrong? How did that happen?
- BR: The data was wrong and I'm not sure why. It may have had to do with behavioral disturbances in these relatively severe Alzheimer's patients. I subsequently went on to describe the symptomatology of behavioral disturbances in Alzheimer's disease (AD) in great detail. However, these behavioral disturbances occur mainly in more advanced AD. The key to understanding more advanced AD is the understanding of the progressive functional changes in AD. In 1983, I described 7 functional stages corresponding to the Global Deterioration Scale stages. In 1984, I began to publish functional substages of the moderately severe and severe AD stages. By 1986, I had described sixteen successive functional stages and sub-stages of the evolution of Alzheimer's disease. However, in 1983, I couldn't determine what was wrong with the study described in our letter which had attracted enormous attention.
- EB: That kind of mistake happens in science. Was there something about working on this illness that was so devastating you ended up believing you must find something that would help?
- BR: I kept uncovering new findings about AD. So at no point did I consider the single unreplicable study finding devastating. In particular, I thought that I was still able to help family members in various ways. I always kept my practice. Seeing patients grounds an investigator. It is good not to just do research. A good clinical investigator has to see patients. I continued to see patients and I continued to learn from my patients. The fact that I was interested in the patients was enormously helpful for family members and this is still true today. I have a unique practice. Many doctors run away from the patients and they don't really look at the person. I look the illness in the eye in every sense of the word. To me, psychiatry is observation, but that observation is not widely practiced.

This is my strength. Most doctors don't look; they think there has to be a new technology before they can see something. If it's only the patient they think there is nothing new to be seen. Today, I'm no longer trying to do descriptive work. I have other goals, but I'm still spending time with families and patients, exploiting this in terms of medication development and in many different ways. But to go back to1983, it wasn't only a debacle. I did a news conference with the Secretary of Health. The disease was just becoming known. It was a new disease, but now it had a name, "Alzheimer's disease". Brain Failure was published in paperback in 1983 under the title, A Guide to Alzheimers Disease . The U.S. Secretary of Health, Margaret Heckler, read an article in the New York Times, Sunday magazine section that was written by the daughter of a patient of mine about her mother. In the article entitled, Another Name for Madness, Marion Roach described the "new illness". Alzheimer's disease. She described how she and her sister. Margaret, came to me for assistance. At that time, Alzheimer's disease was a new word for the public. Marion Roach's article was the first time the US Secretary of Health had heard of this new disease. Therefore, when it seemed I had a new treatment, they rushed me to Washington, D.C. I did a news conference with the Secretary of Health about the new medication. The idea that there might be a medication treatment for dementia was a major event. The government, wisely and properly, exploited this and used it to get funds for the disease. In the end there was no real harm, but on the other hand, although it was only a letter, the claim was explosive. This was a new disease. Everybody had the potential to get it. It did have repercussions. I continued to apply for grants but I had more resistance as a result. I continued the descriptive work and in 1986 I was able to describe the sixteen successive functional stages in the evolution of Alzheimer's disease. I recognized that the sixteen functional stages of AD were a precise reversal of the order of acquisition of the same functions in normal human development. I understood that was very important and that I had to exploit it. I had to follow it and continue the descriptive work.

- EB: Were you continuing the imaging, also?
- BR: We were doing everything. We weren't called a center but that's what we were and we became an NIMH Center in the late 1980's.
- EB: What studies were you doing at that time?
- BR: Well, we were always doing pharmacologic studies and I was trying to get the pharmacological industry to use my measures so that people would learn about them and consequently understand the disease. I came out with a measure called the *SPAD*, *Symptoms of Psychosis in*

*Alzheimer's Disease*, which described some of the characteristic psychotic symptoms in AD for the first time.

- EB: You do a lot of observing, writing and thinking and then...
- BR: It comes together. And, I throw away the symptoms that aren't consistent. I'm looking for consistency and universal symptomatology.
- EB: You sound like you moved from one opportunity to another and that you're guided more by what's in front of you than some overriding objective.
- BR: As you will hear more about later, I did pursue, very consciously, the reversal of normal development phenomenon until the present day. I want to discover what the disease is about, in other words, the cause of the disease, and I want to cure the disease. I want to accomplish things that are real, not an illusion. It is like climbing a mountain. You grab onto what you can get and try to move from there. It's a very useful strategy. However, you still have a vision of the top of the mountain. So, I've been consciously pursuing this, trying to contribute where I felt could. For example when I discovered the treatable aspects of the disease, pharmacologically, I came out with a rating scale, which was an expanded version of the SPAD, and which I had spent several years developing, the BEHAVE-AD, i.e., the Behavioral Pathology in Alzheimer's Disease assessment. This instrument described twentyfive characteristic symptoms in seven major categories, which were separate from the cognitive and functional symptoms, which I had described previously. The BEHAVE-AD covered different symptomatic domains, with different trajectories than the cognitive and functional symptoms, which peak at different points in the AD illness process. It changed the field and the BEHAVE-AD particularly impacted risperidone, the medication that got the furthest in treating behavioral symptoms. Risperidone was approved in thirty nations based on my scale, but the FDA, instead of approving risperidone for treating the behavioral symptoms, decided that these medications were not safe and put out a black box warning, placing them in the dangerous category. I know what went wrong; no one else is treating behavioral symptoms the way I do. I start with a low dose and take my time, I wait weeks, frequently several weeks, before I increase the dose, but apparently no one else is doing that. In terms of psychopharmacology, the cholinesterase inhibitor medications were the first to be developed. The first member of this class to be marketed, tacrine, wasn't safe. The second one, donepezil, is still widely used and the third one, rivastigmine, was developed by a doctor, Ravi Anand, who had come to our center to work as a research clinical fellow in 1982, shortly after he had completed medical school

in India. Ravi subsequently went to work in the pharmaceutical industry where he eventually became the person in charge of the clinical development of rivastigmine for Sandoz, now Novartis. Together, Ravi, Steve Ferris, and I developed a new, global scale to assess the efficacy of the medication using previously validated behavioral and cognitive measures from my other scales. Hence, rivastigmine was eventually approved throughout the world using six of my previously developed clinical rating scales. Four of my clinical instruments, the BEHAVE-AD, a companion measure known as the E- BEHAVE-AD, my functional staging scale, the FAST, and a measure related to and derived from my Global Deterioration Scale, the Brief Cognitive Rating Scale, were used as part of the new global assessment, termed the NYU-CIBIC-Plus. This assessment measure, the NYU-CIBIC-Plus, was the primary outcome measure in the worldwide rivastigmine clinical trials. Additionally, these studies also used the Global Deterioration Scale (GDS) as a stand alone efficacy instrument. These and other measures showed rivastigmine to be efficacious. The medication, rivastigmine, is presently marketed under the brand name. Exelon.

I did a lot of other work with pharmaceutical companies including ten years of work with Bayer to develop the Activities of Daily Living International Scale (ADL-IS), a scale which is very sensitive to mild cognitive impairment.

Another German company, Merz, came to me. It was a very small company and they had a medication, memantine. Merz had a positive study from what were basically six nursing homes in Latvia. The patients studied had severe dementia. The dementia was more severe than the approval range of the cholinesterase inhibitors. The only internationally recognizable instrument employed in these studies was my Global Deterioration Scale. These patients were mostly in stages 6 and 7, i.e., with severe and very severe AD, on my GDS scale. I looked at the data and told them they should replicate it and that I could design the study. These severe patients were a neglected population who needed treatment but had nothing. All the existing medications were approved only for mild to moderate AD, GDS stages 4 and 5.

- EB: Was there a concern because they ended up with a pretty unique indication for, not just an illness, but also severity?
- BR: The FDA was approving medications based only on mild to moderate severity.
- EB: You thought there would be an opening there?
- BR: Yes, and a tremendous need. The severe patients are the most burdened behaviorally. I had done a lot of work on the behavioral aspects

and had all the scales to measure it. I worked with my associate Steven Ferris who had also worked with the FDA and knew their requirements. The study was successful and the question was what to do about it and I thought it should go to *The New England Journal of Medicine*, probably the most prestigious medical journal in the world.

- EB: Have there been drawbacks working closely with the company in terms of your other scientific objectives?
- BR: No, I pursued my other objectives. In any case, going to the New England Journal was a gamble and it was a very extensive review process. It took me years, but it turned out to be worth it. Now, I have the open label study of memantine treatment coming out in January, which will also be important. It seems the medication continues to work, not only for six months, but for a year. Placebo patients, when they were switched to active medication, got better. I've had a similarly productive relationship with industry with regard to the treatment of behavioral symptoms with Janssen, the developers of risperidone. As already described, I previously had a productive relationship with Novartis, the developers of rivastigmine. So, I definitely seek these relationships with industry. I compromise, but I go in my own direction, I have my own vision. I am very conscious of having to seek funds for my research center, but I also see patients.
- EB: What do you say to practitioners or others who aren't so sure these drugs work?
- BR: I think the gains with respect to the cognitively acting medications are modest and difficult for family members and others to detect.
- EB: You have to rely on the scales?
- BR: Yes, completely and additionally, on large numbers of subjects. Memantine is slowing the progress of the disease under controlled circumstances but I don't know what the true, real world, circumstances are in terms of the effects of the medication. I'm not only interested in medications, so let me go to another aspect. I was intrigued that reflexes emerged in dementia patients and in Alzheimer's disease. I knew these reflexes were developmental reflexes, but it wasn't clear where they emerged in terms of the progress of Alzheimer's disease from subjective impairment to severe dementia. I worked together with a neurologist and neuropathologist, Emile Franssen, to focus on studying these reflexes. It was a long pursuit. We developed an instrument that had two hundred items on a seven point scale. Emile was very meticulous. Eventually we published the findings in the *Archives of Neurology* in 1991 and 1993. The reflexes were emerging, more or less, at developmental age appropriate points in the evolution of AD.

So, it's not only cognition and functioning but, also, neurophysiology, neurologic reflexes, which occur in a reverse order to the acquisition patterns in normal development. In 1997 we published data on nearly eight hundred patients in the *Journal of Geriatric Psychiatry and Neurology*. Some of the same reflexes which are markers of continence after infancy, in very young children, are just as robust markers of the emergence of the infantile stage in Alzheimer's disease, as determined by the developmental age equivalent of the FAST stage.

- EB: What do you think it signifies, neurologically and biologically?
- BR: We can explain the behaviors and also behavioral disturbances of Alzheimer's patients on the basis of the developmental stage. For example, Alzheimer's patients develop agitation or catastrophic reactions. If we look up the definition of catastrophic reactions in Ladisdov Volicer's book, Clinical Management of Alzheimer's Disease, published by Aspen in 1988, and the definition of temper tantrums in Webster's dictionary, we find the same definition, just different sobriguets, for precisely the same conditions. The same phenomena apply to the behavioral symptoms which occur in Alzheimer's disease more generally. Many of these symptoms can be explained on the basis of the developmental age of the Alzheimer's person. The so called "delusions", which occur in persons with Alzheimer's are really just fantasies. Just as childhood fantasies are fleeting conditions, the same is true of the so-called "delusions" in person's with Alzheimer's. In Alzheimer's the so-called "delusions" are not firmly held. In contrast, a schizophrenic patient's delusions are firmly held. The developmental age of the AD person also provides an explanation for many other behavioral symptoms. For example, fear of being left alone. If you leave a two year old child alone, they are going to be afraid. The same phenomenon is observed in Alzheimer's persons at the corresponding developmental age based stage. Therefore, the developmental age based severity level explains many of the behavioral disturbances of Alzheimer's disease. The developmental age of the person with Alzheimer's disease also explains many other symptoms. For example, language is acquired over twenty years in normal development; it's lost over a period of approximately twenty years in the course of the Alzheimer's disease. I've known the time course of AD since 1986 when I published it in Geriatrics. Now, it's only a matter of proving it, on the basis of my clinical observations. This effort to prove my clinical behavioral observations of the temporal course of the AD stages will continue for the rest of my life; it's going to take some time. These efforts are termed empiricism in science. In science, you're permitted to look and see, and report what you see. We do it with telescopes and

microscopes. It's allowed in science, but nowadays you're supposed to prove that what you see is real, so that can take time. In 1999, I published a name for the concept of the developmental reversal in AD. I was president of the International Psychogeriatric Association and my presidential paper would be published. I used this opportunity to publish a paper on retrogenesis and the science of management of Alzheimer's disese. This publication explained how a clinician can treat every stage of Alzheimer's disease on the basis of the neurodevelopmental age. For example, a clinician, or a caregiver, or a family member, can understand the needs of the person with Alzheimer's, depending upon the developmental age. The severe Alzheimer's patients in nursing homes are presently neglected. They need the same care as an infant or a child, with all that implies. So, they need to be touched. In a nursing home it is presently considered an assault to touch an Alzheimer's person. The person with severe Alzheimer's continues to need love, but you can't write them a letter. You can't write them a poem. You have to express that love physically. You can't write an infant a poem. And so it goes for every stage of Alzheimer's. I published the science of management of Alzheimer's disease; the management needed is that corresponds to each stage. Later I published additional scientific papers on retrogenesis and the management science of AD. Now, we approach the present. This is retrogenesis. This is what I'm pursuing and what I'm publishing this month, in Alzheimer's and Dementia, in the Alzheimer's Association's new journal.

- EB: You just answered my question.
- BR: I have been searching for the causes, in other words, the mechanisms of the development of Alzheimer's disease. However, the answers have not been accessible. I've been consciously on this search for a long time. I'm also consciously trying to contribute where I can and to make genuine contributions. So, when the nerve growth factor was discovered, it was obvious to everyone that this might have something to do with Alzheimer's disease. I said it in print, however, as an isolated statement, it wasn't particularly meaningful. In 2000, the answers to the origins of Alzheimer's disease began to become more accessible. It's bringing me to basic science. Peter Davies was one of the discoverers of the role of the cholinergic neurotransmitter system in Alzheimer's disease. He subsequently discovered Alz 50, which is a developmental protein present in infants, and which reappeared in Alzheimer's. Peter Davies spoke about Alz 50, and I spoke about the behavioral disturbances of Alzheimer's disease, in a symposium at the American Psychiatric Association's annual meeting, in 1987. The audience was

one the largest I've ever reached. Alz 50 kind of died, as a scientific idea, because it turned out to be tau, which was already known. Tau is the major molecule behind the neurofibrillary tangle. It's the scaffolding molecule that holds up the neurotubules. In Alzheimer's disease, tau becomes hyperphosphorylated. This hyperphosphorylation weakens the neurotubules, which then become tangled. Peter Davies was also apparently the first scientist to note that Alzheimer's disease, in some ways, is like cancer. There is a reactivation of a mitotic process in the neurons in the brain of Alzheimer's patients in response to injury. Peter Davies made this observation in 1996, I believe. It became a field of much broader scientific inquiry in the year 2000, when several papers on this topic were published in the journal, Neurobiology of Aging. I read the papers in that issue three times. The cell cycle was not something I knew much about. For example, the different kinases and enzymes associated with the cell cycle, but I believed I was pursuing a mechanism which might explain the clinical phenomenology which I have been observing in AD. In 2002, I published that the cell cycle reactivation might help to explain the retrogenesis process observed in Alzheimer's disease. Many different people are finding the reactivation of cell cycle factors, but it's not the whole story. In the interim, it was discovered that the hyperphosphorylation of tau is a developmental phenomenon. Tau hyperphosphorylation appears in infancy, and then it disappears. Subsequently, tau hyperphosphorylation reappears in Alzheimer's disease. The specific hyperphosphorylation sites and the magnitude of hyperphosphorylation are basically the same in infancy and in AD. AD hyperphosphorylated tau is said to be a form of fetal tau. So the molecules and mechanisms producing neurofibrillary tangle pathology also are developmentally retrogenic.

I've also continued to search for improved AD treatments. Memantine works as NMDA receptor uncompetitive antagonist. Eric Kandell shared the Nobel Prize in 2001 for work on memory and I began to study the memory process. The growth factor, BDNF, the brain derived neuro-trophic factor, is released from the presynaptic neuron in response to exercise. This then stimulates receptors in the postsynaptic neuron which act on the ionotropic cyclic AMP and NMDA receptors. If too much glutamate accumulates as the result of injury to the presynaptic neuron, then there is an influx of calcium. This is toxic to the postsynaptic neuron and to the long term potentiation memory process. These growth factors are involved with memory, with stimulation of the NMDA receptor. Under pathologic conditions, the hyperphosphorylation of tau is produced by the reactivation of the cell cycle and as noted,

most of the specific hyperphosphorylation sites are identical to those of fetal tau. I don't have all the explanations, but the story is beginning to come together as we learn about the molecular biology of the disease. This has treatment implications, which I'm trying to pursue. I believe Alzheimer's disease represents a new mechanism of disease and that this new disease mechanism applies, not only to Alzheimer's disease, but to other dementias, and it may even apply to brain injury more generally.

- EB: We're going to run out of time but I have a question, before we finish. Is there Alzheimer's disease in your family?
- BR: Coincidentally. I believe most extended families have experience with Alzheimer's disease. This is analogous to the situation with respect to other major late life illnesses, such as cancer. Most extended families will have had experience with cancer. So my grandmother had Alzheimer's disease, but this is later, after I began studying the disease.
- EB: Your grandmother, your father's mother?
- BR: No, my mother's mother, but my father's father had dementia before he died and I've had an uncle who had Alzheimer's.
- EB: Either of your parents?
- BR: No, they both died of cancer.
- EB: Well you've given us the major story of following something from the clinic, watching it and cataloging what you see, systematizing the observation and, then, using those observations to develop an explanatory analogy. Then you provided something futuristic regarding treatment using what you think about the analogy and what's going on in the brain. Altogether there's a really nice complete side to this story.
- BR: I'm consciously pursuing that story. It's not accidental. I do think there is a kind of beauty to the story, a symmetry to the disease, that's increasingly unfolding. I'm extremely satisfied, with the contributions we've been able to make to the understanding and treatment of AD, and our increasing understanding of the likely origins of AD.
- EB Thank you very much.
- BR: Thank you.

## ERIC M. SHOOTER

#### Interviewed by Thomas A. Ban San Juan, Puerto Rico, December 9, 2002

- TB: This will be an interview with Dr. Eric Shooter\* for the archives of the American College of Neuropsychopharmacology. It is December 9, 2002. We are at the Annual Meeting of the College in San Juan, Puerto Rico. I'm Thomas Ban. We should start from beginning. When and where were you born? Tell us something about your education and how you got involved with neuropsychopharmacology.
- I was born in a small village north of Nottingham in England that was ES: part of the original Sherwood Forest. My family jokes that we got our name from our ancestors, who were the shooters in the forest, clearly on the side of Robin Hood and not the sheriff of Nottingham. But, my family moved after about two months and my father, who was a mining engineer, became an inspector of mines in the mining district, which encompassed the counties of Derbyshire, Nottinghamshire, and Staffordshire. The town in which we were situated. Burton-on-Trent. was outside the mining area with easy access to all three counties. It was a major brewing town where beer had been brewed since William the Conqueror using water from the local wells. I lived there until I was eighteen and left for Cambridge and I had a very pleasant childhood. I had one brother, Kenneth, older by eighteen months, so there was always a companion around, for better or for worse. My parents were very loving, but reasonably strict. I went to state schools, first from five till eight or nine, then to an intermediate school and from there, I managed to win a scholarship to the local grammar school, which had been founded in 1521. It was a relatively small school with three hundred pupils ranged in the age from ten to eighteen. It had a good teaching staff, strict but relatively pleasant, a very encouraging atmosphere and a nice place to thrive. We studied the usual set of subjects and played a lot of sports including, cricket, rugby, running and tennis. When it came to specialize it was easy for me to choose the topics, science, math, physics and chemistry. In the small amount of science I'd taken in the first four years, I came to enjoy its logic. You could ask a question and get a reasonably straightforward answer without too many permutations. In those two years of specialization I went through to the second level of examinations, the higher school certificate and gualified for college at age 16. I had a headmaster who was a superb person with a number of great attributes. He was determined to get more of his

<sup>\*</sup> Eric Shooter was born in Mansfield, England in 1924.

students from our school, the Burton-on-Trent Grammar School, into Cambridge. He'd just come from a senior position in Cambridge and knew how to do this. He also insisted that nobody should attempt to go to college before the age of eighteen, so he suggested I stay around for another two years in the Sixth Form retaking and expanding the same subjects. It was very good advice; the third year was with other boys doing the same thing, the fourth year by myself. We were given textbooks of *Experimental Physics* and *Experimental Chemistry* and allowed to work our way through them, which I did with great abandon and pleasure. I recall when I managed to accidentally light the hydrogen jet and blow the apparatus up. It disappeared through the roof and there was a little bill to pay for the repair. Aside from that, I learned a great deal about experimental physics and chemistry, which helped me enormously when I finally went to Cambridge.

- TB: What year did you go to Cambridge?
- ES: I took the exam for Cambridge in the year 1941, passed and was admitted to Gonville and Caius College in 1942. Being wartime, the decision whether I went to college or not was made by a National Board.
- TB: What did you do at Cambridge?
- ES: I had three years at Cambridge studying mathematics, physics and chemistry and an extra subject of mineralogy. Although many of the Fellows of the colleges had gone off to war the teaching was still at a very high level and we benefited from the usual Cambridge system, having a weekly tutorial, one on one or two, with experts in my chosen subjects. I found mineralogy much to my liking, the characterization and study of mineral crystals and their analysis by x-ray crystallography. Given my choice, I would have become a mineralogist but at the end of two years the British government decided that chemistry would be an important subject after the war. So they told a group of us that if we wanted to study chemistry for a third year and specialize we could stay on. There were twelve or thirteen of us who opted for that. I completed the third year successfully in the summer of 1945 as the war was ending and was able to immediately stay on in Cambridge as a graduate student in the Department of Colloid Science, a department committed to the study of the chemistry of large molecules.
- TB: Chemistry of large molecules, could you elaborate?
- ES: Large molecules are the naturally occurring polymers and proteins like collagen or the plant polymers. It was a topic that was to become increasingly important with the manufacture of man-made polymers. Nylon came into being about 1947, during my graduate work, so the subject had enormous importance for understanding the properties,

chemical structures, and the characteristics of these compounds. My supervisor, Paley Johnson, had originally been going to get me to work on rubber as one of the important polymers until he found a postdoctoral fellow to do that and thought I would enjoy working on the proteins of the groundnut (peanut) instead. It was known that you could extract proteins from peanuts and spin them into a fine fiber, which was guite elastic and stable, suggesting the possibility of making cloth and garments out of peanut protein. Before that got very far however, it was superseded by nylon. Interestingly though, the British government thought it could help England where they was still rationing and countries in West Africa nutritionally, if they grew peanuts. So they set out to do this on a large scale in West Africa. Curiously, they'd never done a pilot study, so when they started large-scale production they found there were many animals and insects in Africa, who enjoyed these peanuts, and they only collected a few pounds from many thousands of acres planted. Anyway, I was willing to study peanut proteins because it meant I would learn two of the methods available at this time for studying polymer structure, ultracentrifugation and electrophoresis. These methods required big complicated pieces of equipment in which the movement of proteins in solution under a centrifugal or electrical field was followed with a schlieren optical system.

The first year was spent in the Department of Colloid Science in Cambridge but the Head of the Department then decided to move to take up Directorship of the Royal Institution in London and most of the department members decided to move with him, including myself. The Royal Institution has a long and distinguished history in British Science being the place where Faraday, for example made all his important and original discoveries. It has a rich scientific atmosphere including a magnificent library and is renowned over the years for its Friday evening discourses, given to a lay audience by distinguished scientists with an emphasis on scientific demonstrations. The experimental equipment of many of the previous directors is displayed in the Institution as well as plaques to denote their workplace such as the plaque in the floor of the laboratory where Faraday kept his frogs. One of the more recent visitors to the Institution was Madame Curie who left her own imprint in the form of traces of radium in the drains. This was not discovered for many years until Sir Lawrence Bragg came from Cambridge in the early 1950s to fill the Faraday Chair and restart crystallography research in the Institution. All his X-ray film was fogged up before he started his experiments and the culprit was the radium in the drains.

TB: When did you get your PhD?

- ES: I completed my PhD in 1949 and wrote a thesis describing the characterization of the major peanut proteins. All together it was an extraordinary few years where I was allowed to work essentially independently. At the end I decided this was an area of research that I would like to take further and so I applied for and received a one-year post doctoral fellowship in the Department of Chemistry at the University of Wisconsin, a world-renowned center for macromolecular research.
- TB: This was in...
- ES: This was 1949. In November my wife and I left the UK for America on what was our honeymoon. We arrived in New York with ten dollars each in our pockets, the maximum amount the British government would allow us to export. Ten dollars, I expect, is about a hundred dollars now so it wasn't quite as bad as it sounds. You can do these things when you're twenty-four! I'll never forget the welcome we got when we finally arrived in Madison. My major professor, Jack Williams, came to the railway station to meet us with his car and said, "Hello, Eric and Elaine. I'm Jack and you will call me Jack". We couldn't do that. That was much too much of a transition.

It was a terrific year working under Jack Williams who was a very distinguished professor of chemistry. He was one of the few members of the National Academy at the University of Wisconsin. There was also a very bright and energetic young assistant professor, Bob Alberty in the department who had come from the University of Nebraska and Bob was very much into the theory of the sedimentation and electrophoresis of proteins. I learned a lot from both of them. I worked on the separation of serum from proteins and found you could identify five groups. One of the groups was the immunoglobulins, which were beginning to get a lot of attention.

- TB: What did you do after the year in Wisconsin?
- ES: I returned to England in the middle of December 1950, to take up a position I'd accepted before I went to America, as a scientist at the Brewing Industry Research Foundation. There was a large amount of money in their research fund and they decided to emulate the Carlsberg Laboratories in Denmark. The Carlsberg Laboratories had been deeded into a foundation. All the profits from the brewery went into two research laboratories, the physiology and microbiology laboratories. The idea was to do basic research on the biochemical and microbiological process of brewing. The goal was not principally for brewing but to benefit mankind and they became very distinguished particularly, the physiology laboratory. They did very early work on protein structure using micro methods of analysis. So this is how the Brewing Industry

Foundation in England got started. A number of us were recruited. I went there to characterize barley and malt proteins using the two methodologies of centrifugation and electrophoresis.

- TB: From the Brewing Industry Research Foundation you moved to the University College of London.
- I was fortunate to get a job as lecturer in biochemistry in a distinguished ES: department of Biochemistry at the University College of London, the only department in the University of London that was then teaching biochemistry at the Master's degree level. For me, it was an eye opener and a very good way to learn how to teach, both the experimental procedures and formal didactic lectures. We taught a course in experimental biochemistry, where we devised the experiments and then stayed with the students from nine in the morning until five in the afternoon, mentoring and tutoring them on the experimental procedures. It made teaching much easier and I learned a lesson for later; what it might be like to teach a class of several hundred medical students, the basic aspects of biochemistry and to enjoy it, rather than have it be a chore. Later on, I did get to do research. In the late 1950's, I came to know an anthropologist at the college, who was working in Africa, studying the genetics of blood groups in different populations and he would bring back samples of blood, from which we could isolate the major red cell protein, hemoglobin. Very shortly after that, Pauling showed by electrophoresis that sickle cell hemoglobin was different from normal hemoglobin and Vernon Ingram showed that there was a single amino acid substitution, which changed normal human hemoglobin into sickle cell hemoglobin. This opened up the whole field of hemoglobin genetics, the study of a variety of different hemoglobins and how a single amino acid substitution changed the properties of proteins in such a way that it gave rise to a very definable disease. In the case of sickle cell hemoglobin, that single change made the protein sticky, so unlike normal hemoglobin, which can change from oxygenated to deoxygenated hemoglobin with no change in solubility, deoxygenated sickle cell hemoglobin aggregates into sickle cell shapes that have great difficulty going around in the circulation, causing the concurrent symptoms of the disease. This was the start of biochemical genetics in terms of protein structure. My colleague was a brilliant hematologist, Ernie Huehns, in the Hospital at University College. He was able to collect from the various immigrant populations in London different hemoglobins that we could classify and characterize. We were responsible for discovering hemoglobin G and for characterizing an  $\alpha$ -chain variant. We also, with A.B. Raper, proved that two genes one for the  $\alpha$ -chains and one for

the  $\beta$ -chains controlled the synthesis of hemoglobin. Then, towards the end of the 1950s, I thought I should learn something about this upcoming subject of DNA and went on a sabbatical to join Buzz Baldwin in the Department of Biochemistry at Stanford University.

- TB: So we are now at the end of the 1950s.
- ES: The medical school had just moved from San Francisco and built a new hospital. It provided the opportunity to bring together a new cadre of incredible chairmen in the basic and clinical sciences; David Hamburg, for example, who was appointed Chair of Psychiatry, was one of the first biological psychiatrists in the early 1960s. Norman Kretchmer was Chair of Pediatrics and, Henry Kaplan, Chair of Radiology on the basic science side, Avram Goldstein in Pharmacology, Joshua Lederberg in Genetics and Arthur Kornberg in Biochemistry. The whole place was humming with intellectual vigor and I could not have chosen a better place to visit.

By studying the melting behavior of a hybrid DNA molecule in which one strand was labeled with bromine, Buzz Baldwin and I were able to show that the replicating unit of DNA is the single strand. Although this result seemed obvious from the structure of the Watson-Crick helix it had not been formally proven.

- TB: What did you do after your sabbatical at Stanford?
- I went back to England but only for two years, because I had agreed ES: with Joshua Lederberg that I would join his Department of Genetics and start research in the new field of neurobiology. Joshua, in listening to one of my seminars on hemoglobin I gave at Stanford, said this is a way in which one could begin a study of the brain. You could do the same sort of analysis you did with hemoglobin, just extract the proteins from the brain, separate them by electrophoresis, look for one whose charge is changed, and come up with mutations of brain proteins. This would give you an entry into studying some of the obvious diseases of the brain, like mental retardation on the one hand, and, perhaps, getting to understand how information is stored in the brain. This seemed a very good idea and this was the basis on which I was hired. This is what I came back to do. In 1962, while I was still there on sabbatical, Josh wrote a short grant to NIH, in which he proposed a study to look for these proteins; it was readily accepted. He had a technician start to do something with it so, when I came back in 1964, I inherited this grant which is now in its' fortieth year. I've been very lucky to have the support of NIH for that length of time. So we started to isolate brain proteins by electrophoresis and see what we could find. It became clear, fairly soon, that the important proteins in brain were not readily soluble

in aqueous solutions. What you could extract were the so called housekeeping enzymes and proteins, but really interesting proteins, which were involved in electrical transmission down the axons and passing the signal by chemical means from one cell membrane to the other, were membrane bound and could only be extracted with detergents.

The separation of these proteins was relatively crude and there was no way we were going to see subtle changes. By the time we were discovering you could separate proteins by electrophoresis using and ionic detergent a scientist called Davis discovered the fact that separation was based on size. This detergent, being highly charged, bound in multiple numbers to the proteins so the separation was on the basis of size, rather than charge.

Josh had also suggested that I look at the work of Rita Levi-Montalcini on nerve growth factor (NGF), the name given to the factor that she had discovered that promoted the survival of embryonic sensory and sympathetic neurons. With the help of Stanley Cohen she showed that the NGF activity was associated with a protein isolated from the mouse submaxillary gland but the nature of this protein was unclear. Silvio Varon who had worked with Rita joined me at Stanford in 1964 and together with Junichi Nomura embarked on the purification of the NGF protein. It took almost three years to complete the project, partly because the purification was followed by Levi-Montalcini's sensitive but time consuming biological activity assay and partly because of the need to adapt one of the newer protein screening techniques, acrylamide gel electrophoresis. We finished up isolating an NGF complex, 7S NGF, from the mouse submaxillary gland. The complex contains the basic NGF protein together with a proteolytic enzyme and an inactive enzyme and two zinc ions, which give the complex significant stability. The NGF protein itself is readily released from the complex and, as Levi-Montalcini originally found is exquisitely active at very low concentrations. NGF was found in relatively few locations. It is present in the targets of sympathetic and sensory neurons and is retrogradely transported to the neurons sustaining them at critical periods of development. Later it was found in the hippocampus and as a consequence NGF became a factor of great interest to scientists studying memory and learning.

- TB: Where did the NGF research lead to next?
- ES: We concentrated on the NGF receptors that mediate the effects of NGF and the signaling pathways activated through these interactions. Binding studies identified two NGF receptors on the sensory neurons. We, in particular Monte Radeke and Tom Misko cloned the first one, a

relatively simple single transmembrane receptor, now known as the first member of the TNF family of receptors. It goes by the name p75NTR to indicate its size and its ability to bind all the known neurotrophins. Susan Meakin subsequently showed that the second NGF receptor had tyrosine kinase activity and from its size and location was probably the Trk receptor, a supposition rapidly confirmed by two other groups. A great deal is now known about the way in which the two receptors interact to modify NGF binding.

We identified, with Hans Thoenen's group, the role that NGF and its receptors play in peripheral nerve regeneration and broadened this inquiry to seek other proteins that might be involved in nerve regeneration. We used radio labeling of sciatic nerve proteins and twodimensional gel electrophoresis to characterize proteins whose rates of synthesis were either markedly reduced or increased after peripheral nerve injury. One protein immediately stood out for its decreased synthesis after nerve injury and its recovery during regeneration. Cloning confirmed that it was a new peripheral myelin protein whose peptide chain spanned the myelin membrane four times. It was given the name peripheral myelin protein 22 to indicate its location and size. On exploring the structure of pmp22 in mouse models of peripheral myelin instability, harkening back to my days with the genetics of hemoglobin, Ueli Suter identified two separate amino acid substitutions in pmp22 in Trembler and Trembler-J mice. Since these two mice are models for one of the major diseases of the peripheral nervous system namely peripheral neuropathy (CMT1a) where the myelin sheath disintegrates in late stages of the disease it strongly suggests that changes in pmp22 cause the disease in humans. This was confirmed in a collaboration with Jim Lupski at Baylor College but not guite as we anticipated. Jim and his colleagues had just identified the genetic defect in human CMT1a, not as a mutation but as a duplication of a short segment of a particular DNA sequence in one chromosome. I should add that this brilliant discovery was to have a far-reaching impact on human genetics. This sequence contained the normal pmp22 gene indicating that the duplication of this gene was responsible for the human disease, the first gene to be so implicated. Although mutations in human pmp22 have also been found in CMT1a, Lupski and his colleagues have shown that the duplication of the gene is the most common mechanism behind the disease. These findings clearly open up new ways to explore therapies for the de-myelinating diseases and as anticipated further genes involved in this class of diseases are being identified.

One of the most extraordinary events of my life was to learn a few years after the identification of the pmp22 gene that my own daughter had a peripheral neuropathy. It was diagnosed when she was in her late thirties. Since neither my wife nor I are affected, her disease results from an as yet unknown spontaneous event to her.

In my laboratory further progress came when Jonah Chan, a post doctoral fellow, made the unexpected but highly important observation that BDNF, the second neurotrophin to be identified, enhanced myelin formation in co-cultures of Schwann cells and sensory neurons. The extension of this approach to see if other neurotrophins are regulators of myelin formation seems likely to produce candidates for therapeutic consideration in the demyelinating diseases. It is extremely satisfying for me to see the two major areas of my decades-long research program come together.

- TB: I see.
- ES: After many happy and stimulating years in the Departments of Genetics and of Biochemistry I became the first chair of Neurobiology in the Medical School. Let me give you a little bit of the history behind this. Joshua Lederberg, Donald Kennedy, Avram Goldstein, David Hamburg, and others initiated an inter-departmental PhD program in Neuro-and Biobehavioral Sciences in the early 1960's. Its initial progress was somewhat hampered by concerns at the University level that such a program might be so attractive that it would lower applications to the MD Program. As a consequence advertising the program was limited. Such a concern did not materialize and both programs prospered. With the natural demise of the classical Physiology and Anatomy Departments at Stanford the opportunity came to create new Departments. The Department of Neurobiology was formed in 1975 and we moved into a new building in 1977. The initial members were John Nichols and Denis Baylor from Harvard's noted Neurobiology department who had joined the Physiology Department at Stanford two years earlier in anticipation of the expansion of Neurobiology, Jack McMahan also from Harvard Neurobiology, and myself. We took over the Neuroscience teaching for medical students and became a focal point for the PhD program including adding more specialized graduate courses. With the three faculty named above, and other Neuroscience-oriented faculty from the Medical School and University the course soon became highly rated. The department expanded with the recruitment of Carla Shatz, Eric Knudsen, Richard Aldridge, and Bill Newsome and reached an enviable level of distinction in both teaching and research. With increased stellar representation of neuroscience in other departments in the Medical

School and University, Stanford is well poised for great success in this field.

- TB: Are there any other areas of significant interest you want to tell us about?
- ES: Yes, my involvement in biotechnology. In the late 1980's I heard a most stimulating lecture by a young neurologist Dr. Len Schleifer from Cornell Medical School on the potential application of the neurotrophins, all four had by then been discovered as well as others such as CNTF, to diseases of the nervous system. Sometime later he contacted me to see if I would be interested in joining him to start a biotechnology company focusing on the potential of neurotrophins to maintain neuronal survival. I agreed, as did Dr. Al Gilman, Len's mentor in his MD, PhD program. We put together an impressive Scientific Advisory Board while Len, realizing he had hidden talents in fundraising, became the CEO, set up laboratories on the old Union Carbide Campus in Tarrytown, NY. The first scientist hired was George Yancopoulos recently graduated MD, PhD from Columbia and soon after Ron Lindsay from the MRC in London. The first disease tackled was the motor neuron disease ALS using CNTF because it would be easy to deliver it to the appropriate muscles for its uptake and retrograde transport to the motor neuron. Experiments in culture amply confirmed CNTF's role as a survival factor as did treatment of mouse models of motor neuron disease. However, CNTF failed completely in human trials. What CNTF did was to make the patients loose weight. The explanation came later. CNTF receptor is homologous to the leptin receptor whose natural ligand leptin is a regulator of appetite. Whether CNTF is a drug for obesity remains to be seen.

A second attempt in a clinical trial using BDNF also failed even though markers showed that the patients received a biologically effective dose of BDNF. At the present it is not possible to try the combination of CNTF and BDNF that also prevents motor neuron disease in mouse models because of the FDA requirement that the components have to be effective and safe when administered singly before they can be used in combination. These examples show how difficult it is to develop a new drug.

- TB: How would you summarize your career?
- ES: It has stretched over 50 years of research and teaching mainly at two institutions, University College London and Stanford. At both institutions I have been privileged to work with a series of bright undergraduate and graduate students, postdoctoral fellows and sabbatical visitors. I have learned much from them and gained great satisfaction from their

subsequent successes. Each institution has provided a wealth of distinguished colleagues and I cherish the friendships that have formed over the years. Thanks to the flexibility of research funding, particularly from NIH I have been able to follow projects with unforeseen but highly profitable directions. My elder granddaughter when asked in high school what she would like to be replied, "a neurobiologist". When asked to explain she answered: "My Grandfather is a neurobiologist and he enjoys his work very much". That just about sums it up.

- TB: Where would you like to see things nove in your area of research?
- ES: Very much along the lines on which science has developed in this country. The NIH support of research, both intramurally and extramurally, is excellent and the recent doubling of the appropriations by Congress speaks volumes to the high regard NIH has held in Congress. It is indeed one of their major successes.
- TB: I think this would be the right note to conclude this interview. Thank you very much for sharing all this information with us.
- ES: It was my pleasure.
- TB: Thank you.

## **MYRNA M. WEISSMAN**

#### Interviewed by Thomas A. Ban Waikoloa, Hawaii, December 12, 2001

- TB: This will be an interview with Dr. Myrna Weissman\* for the Archives of the American College of Neuropsychopharmacology. We are at the 40th anniversary of the college in Waikoloa, Hawaii. It is December 12, 2001. I am Thomas Ban. Could you tell us where you were born, brought up, your early interests, education and so on?
- MW: I was born in Boston, Massachusetts and was an only child. My father had a small business and my mother stayed home. I went to Brandeis University and graduated when I was about twenty. The fields women were shunted into were nursing, social work or teaching. I did social work, got married and had four children. I didn't like social work.
- TB: Where are we time wise?
- MW: In the late 1960's.
- TB: Late 1960's.
- MW: Right. In 1970 I entered graduate school at Yale for a PhD. My four children were age six and under, I was thirty and decided I had to do something with the rest of my life. Fortunately that was the beginning of the women's movement, because otherwise, they wouldn't have let me into graduate school, especially at Yale. My first plan had been to develop real estate. We lived in Bethesda, Maryland, my husband was a scientist at NIH, and real estate in the area was rapidly developing. I saw an opportunity to do something creative that was also very lucrative. So, I took out my real estate license but then my husband accepted a job at Yale. We arrived in New Haven and I realized it was not a place for real estate development, so I'd better find something else. I got the most interesting job of my life with Gerry Klerman, working two days a week on a study of the maintenance treatment of depression to prevent relapse and recurrence. I was the social worker with no experience and small children who didn't want to work more than two days a week or an academic career. I wanted something fun and this seemed like an important project. I was hired to help get started until they found an experienced fulltime social worker to run the project, travel and do psychotherapy. It was difficult to work with young children. My first day of work, the baby sitter didn't show up. I remember Gerry saying, "Well, bring them along". My 18-month old and I arrived and the meeting was about life events. Gene Paykel was there with Gerry gearing up for the maintenance study and they had just obtained their first data

<sup>\*</sup> Myrna M. Weissman was born in Boston, Massachusetts in 1940.

on life events. It showed more life events in six months prior to onset of depression compared to controls in the same time period. Life event exits seemed more important than entrances.

- TB: You had your degree in social work but no prior experience?
- MW: I was quite inexperienced but I knew this was an important study. It was interesting and I didn't want to spend my time doing something boring.
- TB: So you found the people stimulating?
- MW: Oh, they were so interesting. There were no guidelines on what to do and they had a hard time finding this super social worker to run the project. Gerry didn't like to waste time and gave me Aaron Beck's hand written manual on cognitive therapy, about a hundred pages long. He told me to design the psychotherapy component and specify the procedures for the depressed patients, mostly women. I was the perfect person to do that because I had no pre-existing ideologies. I started reading. I read Bowlby & Rutter, the life events literature and Parsons and Bales, working very closely with Gerry. I suggested we should define the dose of the psychotherapy like a drug, then the duration, quality, and who does it. That was easy. Then we started to get into the tough part. What's important in depression with depressed middle-aged women who have children? I knew something about children. I remember saying, these patients should know they have depression; it shouldn't be a mystery. So, we began by going through a diagnostic procedure with the patient explaining what depression is, its symptoms and its course. Then we needed to figure out how it started. We developed the idea of an interpersonal inventory enquiring what was going on, and who, were the important people in the patient's life. While depression is a biological disorder what's happening in life, probably triggers it. We developed a draft manual and Gerry used to say, "You have to be specific, you can't just say, be supportive. You have to specify what you do to be supportive, write scripts". I was working two days a week, but most of this was done on the other days at home. I only had the obligation to go in to work two days a week, which freed me up.
- TB: So, you did some of your work at home?
- MW: I did most of it at home. Finally, we had a manual, maybe 50 pages. Then Gerry said to me and to Gene Paykel, "Now you have to define the outcome. Social function should be the outcome of psychotherapy. We expect that drugs will help symptoms, make people sleep better and eat better, feel less hopeless, but psychotherapy will have effects of how people function, so define the social functioning". I remember going home with a stack of papers, all the articles I could find on social

functioning. After that, at Gerry's request, I wrote a review for the FDA on Social Functioning Scales, which was one of my first publications.

- TB: When was that?
- MW: It was in the early seventies. Gerry had left for Harvard but he called and said, "The FDA needs a review of social adjustment scales, could you do it, and make it like a consumer report"? I did, and we published it in Archives. As a review it was guoted a lot. The scales fell into two categories: Those designed for studies of schizophrenia, where functioning was assessed at a low level. For example, do you brush your teeth and take your own bath? Our patients were depressed women, living at home taking care of families, so these scales were not appropriate. The other scales were for college students and assessed dating. Again, our patients were married and had children. Barry Gurland had a scale that he'd been working on for years that had many items appropriate for us, but it didn't cover children and extended family, so, working with him, we developed the Social Adjustment Scale. Now that we had the scale and a manual, we were ready to begin the study but Gerry pointed out we had to validate the scale. Not having studied psychometrics I wasn't sure what was needed. With the help of Jerry Myers in New Haven, who worked with Hollingshead and Redlich, we identified an appropriate normal sample. This led to a book, The Depressed Woman, a Study of Social Relationships, published in 1974 by the University of Chicago Press. After Gerry left for Harvard and Gene returned to England I went to graduate school. I completed graduate school very guickly because Brig Prusoff and I were running the remaining studies left at Yale. Gerry was the Principal Investigator and subcontracted the studies to us.
- TB: So your book was published before your graduation?
- MW: It came out in 1974, the year I got my degree.
- TB: Did you use it for your dissertation?
- MW: No, they wouldn't let me because the writing began before I started graduate school.
- TB: What did you do for your dissertation?
- MW: My dissertation was much less interesting than the book. It was the follow-up of the maintenance study.
- TB: Could you use the data from that study for your dissertation?
- MW: I could, because I had been heavily involved in the study. I designed the psychotherapy and the major outcome measure and had been involved in data collection and supervising the staff. I didn't do it alone and could never have done it without Gerry, Gene Paykel and Brig Prusoff.
- TB: Could you tell us something about the results?
- MW: One hundred and fifty depressed women received either drugs or high contact psychotherapy with placebo or no pill. First, they received an open trial of amitriptyline. If they responded, they were then randomized into the six cell factorial design. The major finding was that amitriptyline, over eight months, prevented relapse compared to placebo or no pill. Psychotherapy had no effect on preventing relapse but had an effect on social functioning. Since patients had problems in both areas, those who had both medication and psychotherapy had the best outcome. This was the first evidence for the efficacy of combined treatment. Gerry and Gene were very dubious about the efficacy of psychotherapy. No one had ever shown a psychotherapy effect so they were surprised to find one.
- TB: Were you also involved in the "life events" studies?
- MW: No. That was Gene and Gerry's work.
- TB: I see.
- MW: My one involvement in life events came from a graduate school course. I was learning new statistical approaches and concepts in a class on relative and attributable risks. I suggested to Gene this might be useful in presenting life events data. So he did that and published a paper which showed that attributable-risks were much higher for depression than other disorders. So, we collaborated closely, even from afar.
- TB: And, then, Gerry and Gene left?
- MW: Right. When Gerry and then Gene left Yale, I finished the follow up of the maintenance study. Then we wrote another grant on acute treatment with drugs and interpersonal therapy. Mason DeLaverne was hired as the treating physician. He was a semi-retired internist, a very nice man, who took care of the patients. One morning I arrived to find a waiting room full of patients and no Mason.

I called his wife and learned he'd had a heart attack and stroke and died that night on the stage, while performing on the violin. So there we were Brig and I, no doctorate degree between us, and patients. That was trial by fire. We hired another doctor and just continued. We were off campus at a little house on Park Street so we didn't cost the University anything. In fact, we brought in money from overhead on the grants so nobody paid much attention to us. We did what we wanted and had a great deal of fun.

- TB: When did you finish your dissertation?
- MW: I finished up my dissertation in 1974. Then we wrote a collaborative grant with Gerry as the principal investigator at Harvard while I was the principal investigator at Yale, now I had my PhD. This was an acute treatment study, because we argued that psychotherapy would have

more of an effect from the beginning, not just after patients responded to medication. It was much easier to do a 16-week acute treatment trial, using amitriptyline and what we had now named high contact, Interpersonal Psychotherapy (IPT). Bruce Rounsville and Eve Chevron began to work with us and we put together a comprehensive manual, which was published in 1984. Gerry and I did not want to train people in IPT when it had never been used outside of Yale and Harvard. We wanted to wait until there was more evidence for efficacy.

- TB: Did you work full time by then?
- MW: After I got my degree in 1974 I went full time.
- TB: I suppose by then the children were in school all day?
- MW: They were still young, but I worked at home a lot, so I never worked nine till five. I would go to work very early after the children went to school and I was always back when they got home. I would work in the evenings and on weekends, but we were a working family. We all worked. If I had any major writing to do, I would stay home. I was very close to home, so if I wanted to go to the children's performance or help at the school, I did. I had no bosses.
- TB: Did you have your own projects?
- MW: I had several grants, because it wasn't difficult to get funded if you had ideas. I was also involved in research with Herb Kleber at the Drug Abuse Unit. We were outside the main stream in psychiatry, the Department was very psychoanalytic. Herb was next door in the same complex a couple of blocks from the medical school. He had a big government contract to study methadone for heroin addicts and invited Brig and I to do the part on depression. Brig and I had a weekend to get the project written. I knew nothing about methadone but Brig's husband was a very prominent pharmacologist, so we decided she should take the methadone part and I would write the depression part. We wrote that portion of the grant on the effects of methadone on mood using the assessments from our clinical trial. We only needed an additional section on the pharmacology of methadone and its effect on mood. The grant was funded and, suddenly, I was studying drug abuse. There were two other grants that came soon after. One was a very large grant to study co-morbidity in drug addicts and the other was to do psychotherapy, IPT, added to a standard program for drug addicts to see if it improved the outcome of methadone treatment. This was in collaboration with Bruce Rounsaville at Yale. ITP didn't have an effect and it was also negative in another sample of drug addicts. That, to us, was reassuring. If you have something that works for everything, you probably don't have anything.

- TB: Were you on the faculty by that time?
- MW: I was an Assistant Professor and I had the maintenance study follow up, the acute treatment study, the methadone depression study, the co-morbidity study and psychotherapy opiate studies. It was a big operation.
- TB: You moved ahead fast on the academic ladder.
- MW: I got promoted to Associate Professor and I can't remember when I was made full Professor, but I was the first woman to get tenure in the Department of Psychiatry at Yale and I was a PhD. Interest in research became salient and Boris Astrachan, head of Community Mental Health, was a supporter and really pushed for my tenure.
- TB: Is your PhD in Epidemiology?
- MW: It's in Chronic Disease Epidemiology.
- TB: You had joint appointments in psychiatry and epidemiology?
- MW: Yes.
- TB: How long did you stay at Yale?
- MW: Well, I stayed with Yale until 1987.
- TB: 1987?
- MW: Yes, a long time. I liked Yale. I was very happy there, but, by that time, Gerry and I were married, living in different cities and I did not like that. My career was not as important as having a real life and my children were older. I was going to move to Boston, but there was no tenure job with Harvard. I was afraid to move to a non-tenured position. Gerry was willing to move to Yale, but they didn't have anything for him. Then we got these great job offers in New York.
- TB: So, you moved to New York?
- MW: Gerry moved to New York in 1985 and I moved in 1987. Gerry was working at Cornell and it was easy, because he worked a couple of days in Westchester and we lived in Woodbridge, a forty-minute trip. We wanted to be in the same city, so we moved.
- TB: Did you work together or did you have your own projects?
- MW: We worked together, but also had different projects. When I was at Yale, in the 1980s, we had the Epidemiologic Catchment Area (ECA) study. We obtained the first rates for psychiatric disorders in the community, using modern diagnostic criteria. That was like a dream for someone who was an epidemiologist. Jerry Myers, who was a sociologist, had done major work on community surveys, using the older techniques measuring symptoms, not diagnoses. Together we wrote the first application to do the ECA and got the first grant. That was followed later by sites in St. Louis, Baltimore, North Carolina, and California.
- TB: Could you tell us about the study?

- MW: The ECA surveyed eighteen thousand people in five US communities, using the Diagnostic Interview Schedule, which became DSM-III. It was developed by Lee Robins, PhD. and could be used by lay interviewers, because it was highly structured but generated the diagnoses used in clinical psychiatry. In the New Haven site, we surveyed eight thousand people with an over sample of the elderly and Black Americans. North Carolina had a rural sample. People developed their careers from that study. Marty Bruce, who is here at the ACNP, was my post-doc and she got interested in geriatric psychiatry. She took over a follow-up sample and wrote her own grant. So, there was a lot going on. We still had funding from the ECA. Gerry wasn't involved in that. But while Gerry and I sometimes did separate studies, he had some on HIV we always talked with each other about what we were doing.
- TB: What did you find in the ECA?
- MW: In the ECA, we found that the rates of depression were fairly high, the rates of schizophrenia were what we had expected, about one percent, and so were the bipolar rates. Sex differences in depression were what we expected; about two to three fold greater in women than men. The major surprise was that most of these disorders begin in the young. We thought of depression, bipolar and the anxiety disorders as conditions of middle aged people. What we found, consistently, across all the sites was that these disorders begin often in adolescence, and certainly, by young adulthood. That didn't mean that older people didn't get depressed, but these were usually recurrences. So, the biggest contribution of the ECA was turning the focus on young people and their high rates of psychiatric disorders. There have been similar findings in subsequent studies like the National Comorbidity Survey (NCS). I then got interested in Genetic Epidemiology and started to do family studies of depression and panic disorder. These continue and I still am studying the grandchildren of our sample from New Haven. Now we are doing Magnetic Resonance Imaging (MRI) studies of three generations at high and low risk for major depression (MDD). We presented the first findings from the three generations study at this meeting.
- TB: What did you find?
- MW: We found that the children of depressed parents have very high rates of depression; as compared to children of controls and that these depressions begin early, continue and recur. The relative risk is about a three or four fold increase. We have followed them to adulthood and now find that the grandchildren carry the same risk. The sequence that we saw in the grandparents, the parents, the second generation and other grandchildren is that they begin with pre- pubertal anxiety disorders.

Around adolescence, you see the emergence of depression and for some, in adulthood, substance abuse, especially for males. The risk is carried to the grandchildren of whom we have data on the first one hundred and thirty individuals. It's a first look, it's not clean data, but you can see there is over a fourfold increased risk in the grandchildren, based on their grandparents' depression status. That's a sturdy finding and others have found the same. The grandchildren are all in New England. We still have a team at Yale and have added neuropsychological measures, EEG, startle response and now MRI and genetic studies.

- TB: How did you measure the startle response?
- MW: This is work done by Christian Grillon, who was at Yale and is now at NIMH. They use a puff of air and measure the startle response. There's work in animals to show which neural circuits might be involved in anxiety, as reflected by the startle response. Brad Peterson is now at Columbia and is an excellent neuroimager, who was at Yale, and still has a team there. The next phase will be neuroimaging in these children and their parents and grandparents. That doesn't mean the environment isn't important, but we know that these children are carrying a risk that is stable and sturdy across the generations. That work continues and we are now collecting blood for DNA.
- TB: What would you consider your single most important contribution?
- MW: I don't know.
- TB: You did several studies which had an impact on the field.
- MW: A lot of the things were done that are now standard. So no one is going to say, "She did it". That's good, because it means it's been incorporated. I feel that I helped bring epidemiology to psychiatry. I think IPT is a contribution. There are now numerous clinical trials and adaptations with an international society of IPT. We have a book on that which came out in 2000 and another in 2007. The Social Adjustment Scale has been translated into numerous languages. The high risk studies showing the transmission of depression across generations is a finding of major importance.
- TB: You mentioned that you brought in psychiatric epidemiology. Is there anyone else who had been involved about the same time doing the same kind of research?
- MW: Lee Robins, of course. She was over a decade ahead of me and did those wonderful studies of disturbed children growing up. I modeled my thinking about depressed children growing up on her work. It was Lee with Bob Spitzer who developed the Diagnostic Interview Scale (DIS), which made the first epidemiologic studies in the community possible.

She has made major contributions so I would say that she was there before I was.

TB: So she was there before you?

MW: Yes.

- TB: Anyone else you would like to mention?
- MW: In epidemiology?
- TB: In epidemiology.
- MW: Bob Spitzer is a psychiatrist, but his work standardizing DSM diagnoses made epidemiology of psychiatric disorders in the community possible. There's a whole new generation. Ron Kessler is a leader in psychiatric epidemiology. His work began in the 1990's and he's doing major work on cross national epidemiologic studies with the World Health Organization (WHO). He has an industry going and has done incredibly good work. I would consider him a leading person in psychiatric epidemiology. Adrian Angold, Jane Costello and Peter Lewinsohn have done epidemiologic studies in children.
- TB: Your research was not been restricted to epidemiology but extended to genetics, biologic measures and treatments. Is that right?
- MW: We have a field that is much more developed and is now making the translation to biology. I don't want to keep doing the same thing. I could do another four high risk studies and show that the children of depressed, anxious or alcoholic parents have different patterns, but it wouldn't be very interesting. Having laid the groundwork the next step requires a serious collaboration with people in biology. In this phase of my research, I am working in close collaborations with other investigators. I have a genetic linkage study in panic disorder; a sib-pair genetic study in depression, and a study of fear and anxiety where I work with molecular biologists. I'm not a molecular biologist and never will be. I don't even understand it at a deep level, because I don't have that background, but we work very closely together. I lead the collection of the families, the design, and the definition of phenotypes. I collaborate with Brad Peterson and others at Columbia on neuroimaging. I am very happy to have the people I collaborate with write the papers, and lead that part of the research.
- TB: Can we get back to the IPT? What is its current status?
- MW: It's been adapted for many conditions and used in a recent study on bipolar disorder. There's much more enthusiasm about it in Europe, Canada, Germany, Australia and New Zealand, where it's required in some training programs. Our study of depressed patients in Uganda using IPT is one I am the most proud of.

- TB: It was a treatment developed by Gerry and you, right?
- MW: Gerry was the major thinker in IPT. It came from his simple notion that despite the obvious biological basis of depression, the episodes are triggered by events, usually interpersonal. This notion is now supported by genetic studies done by Caspi.
- TB: I see.
- MW: What people are asking now is: what are the components of IPT that might be combined with other treatments? I don't have a problem with that. There is great satisfaction in doing something well and seeing it endure. It feels very good.
- TB: Opening up a new field?
- MW: Opening up a field.
- TB: What are you working on now?
- MW: What I try to do is things that are interesting to me that I can believe in. To do the same thing is easy, but not interesting, I'd rather go shopping. There's a lot of mechanics in research that are not pleasant, getting through Institutional Review Boards (IRB), writing grants, dealing with the administrative issues. It can be tedious. But, if you're not doing it in the service of something that's interesting, or that might provide an answer, it's not worth it. So, I've tried to keep in the areas that I believe will lead to answers. The most interesting study we're working on now has to do with answering a question that comes from the highrisk studies. We have shown that the children and the grandchildren of the depressed parents and grandparents don't have a very good prognosis. On average they don't do well. It's incumbent on us to do something clinically to figure out how you would intervene. We don't know very much about the treatment of children but we know a lot about the treatment of depressed adults. What if you vigorously treated a depressed mother? Could you have an impact on forestalling or preventing the illness in a child? We completed this study and remission of the mother's depression resulted in significant improvement in her children's symptoms. This was published in JAMA in 2006 and attracted considerable attention.
- TB: Your work is widely known. Are there any awards you received you would like to mention?
- MW: Awards are only important if you don't get them. I was very pleased to get into the Institute of Medicine. In May 2007 I am getting an award from the Society of Biological Psychiatry. That really pleases me as I am not a biologist.
- TB: Didn't you get the prestigious Anna Monika award?
- MW: Yes, but that was really Gerry's.

- TB: When did you get involved with the ACNP?
- MW: When the maintenance study results came out and we presented them at the meting. People were really interested.
- TB: Have you served on any of the committees?
- MW: I have been on many different committees and on Council. I rarely miss an ACNP meeting. It's like family.
- TB: Is there anything else you would to add, personal or non-personal?
- MW: Well, my biggest loss was Gerry. He died April 3, 1992.
- TB: But, you seem to be keeping very active?
- MW: Yeah, I'm very active and I have great children. I have a son, who is a successful scientist. He has a Howard Hughes Unit at UCSF and is a structural biologist. I remarried last year to Marshall Nirenberg, a great man who won the Nobel Prize for deciphering the genetic code. I have three wonderful daughters, one who left law to become a psychiatric epidemiologist.
- TB: So she follows you?
- MW: Only a little. She is her own person. And, I have another daughter who is also an epidemiologist and a physician. She's in infectious disease at Yale, running AIDS programs. And, I have another daughter, who has an MBA, taking a business route and is running a big medical practice.
- TB: So all of them seem to be following in your footsteps?
- MW: Yes, in that they all have careers that they enjoy. I also have seven grandchildren.
- TB: You have seven grandchildren? That's great.
- MW: Yes.
- TB: Well, I think I would like to thank you for sharing all this information with us.
- MW: Thanks for asking me.
- TB: Thank you.
- MW: It's an honor.

## PAUL H. WENDER

### Interviewed by Thomas A. Ban San Juan, Puerto Rico, December 11, 2002

- TB: This is an interview with Dr. Paul Wender\* 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 11, 2002. Could you start, Paul, from the very beginning?
- PW: I was born in 1934 in Manhattan, the offspring of a psychiatrist who was psychoanalytically trained by one of Freud's disciples and a mother who was a social worker. One result was that I become interested in psychiatry from an early age. I went to private school and then to Harvard College where I majored in biochemistry, but became guite interested in behaviorism and learning theory because these were relatively hard psychological sciences. I'd asked my father when I was a freshman to let me read something of Freud's to get a feeling for psychoanalysis, and he sent me a copy of a General Introduction to Psychoanalysis. I peppered the margins with "how does he know this", "what evidence does he have for making this statement", and came to question Freud's provocative, but unsubstantiated statements. I went to Columbia Medical School where I did my physiology thesis on a certain aspect of Pavlov's work and, following an internship in medicine at Washington University, I began training in psychiatry at the Massachusetts Mental Health Center in 1960. It was totally psychoanalytic. I found myself in the position of the little boy in the fairy tale of the emperor's new clothes. None of these people had scientific clothes on. I found it entirely impossible to comprehend schizophrenia on the basis of psychodynamic theory. I read the descriptive literature, the German literature on twins and on family studies, and became convinced that schizophrenia was a genetic disorder. I realized that neither family studies nor twin studies would prove the role of genetic factors because individuals who developed schizophrenia usually grew up under the psychological influence of schizophrenic parents. So the effects of heredity and environment were confounded. I was so dissatisfied with the teaching and non-teaching I received during my residency that I and a number of other residents organized a seminar on schizophrenia in which we presented papers. The most prestigious member to be of our group was Eric Kandel who was at that time a fellow psychiatric resident; many of the group later went into research. I wrote my paper on the origins of the concept of dementia praecox, taking advantage of the fine medical

<sup>\*</sup> Paul H. Wender was born in New York, New York in 1934.

libraries in Boston. In 1962 I was drafted into the army and by a great fluke of luck managed to go to the National Institute of Mental Health and avoid doing psychiatric service in Korea. There I did some work with Bob Feinberg who was studying sleep and dreaming in schizophrenia and also did some research on the relationship of early social behavior in children and their later cognitive functioning. I submitted my seminar paper to the editor of the *American Journal of Psychiatry*, a man who had been trained by Kraepelin, and he accepted the paper and requested that I make one addition to the paper; a quote from Kraepelin. It was Kraepelin's modest statement, "We are always standing at the beginning".

- TB: When was the paper published?
- PW: The paper, my first, was published in 1963, and that was a delight to me, my mother, and my father. About 1963, I was still reading extensively about schizophrenia, and I hit upon the idea of using adoption to separate the effects of nature and nurture in the etiology of the disorder. The beautiful thing about studying adoption is that the people who supply the genes and the people who supply the environment are two separate groups. My first approach was to study the adoptive parents of patients with schizophrenia at Johns Hopkins. To continue the study I needed more money, so I went to the head of Intramural Research at NIMH, Bob Cohen, told him what my research needs were and how the research might be expanded. He told me that within the past several weeks two senior investigators had come independently to him to request money for adoption studies. One was Dr. David Rosenthal, chief of the Laboratory of Psychology, and the other was Dr. Seymour Kety, chief of the Laboratory of Clinical Science. Bob Cohen suggested I talk to them, and I did. I was not sure whether they would want me to collaborate with them. They had discussed their idea with Bob earlier than I did but they welcomed me as a full collaborator. This led to the Danish adoption studies of psychiatric disorders. One of the things that I wanted to do was to study individuals born to schizophrenics and adopted by normal parents. But it was very difficult to acquire such a sample. At that juncture, a visiting psychologist came to the NIMH and told us about his research in Denmark and about the existence of superb registers which would enable us to do this kind of study. He put us in touch with the Danish psychiatrists with whom we then collaborated, Drs. Fini Schulsinger; Joseph Welmer; and Bjorn Jacobsen. We initiated two studies. In the first study, in which Seymour Kety was the principle investigator, we wanted to investigate the biological and adoptive relatives of adopted schizophrenics and as a comparison group

the biological and adoptive relatives of adopted normal subjects. The issue was how to find them? The Danish registers contain information about all child adoptions by non-family members; in Copenhagen there were 5500 and we decided to examine all those who were between the ages of 18 and 45 and who had been placed in adoptive homes at an early age. The question was how to find which of them had schizophrenia? This was easy to determine because there was another register; the Institute of Human Genetics which listed the names and diagnoses of all Danes admitted to psychiatric hospitals. We determined that 600 of the adoptees had a psychiatric hospitalization of which 33 were diagnosed as schizophrenic. As a comparison group we chose age and sex matched adoptees who had never received a psychiatric hospitalization. The names of the biological and adoptive parents of the schizophrenic patients and controls were given in the adoption register. The next question was how to locate them. Once more a register came to our aid. Every time people move in Denmark, they must register with the police, report their address change, and state the names of all people with whom they live. This enabled us to find the names of what other children had been born to the biological parents of the schizophrenic adoptees. Similarly, we were able to locate the adoptive parents and siblings of the adopted schizophrenics. We had the participation of a very vigorous young Danish psychiatrist, Bjorn Jacobsen. He had marched all over the peninsula, Zealand, where Copenhagen is located, and Jutland, which protrudes from Germany to interview all the adoptees and their relatives. One of the things I had also become very interested in was what was then called borderline schizophrenia, or "schizoidia".

- TB: Schizoidia?
- PW: This was not a recognized diagnosis in DSM II, but it was a pet love of mine, and I had designed a structured interview for diagnosis which examined signs and symptoms of "borderline" schizophrenia. Hospitalization records and interviews, when possible, were obtained from all the relatives, biological and adoptive, and blind diagnoses were made by Drs. Kety, Rosenthal, Schulsinger and me. The most exciting day I ever experienced in science was the day after Drs. Kety, Rosenthal and I had diagnosed all the relatives blindly. With our Danish collaborator, Dr. Fini Schulsinger, we opened the envelopes which had been sealed by research assistants. Lo and behold, we found the genetic hypothesis substantiated; there was an increased frequency of schizophrenia and schizophrenia-like disorders only among the biological relatives of the adopted schizophrenics. This proved two things. First,

there was a genetic contribution to schizophrenia. The early family studies and the twin studies had been correct. Second, and this was of great interest to me, schizophrenia occurred along a phenomenological continuum, which we referred to as a schizophrenic spectrum. The individuals we called "borderline schizophrenics" were included in DSM-III and designated as "schizotypal personality disorder". That was a major contribution, because the word "spectrum" became widely used in the description of many psychiatric disorders. There is an OCD spectrum, an autistic spectrum and a depressive spectrum. So the idea caught on.

#### TB: What about the second study?

PW: The second major study used a different strategy to evaluate the psychiatric status of four groups. First we examined the adopted away individuals who had a biological parent who was schizophrenic, second, people born of normal parents who were adopted, third, the most unfortunate group, people who had the good fortune to be born to normal parents but the misfortune to be adopted by schizophrenics, and fourth, people born to and raised by schizophrenics. The interviews of all these subjects were performed by Dr. Joseph Welner. What we found was substantiated the other study; compared to the biological offspring of normals the adopted away offspring of schizophrenics were at increased risk of schizophrenia and "schizotypal personality disorder". The way DSM-IV constructed this diagnosis was by studying all the people who we had designated as borderline schizophrenia and extracting our clinical descriptions. Another finding was that being adopted away from a schizophrenic parent did not attenuate the disorder. These subjects did just as badly as if they were raised by their biological parent. That is not to say that these unfortunate individuals may not have had a more difficult experience having a biological parent who was schizophrenic, but it did not increase their risk of schizophrenia. The last comparison group consisted of people born to normals and adopted by schizophrenics. There was no increase in schizophrenia, but they told the interviewing psychiatrist that they had very unusual and peculiar adoptive parents. To study so called "schizophrenogenic" parents we did a study in the States where I interviewed the adoptive parents of schizophrenics compared with the biological parents of schizophrenics and a comparison group of normal subjects. Here we found that the adoptive parents were more psychologically disturbed than the parents of normals; they were depressed and anxious. They had one child, they were now 65 to 70 years old, and they were concerned about what would happen to their chronic schizophrenic child when they died. To control for the effects of parents on the child, we replicated this study with one change. We studied the adoptive parents of schizophrenics and the biological parents of schizophrenics, and the biological parents of non-genetic patients with mental retardation. The parents of the mentally retarded children were in the same position as the adoptive parents of schizophrenic children. They were 65 or 70, had a seriously impaired child who they had been caring for an entire lifetime, and they were terribly concerned about what would happen when they died. The adoptive parents of schizophrenic children were no more anxious and depressed than the parents of retarded children. The psychological difficulties in both groups could be seen as the effects of rearing a seriously disabled child. Lastly, we used the adoptee method to study major mood disorders. Our study groups consisted of the relatives of patients with unipolar and bipolar depression, we didn't separate the two diagnoses in those days, and the relatives of a group of normal control adoptees.

- TB: What did you find?
- PW: We found significantly increased risk of affective disorder only among the biological relatives of the major mood disorder patients and, most striking, a 15-fold increase in suicide in the biological relatives of the adoptees with affective disorders compared to the biological relatives of the normals. This was presumably mediated by mood disorders experienced by the biological parents and siblings of the adopted patients with major mood disorders. We turned our methodology and our population register over to other psychiatrists who used the adoptee method and the registers to explore genetic contributions to alcohol abuse, criminality, and to psychopathic personality. The results here were more complex. There were environmental contributions to these disorders in that someone born to a criminal and adopted by a criminal was more likely to be criminal than someone born to a criminal and adopted by a non-criminal. But the major discovery was that there was a genetic contribution to criminality, alcoholism and "psychopathy". I consider these studies to have done useful work historically. They documented the fact that there was "gold in them there genetic hills". If geneticists approached these disorders with appropriate methodology, they would be able to elucidate the specific genetic factors that were mediating the phenotype of these disorders. Back in 1967, this was in the distance, and I turned my attention away from adoptive studies in psychopathology to study another interesting area, which I consider to be my second major contribution to psychiatry.
- TB: What was that?

PW: The awareness that adult psychiatry could not really explain the etiology of psychopathology very well. I wondered, if one studied children, whether one could learn more about the development of psychopathology. Accordingly I decided to take a fellowship in child psychiatry at Johns Hopkins in 1964. The chairman was Leon Eisenberg who was a critical psychiatric free thinker and who provided a congenial atmosphere. Early in my training I became interested in a group of children diagnosed with minimal brain-damage who were active, disobedient and oppositional, impulsive, inattentive, did badly in school, had difficulties with their parents, siblings, and peers whose symptoms all but disappeared when given d-amphetamine. Theirs was the most rapid and striking response to drugs that I had and have seen to this day. The only response to somatic intervention comparable to that is ECT in involutional melancholia. D-amphetamine began to work in 45 minutes, and when continued, the child functioned better than he ever had in his entire life. Mainly, in psychiatry, we try to get people back to the status quo ante, the best they have functioned before their illness, not better than they have ever functioned in their lives. I became interested in the phenomenology of these children and started studying their clinical characteristics. Because I was interested in experimental psychology, I was struck by the similar response of rats and children to dextroamphetamine. D-amphetamine in rats potentates some of the effects of positive reinforcement, as in the electrical stimulation of the brain, and strengthens negative reinforcement-avoidance behavior, in those which don't learn to avoid punishment in the shuttle box. Given d-amphetamine, most of the non-avoiders who did not learn to avoid punishment do so. It struck me these children were fairly unresponsive to positive reinforcement from their parents and also to punishment, i.e., negative reinforcement. I then became interested in the mechanism of action of d-amphetamine. Since d-amphetamine is an indirect agonist for dopamine and norepinephrine, I hypothesized that minimal brain dysfunction, as it was then called, now attention deficit hyperactivity disorder (ADHD), was mediated by decreased dopaminergic and /or catecholaminergic function. To be immodest, my hypothesis was prescient, because there have been several meetings at ACNP about the dopamine transporter and the dopamine receptor in ADHD in children.

In 1973, after 11 years at the NIMH, I received a research professorship at the University; a hard income appointment which enabled me to do research for 26 years. I had been impressed with the fact that the parents of ADHD children often had problems similar to those of their children. To learn more about this, I began to talk to the parents

and asked them, "Did you have problems like Johnny when you were a child"? And, the spouse would say, "What do you mean USED to have problems"? And, then, because of my psychoanalytic training, I'd spend two hours talking to them. Many had symptoms of minimal brain dysfunction expressed in an adult form such as inattention, hyperactivity, mood liability, overactive responses to stress, disorganization, impulsivity, and hot tempers. On the basis of these observations, I had residents obtain patients from the outpatient clinic who had this group of symptoms. Because ADHD in childhood is a mandatory prerequisite of ADHD in adulthood, and because many of our patients' memories were unclear, we obtained permission to question their parents about their childhood. When parental reports described ADHD behavior in childhood and when the patients had several of the adult symptoms, we diagnosed them as ADHD adults. The next step was to perform a drug trial. Since methylphenidate was the drug of choice for children in 1976 we did a double-blind crossover trial of methylphenidate and placebo in the treatment of these supposed ADHD adults.

- TB: What did you find?
- PW: Treatment was very effective. It reduced symptoms extensively and two-thirds were rated as much or very much improved. This was a small sample: one of the problems of interpretation was when you're taking people with a mélange of psychiatric symptoms, and treating them with a euphoriant drug, the results might be similar to those we could have obtained with morphine. We had to make sure this wasn't the case. So what we did next was treat another sample of ADHD adults with pemoline (Cylert), in a double-blind placebo controlled trial. Now, pemoline is effective in ADHD, but it is not a good recreational drug, and it's insoluble. If you inject it intravenously, all you will get for your efforts is a pulmonary infarct. Our finding using pemoline supported our view that ADHD exists in adults and its symptoms respond to pharmacological treatment with a non-euphoriant drug effective in children with ADHD. After these two drug trials, we initiated a number of studies. First we decided to replicate our methylphenidate findings with a larger sample, in which we studied the concentration of the principal metabolite of dopamine, homovanillic acid (HVA) in the CSF of ADHD patients and controls. Our hypothesis, advanced by me in 1971 was, that ADHD was produced by reduced dopaminergic activity and that the levels of HVA would be lower in the CSF of patients than in controls. Obtaining a group of a control group of normal adults presented a problem. What we did was to ask the healthy partners of the patients to participate and most of them did. To minimize trauma, we enlisted the participation of

the Chairman of the Department of Anesthesiology. Analysis of the CSF found a significant decrease of HVA in the CSF of ADHD patients compared to controls. The clinical findings replicated those of our previous placebo-controlled studies of pemoline and methylphenidate. ADHD patients experienced a substantial and highly significant benefit from treatment. There were other ways I wanted to look at dopamine, and one was administering precursor amino acids: phenylalanine, L-DOPA, and tyrosine. To summarize our results, phenylalanine did nothing and L-DOPA made people cloudy, and produced nausea and fatigue; it did not improve concentration or benefit any other ADHD symptoms. The response to tyrosine was different. After about two weeks it had a marked beneficial effect. Now, it was an open study, but we had run trials of two other amino acids in which no benefits occurred so we didn't think the tyrosine effect was a placebo effect. An interesting thing that occurred in the trial was that one patient started getting more and more paranoid. After we stopped the tyrosine the symptom remitted. We had erroneously picked someone with schizotypal personality disorder who had symptoms in common with ADHD and had given him an amphetamine-like drug which will, of course, increase the severity of paranoia. The other patients showed as much benefit as they had on stimulants, but after about six-weeks they became tolerant, and further increase in the dose of tyrosine had no effect.

- TB: But after about two-weeks of treatment tyrosine had a beneficial effect?
- PW: Since tyrosine is the immediate metabolic precursor of dopamine, we felt that the results supported that hypothesis that dopaminergic function plays a role in the pathogenesis of ADHD.
- TB: You measured HVA in the methylphenidate study but not in the tyrosine study?
- PW: Yes. As I said, studying ADHD is adults allowed us to get informed consent to perform studies which would be difficult to perform with children. Among these was the administration of monoamine oxidase (MAO) inhibitors, as a partial test of the dopamine hypothesis. We chose first to study pargyline, which in low dose is a relatively pure inhibitor of MAO-B. Monoamine oxidase B metabolizes phenethylamine and dopamine. We reasoned that if these were critical neurotransmitters, treatment with MAO-B inhibitors should produce therapeutic benefits in ADHD adults. It did. A problem was that although pargyline was as effective as methylphenidate in some patients receiving low doses, others responded only when we increased the dose to levels where it was probably beginning to inhibit MAO-A as well. So, we decided to perform a therapeutic trial with L-deprenyl, which is also a fairly specific MAO-B

inhibitor and to confine the trial to low doses of the drug. We found that the same percentage of ADHD patients, about two-thirds, manifested much or very much improvement, but they also experienced some subtle dysphoria. None wanted to continue on L-deprenyl, even though their ADHD symptoms were relieved, while many patients chose to continue treatment with pargyline.

- TB: Did you measure CSF HVA in these experiments?
- PW: We measured HVA only in the methlpendiate study. One important feature of doing invasive studies was that we could obtain informed consent from adults. Of course, we could never have done a lumbar puncture study in children.
- TB: You obtained dysphoria with L-deprenyl, which is kind of unique, because one would have expected the opposite.
- PW: That's right. I should say something about our experience with methylphenidate and amphetamine in ADHD adults. We continued to treat many of our patients with stimulants and found their symptoms and their social functioning improved. For example, rather than being fired from jobs, they got promoted; rather than dropping out of school, they progressed; difficult marriages and relationships improved. Accordingly we decided to conduct a one year trial of methylphenidate to determine if we could systemically document these observations. We began with a double-blind crossover trial of methylphenidate and placebo and found, as before, that two-thirds of the patients showed much or very much improvement on the active drug. The effect size was large, 0/8 comparable to 0/3-0/4 in trials of novel antidepressants. The 75% of our sample who showed much or very much improvement on methylphenidate were then entered into a year long trial of the drug. We measured the symptoms which characterize adult ADHD, such as inattention, hyperactivity, mood liability, over reactivity, disorganization, stress intolerance, and impulsivity. In addition, we measured social adjustment with the Weissman Social Adjustment Interview and Scale. Symptoms and social adjustment were measured at baseline and at six and twelve months. There was an 80% reduction in severity of all seven ADHD symptoms. Their average severity was between "not at all" and "slight". In addition, we found a substantial improvement in social adjustment which measured relationships with his/her partner, children, extended family, work, and economic functioning. Patients improved from "moderate impairment" to "slightly less than good functioning" over the year. The effect sizes of symptom and social functioning improvement was greater than 2. So we documented systemically what we had noticed clinically, that long-term treatment of ADHD in adults results in much better functioning

in all respects. This can be illustrated by one case vignette. This was a 21-year-old woman who entered our study at the suggestion of her social worker aunt. She had had two children out of wedlock in high school. had been using drugs but had given them up, and was currently living on welfare. During a short term trial she became very much better on methylphenidate and we continued medication on an open basis. She became interested in getting a general equivalency for her high school degree and attained it. She didn't like being at home all the time, so she got a part-time job while her mother gratefully baby sat the children. In a few years she had a full-time job and was promoted. Then she had the good fortune to meet a nice guy. Luck plays a huge role in human affairs, but is never commented on by psychiatrists. He was willing to marry her despite the two illegitimate kids. They had a very good marriage, and she decided she would like to get a college degree. No one in her family had ever gone to college. She entered the University of Utah and graduated with a 3.8 average. In her senior year, she decided that she would like to study cognitive psychology, and she got into graduate school on a full scholarship. This fall she e-mailed me to let me know that she had obtained a second scholarship. I have treated many patients with similar outcomes. While anecdotes prove nothing I wanted to illustrate what an effect size greater than two means in the real world. It's not the same as a 50% response to an antidepressant drug versus a 35% response to placebo in controlled trials of antidepressants. So I consider my two contributions to have been in the area of minimal brain dysfunction, now ADHD, and the adoption studies of psychiatric disorders. ADHD has now become the disease of the decade and is plastered all over magazines and on the web. I contributed to that explosion when I wrote the first monograph on minimal brain dysfunction in kids in 1971, and the first monograph on ADHD in adults, in 1995.

- TB: What are you doing these days?
- PW: I am in partial retirement in Andover, MA, where I am seeing private patients.
- TB: Could I ask you a couple of more questions?
- PW: Of course.
- TB: It seems you were first to have the idea of using the adoption methodology in the Danish studies...
- PW: Yes, but at the same time so did Seymour Kety and David Rosenthal. Our projects were collaborative. It is amazing.
- TB: The research continued over a period of...
- PW: About ten years. And then we gave the research registers to other people to do other kinds of research. One of the great joys of my life was

working with these two men. Dr. Rosenthal and Dr. Kety treated me as a peer. Dr. Kety was a great man whom I loved and whom I miss very much. Every time an interesting thing happens in the world of schizophrenia, I think I must call Seymour right away, and now I can't; I know what pleasure he would get out of it. Did you know him?

- TB: Yes. So you were close to him?
- PW: Yes, we were dear friends.
- TB: What about the others?
- PW: Dr. Rosenthal?
- TB: Yes.
- PW: I was also very close with Dr. Rosenthal. He mentored me and taught me a great deal of psychology. Just as I was leaving NIMH he developed rapidly progressive Alzheimer's.
- TB: I see.
- PW: He died in the 70s.
- TB: What about Fini Shulsinger?
- PW: Fini Shulsinger is in Denmark and still alive. He is a Past president of the World Health Organization. I saw him several years ago. He is still going strong so far as I know. To repeat his role in our research, Dr. Schulsinger searched through the central registry of all patients in Denmark admitted to psychiatric hospitals with presumably genetic disorders. Fini quickly eliminated those who had multiple sclerosis or epilepsy. He then dictated summaries of all the severe psychiatric disorders. He has a low, quiet drawl in English. I remember sitting in Dr. Kety's office together with Dr. Rosenthal listening to endless audio tapes of Dr. Shulsinger. Dr. Kety smoked a pipe, and in that era I smoked cigarettes. We'd listen to three or four hours of Fini's tapes in English with a Danish accent, in a smoky room. He was an invaluable collaborator. Without his participation we could never have conducted our studies.
- TB: What about Jacobson?
- PW: I don't know what happened to Dr. Jacobson. I believe he is still alive and functioning well.
- TB: After the adoption studies your research interest moved from schizophrenia to...
- PW: To bipolar disorders. The important thing is we and others, using our method, showed a genetic contribution to a variety of psychiatric disorders. This was different from twin studies, in which one could account only for genetic factors. Our method measures the amount of variance due to genetic contributions. In the case of schizophrenia we could find no evidence supporting the role of non genetic familial factors in the development and degree of schizophrenic symptoms. That set the

stage for the molecular the geneticists to do their stuff, which in 1967 wasn't much.

- TB: And the adoption studies showed that in certain disorders environment also plays an important role?
- PW: Right. As this particular ACNP meeting has shown, the interaction of genetic factors with early environment can actually change gene expression in some disorders. Our research influenced the whole field of psychiatry and produced a sea change. I hope this does not sound like an arrogant statement.
- TB: Your findings in the adoption studies certainly influenced the whole field and you also pioneered in ADHD in adults.
- PW: Yes, it has. And I can't figure out how I did this, because I still think of myself as 21-years old; not 68 giving an oral history because I'm an aging neuroscientist.
- TB: You are in partial retirement you said.
- PW: And seeing patients which I enjoy a great deal, mainly on a consultation basis.
- TB: You trained many people. Would you like to mention just a few of them?
- PW: Dan Safer in Baltimore. He has done a lot of creative work on ADHD. Ron Reider worked with me at the NIMH; he is head of psychiatric training at Columbia. Jim Harris is a neuroscientist at Johns Hopkins, who has done basic work on all aspects of Lesch-Nyhan syndrome and has written a seminal two-volume text on developmental psychopathology. He is a multi-faceted man who writes the commentary on the paintings the *Archives of General Psychiatry* uses on its cover.
- TB: When did you become a member of ACNP?
- PW: I think 1975, I'm not sure.
- TB: And you have been active in the college? Did you serve on any of the committees?
- PW: I've always abjured sitting on committees and avoided department chairmanships.
- TB: So you did what you liked to do? You were involved in research and teaching mainly?
- PW: Yes and also treatment throughout. I was always in practice. I can spend only so much time doing research. Practice in the real world that has been both a basis for my research and a gratifying and rewarding activity.
- TB: On this note we should conclude this interview with Dr. Paul Wender. Thank you, Paul for sharing this information with us.
- PW: Thank you.

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