Treating the Brain: *An Odyssey*

By

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Treating the Brain: An Odyssey

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FOREWORD

By

Edward Shorter, PhD

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Barry Blackwell, a psychiatrist and psychopharmacologist with an international reach, has been known for his fluent pen and quick mind. He worked for a while in industry and has spent many years laboring in the trenches of clinical psychiatry, and is therefore well positioned to write authoritatively about the disaster that psychiatry's encounter with psychopharmacology has become. The author is a rare combination of someone who has his psychiatry chops, a strong basic science background in psychopharmacology and an adept historical pen. When, therefore, he produces a big book like this and modestly says – more or less – that it's something he chipped away at in his spare time over the years, he must be attended to carefully. The book is worth the read: Some of it reprinted, some original text, it is a triumph of historical scholarship and of wise, mature reflection on the part of someone now in his 80s looking back on a history of triumph and tragedy.

The triumph occurs in the first part of the story, the years from 1940 to about 1980, when one successful drug class followed another and psychiatry acquired, for the first time, the ability to relieve misery of the mind. The tragedy is from 1980 to the present, as enmeshment with industry has corrupted the discipline, trivialized (or falsified) its intellectual content and watered down the pharmacopoeia to the point where one asks of the many "antidepressants" if they actually work at all.

Blackwell's path to psychiatry was not a direct one. He writes disarmingly: "I was uncertain about a career in psychiatry. Clumsy from birth, I was not cut out for the fine finger work required for animal research: I shattered expensive glass pipettes and smudged endless smoked drums. Besides, I preferred humans to rodents and felt reluctant to relinquish the breadth of medicine for the narrower scope of psychiatry. The commanding officer of my reserve army Field Ambulance was a close friend and looking for a partner in his suburban London practice. So, I decided to try my hand at family medicine." After further misadventures, and despite his hatred of organic chemistry, he does in fact end in psychiatry.

And so he sets out to offer us what is essentially the lived experience of a life in psychiatry, set within a scholarly framework. How to approach this vast subject?

First there is what might be called the omnium-gatherum approach; Blackwell moves like a vacuum cleaner across the expanse of psychiatric history, picking up piquant little details in no particular order: Heinz Lehmann's wife was a nurse; Jean Delay had an improbably large number of publications only because he attached his name as first author to everything that his assistants wrote. This actually makes for fascinating reading.

We find John Smythies opining that, "The way that the English girls I knew moved was honed by many hours playing hockey and by many hours astride the saddle – Italian girls did not play hockey. They flow and do not jerk." Exquisite.

In one chapter the vacuum cleaner lands, quite unexpectedly on "women pioneers" in psychiatry, a vastly understudied subject. Blackwell then treats us to wads of detail on the lives of nine women – such as Victoria Arango and Rachel Klein – some of whom are well known, others not.

Out of the blue appears a chapter that Blackwell wrote in 2014 on "the anxiety enigma." This is not part of a systematic assessment of the nosology, which Blackwell would certainly be capable of offering, but doesn't. Nonetheless, anxiety occupied center stage in psychiatry from the 1960s to the 1980s and these recollections are most welcome.

Yet, as I said, there is a second approach, and that is to identify great themes in psychiatry and to return to them time and again midst the flurry of detail. And for Blackwell the big themes are (1) The tension between biological, psychological and social features of mental illness and its treatment that he identifies both in his own practice and as prevalent among the pioneers in psychopharmacology; (2) a kind of "great man" theory of history, in which advances are made by brilliant flashes of insight and determined action; and (3) the pharmaceutical industry has corrupted the inheritance that these pioneers left to psychiatry – and to society.

Apropos individuals who made a big difference in the psychiatry narrative, Blackwell introduces us to the whole world of Edward Mapother and Aubrey Lewis at the Maudsley. These are among the most riveting sections of the book as so many people today have fond memories of these precincts. But were it not for Lewis's genius at inspiring – and were it not for the German influx of refugees from Hitler – English psychiatry would have been an inconspicuous presence internationally. So, the little round of clinicians that Lewis regularly convoked at the lunch table meant that England punched far above its international weight. This is "great man" grist. Karl Rickels, Heinz Lehmann and others get a similar fond treatment.

Blackwell knows his figures well enough that he refers to them affectionately by first name. Idolizes would be too strong, but it is clear that Blackwell greatly admires the men and women who parade through these pages. Of Frank Berger, the originator of meprobamate, he writes: "Berger [offers] a lifetime's treasure trove of wisdom; of truth in action." I share these sentiments, but wish merely to say that the approach is not skeptical nor critical.

On the drugs sponsored by these men and women, Blackwell's view is that, generally speaking, meds are a great benefit. But how about "prophylactic lithium"? Blackwell and Michael Shepherd became famously embroiled in controversy with Mogens Schou in 1968 on this issue. Here Blackwell rows back a bit, but not a lot, and still expresses dubiety about what other observers consider the most effective agent in psychiatry.

Some of the great figures are historically not without blemishes. John Smythies, once he reached Saskatchewan, was on the wrong side of transmethylation theories and his reputation has suffered accordingly. But Blackwell's sympathetic account rehabilitates him as a contributor.

In one section, Blackwell tells of his own encounter with "the cheese factor" and the malentendu with Gerald Samuels.

On industry: Blackwell is scathing about the recent impact of the pharmaceutical industry. He writes of industry-sponsored trials: "While they adhere to FDA minimal requirements for controlled studies, [the companies] have adopted other dubious ways to degrade the process and bias the outcomes."

Industry has always existed to make a profit. There is nothing sinister about this, although the companies were not supposed to invade the practice of psychiatry in order to pursue their commercial rivalries. Yet Blackwell also laments the invasion of medical practice itself by the greenback. He closes the book: "At age 84, I now live at the distal end of the stethoscope, a problem to be solved, seldom a person to be understood, often an aggrieved patient, greeted by Mammon in a doctor's office."

There is so much here, and it is so delectable, that this should be a book that readers take to the beach and relish as the children splash in the water. These memories will live on for future generations. We owe a debt to Blackwell.

August 8, 2019

Acknowledgments

Treating the Brain is dedicated to three scholars who mentored my development as a professional psychopharmacologist and amateur historian.

First, **Sir Aubrey Lewis** at the *Maudsley Hospital and Institute of Psychiatry* in London who recognized something about me worth encouraging and tutored all his registrars in rigorous epistemology,descriptive psychiatry and critical thinking.

Second, **Frank Ayd,** a fulltime private practitioner, consultant to pharmaceutical companies as well as to the Vatican and Pope, a co-founder of the ACNP and senior editor of our book, *Discoveries in Biological Psychiatry* (1970). A mentor who became a friend and colleague.

Finally, profound gratitude to **Tom Ban** who invited me to help edit the 10 volume *Oral History of Neuropsychopharmacology* (2011) and then asked me to become a founding member of the *International Neuropsychopharmacology History Network*, responsible for Biographies and Controversies that provides much of the material for this volume, posted on the INHN website from 2013 to the present.

I also express appreciation and gratitude to **Olaf Fjetland** for diligent and patient editing of this volume throughout all stages of its development.

Introduction

The International Neuropsychopharmacology History Network (INHN.org) was founded in 2013 by Tom Ban and a few like-minded colleagues, including myself. The core material for this volume, 22 biographies of selected pioneers and six significant controversies were penned and posted on INHN.org in five years between 2013 and 2017. Together they provide a colorful portrait of some of the organization's early activities in an historical context.

Technically, this is a convenience sample which raises the question of how representative it is of the larger population of pioneers and range of controversies. By definition most, if not all, controversies are unique with little content in common so this question may be moot. Nevertheless, all six controversies touched my own 50-year career in some manner or degree (Blackwell 2012).

Controversies were also sometimes imbedded in the individual biographies. The anti-psychiatry agenda touched the careers of Jean Delay, Jose Delgado, Heinz Lehman and Karl Rickels. Squabbles about the priority, significance or methodology of a discovery are evident in the biographies of Thudichum, Cade, Smythies and Charalampous as well as the Anxiety Enigma and Lithium Controversy.

The selection of pioneers was dictated by several considerations. If we define pioneer as activity in the period 1949-1980, age and mortality winnowed the field. Joel Elkes was 101 years old when I interviewed him, Martin Kassell was 100 and many who merited a biography were deceased. Five biographies are a synopsis extracted from personal memoirs of Callaway, Berger (post-mortem), Smythies, Rickels and Varga (in part). Two are derived from post-mortem biographies by other authors of Cade and Delay. Four are based on in depth personal interviews of Elkes, Varga, Charalampous and Kassell and two from detailed literature reviews and other material about deceased pioneers, Lehman and Delgado.

A general familiarity with the careers of pioneers, available for reflection and comparison, was obtained between 2008 and 2011 working with Tom Ban on the Oral History of Neuropsychopharmacology (OHP) for the 50th anniversary of the American College of Neuropsychopharmacology (ACNP). I edited Volume 7 (Special Areas; *Desiderata*) and Volume

9 (Update) in the 10-volume series and also wrote 57 mini-bios (dramatis personae) published in Volume 4 (Psychopharmacology) and Volume 7 (Special Areas; *Desiderata)*.

Further details about each biography or controversy and its place in the chronology are provided in the text.

A diversity of cultural origins is displayed in the chronology beginning in the 19th century with Thudichum, who trained in Germany and migrated to Britain. The onset of the Pioneer Era (1949-1980) began halfway through the 20th century with Elkes in England and Cade in Australia. Following, in a flourish of creativity and serendipity, were Delay in France, Lehman in Canada and Berger in America, from Germany via Britain to America. He was joined by Delgado from Spain and Elkes from Britain. Later arrivals in America were Rickels from Germany, Varga from Hungary and Charalampous from Greece. The only pioneers born and raised in America were Calloway, Kline and Kassell.

We can compare this convenience sample with a control group of 57 mini-bios (dramatis personae) written by me for the OHP in volumes 4 and 7. There were 13 immigrants (28%) and 10 women (18%) in this cohort. The oversampling of immigrants or foreigners in the convenience sample is partly explained by a chronological difference in time frames. The convenience sample is from the first 15 years of the Golden Era (1949-1964) while the control cohort covers a lengthier period. The high incidence of immigrants from Europe in the convenience sample is contributed to by scientists fleeing the Nazi and Communist regimes in the pre-and post-World War II years.

The absence of women in the convenience sample compared to the control cohort is due to the fact that the Pioneer Era of psychopharmacology was also a time of a cultural phenomenon - misogyny. The organizing committee of the ACNP (1961) included no women. The first women council members were not elected until 20 years later (1981). Eva Killam became the first woman President in 1988 and there were only two other woman presidents in the next 20 years.

However regrettable the absence of women in the convenience sample, it is compatible with the ACNP's organizational and recruitment policies. There are several women members in the control cohort born between 1920 and 1940 (almost all of the pioneers in both genders were born in that time), whose careers clearly merit a biography and seven of their stories are told in Chapter Nine, taken from Volumes 4 & 7 of the OHP.

In Chapters 1 thru 9 in this volume biographies discoveries and controversies are intermingled in conformity with the time sequence and leading to chapters that highlight the differing points of view between Early Optimism and Ambiguity (Chapter 10) as opposed to Cautious Appraisals and Skepticism (Chapter 11).

The next two chapters deal with major controversies, Lithium (Chapter 12) and The Anxiety Enigma (Chapter 13), followed by Karl Rickels biography; a psychopharmacologist who played a major role in the latter controversy (Chapter 14).

Two chapters that follow cast light on broader aspects of the Pioneer Era; withy biographies that illuminate how vicissitudes and changing zeitgeists influenced the careers of three pioneers (Chapter 15) and the manner in which the early history of the period cast light on the later years (Chapter 16).

The five final chapters discuss broader considerations affecting the entire field including Changing Medical Education and Practice (Chapter 17), The Biological Basis of Psychiatric Diagnosis and Treatment (Chapter 18), Corporate Corruption in the Psychopharmaceutical Industry (Chapter 19), the ADHD Controversy (Chapter 20) and an epistemological conundrum about what to believe; The Baby and the Bath Water (Chapter 21).

. The volume ends with an Epilogue placing the two contrasting eras of psychopharmacology in their historical context (1949-Present).

Prologue and Personal Perspective

The title for this book emerged as it was being written. Originally it was to be a compendium of the biographies of selected pioneers in psychopharmacology and early controversies in the field published on the INHN website between 2013 and the present. Instead it morphed into something more substantial and significant influenced both by the historical material but also embedded in my own career.

The material invited a comparison between two distinct epochs in the history of the field. The “Pioneer Era”- three decades from 1949 to 1980, was an innovative period when all the first drugs for psychiatric disorders were discovered, leading to the emptying of asylums and initiating care in the community, thus creating an optimistic, proud and highly productive profession. This

contrasts with four decades, from 1981 to the present, characterized by dwindling innovation, corporate corruption in the pharmaceutical industry, professional and academic complicity in a cultural climate of avarice, political malfeasance, ethical lassitude and research gridlock.

This comparison between two distinct eras deserves the metaphor of "An Odyssey" – the Greek term Homer chose to describe the vicissitudes of Ulysses' sea voyage back home from Troy to Athens. OED defines an Odyssey as "A long and adventurous journey or process." Such journeys often include triumphs and tribulations, victories and defeats, sometimes triggered by the Greek emotions of Hubris (excessive pride) leading to Nemesis (downfall or retribution). An outcome that seems to distinguish the two eras this book examines.

A Career Synopsis

The topics examined and opinions expressed in this book are colored by the experiences of my career. This began after pre-med at Cambridge University at Guy's Hospital in London, graduating in 1961, which led to psychiatric residency and a basic psychopharmacology fellowship coupled with general training at the Maudsley Hospital and the Institute of Psychiatry that emphasized epistemology, descriptive psychiatry and rigorous formulation of clinical problems.

This was followed by a brief interlude of family medicine in suburban London that included collaborative work with the Maudsly Social Psychiatry Unit on the validation of the General Health Questionnaire (GHQ) devdloped by David Goldberg,, among the first rating scales to record the symptoms and natural history of affective disorders in primary care, the settingt in which a majority of psychotropic drugs are used.

In 1968, aged 34, I migrated to America to become the Director of Psychotropic Drug Research for a pharmaceutical company in Cincinnati that was recovering from their disastrous research and marketing of thalidomide as a hypnotic for pregnant women That catastrophe led Congress to establish the FDA parameters for proving the safety and efficacy of all drugs, early research in which I became involved. I was mentored by Frank Ayd, a consultant to the company and early pioneer as well as a founding member of the ACNP. We both did research in prison volunteers, Frank sponsored my membership in the ACNP and together we planned and implemented the unique Taylor Manor Symposium in 1970, ***Discoveries in Biological***

Psychiatry to which Frank invited all the scientists and clinicians involved in the discovery of each of the first drugs to treat every category of mental illness.

After two years I was appointed Professor of Psychiatry and Associate Professor of Pharmacology at the University of Cincinnati. The first faculty member not an analyst I took over the Psychosomatic Unit founded by George Engel and extended its research activities by developing a cognitive-behavioral treatment model for forms of abnormal illness behavior.

In 1974 I became Professor and Founding Chair of Psychiatry at Wright State University in Dayton – a community-based program, one of more than 30 funded by the Federal Government in the hope of graduating humanistic primary care physicians willing to work in under-served urban and rural settings. Also, as Professor of Pharmacology and Medicine, I developed interdisciplinary innovative educational programs and a broad research palate. Inevitably the experiment failed and when the charter class graduated I resigned and accepted another innovative challenge.

In 1980 I became the founding Professor and Chair of Psychiatry at the urban Milwaukee Campus of the Wisconsin School of Medicine in Madison. Its goal was to offer medical students and residents an inner-city experience in a largely Medicaid population. We recruited faculty and built a successful psychiatric residency program. I managed the consultation-liaison program and became involved in research and practice among the homeless population with mental illness, leading to a sabbatical at the NIMH as staff person to a federal inter-agency task force on homelessness.

In the early 1990s managed care evolved, mental health was separately capitated and within a relatively short space of time seven inner city hospitals merged and/or went bankrupt. Increasingly large healthcare "not for profit" corporations evolved with the mantra, "No Margin, No Mission," and an eagle eye on the bottom line. Primary care disciplines couldn't compete economically. The large corporation that acquired our bankrupt inner city hospital closed our inpatient program, effectively terminating the residency program in psychiatry. Soon afterwards the corporation gave the family medicine faculty the choice of ceasing to treat Medicaid patients or being fired. The chair of family medicine moved to join the corporation and within a few years became its CEO, now earning almost $4 million annually.

These events marked the end of my academic career and for a brief time I worked as a consultant to Blue Cross and Blue Shield, then as Medical Director of a small managed care company where I enjoyed the challenge of overseeing the management of my colleagues' difficult cases until I retired for the first time.

My academic career in all its settings included research on the educational and clinical challenges faced, funded from salary and never by industry, federal agencies or foundations. It incorporated students in the design and implementation as well as including residents and faculty in medicine, psychiatry, pharmacology, pharmacy and other allied disciplines with results often published in leading journals.

In 1998, aged 64, I took down my shingle and embarked on a three-year exploration of my spiritual life at the local Catholic Seminary where I enrolled in a Master's program studying religion and philosophy alongside male seminarians and women seeking a second career as parish administrators. With the help of a spiritual director (a very kind and wise nun) I recognized I was spiritually handicapped, quit the seminary and went back to work as the only psychiatrist at four Catholic Charities clinics in Milwaukee and neighboring counties where I saw a Medicaid or uninsured population of folks unable to find a private psychiatrist willing to treat such patients. It was rewarding work, collaborating with well-trained social and psychological therapists in adjacent offices and soliciting free drug samples from pharmaceutical representatives. This job ended abruptly when the pedophile crisis threatened to bankrupt the Archdiocese and they could no longer afford the portion of my work that was not pro-bono.

Around 2004 I accepted a job in the Wisconsin Correctional system as the only psychiatrist in a women's minimum-security prison where half the 200 inmates had a mental illness, testimony to the inadequacy of community mental health. It was highly rewarding professionally and economically – I earned enough to pay my youngest son's medical school tuition of $40,000 annually, but which provided him and his family no medical coverage despite a large faculty practice. The Dean's office offered to loan him an additional $10,000 a year to buy insurance. Adam declined and applied for Medicaid which was granted plus an offer of food stamps.

In 2008 my son graduated, I quit paid work and began a new life as an amateur historian, a vocation in which I have been mentored by Tom Ban. For three years I assisted Tom with his work as senior editor of the 10 volume *Oral History of Neuropsychopharmacology* (OHP). .

After a brief hiatus, in 2013 I joined Tom in helping to found the International Network for the History of Neuropsychopharmacology (INHN.org) with responsibility for Biographies and Controversies creating the material for this book. Our work is unremunerated and free from all outside funding.

The components of this Odyssey are primarily the fruit of our collaboration and *Treating the Brain* is dedicated to Tom Ban and Frank Ayd, two of the earliest pioneers and to Sir Aubrey Lewis, head if the Maudsley Hospital and London Institute of Psychiatry. That the Prologue includes a synopsis of my own career is a reflection on something I learned in my historical writing. Biographies and controversies are strongly influenced by the cultural climate of their time and often colored by the innate idiosyncrasies and experiences of their author. This may emerge more clearly in the Epilogue.

The chapters in this volume are arranged in roughly chronological order, each with a preamble to clarify linkages between different postings on the INHN website and to emphasize the conceptual framework. This structure creates more of a mosaic than a portrait, another Greek word conveying a pattern created from an assembly of individual pieces (OED**:** Fr. Gk. *Mousa;* muse).

Chapter 1

Ludwig Thudichum, "Father of Neurochemistry"

Preamble

As a young resident in psychiatric training I heard Thudichum's name bandied about, but in pre-Google days that was all I knew of the man. When in 1994, aged 60 and Chairman of an academic Department, I wrote the poem below, *Our Fathers*, I remained ignorant. That changed in 2015 when I decided to write Thudichum's biography for the INHN website. The poem, which sets the tone for that work, conveys the occasional frustration and sense of inadequacy a psychiatrist feels when confronted by a complex patient whose illness fails to respond to the therapeutic claims of either psychological (Freud) or chemical (Thudichum) interventions.

The poetic metaphor is prelude to this volume that spans almost 70 years, beginning with asylum care which persisted despite speculative chemical and psychological theories of etiology. Next came a golden and optimistic era of serendipitous drug discoveries that shifted people suffering severe, persistent, mental illness from custodial care into communities (and prisons). That main theme is told in the biographies of pioneers and scientific controversies, leading to today's more skeptical appreciation of the complexity and sometimes intractable nature of the disorders we still aspire to treat and, even more hopefully, to cure.

When I set out to write the story of Thudichum's life I discovered a biography written in 1958 by his fellow biochemist, David Drabkin, and obtained a second-hand copy from Amazon which provided the framework for my own work.

Two years earlier I had written a biography of Jose Delgado (see Chapter 10) when a similar claim of "Father of Neuroscience" had been made for his Spanish mentor, Santiago Ramon y Cajal, a Nobel Laureate in Physiology and Medicine, for his research with Golgi on the structure of the nervous system. There is, however, a distinction between these seemingly rival claims – between the specific terms "Neurochemistry" for Thudichum and "Neuroscience" for Cajal.

In a comment on my essay Ed Shorter, a distinguished historian of psychiatry, makes more substantial criticisms of the Thudichum claim. He points out that in the mid to late 19th century the

idea that psychiatric illness stemmed from biological disorders of the brain "was not an original idea." He correctly notes that work at this time was almost entirely on the chemical composition of the brain rather than function. This is confirmed by Appendix One in Drabkin's book which lists Thudichum's entire body of work: 213 citations in the English and German literature, both books and scientific articles, published between 1846 and 1901. Only 11 (5%) directly relate to the brain and almost all are on its chemical composition. Perhaps this justifies Shorter's suggestion that a more correct title might be "An influential early biochemist," although Thudichum's major thesis, *"Chemical Composition of the Brain,* was, I believe, without a rival when it was published in 1884, making the case that aberrant chemistry was probably the cause of mental illness. A tendency to inflate Thudichum's status as a leader in the field may be due to his reputation as "The Multiple Man." A practicing surgeon, physician and biochemist, he was adept in Public Health matters and the range of topics about which he published was encyclopedic including bones; arteries; the uterus; lungs; the kidney and urine; the gall bladder and gall stones; the liver and bile; as well as the spinal cord. He also published as an expert in horticulture, cooking and oenology. He did not have a "school" because Britain lagged behind Europe in biochemical matters. However, he was an employee of the British Parliament and their consultant on health elated matters.

That he was disparaged by ambitious contemporaries is also true, part of a long lasting and bitter dispute between himself and leading academic rivals in his native Germany; chief among them, Hoppe-Seyler engaged in a lifelong denigration of Thudichum documented by 27 references throughout Drabkin's book, allegations against which Thudichum "fought back with Jovian wrath." As Shorter notes, Hoppe-Seyler called Thudichum "a fool and charlatan" in his review of a paper published in a journal edited by Virchow. When Thudichum demanded a retraction, he received a letter from Hoppe-Seyler, reproduced in Drabkin's book (Fig.19). He apologizes and offers a rather lame excuse, blaming Virchow for not sending him proofs in time to amend or retract his slander.

A burr under Thudichum's saddle (he was an accomplished equestrian) was the unpleasant tendency for his German rivals to replicate his research, rename the chemicals he had discovered in German and then claim priority for the discovery themselves.

Finally, Shorter suggests the title "Father of Neurochemistry" would be better bestowed on Bernard Brodie for the work in his lab at NIMH in the 1950s using the newly invented fluoroscope to identify chemical processes in the brain. This seems an odd title to bestow on a contemporary colleague when clinicians like Elkes, Cade and Delay had already made their chemical and clinical discoveries, so it seems unrealistic to assign paternity. Perhaps a kind friend or a brother, but surely not "father."

Squabbles about priority between scientists are common (see Adumbration in Chapter11), a fact demonstrated by Donald Towers, previous owner of my copy of Drabkin's biography. Also, a historian, he discovered that the 17th century German chemist Johann Hensing studied cerebral chemistry and discovered phosphorus in the brain, anticipating Thudichum by about 200 years. Perhaps "The Grandfather of Neurochemistry"?

In defense of Thudichum and the patronym he justly deserves, Hector Warnes rightly took me to task, as does Ed Shorter, for failing to be more specific about the precise contributions Thudichum made to understanding the composition of the brain. I plead guilty to relying entirely on Drabkin's 273-page biography in which this pre-eminent contemporary biochemist also fails to document the substances Thudichum identified and which Hector painstakingly names; cephalin, sphingomyelin, galactose, lactic acid and sphingosine. Drabkin cites the same source as Warnes (Thudichum 1896) but does not discuss it in detail.

About phosphorous I do not yield so easily – why name a substance known to be present in the brain for centuries? Thudichum was averse to false claims of priority. In the preamble to my brief biography of Thudichum I relate the tale of how Donald Tower wrote his own monograph of Johann Hensing, attributing his identification of phosphorus to the year 1719 in a volume which received an Award of Distinguished History from a German University (Tower, 1983). If indeed an alchemist named Henning Brand preceded Hensing in 1669, it is not ratified by a citation, but may be yet another example of disputed priority in scientific discovery.

So, we may have another controversy on our hands. Who is the "Great Grandfather of Neurochemistry" – Brand or Hensing?

Thudichum: "Father of Neurochemistry"

<u>Our Fathers</u>

"*The poets and philosophers before me have discovered the unconscious; I have discovered the scientific method with which the unconscious can be studied*."

Freud, Father of Psychotherapy

"Many forms of insanity are unquestionably the external manifestations of the effects upon the brain substance of poisons fermented within the body"

Thudichum, Father of Neurochemistry

She wakes me up in early morning doubt.
Crazed eyes and alien name, Luz Medino;
both fuel the need in me to know about
her persona, gene pool, Puerto Rico.

Sour culture and unruly cells enslave
her brain in bitter juice. It can't go free,
slumped sad inside its melancholy cave,
bound by its own unraveled chemistry.

The day they cut her breast away she wept,
her hardwood face dissolved in acid tears.
Except for dream-infested nights she kept
slammed shut that angry door to all her fears.

She doesn't rage against her fate. So sure
she is a devil who deserves to die
that words or drugs have not produced a cure
and Freud or Thudichum can't tell me why.

More than twenty or more years ago, I composed and published this poem dedicated to "Our Fathers" (Blackwell 1994). As befits the topic, it is in a classical form with four stanzas, each of four lines with 10 syllables and alternating end rhymes.

The poem portrays the frustration we all feel when our best therapeutic attempts and all our tools fail to benefit the patient. When it was penned, all I knew about Thudichum was his paternal eponym as "Father of Neurochemistry." Then Tom Ban suggested I write a biography of Joel Elkes, born only 12 years after Thudichum's death in 1901 and described by Jean Paykel as the "father of neuropsychopharmacology" (Paykel 2003, cited by Shorter 2011).

To accomplish that task, I needed to learn more about Thudichum and I was surprised to discover a copy of his only biography (Drabkin 1958) on Amazon for the bargain price of $3.50. It was a second-hand copy in pristine condition, its former owner identified by a rubber stamp on the fly leaf.

Donald B.Tower M.D.

National Institute of Neurological Disease and Blindness

Bethesda, Maryland.

Knowing more about the book's former owner might enlighten my understanding of Thudichum. Donald Tower's own autobiography was available in Volume 3 of the series The History of Neuroscience in Autobiography" (Squire 2001).

A medical graduate of Harvard (1944) with a Ph.D. in neuroscience from McGill (1951), Towers trained in wartime as a physician and post-war began neurological and neurosurgery training under Wilder Penfield at the Montreal Neurological Institute where both clinical care and laboratory research were mandatory. This involved neurosurgery on the foci of seizures and bench work on the excitatory role of acetylcholine in epilepsy. After graduation he chose to pursue the research track with work in humans and animal species from rats to whales and elephants.

At the outbreak of the Korean War Towers satisfied his reserve military obligation in an assignment to the National Institute of Health's Institute of Neurological Diseases and Blindness (1953) where he moved up the ladder to become Director of Neurological Diseases and Stroke (1974-1981). Like Thudichum, he engaged in both clinical and chemical work on the brain, on the manifestations of disease and its putative origins.

Following retirement from the NIH, Donald Towers pursued his hobby and delved into the history of neurochemistry. From the German edition of Thudichum's monograph on the Chemical Composition of the Brain (1901) David learned of the 17th century career and contributions of Johann Hensing who, like Thudichum and Tower, was both a clinician and neurochemist. Tower obtained a photocopy of the only known text of Hensing's monograph on cerebral chemistry that included the discovery of phosphorous, the first specific chemical substance to be isolated from the brain. Tower published his own monograph of Hensing (Tower 1983) which received an Award of Distinguished History from a German University.

Thus, we have a four-century chain of distinguished clinician-scientists through Hensing, Thudichum, Tower and Elkes from a single simple chemical substance in the 17th century to the elegant but baffling complexity of contemporary 21st century neuroscience.

The origin of Drabkin's interest in Thudichum appears to date from 1925 when their paths crossed over an unlikely scientific problem they shared in common concerning the color of urine and its biochemical significance. When Drabkin became interested in this topic (Drabkin 1927) an intensive search of the literature turned up Thudichum's early "Treatise on the Pathology of Urine" (Thudichum 1858) and his later discovery of urochrome (Thudichum 1868). While Drabkin was developing his own paper (1925-1927), he sought further information about Thudichum and received a message from Irvine Page, Research Director of the Cleveland Clinic Foundation, making him aware that Dr. Otto Rosenheim, an outstanding steroid chemist, had collected a substantial amount of archival information about Thudichum. Rosenheim's interest was stimulated by his own early research when he found proof in defense of Thudichum's controversial view that Liebreich's "Protagon" was not a discrete chemical entity but a combination of two others. (Rosenheim and Tebb 1910). This debate sparked a contentious dispute, described later, that tarnished Thudichum's reputation and career.

In his biography of Thudichum, Drabkin devotes an entire appendix to Rosenheim's distinguished career (he discovered ergosterol, precursor to Vitamin D) and acknowledging the material about Thudichum he provided. He also dedicates the biography to Rosenheim noting that "With characteristic generosity he put at my disposal many salient facts he gathered on Thudichum's life." We do know that Drabkin and Rosenheim corresponded with one another beginning in 1929 and Drabkin promised that in return he would produce a biography on Thudichum in the future. Eighteen years later he published a brief historical synopsis in two chapters for a history of biochemistry (Drabkin 1947) and in 1954 he gave two unpublished lectures in Chicago on "Thudichum a Neglected Genius of the Nineteenth Century: His Times and Contemporaries."

In the prologue to the biography Drabkin berates himself for the dilatory implementation of his promise to Rosenheim made a quarter century earlier.

He then relates how this "writer's block" was overcome after a meeting with another scientist enthused about Thudichum. Drabkin's friend Harold Himwich introduces him to Percival Bailey, a neurosurgeon who served as research consultant to the State of Illinois. Together they are planning a ceremony to name the new Laboratory of the Galesburg State Research Center in honor of Thudichum. Bailey invites Drabkin to give the opening lecture, acknowledging "You are the man who knows more about Thudichum than anyone" and then relates the origins of his own interest which are retold in his introduction to Thudichum's biography.

It began 40 years earlier in 1913 when Bailey attended a course in biochemistry at the University of Chicago and the lecturer, Fred Conrad Koch, made frequent reference to Thudichum. This knowledge lay dormant for several years until Percival married into a family of grape growers in California. Becoming an oenophile, he browsed second hand book stores in search of texts about wine making and came upon an author named Thudichum (Thudichum 1894). Sensing this might be the same man he began a search for Thudichum's classic monograph *"The Chemical Composition of the Brain"* (Thudichum 1884) a prominent London bookseller had a dozen requests on a waiting list, but a copy had not been found in as many years. Quite by chance, in a pile of catalogues he was about to discard, he noticed a copy selling for $4.50. This began his own search for historical material.

After telling his own story Bailey unveils a strategy designed to enable Drabkin to fulfill his promise to Rosenheim. “You must get rid of your guilt complex; I shall arrange it.” Within weeks Drabkin receives “the following guilt purging program.” It outlines a four-lecture series incorporating the two he has already given on “The Neglected Genius” with a lecture to be written for the naming ceremony on “His Works” to be followed by a final named lecture at the University of Illinois on “Thudichum: Chemist of the Brain.”

The specificity of this strategy, building on previous work and defining two future distinguished lectures, produced the desired results and became a framework for the long-awaited biography which was finished within a year.

In January 1955 Drabkin set sail for England on the Queen Mary to deliver his completed text (not yet published) to whom it was dedicated and long ago promised. Sadly, Max Rosenheim was too sick to receive visitors so David placed the document in the hands of his mother. The next day she telephoned to report that Max was “excited that the work was completed and very much moved by the dedication.” David Drabkin returned to America where four months later he received a letter reporting that Max Rosenheim had died peacefully in his sleep.

With the provenance of the biography unveiled by this voyage of discovery its form and content will be reviewed for the main purpose of familiarizing the reader with the source of my briefer biographical synopsis of the character, career and accomplishments of “The Father of Neurochemistry.”

“*Thudichum Chemist of the Brain”* (Drabkin, 1958)

No source of information compares with Drabkin’s biography of Thudichum. It is scrupulous in design and encompassing in its scope. The text is 309 pages, including a Forward by Percival Bailey, an author’s Prologue and Epilogue and five Appendices: **I**: An annotated bibliography of Thudichum’s 213 publications (1846-1901); **II**: A chronological Outline of Thudichum’s Life; **III**: ‘Belated Honors’ documenting efforts in England and America to raise resources to support his bereft family as well as founding the kind of research institutions

Thudichum envisaged such as at NIH and Galesburg, Illinois; **IV**: Transcriptions of letters in his native language to colleagues and critics; and **V**: A brief memoir of Otto Rosenheim documenting a career-long devotion to collecting information and memorabilia about Thudichum that forms a foundation for Drabkin's Biography.

The main text (pp. 29-183) is divided into three chapters: "The Man", "His Time and Contemporaries" and "His Works." The first of these includes 15 pages of memorabilia including photographs of Thudichum at different ages; the spectroscope he used; instruments given him by Liebig; drawings from his texts; title pages of his books; lecture notes; letters; his degree Diploma; the title page, in German, of his classic monograph "*Chemical Composition of the Brain"*; pictures of his homes in London; pencil drawings made while a surgeon in the Danish war; a poem to his favorite daughter Lottie on her birthday; and photo reproductions of his unpublished books on "*History of Beer and Ale"* and *"Cape of Good Hope Wines."*

Drabkin's literary style is impressionistic, reflecting thoughts, feelings and events as they occur during his excavation of Thudichum's life. Reconstructing this treasure trove in a coherent chronological sequence was challenging, an invitation for a synopsis to become plagiarism. So, this text makes liberal use of quotation marks to preserve the flavor and provenance of the original biography.

Ludwig: The Man

Ludwig Thudichum was the progeny of forbears who toiled with their hands, traced back to the 17th century, including a cloth maker, cooper and coppersmith. The original family name was Dudichum, a condensation of three German words, *du dich um* which translates roughly to "bestir yourself," "get to work," a "wonderful admonition and motto for a man who once wrote to his friend and mentor, Liebig, proudly proclaiming he had "done the work of three men."

In the early 18th century the family changed its name to Thudichum and began to climb the social ladder moving from handicrafts to intellectual pursuits. Ludwig's father, Georg, was a minister in the Reformed Lutheran Church, Principal of the local Gymnasium (high school) and Doctor of Philosophy, an authority on the epic verse and prose of ancient Greece. He would sire three sons and three daughters. Ludwig was the eldest son, another would become Vice President of a German University and the other founded a famous boys' school.

The family lived in Budigen, a small medieval town unspoiled and idyllic, "with narrow cobbled streets and inner court yards glimpsed through stone archways, its castle and hilly vineyard." Thirty miles north is the "University town of Giessen where the great Liebig founded a chemical dynasty." Ludwig's birth on August 27th 1829, and his subsequent baptism, is recorded in documents dating from 1630. He was named Johann Ludwig Wilhelm, later anglicized to John Lewis William, alternatives he "abhorred." His close friends in England and Germany all called him Ludwig.

Ludwig led a charmed childhood. He was talented in amateur theatricals and his writing skills at age 17 earned him an offer to edit the town weekly newsletter. He belonged to a coterie of talented children, two of whom also became physicians and in whose company he became an excellent swimmer in the local river during the summer and a fine figure skater on its ice in winter.

The family dwelt in a large house, beautifully situated in a lovely park, leading life "on a modestly elegant scale." Parents and children toiled together to turn a plot of land behind the house into a terraced garden growing fruit and nut trees along with grape vines that yielded a wine "as good as any on the Rhenish slopes," as well as a garden "to rival any in England." Clearly these endeavors were the seedbed for Ludwig's lifelong interest in viniculture and horticulture.

Inside the house his father's study was a shrine to his own scholarly accomplishments, translating Greek poetry and tragedies, playing a piano with a "noble tone" alongside his guitar with a compilation of 100 lieder songs. "In this room the Classic and Romantic, song and wine, were wed, a marriage proclaimed by three busts of Zeus, Goethe and Schiller. These symbols were for the children ingredients of the growing up process, much as the garden was."

The climate of the Thudichum household must have resembled that of the European "Salons" of that era -- popular intellectual and social gathering spaces. "The important medical and scientific achievements in Germany in this period were co-linked with the extraordinary liberalism of its great universities." A prevailing sentiment was Goethe's view that "conflict of opinion does not determine truth but states the problem to be solved." Ludwig absorbed this truism in a life devoted to problem solving although the debates that ensued were often mired in controversy

Ludwig was the most apt of the six children in absorbing the fruits of the environment in which they lived. He became a gifted pianist and singer with vocal training from a famous Italian tenor that equipped him to sing in an amateur opera. Georg Thudichum's "scholarship and broad interests brought distinguished people to his door." Among them was the renowned chemist Justus von Liebig. "Georg, the Greek savant, attended some of his lectures at Giessen." In his diary Ludwig's father recorded his admiration and critical analysis of Liebig's lectures: "Without doubt chemistry will bring new light to agriculture and to physiology, perhaps also to medicine? At the best, if the true principles of life were known, the ancient diseases which have plagued man could be prevented."

Impressed with Liebig's talents, Georg consulted him about an analysis of mineral waters from a newly discovered spring on his property to determine if they justified building a spa. Liebig advised otherwise, but visited the Thudichum property when Ludwig was 18 years old, preparing for university. Little did any of them realize that Liebig would become Ludwig's mentor and Ludwig would become Liebig's torch bearer, seeking the fruits of chemistry to illuminate the diseases of body and brain just as his father had imagined might be possible.

At 18 Ludwig graduated from the Gymnasium and embarked on medical school. At the time it was quite usual in Germany to obtain training at more than one university, Ludwig opted to go first to Heidelberg and then Giessen. In Heidelberg, from 1847 to 1851, he was taught by Wilhelm Bunsen, the inventor of the spectrograph and in Giessen he was mentored by Liebig in novel methods of chemical analysis, techniques he employed in his life's work. In Heidelberg he wrote a prize-winning essay on "Urea in Amniotic Fluid" (Thudichum 1850), but his M.D. thesis in Giessen was on "Fractures of the Upper End of the Humerus" (Thudichum 1851).

At age 19, during his first year as a medical student, Ludwig visited the Dupre family in Frankfurt and met his third cousins, two boys and a girl, Charlotte, "small and warm, with dark hair, French-like." In two weeks they bonded, but six years would elapse before they married in London (1854). "But from the first this small woman became the refuge of the big man."

Despite having trained under powerful mentors Ludwig's career did not prosper following graduation principally because he became politically compromised after volunteering for military service on the revolutionary side of the 1848 movement that attempted to establish a democracy

in Germany. When he was denied a post in the Pathology Department at Giessen University in 1853 he knew the reason. “The impetuous young and older men associated with it (the revolution) were destined to pay the price for non-conformity. Many, like Thudichum, found the aftermath unpropitious and migrated to other lands.” For Ludwig this meant London

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Thudichum’s Time and Contemporaries

Of Thudichum’s 72 years on earth 50 were spent in Queen Victoria’s England until she died, just eight months before he did in 1901. Within 10 years of arriving he had established himself as a prominent physician, surgeon and scientist. Regarded by some as England’s leading biochemist (there were not many), his reputation was cemented by winning the prestigious Hasting’s Gold Medal for work on urochrome also leading to appointment as the Honorary Lettsomian Professorship. “It was the heyday of Thudichum’s life.”

Dobkin provides an itinerary of Thudichum’s dwelling places in London (1853-1901) and vignettes of his life in them. The principal and final of these was an elegant house in Pembroke Gardens (from 1876). Adjoining it was a converted greenhouse where Ludwig housed his private laboratory stocked with analytical equipment (some of it from Liebig’s own lab) and where he did much of his research.

Thudichum became a British citizen six years after his arrival (1859), but “frequently made trips to Germany for scientific meetings and particularly to visit loved ones.” At home he preserved a climate “of good things, music, gardens (the best dahlias in London) and subtle family customs. This is the real Thudichum, a man of love and fun.” He sired six daughters and two sons, all proficient pianists with fine singing voices. Strongly built and athletic, he was an expert duelist and a fine horseman who owned two steeds he rode daily in Hyde Park.

Thudichum “was a prodigious worker and maintained a strict routine.” An early riser he made time for his dogs, horses and garden before patients arrived at eleven, followed by two hours in the laboratory. After lunch he took 10 minutes rest before returning to research. He read the literature late at night, rarely went to bed before two, and slept for only four hours – all he needed.

Overall "he was somewhat of an eccentric and epicure. But he was also an indulgent father and had a lusty, boyish humor." Ludwig smoked three carefully selected Havana cigars a day, an indulgence he viewed as "an ambrosial offering to Apollo… to compose my shattered nervous system." He was also a lifelong oenophile for whom "wine was truly God's gift to man."

Thudichum's capacity to unite work with pleasure is reflected in an occasion when, as the first Professor of Clinical Pathology at Saint Thomas' Hospital, he designed a study of the conversion of alcohol to energy "in the course of wining and dining a large group of medical students in the garden. "There were 33 in number, including myself. We drank from two in the afternoon till seven in the evening, 44 bottles of wine consisting of white and red, Hungarian, Burgundy and Sauterne – the alcoholic contents were an aggregate of 4.000 grams of acute alcohol. All the urine passed from two in the afternoon till six next morning was collected and distilled – only ten grams of alcohol were collected. The rest was burned in the system" (Thudichum 1866-67).

Ironically, all the London homes Thudichum lived in were destroyed by German bombs during the Blitz of World War II. His children survived and the last to die was his favorite daughter Lottie on September 30th 1947, at age 85.

During this first decade in London, Thudichum made friends and enemies. First among the former was John Simon (later Sir John). Like Liebig in Germany, Simon became Thudichum's major support in England, funding and sponsoring his research with the Royal Society of London. Sir John was also Chief Medical Officer for the Medical Department of the Privy Council (later the Medical Research Council). It was to him Thudichum dedicated the second edition of his book, "*A Treatise on the Pathology of Urine"* (Thudichum 1877), "as a small tribute of admiration for his many and eminent public services in improving the health of the people." It was this relationship between a leading and innovative public health administrator and a talented physician-biochemist that led to Thudichum's "*Further Reports on Research Intended to Promote and Improve Chemical Identification of Diseases"* (Thudichum 1867). These reports covered fundamental contributions to the chemistry of pigments in gallstones, bile and blood (the "luteins").

It was at the age of 40 (1869) that Thudichum, supported by Sir John Simon and government funding, began his seminal work on the chemistry of the brain, resulting in a series of reports called "Parliamentary Blue Books" beginning five years later by which time he had studied 1,000 brains. It was this work that led eventually to "*The Chemical Composition of the Brain"* (Thudichum 1884), translated promptly into Russian but not into German until just prior to his death (Thudichum 1901).

During this epoch, seeds of enmity had been sewn among his less talented detractors irked by "his non-conformity, individuality and obvious virtuosity." His work on the brain was vigorously attacked and "at fifty-five Thudichum was a discredited man"; he lost his government funding and, although he was able to continue research in his private well-equipped laboratory, he was forced to spend more time on income-generating medical practice and less on research. Although this was the nadir of his reputation, opposition to Thudichum's original ideas and challenging personality began much earlier, within a few years of winning the Hasting's Gold Medal. "Vilification by powerful members of the biochemical fraternity would be his lot; he would have to wage a ceaseless bitter struggle to maintain his place in the sun."

In 1868 Hoppe-Seyler, Germany's leading biochemist, published a slanderous review of Thudichum's discovery of "cruentine" (hematoporphyrin) in a German journal, accusing him of falsifying his results (Hoppe-Seyler 1868). Thudichum appealed to the journal editor, Virchow, requesting a public retraction. This produced a letter of apology for "possibly one-sided and too categorical a judgement" coupled with promise of a future report which never appeared. Fearful his reputation was in jeopardy, Thudichum wrote to Sir John complaining that his position as Professor of Chemical Pathology at St. Thomas was inadequate to support the expense of his research (which he carefully itemized). The result was a generous increase in government research, given although "he was under a cloud."

Although the results of Thudichum's research were appearing in Government reports and Blue Books, they were being "effectively buried" by "garbled re-abstraction or willful misinterpretation." In a "valiant attempt" Thudichum founded his own biomedical journal, *"Annals of Chemical Medicine,"* which foundered after only two issues (1879 and 1881) largely because the contents were made up almost exclusively by Thudichum's own research, inviting virulent rebuttals from his European detractors, Hoppe-Seyler, Stadeler and Maly.

The dispute with Maly was typical of those which plagued Thudichum. Maly, the influential editor of a German journal, critiqued Thudichum's finding that bromo-bilirubin was a bromine substitution product of bile pigment. Maly maintained it was an oxidation product (Maly 1877). Thudichum's correct analysis was based on use of the spectroscope, an instrument with which Maly was not familiar.

Disparagement of Thudichum's research also took the form of "re-discovering" the substances he found and re-naming them in a different journal. Dobkin gives several examples and names the scientific miscreants: Salomen, Abderhalden, Geheimrat and Otto Von Furth, all tucked away in German journals safe from English eyes.

Not everyone in Germany was a detractor. Liebig, Thudichum's lifelong friend and mentor, continued to lavish praise: "It is hard to understand how you find time for these difficult investigations" and "you are remarkably active in fields in which work is extremely difficult."

Thudichum also had powerful enemies in England. Chief among them was Arthur Gamgee, the country's first physiological chemist who "came to loathe him with unreasonable and self-damaging fury." Drabkin makes an effort to uncover the source of this "Thudichumphobia" and attributes it to twin sources: Gamgee's unstable mental temperament and controversy over his discovery in the brain of a compound he named "protogon" which Thudichum considered inaccurate. "The verbal fireworks on both sides became ill-mannered and intemperate." Gamgee criticized Thudichum in his "Textbook" which Thudichum destructively reviewed for a journal titled, "Modern Textbooks as Impediments to Animal Chemistry." This contentious debate stirred up "new and powerful enemies."

Criticism of Thudichum survived into the early 20th century gradually reversing after Rosenheim's research proved Thudichum correct about "protogon" while his interest and admiration grew (Drabkin 1958). Furth's "glowing tribute" also served to further restore his reputation and credibility in Germany (Furth 1928).

Ludwig Thudichum's Diverse Interests and Philosophy of Science

Drabkin's synonym for Thudichum is "Multiple Man." This seems paradoxical since he points out that Ludwig was accused of "dilettantism by his detractors, the Brahmins of his day,

(Hoppe-Seyler, Maly and Gamgee and Co.)." Thudichum, in his own words, says in a lecture to the Medical Society of London titled "*Rise of Specialism Limited"* (Thudichum 1864): "Do not spread yourself too thin; do not dissipate your energies in breadth." Drabkin resolves this paradox by noting, "Thudichum plumbed deeply and yet allowed himself the broadest latitude in casting his lines." Metaphorically, wherever Ludwig cast he caught big fish. Only by shrinking his catch to minnows did ignorance and envy enable detractors to call him a dilettante.

To make his point, Drabkin lists Thudichum's accomplishments across the oceans he fished and furrows he ploughed: "Thudichum and Public Health, Thudichum the Physician (Thudichum's test for creatinine), Thudichum the Surgeon, (Thudichum's speculum for nasal polyps), Scientist, Chemical Pathologist and Physiological Chemist, Thudichum the Historian, Thudichum Chemist of the Brain, Thudichum the Humanist, Poet and Musician." And Drabkin's list does not include viniculture and horticulture. This is the repertoire not of a dilettante but a polymath. No wonder he infuriated lesser mortals!

Drabkin illustrates each of these domains in detail for which the reader of this brief biography must consult the original. Suffice for this biography and its home at the International Neuropsychopharmacology History Network (INHN) to note Drabkin's comments on Ludwig Thudichum's views as an historian: "To him it was a most necessary phase in which the current literature not only is casually scanned, as is usual, his was a deep approach from the very roots – a critical sifting of past errors from adequately established fact, which in the long run saved valuable time by avoiding unprofitable pathways. His appraisals and opinions were never based upon the past evaluations of others. He read the contributions in their original and weighed them carefully, whatever may have been the contemporary opinion of their merits."

Drabkin concludes that "Thudichum's introductions to his various treatises are truly masterful historical contributions… although this aspect of his work has received no notice whatsoever." The introduction to the German edition of his classical monograph (Thudichum 1901) expresses a philosophy of science linking medicine to chemistry.

"My medical soul hangs, expressed in poetical language, in ardent affection on the infallibility of the chemical method. It was for me a spiritual guide in the agitated sea of medical conjecture, on which one so often lacks that compass. The chemical method of investigating and

managing disease, together with the development of etiology and diagnosis, has convinced me that the healing art, aside from its practice by men of genius and its sway over human minds, is capable of perfection into an exact science and of being applied with an almost astronomical precision. For this purpose, however, as in theology the falsification of the records, so also in medicine, to make use of an expression of Darwin, the 'false facts' must be rooted out and the scientific bases for judgement and all intelligences must be established." This is translated into English and quoted by Percival Bailey in his Foreword to Drabkin's biography.

This said, Ludwig Thudichum died a happy man. On May 24th 1901 his monograph on "The Chemistry of the Brain" was published in Germany, 17 years after it was available in England and Russia. Three months later on August 23rd he received an Honorary Degree Diploma from Giessen University celebrating the 50th anniversary of his graduation. After he returned home he celebrated his 72nd birthday on August 27th. On September 6th, walking with a colleague in the evening he was noted to be "unusually elated" due to these recent events. The following day, September 7th, while dressing in the morning and preparing to tend his garden, he suffered a cerebral hemorrhage and died a few hours later. "Death came with kind swiftness" (Obituary, West London Med. J. 6 (1901), 297).

One cannot help wondering what Ludwig Thudichum might think and feel if he were alive today, 114 years after his death, at that time a happy, contented chemist, physician and scientist. He would find his expectation that neurochemistry could achieve "almost astronomical precision" in the treatment of diseases of the mind was tragically unfulfilled. Instead our generation is engaged in rooting out "false facts" while attempting to find better "scientific bases" for judgement. Aware of all this, Ludwig, the skilled physician and occasional poet might empathize with Luz Medino and her frustrated doctors, impotent to find a cure for her psychotic melancholia brought about in an unknown manner by upbringing, persona, culture, genes, gender and mutilating surgery. Thudichum knew chemistry had shone light on the brain's structure, but how that organ orchestrated its miracles and misfortunes remains a mystery. Much work remains to be done; ***Du Dich Um.***

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Chapter 2

Early 20th Century Asylum Care

Preamble

Enoch Callaway

A full understanding of the impact of modern psychopharmacology on the practice of psychiatry and the benefit to patients requires an understanding of conditions in the asylums portrayed in popular media by the Oscar winning film *"The Snake Pit"* (1948) which was alleged to have triggered reforms in asylum care co-incident with the arrival of effective medications that ushered in the era of closure and de-institutionalization of inpatients into the community during the 1960's.

Brief portraits of these events are touched on in several other chapters but Chapter Two is exemplary. It is a synopsis of Enoch ("Noch") Callaway's memoir, *"Asylum; A Midcentury Madhouse and its Lessons about Our Mentally Ill today."* First because it records the experiences and opinions of a leading psychiatrist working as a resident during his two most formative years (1948-1950); between his own personal and training analysis, confronting and attempting to help many patients who had failed to benefit from that form of treatment. During this time Cade, in Australia. discovered lithium for acute psychotic mania (Chapter 5) and chlorpromazine was on the near horizon in France, discovered by Delay's team (Chapter 6).

Important secondly, because Worcester Insane Asylum fulfilled a key role and "best case" example of the evolution and history of asylum care. It was among the first State asylums built, opening on the outskirts of Worcester, Massachusetts in January 1883. It became a model of compassionate "Moral Therapy" better than the fate of the mentally ill confined in prisons, poor houses and other States exposed by Dorothea Dix in the same year the Asylum opened.

Worcester Insane Asylum had an enlightened history under mostly talented medical and administrative leadership. On the cusp of the 20th Century Adolf Meyer was its Medical Director

for six years going on to become America's leading psychiatrist and President of the American Psychiatric Association. Subsequently excellent administrators acquired extensive academic affiliations, recruited outstanding faculty and attracted the best psychiatric residents and trainees from allied mental health disciplines.

Never the less the patient population was typically chronic, severely psychotic, often medically impaired and mostly refractory to a slim repertoire of existing treatments which included insulin coma, ECT and lobotomy.

Noch describes his encounters and adventures in this environment in lively, entertaining, prose in Chapter Two (Parts 1 and 2 of his memoir). How these illuminated his entire distinguished career and some of the predicaments and controversies he encountered are described in Chapter 16 (Parts 3 and 4 of his memoir).

Asylum: A Mid-Century Madhouse and It's Lessons about Our Mentally Ill Today by Enoch Calloway

Enoch ('Noch') Callaway's memoir is a striking accomplishment in format, content and style. Only 187 pages long, it has 54 chapters (average length 3-4 pages) divided into four parts. Its intent is to relate the author's anecdotal experiences as a resident at Worcester State Hospital (Parts 1 and 2) using them as a metaphor (Parts 3 and 4) for the broader clinical, administrative, educational, research and philosophical considerations that have shaped the author's long and successful career.

'Noch' achieves his literary goal in exemplary prose enlightened with humor, wisdom, humility and razor-sharp insights that fulfill his hope that, "These anecdotes from that forgotten world will add a new perspective to dilemmas of freedom and asylum we face."

The memoir's structure makes for an easy read, one anecdote at a time, but its impact has more to do with the forest than its trees. So, this review accomplishes its task in reverse order. First the life history of the asylum and then selected anecdotes that illuminate today's controversies and challenges. This should encourage a reader to consume the entire volume.

A more than a century and a half long history of the Worcester State Hospital portrays the shifting sands of institutional care for mental illness in America, from overcrowded asylums in the

mid nineteenth century to empty beds and community care in the late twentieth century. It paints a picture of how changing political, social and scientific zeitgeists have shaped evolving patterns of care.

In January 1833 the Worcester Insane Asylum opened its doors to 164 patients. Situated on the outskirts of the town of Worcester, Massachusetts, it was one of the first State mental asylums in America. Its enlightened Superintendent, Samuel Woodward, created an environment of kind, compassionate and individualized care, free of restraints that became "an international model for moral therapy." Noch remembers an early photograph of a lawn party from around 1840: "They are elegantly dressed, and the women have parasols, the whole thing looks quite upper middle class." This is all the more remarkable coming just before Dorothea Dix returned to her native State of Massachusetts to commence pioneer advocacy for humane care of people with mental illness. Her investigation revealed the fate of those in prisons and poor houses: "confined within the Commonwealth in cages, stalls and pens! Chained, naked, beaten with rods and lashed into obedience." (Her fiery report, "Memorial" was submitted to the State legislature in 1843, the year the Asylum opened).

By 1877 enthusiasm for moral treatment had waned, overwhelmed by the influx of immigrants from different cultures and languages poorly equipped to benefit "from large doses of white, Anglo-Saxon, Protestant values." Care became more custodial than therapeutic and the population expanded. The State built a new, larger and more impressive asylum which Noch would later describe as "a baroque architectural anachronism." It stood on a 500-acre working farm, built like a fortress, "defending the mentally ill inmates from society."

The institution underwent a brief six-year renaissance from 1896 until 1902 when Adolf Meyer was hired as "Director of Clinics and Pathologist." Trained in Zurich as both a psychiatrist and neuropathologist Meyer migrated to America at the age of 36 to become one of the most influential psychiatrists on the world stage and eventually President of the American Psychiatric Association. He espoused a clinical approach that combined all the biological, psychological and social influences as well as a rigorous attention to detailed history taking and integrative thinking.

Despite his brilliance, Meyer's influence on the institution failed to raise it above the custodial level where it remained until 1920 when a combination of circumstances lifted it out of

the doldrums. The Flexner revolution had moved medicine from a community based apprenticeship to an academic discipline in urban medical schools. Although psychiatry lagged behind the rest of medicine in innovation and discoveries the first partially and selectively effective treatments began to appear; barbiturates, chloral and paraldehyde followed by amphetamines, ECT, insulin coma, the EEG and eventually lobotomy.

Skilled administrators exploited these developments to recruit faculty, build academic collaborations, raise money and create programs initiating a Camelot era that would last until the mid-twentieth century and into which Noch would step. First was Dr. William Bryan (1920-1941), followed by Dr. Bardwell Flower (1941-1969). Two major affiliations came with money and talent, bringing recognition and attracting students from the allied mental health disciplines. In 1924 a wife whose husband failed to benefit from psychoanalysis endowed the biologically oriented McCormack Schizophrenia Foundation which lasted until 1944. An affiliation developed between Clark University Physiology Department in laboratory space provided by the hospital and blossomed into The Worcester Foundation for Experimental Biology, headed by Hudson Hoagland from 1930 and joined by Dr. Gregory Pincus in 1938. Together they undertook endocrine research in women hoping to shed light on mental illness, a collaboration that led to the contraceptive pill – an example of serendipity that matches the discovery of Viagra; dual discoveries that perhaps outstrip any in psychopharmacology during those eras!

Noch entered residency training in psychiatry in 1948 and stayed for two years. He chose the specialty while it was still the "Cinderella of Medicine" because (like Jean Delay) he was too clumsy to follow in his father's footsteps as a surgeon and fell in love with the discipline. He was member of a class of seven men and a token woman fresh from medical school, "intellectually over trained and emotionally under developed." All were from first rate medical schools. It was a time on the cusp between total hegemony of psychoanalysis over academic medicine and the impending discovery of chlorpromazine in 1952 that ushered in the Pioneer Era in psychopharmacology. To Noch the environment mirrored the image of the 1948 movie, "The Snake Pit" identifying himself with the film's eager and serious minded, psychoanalytically oriented, young psychiatrist.

By the time Noch arrived the institution housed 3,000 patients, 1,000 employees and 30 physicians including a staff surgeon and an internist with an operating suite and X-Ray facility. It had its own laundry, dairy, farm and industrial therapy unit. Residents, faculty and researchers lived in the hospital as well as wives, some of whom served as nurses or other staff. "The setting was bizarre, the food lousy and the conditions shocking at first; our heterogeneous group lived and worked together in enforced isolation with amazing enthusiasm and good humor. In a sense we were all inmates at Worcester." Patients were segregated by gender, severity and treatability; a single nurse or attendant might have to care for a hundred patients at nighttime.

What ameliorated this dismal institutional environment was a vibrant intellectual climate dedicated to learning and the best treatment possible. In addition to many of the world's leading psychoanalytic thinkers "almost every star in the fields of brain and behavior paid us a visit." All this fed Noch's self-professed, "ravenous curiosity."

The mid 1950s saw the beginning of a 40-year decline in prestige and influence as psychopharmacology and neuroscience began to dominate the field followed by de-institutionalization that ushered in community based care. Eventually the institution Noch knew and loved burned down in the spring of 1991.

The research done at the asylum would be archived, but for the inmates and staff, deprived of immortality, Enoch Callaway wrote this "memoir" as a metaphor. But metaphor for what? Surprisingly, not for his distinguished career but to illuminate the shifting sands that engulfed psychiatry over the next 60 years. Those interested more in the man and his career will find it documented in Volume 2 of the Oral History of Neuropsychopharmacology (ACNP 2011) which includes a brief biography of his contributions to clinical research by the volume editor, Max Fink, and an extensive personal interview by the series editor, Tom Ban, which together detail his exemplary career as Emeritus professor at the University of California, San Francisco; Director of Research at Langley Porter Psychiatric Institute; Distinguished Life Fellow of the American Psychiatric Association; and Fellow Emeritus of the American College of Neuropsychopharmacology. Even here, Noch's inherent modesty identifies his two most enduring life-long interests as being devotion to seeing patients and to mentoring students – themes already

apparent in the young resident 50 years earlier as he learned from those he treated and the faculty who mentored him.

Part One: *"In the Home of Broken Minds*" paints a colorful picture of the patients, the bleak environment and the primitive but partially effective tools of the trade available to an aspiring new psychiatrist. To appreciate the impact asylum care would have on a neophyte young resident one must remember that in 1948 almost every department chairman of psychiatry was a psychoanalyst, most residents were in analytic therapy with a faculty member and the normal rite of passage to an academic career was a personal followed by a training analysis. Exposure to the asylum was a two-year interlude where, paradoxically, a newcomer fresh from medical school was confronted with patients who were unsuitable for or had failed analytic interventions.

The "backwards" housed untreatable neurological and psychiatric disorders. Women wore heavy canvas attire, "their straggly unkempt hair made the witches of Macbeth look chic… most of them milled about in aimless agitation, defecating and urinating as the urges arose. Patients no longer recognized their visitors and the visitors ceased to visit." Nonetheless, Noch says, "I absolutely loved my work, despite the grim surroundings, the skimpy pay and the lack of reinforcement that our fantasies of healing the mentally ill received." The lesson learned and later taught by Noch to his own students was the preservation of compassion in the face of pathology.

Asylum was an environment in which the smallest success was powerful reinforcement and Noch tells how this came about. A tall black man was brought to the asylum in handcuffs and leg irons by State Troopers who found him directing traffic as "God's chief of police on earth." Made worse by the stimulating environment of an acute ward, Sam was placed on the hospital farm, got along famously with the cows and thrived. Noch relates this improvement to research by Gerald Hogarty 30 years later showing how a "low expressed emotion environment" was an important adjunct to drug therapy in schizophrenia, but bemoans the fact that such farms no longer exist "due in part to the misguided do-gooders who feared that the farms were exploiting mental patients."

Also in Part One are meticulous descriptions of each of the therapeutic tools in vogue at the time. Insulin coma therapy was in its heyday, safely employed and sometimes effective (perhaps because of the close personal attention it demanded). But it faded fast as quicker, safer

and less complex drug treatments took over during the next decade. Electroconvulsive therapy (ECT) is also described in its pre-anesthesia days, widely regarded by inexperienced residents as "a confession of therapeutic incompetence" and a treatment still widely maligned and misunderstood today. Noch tells how he learned otherwise after he was assigned a middle aged, intelligent and obsessive business man with melancholia leading to a workman-like attempt to hang himself. After a month of five-days-a-week hourly therapy sessions went nowhere Noch's supervisor recommended ECT. After the second treatment the patient began to improve and three weeks later was discharged. Noch continued to receive thank you cards and small gifts from the family for many years until his former patient died of a heart attack.

The Last Resort, (Chapter 10), describes working as an assistant to the visiting neurosurgeon performing lobotomies, an intervention "totally against the grain of the psychoanalytic zeitgeist." Noch describes two highly successful outcomes though each was marred by an "associated adverse event"; techno-speak for side effects. A schizophrenic became a prominent Boston politician whose attenuation of moral concerns did not hamper his career; "morals and conscience do not seem essential to a career in politics." After a year of futile psychotherapy for severe compulsive hand washing, Mary Burns underwent a lobotomy with "miraculous results" if it were not for short term memory impairment that prevented her return to an unsupervised outpatient setting.

Paradoxically, the best gift offered a neophyte psychiatrist like Noch was the ability to "observe the course of untreated diseases without any insurance driven compulsion to name everything." *Some Comments on the Subject of Schizophrenia* (Chapter 12) tells how this encouraged an appreciation for the individual biography of schizophrenia, its often unpredictable course and its distinction from drug induced psychoses and organic delirium. Noch contrasts this with current "clinical self–deception… abetted by statistical pseudo-descriptions." He limns the contemporary DSM system of diagnosis as a monochromatic Chinese menu approach; "such cut and dried definitions mask the mystery of the disease but give the impression that one knows what one is talking about."

Pet Paranoid (Chapter 16) offers another feature of asylum life: "It is natural for public institutions to be generally ignored when they function well, but if there is any trouble, they get attacked promptly by members of the public." Noch gives an amusing anecdote as illustration. A

local attorney decided "the hospital was keeping people locked up for evil reasons and that unscrupulous devious physicians were behind the sinister cabal." The hospital Superintendent decided to allow the attorney free access to the inmates in the unlikely event he might "get constructive work out of a critical crusader." It was not long before the attorney attracted the attention of a manipulative psychopath whose paranoid ideas matched those of his advocate. When the attorney lodged a formal complaint demanding the patient's release the Superintendent concurred providing the attorney take the patient "into his own home and vouch for his behavior." A few days later the attorney crossed his new lodger, evoking rage and causing the host to flee his home in fear. On return he discovered the patient had absconded with "a bedside clock and modest sum of money."

In *Never Say Die* (Chapter 19) Noch learns a new lesson – prognosis is supposedly, but not inevitably, the mark of a good clinician. Exposure to the natural history of disease teaches how to predict its outcome and, in this case, the lesson was amplified by living alongside his patient in the asylum. Mr. O'Malley was the wealthy head of a large clan eager to inherit his money and anxious for how long they might have to wait. Admitted after a stroke that left him confused and aphasic and based on previous experience with similar cases, Noch felt recovery was unlikely and, in communicating this, learned that the family considered the patient to be "a tight-fisted tyrant and they would be willing to take over financial responsibilities." The relatives disappeared to await their good fortune but, contrary to expectations, the patient made a rapid and remarkable recovery attended daily by an attractive and devoted young lady who proved to be his mistress. Upon leaving the hospital and learning what was afoot Mr. O'Malley "promptly disinherited the bunch and married Sally."

Part 2: *Doctor Make the Voices go Away* (Chapters 22–39) is devoted to the various forms of treatment available in 1948 and some broader implications.

Noch is at pains to make it clear that the asylum, circa 1948, was "not a run-of-the-mill State Hospital." It was awash with students and trainees in all the mental health disciplines, taught by competent mentors in a stimulating intellectual atmosphere that bred a great camaraderie." Although the available treatments sound primitive today they were administered by well-trained staff in a humane manner, often with impressive results. *Hydrotherapy* (Chapter 25) is an example.

Closeted with their patients and immersed in their treatment "residents felt they were learning at warp speed because there was nothing else to do."

Exposure to the real world of mostly rejects or failures to benefit from psychoanalysis did little to dampen the enthusiasm or residents' ingrained beliefs although their spouse's skepticism (Chapter 26) created "the first inkling I had that, for at least some psychoanalytic theory, someone had just 'made it up out of whole cloth.'"

This tension between the ex-cathedra dogma of psychoanalytic ideology and the nuggets of wisdom embedded within would be an evolving influence on Noch as he became exposed to both the fruits and false starts of scientific methodology.

In *A Saint for Schizophrenia* (Chapter 27) Noch is exposed to the charisma of Frieda Fromm Reichmann with her insights into the inner workings of a psychotic mind expressed with warmth and acceptance, devoid of narcissism. Equally important (and pedagogically unusual) was her "willingness to acknowledge an error and to explain how she had learned from experience."

Coarse Brain Damage (Chapter 29) juxtaposes prevailing psychoanalytic dogma that absence of demonstrable neuropathology implied a psychiatric disorder inevitably sprang from psychological roots compared to the innovative, sensitive psychological tests developed by Dr. Kurt Goldstein. Noch's patient suffered from "jargon aphasia" and when an EEG indicated a possible left temporal lobe tumor Noch advocated for neurosurgery although the nameless patient was unable to identify anyone to give consent. In a clinical examination Dr. Goldstein's request that the patient provide his name produced the response "Shit." Moving closer, talking gently, touching the patient, inviting him to relax and quietly repeating the question eventually produced the wanted answer. Astonished by this "miracle" and shocked by Goldstein's willingness to ignore the analytic dictum against laying hands on a patient the residents sought an explanation. He replied: "I use visual, verbal and tactile input together to reinforce each other." Also impressed by the similarity between Goldstein's demeanor and Fromm Reichmann's the residents inquired if Goldstein had studied under her? "The great man exploded. She was my pupil." By the time the patient's new-found relatives were contacted it was clear the brain lesion was an inoperable glioblastoma and he left the asylum to die at home.

Psychosomatic Medicine (Chapter 30) paints a somewhat similar picture turning traditional wisdom on its head. Tom, a 24-year-old married man, was referred to Noch at his own request with a complaint of severe epigastric distress after a normal physical work-up. Sixty years ago, such patients were almost universally labelled as suffering from an incipient peptic ulcer secondary to "unresolved dependency needs." Today the cause is almost invariably due to an infection with *Helicobacter pylori* and treated with antibiotics. In blissful ignorance of today's scientific knowledge Noch embarked on a traditional series of psychoanalytic sessions with Tom who was "intelligent and well read" hoping to uncover "deep psychological problems." In their first session Tom talked about his undercapitalized new business and the associated financial fears which he had not shared with his wife because she idealized him. At the end of the session Noch could not restrain himself "from committing a psychoanalytic no-no." He asked Tom, "Do you really think your wife wants to be kept in the dark about what you are thinking?" Tom "doesn't know." Over the next five sessions Noch relentlessly explores Tom's early life and concludes: "He was in better shape psychologically then than I was." To Noch's surprise, at the beginning of the seventh session Tom announces, "That about raps it up" and in response to the question, "What about the stomach pains?" Tom discloses that they stopped after the first session. Following Tom's "misguided" advice he discussed his feelings with his wife who then joined him in helping to run the shop, resolving their financial worries. Unasked and unanswered is today's question: if Tom had only been prescribed an antibiotic what would have happened to his marriage?

Probably the most remarkable aspect of life at Worcester State Hospital was not what it did for the patients or for the resident's love affair with psychoanalysis but how it shaped the resident's attitudes and behaviors in a scientific direction. Noch provides an answer in *Gather Ye Labwear Where Ye May* (Chapter 34). At least three quarters of the residents published papers in edited journals and Noch comments, "Since then I have not encountered such a productive group of residents." They were surrounded by role models: career psychologists, physiologists and biochemists supported by an excellent library, an enormous patient population and remarkably good clinical records, a data base for almost any enquiry. There were no distractions to discourage them; no grant proposals, no human subjects committee, only a competitive environment and freedom, "so when one had an idea for a study one simply did it." As yet the Federal government was not involved in funding and scientists who staffed the labs were motivated by a "sense of playful improvisation." It is important to note that this kind of milieu at Worcester and a few other

select State and Veteran's Administration Hospitals would form the seed bed for the coming psychopharmacology revolution where the earliest discoveries, measuring instruments and trial methodologies were forged rather than in the halls of academia. The atmosphere and attitudes Noch describes are echoes of the consensus expressed by scientists who worked in those environments during the early days (ACNP 2011).

Some of Noch's own ventures at playful improvisation are described in *Miscellaneous Misadventures* (Chapter 35). They include attempts at repairing an EEG machine, building a high-fidelity sound system from spare parts and attempting to boost the alcohol content of apple cider brewed for resident consumption. Noch also learned through experience that science, like psychoanalysis, is often confounded by difficult to measure or predict variables. In *The Fortunate Failure* (Chapter 36) he learns firsthand about the placebo response, double blind studies, the problems of collecting urine samples from a psychotic patient who likes to pee in his pants – despite the fact that male psychotic patients are more tractable than females, can more easily pee into a bottle and don't menstruate. Finally, he learned how extraneous variables can invalidate the most carefully planned experiments. Their finding that schizophrenic patients had low urinary corticosteroids was not due to the disease but the fact that so many patients had sub-clinical scurvy because the study was done in the winter and there was almost no vitamin C in their diet.

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Chapter 3

Joel Elkes; Father of Modern Neuropsychopharmacology

Preamble

This Chapter is one of four biographies based on significant personal interaction (See Chapter 15, 1, 2 and 3). I first met Joel Elkes in 1970 at the Baltimore Conference on *Discoveries in Biological Psychiatry* where, at age 57, he presented his paper, "*Psychopharmacology: On Beginning in a New Science."* I learned more about him when I collaborated with Tom Ban on *The Oral History of Psychopharmacology* for which he was interviewed at age 82 by Fridolin Sulser in 1995 (Volume 1: Starting Up). When Joel celebrated his 100th birthday in 2013 Tom suggested I write his biography for the INHN website. After some reading and research, I met Joel Elkes and his wife Sally Lucke at their summer home in Chicago and spent several hours interviewing him and socializing with them.

After the biography was complete and presented to Joel and Sally they invited my wife and I to attend a public showing of Joel's much admired art, combined with a celebration of his 102nd birthday. A few weeks before it was due Sally called from a hospital where Joel had been admitted and was recovering from a mild heart attack. I was able to speak to him; he was in his usual optimistic frame of mind and looking forward to seeing us at his birthday. It was not to be; a few days later Sally called again to say Joel had died due to a fatal heart attack so the art showing would now be coupled with a memorial service. I joined several colleagues in brief eulogies and we returned home with one of Joel's much-admired paintings. It serves as a daily reminder of a true pioneer whose accomplishments are inadequately appreciated or acknowledged today.

Joel Elkes: An Integrative Life

This brief biography and review of Joel Elkes' scientific, literary, artistic and other accomplishments are in three parts.

First, a synopsis of Elkes'singular and pre-eminent historical role as the first modern neuropsychopharmacologist. Then a chronological account of his early life, followed by the three epochs of a professional career, in Birmingham, U.K., the National Institute of Mental health at St. Elizabeth's Hospital in Washington D.C. and Johns Hopkins University. Finally, a review of Joel's later life activities including his literary and artistic accomplishments.

Historical Role and Singular Accomplishments

At this writing, Joel Elkes is now in his 102nd year of a distinguished life and is the oldest living pioneer in our field, recognized as the "Father of Modern Neuropsychopharmacology" (See Paykel 2003; Shorter 2011); a worthy successor to Thudichum, the acknowledged founder of neuroscience and the first "Chemistry of the Brain." Both men are polymaths with wide ranging interests, Thudichum, dubbed by his biographer as "The Multiple Man," who "lived broadly and deeply" (Drabkin 1958) akin to Elkes' integrative life portrayed here.

Joel was born in 1913, 12 years after the death of Thudichum. Elkes' early research on the molecular structure of myelin (Elkes and Finean 1949) is an echo of Thudichum's work in "The Chemical Composition of the Brain" (Thudichum 1884).

Joel Elkes' designation as the "Father" of modern neuropsychopharmacology is bolstered by many "firsts" in the field.

In 1951 he established a Department of Experimental Psychiatry in Birmingham, the first in the world (Ban 2001). With his wife, Charmian, he conducted the earliest controlled trial of chlorpromazine in overactive states (Elkes and Elkes 1954), an early empirical approach, "one of the first in any medical specialty" (Silverstone 1998).

Later in life (Elkes 2011a), Joel describes the wisdom derived from this seminal controlled study: "The research instrument in a trial of this sort being a group of people, and its conduct being inseparable from the individual use of words, we were impressed by the necessity for a 'blind' and self-controlled design, and independent multiple documentation. Furthermore, we were equally impressed by the false picture apt to be conveyed if undue reliance was placed on the interview alone, as conducted in the clinic room. The patient's behavior in the ward was apt to be very different. For that reason, the day and night nursing staff became indispensable and valued members of the observer's team. We were warmed and encouraged by the energy and care with which they did what was requested of them, provided this was clearly set out at the beginning. A chronic 'back' ward thus became a rather interesting place to work in. There may well be a case for training senior nursing staff in elementary research method and in medical documentation. This would make for increased interest, increased attention to, and respect for detail and the availability of a fund of information, all too often lost because it has not been asked for."

Not only is this an early endorsement of controlled trial methodology which would henceforward become the gold standard, but it is a prescient statement of what would be helpful as the State Hospitals and VA in America became the seed bed for early trials of future psychotropic drugs. It was an approach other pioneers would emulate or discover for themselves as demonstrated by Martin Kassell. (Ch.15)

Another innovation, before the foundation of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) or American College of Neuropsychopharmacology (ACNP), and in the wake of the chlorpromazine discovery, was Joel's role in initiating the First International Neurochemical Symposium representing 11 countries held at Oxford in1954 (Elkes 2011a). It was attended by Seymour Kety, Heinrich Walsh, Louis Flexer and Jordi Folch-Pi from the USA, with Geoffrey Harris, Derek Richter and Elkes himself from the UK.

After moving to the USA, the scope of Joel's interests and influence expanded and, in 1957 as a consultant, he convened the first World Health Organization (WHO) group on psychotropic drugs that issued its report in the following year (Elkes 1958).

As the science of neuropsychopharmacology grew its pioneers coalesced into collegial organizations. Joel Elkes became the first President of the ACNP in 1962 and when the history of the CINP was written the first chapter was by Joel Elkes titled, "Towards Footings of a Science: Personal Beginnings in Psychopharmacology in the Forties and Fifties" (Elkes 1998). At a later meeting in Glasgow he was awarded the CINP Pioneer award for his help and guidance at the organization's inception (Bradley 2001). The Department at Hopkins he inherited from Adolf Meyer and John Whitehorn was named by Joel as the first Department of Psychiatry and Behavioral Science, a title soon and often emulated elsewhere.

When the pioneer discoverers of all the first-generation psychotropic drugs were convened to honor them in 1970 (Ayd and Blackwell 1971) Joel Elkes, then aged 53, delivered the opening paper titled "Psychopharmacology: On beginning in a New Science" (Elkes 1971). He described his early approach to a discipline as "resting on the assumption that the various manifestations of gross mental disorder and milder dysfunction have their counterpart in the disturbed physiology of the brain, and that the study of the chemistry, cellular constitution and the electrical activity of the brain may contribute to an understanding of its functions as the highest integrating organ."

Joel was a founding member of two editorial boards, The Journal of Psychiatric Research and Psychopharmacologia (now Psychopharmacology). In addition, he was also a founding Council member of the International College of Psychopharmacology and of the International Brain Research Organization (IBRO/UNESCO).

The Child as Father to the Man

Joel's recollections of his early life and the manner in which they may have influenced his future career are derived from three sources, (Elkes 2011a; Ban 2001; Elkes 1997).

Joel Elkes was born in Koenigsberg, capital of eastern Prussia, on November 12, 1913. His father, Elkhanan, became a medical officer in the Russian Army during the First World War and the ensuing Russian Revolution, so Joel's first five years were spent in Russia before they settled in Kovno, capital of the new Lithuanian Republic. His father was the leading physician in the region and, while his "waiting room was always full of patient's who could not pay," he also cared for the President, Prime Minister and Diplomatic Corps. Joel describes his father as follows: "I recall his clean features and his smile. His movements were small and graceful. He rarely raised his voice in public, but when he spoke there was warmth and interest and humor in it, which gave anyone in his presence a sense of closeness and courage. Human frailty – including his own – was to him part of the Almighty's prescription for a good and full life. Only in the presence of bigotry, prejudice, and cruelty would his demeanor change. He would then grow silent: a silence often followed by a statement of such devastating directness as to render his hearer dumbfounded and confused. On his desk rested a little tablet carrying an inscription of Emmanuel Kant, 'Two things continue to astonish the mind, the more it dwells on them. One is the starry sky above me, and the other is the moral law within me'" (Elkes 1997).

In the same memoir he also paints a picture of his mother. She was, "blessed with warmth, vitality, curiosity and extraordinarily well read, she assimilated the best of German and French culture, while always drawing on the wellsprings of Jewish heritage. Much was self-taught. Her cheerful temperament complemented my father's somber mood. She was his complete confidante and life companion. She was a wonderful mother, a fount of joy, optimism, adventure, sheer lifemanship, and full of sound practical advice. I still treasure some of her letters from my student days, written in impeccable copper-plate."

Joel attended a Jewish high school (Schwabe's Gymnasium) founded by a group of idealists to provide a good education and prepare students for a hoped for future life in Israel (Palestine). Lessons were taught in Hebrew, although German was spoken at home. Joel was an excellent, prize winning student, graduating with honors and described by a teacher as a "mature poet" in Lithuanian. Initially, he developed a deep interest in physics, fascinated by structure, particles, force-fields and "how the world is held together." Lacking mathematical skill, he switched his main interest to chemistry as a means to enter medical school, inspired by his father as a role model and aspiring to become a "scientist serving medicine." He states: "I went to medicine because I had a secure example of good physicianship and a good person in my father and because I also hoped that medicine would lead me to a sort of relationship of science to life and nature" (Elkes 2011a). In a talk to the ACNP Joel also identifies three other "heroes" who inspired him: Einstein in physics, Ehrlich and his work on receptors and Goethe as an example of "the rare combination of humanism, scientific creativity and spirit… a master of both prose and poetry." He also read Freud and was impressed by "his view that the future would produce physical markers for mental events" (Elkes 2011a).

After graduating from the Gymnasium Joel studied for a year in Koenigsberg to matriculate from a German school and quickly caught up with his peers in German literature and the French language, graduating at the top of his class. Following this he spent four months in Lausanne, Switzerland, attending lectures at the University on pre-medical topics as a prelude to medical school in England. His father was physician to the British Ambassador to Lithuania who encouraged Joel to seek training in his country and provided a letter of recommendation.

In 1930 Joel left Kovno for England where he eventually enrolled in medical School at Saint Mary's Hospital in London, taught by a distinguished faculty that included Sir Charles Wilson (later Lord Moran, Churchill's physician), Sir Almroth Wright who developed a typhus vaccine, Alexander Fleming, who discovered penicillin, and Alec Bourne, a distinguished obstetrician, who later became his father in law.

Despite this cadre of brilliant clinicians, the hospital was devoid of role models in the as yet unborn field of psychopharmacology. So, while still a student, in the mid-1930s, he was invited to join Alastair Frazer, Senior Lecturer in physiology as a Student Demonstrator. Frazer was working on the absorption of fat from the gut and concerned about the structure of chylomicrons

entering the circulation from the thoracic duct following a fatty meal. Joel developed a micro-electrophoretic cell to study their mobility in an electric field. This resulted in his first publication in the *Journal of Physiology* while still a student (Elkes, Frazer and Steward 1939), work that was cited by Starling in his classic textbook *Principles of Human Physiology.*

While still in medical school in 1937, Joel embarked on a Training Analysis at the renowned Tavistock Clinic at the suggestion of John Bowlby, one of his mentors and a friend. This venture was interrupted by the war when his analyst (Bion) was inducted into the Army. Joel later completed his analysis in 1955 in Washington D.C. under Winifred Whitman, a training requirement the head of NIMH stipulated for his entire faculty. One can only speculate on how this experience stimulated and informed his later integration of social and psychological factors with his primary early interest in biological matters.

At the start of World War II Joel was cut off from support sent by his father and having financial difficulty supporting his sister and only sibling, Sara, who had joined him in 1937. Alastair Frazer found him a job at the Transfusion Service, where he met his future wife, Charmian Bourne, daughter of his obstetrics professor.

Joel graduated in 1941 and fulfilled the obligatory pre-licensing requirement as a rotating intern in orthopedic surgery, ophthalmology and internal medicine. Enjoying clinical work, he contemplated opening an office in London to practice medicine, but fate intervened when Alastair Frazer was appointed Chairman of the Department of Pharmacology in Birmingham UK and invited Joel to join him as his research assistant.

We shall see how his upbringing, experiences, education and opportunity would shape Joel's future career but, meanwhile as the war raged on, events in Lithuania were unfolding in tragic fashion that he would only learn about after the war's end and would eventually incorporate in a memoir, *"Values, Belief and Survival: Dr. Elkhanan Elkes and the Kovno Ghetto"* (Elkes 1997). In the first 18 months of the war the Nazi regime established the apparatus of the Holocaust in the homeland, but in June 1941 they began to export *The Final Solution* to nearby Lithuania. The Jews in Kovno were herded into a Ghetto and instructed to nominate a leader (*Oberjude),* expected to serve as a trusted servant of the community as well as the conduit for Nazi directives, not to be questioned on fear of death. As the most respected member Elkhanan accepted this

impossible task under considerable pressure and with great reluctance. For more than two years he fulfilled this role with skill, integrity, exceptional dignity and courage while the Nazi juggernaut rolled on. As the balance of war shifted in the Allies direction, the Nazis moved to bring *The Final Solution* to a speedy and complete conclusion. In mid-1944 the Ghetto was destroyed and the remnant of the population murdered or transferred to concentration camps.

In frail health, Dr. Elkhanan Elkes pens a last long letter to his children dated October 19th 1943 that is smuggled into England after the war ends, and which Joel does not read until the autumn of 1945. It ends:

> "I am writing this at an hour when many desperate souls – widows and orphans, threadbare and hungry – are camping on our doorstop, imploring us for help. My strength is ebbing. There is a desert inside me. My soul is scorched. I am naked and empty. There are no words in my mouth. But you, my most dearly beloved, will know what I wanted to say to you at this hour.
>
> "And now, for a moment, I close my eyes and see you both standing before me. I embrace and kiss you both; and I say to you again that until my last breath, I remain,
>
> Your loving father."

On July 13th 1944 Dr. Elkes leads a small group of his surviving community to the railway station and, transferred like cattle, they arrive at Landsberg-Dachau around July 15th. He lived barely three months, striving till the end to help and serve others until finally, his brother, a fellow prisoner, in a letter to Joel describes Elkhanan's state of mind in his own words: "Such a life is unseemly. I cannot watch this suffering; I must be away." He begins a hunger strike and his brother tells of his final days: "He laid there for 14 days, a few teaspoons of water his only nourishment. He remained conscious until his last breath, and, on the 17th of October, 1944, at 4.15 am was gone."

Joel's mother mercifully survived concentration camp, joined him in London and eventually moved with Sara to Israel where she died 20 years later.

Blessedly unaware of the unfolding events during the remainder of the war, in 1941 Joel was ready to begin his career, turning his experiences, ideals and hopes into reality.

Joel Elkes' Career

Joel's career extended from the end of medical school in 1942 to official retirement in 1974, During these 32 years he worked in three settings: Birmingham UK (1942-1957), NIMH at St. Elizabeth's (1957-1963) and Johns Hopkins (1963-1974). During this period his CV records 40 publications, but their quality and impact far outweigh their quantity partly because of his reluctance to add his name to the work of those he mentored – an unheard of and mostly unfollowed precedent.

In 1942 he joined his friend and mentor, Alistair Frazer, as the Sir Halley Stewart Research Fellow in Pharmacology. Among the first papers published was a continuation of his research as a medical student. Three of the authors were Sir Halley Stewart Research Fellows (his mentor Frazer and Stewart, his colleague at St Mary's, as well as Schulman from the Colloid Research Center at Cambridge University). The paper was presented in 1944 at the Royal Society in London (Elkes, Frazer, Schulman and Stewart 1944). In 1945 he was promoted to Lecturer and in 1948, only six years after joining the Pharmacology Department, he became Senior Lecturer and Acting Director of the Department.

His research accomplishments during this time were significant, producing 16 publications. He began work on the physical chemistry, constitution and structure of biochemical membranes, the lipoproteins. "Suddenly I realized the nervous system was full of lipoproteins. It was myelin, a beautiful para-crystalline structure ubiquitously distributed in the nervous system." Aided by his first Ph.D. student, Bryan Finean, a crystallographer, they developed a technique for the X-ray diffraction of the living frog's sciatic nerve in response to temperature changes and chemicals, including ether. "I suppose it was in the vain hope of seeing the penetration of molecules of an anesthetic into the molecular structure of myelin... Suddenly I was in the nervous system" (Elkes and Finean 1949). "At that time there was no real neurochemistry and very few people I could talk to." Between 1949 and 1953 they produced five publications. At this time Joel also began to study the anticholinesterases and the role of acetylcholine, "the main molecule in the central nervous system" in the firm belief that pharmacology was the path to understanding physiology.

A few years after moving to Birmingham UK, Joel and his wife Charmian (a family physician) began clinical training and part time clinical work at the City Mental Hospital working with both inpatients and outpatients. During this time (1944-1950) they began to study the effects of amobarbital, amphetamine and mephenesin on patients with catatonic schizophrenic stupor. This work yielded paradoxical results. Amobarbital caused awakening from catatonic stupor; amphetamine deepened the stupor and mephenesin led to muscular relaxation without affecting states of consciousness. This suggested specificity of the action of drugs and possible regional chemical differences in distribution of controlling cells within the brain. This experiment also established the Elkes' place in the mental health culture in England.

Difficulty translating his pharmacology from lab animals to humans convinced Joel "we needed another intermediate point." The missing piece fell into place when his second Ph.D. student, Philip Bradley, developed techniques for recording electrical activity in conscious and unrestrained cats. Now they could study the effects of anticholinesterase, acetylcholine blockers and amphetamine on electrical activity of the brain and behavior.

The development of this methodology continued while Joel was awarded a Fullbright Travelling Fellowship in America (1950) where he worked as a resident at the New England Hospital in Boston (under John Nemiah, later Editor of the American Journal of Psychiatry) and at Norwich State Mental Hospital (under Dr. Kettle).

Upon his return from America in 1951 he was appointed Chair and Professor of a new department he named "The Department of Experimental Psychiatry" at the University of Birmingham UK.

Joel's ground-breaking work with Philip Bradley now began to bear fruit in these techniques and results (Bradley and Elkes 1953); (Elkes, Elkes and Bradley 1954); (Elkes and Bradley 1957). It was into this environment that the serendipitous discovery of chlorpromazine in France intruded leading to the first controlled trial of its efficacy in schizophrenia described earlier and published in the *British Medical Journal* (Elkes and Elkes 1954). Joel's work in Birmingham laid the foundation for developing a concept of regional neurochemistry leading to the first International Conference focusing on this topic in 1954. Joel describes this evolution thus: "We began to talk about regional neurochemistry. Seymour Kety thought about regional differences in

cerebral circulation and I thought about regional differences of neurotransmitters and families of naturally occurring compounds that had arisen in evolution to modulate and guide the interaction of neurons, and regulate excitation and inhibition in the nervous system. I thought of regional field effects in the nervous system" (Elkes 2011a).

Joel's visit to America must have made him aware of the burgeoning interest in neuroscience coupled with vast resources available to support research in the Eisenhower years when America was indeed "the land of opportunity." By the mid-1950s Joel's research was increasingly bearing fruit and he had established an international reputation in the emerging field of psychopharmacology for leadership and innovation. The coupling of talent and resources made it inevitable that he eventually move to greener pastures. And so, when he was invited to develop the first Clinical Neuropharmacology Research Center in America, he decided the time was ripe to make the move from Birmingham to Washington D.C.

Joel's work during the six years he was at Saint Elizabeth's yielded nine publications of his own and many more by young scientists he mentored. His own publications included eight ground breaking book chapters in five years on diverse topics including, *Psychopharmacology: the Need for Some Points of Reference* (1959); *Psychotropic Drugs* (1961a); *Drugs Influencing Affect and Behavior* (1961b); *Schizophrenia in Relation to Levels of Neural Organization* (1961c); *Regional Neurochemistry* (Kety and Elkes 1961d); *Amines in Relation to Behavior* (1962a); *Behavioral Pharmacology in Relation to Psychiatry* (1962b), a large review paper comprising over 500 references; and *Biological Bases of Psychiatry* (1963).

Among the distinguished alumni Joel recruited was Mayer-Gross the German psychiatrist who persuaded him to write an article for the prestigious handbook he edited, *Psychiatrie der Gegenwart*; this paper, "Behavioral Pharmacology in Relation to Psychiatry," was *a tour de force* worthy of a book in its own right. Its publication was delayed and it did not appear until 1967 and was not published in English until his *Selected Writings* in 2001.

But the value and influence of what Joel Elkes created at Saint Elizabeth's was reflected not only in the literature published, but in the atmosphere he initiated and the work of the scientists he recruited and mentored. Joel regarded the Institute as a "greenhouse" in which he toiled as "a good gardener." He describes the culture as follows (Elkes, 2011a): "It was a wonderful, heady,

exciting time in the middle of a very chronic mental hospital. There were people coming virtually from all over the world and there were talks and discussions and excitement. At the same time, there was always and always, which is what we had hoped, the presence of the patient. For example, you go to the canteen for lunch and there's a patient with schizophrenia hallucinating under a tree. You're never very far away from the problem that brought you here. And, gradually there developed a sense of place, of belonging. Gradually, I realized that, my God, together we created something pretty wonderful."

Joel relates his capacity to nurture others to his upbringing (Elkes 2011a). "That brings me back to my parents. They were extraordinary, nurturing people. They made me feel wanted and secure, and at the same time, there was always, always the questioning spirit, the wish to understand."

In 1963 Elkes left the research center he created to become Chairman of Psychiatry at Johns Hopkins. Satisfied as he was with the accomplishments at St. Elizabeth's Joel may have wished for a broader palette, one where he could exert an influence on the place of psychiatry in medicine and the training of future practitioners in both disciplines. He joined an already talented faculty whose interests ranged from biology and sexuality to psychoanalysis. The breadth of his own aspirations is reflected in renaming his new domain, "*The Department of Psychiatry and Behavioral Sciences,"* possibly the first academic program to employ "behavioral" as a semantic link between psychiatry and the rest of medicine. To demonstrate and cement this relationship he invited the Chairs of all the other departments in the School of Medicine to give lectures in the students' introductory course. Joel's first two papers in this period reflect these widening interests: "On Meeting Psychiatry: a Note on the Student's First Year" (Elkes 1965a) and "Psychoanalysis and the Community" (Elkes 1965b).

Joel's educational innovations included all levels of care and different disciplines. Not surprisingly his Department's reputation attracted stellar psychiatric residents, among them Sol Snyder, Joe Coyle, Ross Baldessarini and Joe Brady. In addition, Joel founded and was first chair of the Hopkins M.D.-Ph.D. Program in Medicine and the Behavioral Sciences. He was also Founder and First Chairman of the Board of Fellowship House a residential, intermediate care facility for people with mental illness. Sol Snyder's meteoric rise led to the development of a

separate Department of Neurosciences. Finally, Joel and Charmian founded a Master's program for Mental Health Counsellors.

Joel's bridge-building, integrative cognitive and administrative style, carried with it drawbacks as well as benefits. In his time at Hopkins Joel was at the cusp of a changing Zeitgeist; between the hegemony of psychoanalysis and the burgeoning field of neuroscience he pioneered. Joel's efforts to integrate these two poles, to bring psychodynamics, biological psychiatry and medicine closer together were, perhaps inevitably, disparaged by those whose polarizing viewpoints were devoted to the integrity and dominance of their own domains. This discomfort would contribute to his decision to move on.

Upon leaving Hopkins Joel accepted a named professorship at McMaster University in Canada where he stayed six years (1974-1980) "seized by interest in the laboratory of everyday life" (personal communication). His adolescent attraction to Freud's prediction that physical markers underlie thoughts and feeling was fulfilled with his pioneer work in neuropsychopharmacology; what lingered on from his experience in analysis was the need to complete "the inner examination of the self" an idea expressed in his essay "On Awareness and the Good Day" (Elkes 1981). As usual with Joel, this personal insight soon translated to the broader context of holistic and behavioral medicine, integrating social and psychological dimensions with the biological foundations he had already created.

The ideas incubated at McMaster blossomed in full after he became Emeritus Professor of Psychiatry at Louisville University when public and professional concerns were increasingly expressed about the dominance of technical over humanistic skills in medical education and practice (Blackwell 1977). Here Joel collaborated with like-minded faculty and therapists in efforts to "humanize medical education." At first, this involved a four-day voluntary Health Care Awareness Workshop for incoming medical students (Dickstein and Elkes 1985). The curriculum included mode of life as a factor in illness and disability; stress and the stress response; the physiology of nutrition, exercise and relaxation; the psychology of time management and study skills; dyadic listening; the place of beliefs in healing; and the ethics of medical practice.

This pioneer work became the platform for a more ambitious program, "Arts in Medicine," for which he obtained funding, designed to integrate the twin cultures, "soft Arts" and "hard

Sciences" in a well-established School of Medicine (Ban 2001). The program's objectives were to demonstrate the value of this unity in therapeutics, biomedical research, self-awareness among health professionals, as well as personal well-being and creativity.

Asked in 1995, at age 82, to put modesty aside and name his greatest contributions at the three major institutions he headed, Joel names four (Elkes 2011a). First, "the role of regional neurochemistry in understanding the mode of action of psychoactive drugs." Second, "pharmacology as the gateway to physiology, to understanding how the brain works naturally without the chemical prostheses of drugs; as a way of exploring the phenomena, the layering, the organization of mental life, and giving us an insight into schizophrenia as a disorder of information processing in the brain." Third, "the importance of understanding the environment, the social setting, the action and even the dose of a drug on these variables." And last, "providing a setting where intelligent conversation between, neurochemistry, electrophysiology, behavior and subjective experience could take place, and where experiment interacts with clinical experience."

Family Matters

Like other pioneers in our field Joel Elkes' professional and family life have been intertwined in collaborative and creative ways, with rare tragic moments. Joel's first marriage incubated in medical school when he met Charmian Bourne, daughter of a leading obstetrician at St. Mary's Hospital. It was a relationship built on the future hopes of a young couple facing the vicissitudes and uncertainty following World War II, later cemented by joint work in psychiatry and their seminal early research on chlorpromazine (Elkes and Elkes 1954), collaboration that became part of their dream. The marriage bore fruit with a daughter Anna and, in turn, a grandchild Laura, both deeply involved in Mindfulness and Spirituality, twin fields akin to Joel's lifelong interests. This marriage sadly ended in divorce. Charmian died in 1996.

Joel's second marriage was to Josephine Rhodes, afflicted with severe, painful and crippling rheumatoid arthritis who Joel hoped vainly to comfort and help, consistent with his nurturing nature. It was a relationship that ended, unfortunately, in a mix of fond memories and deep disappointment.

Joel's present marriage is to Sally Lucke, an innovator and educator in Sarasota; Sally founded a major Art Museum and a Holocaust Library in the Liberal Arts College she had

envisioned. She lectured at Harvard on Art Therapy, taught at the Museum of Modern Art and was a scholar at the National Gallery. Sally also created a Public School for the Gifted and another for the Visual and Performing Arts. Their shared interest in healing through the Arts, Mindfulness and Meditation, brought Sally and Joel together at the beginning of their relationship and they continue to develop this knowledge and create organizations reflective of their shared commitment.

Sally also shares Joel's nurturing instincts and talent; while still his fiancé she took into her care and shelter a homeless minority high school student in the seventh grade, tutoring him till Larry became a National Honor Scholar, then a graduate of a renowned law school and now a practicing attorney and much beloved member of their family.

Life as a Whole

It is likely that "retirement" was a notion or a word unlikely to appear in Joel Elkes' mind or lexicon. He left Johns Hopkins in 1974, age 61, with a 32-year career behind him, and added 41 productive years to that – and still counting! As events would unfold he had much left to explore and contribute, some of it described above. Why he made such a change at a relatively early age is speculative but may be enlightened by reciting Joel's own description of his father's determination to conserve energy for what he did best and "to keep away from committees and councils" (Elkes 1997). Perhaps Joel's fertile integrative mind was seeking fresh fields to plow, free of administrative burdens and constraints.

Elkhanan Elkes' reluctance to seek or accept organizational responsibility was tragically prescient, ending in heartbreak and disaster during the Holocaust despite heroic efforts to serve his community. Joel's administrative skills were considerable when deployed in a fruitful era and environment. But nevertheless, perhaps they sapped energy needed to pursue broader horizons.

His CV, between 1974 and when it was last updated (1987), lists an additional 10 book chapters on educational, public health, behavioral medicine, community affairs, psychotherapy, self-regulation and self-awareness.

Throughout his lifetime Joel has been dedicated to supporting the affairs of his Jewish faith, a member of the Board of Trustees of Hebrew University in Jerusalem and Chair of the Israeli Center for Psychobiology. When his sister Sarah Elkes established a lecture series in honor of their

parents, Joel gave the inaugural address in 1991 at the Stanley Burton Centre for Holocaust studies in Leicester, England, and six years later published the material as a memoir (Elkes 1997).

Over the span of his life Joel has been a member of several international organizations dealing with his major areas of interest in brain research, psychopharmacology and psychotropic drugs. He has served on the Editorial Boards of six journals, been an invited participant in more than 35 international symposia and given many invited or named addresses to professional organizations, institutes and universities at home and abroad.

Joel is a Distinguished Professor Emeritus of Psychiatry at the Universities of Johns Hopkins and Louisville. He is also a Charter Fellow of the Royal College of Psychiatrists of Great Britain, a Fellow of the Royal College of Physicians of Canada, Life Fellow of the American Psychiatric Association, Life Fellow of the ACNP and a Life Fellow of the American College of Psychiatrists.

Over the span of his life Joel has been a member or fellow of almost 50 societies or professional organizations, testimony to the breadth of his interests, gregarious temperament and abundant energy.

Among the prestigious awards he has received are the Salmon Medal (1964); Taylor Manor Award (1969); Governor's Citation for Distinguished Service, State of Maryland (1969); Benjamin Franklin Fellow, Royal Society of Arts & Sciences (1974); and the Pioneer Award, CINP (1998).

To celebrate Joel's 100th birthday, the CINP published a selection of his writings (Ban 2011). Titled "*Selected Writings of Joel Elkes,"* the book is organized thematically in a manner that reflects Joel's breadth of interests and span of influence. The 12 topics are: Overviews; Early Papers; Electrophysiological Studies in Birmingham & an Early Clinical Trial; Reviews; Schizophrenic Disorder, a disorder of information processing in the Brain; Humanizing the Education of Physicians and Behavioral Science in the Service of Medicine; Five Named Lectures; The Community as an Agent of Proactive Health Care & Health Enhancement; Holocaust & Israel; Two Friends (Jonas Salk & Norman Cousins); and On Art & Healing. This alone is testimony to a multi-tiered life, but it also speaks to abundant and prevailing energy. There are publications from every decade of Joel's career from the 40s (1), 50s (4), 60s (10), 70s (4), 80s (3) and 90s (6).

This surely gives the lie to William Osler's opinion about, "The comparative uselessness of men above forty years of age" (Osler 1932).

In 2011 the ACNP celebrated its 50th anniversary, a few weeks past Joel's 98th birthday, when he presented a History Lecture, supported by more than 100 references and a pamphlet (Elkes 2011) reprint of three seminal papers included in his *"Selected Writings"* (Ban 2001). Together these cover a span of 43 years (1952-1995) and, perhaps, represent his most treasured contributions, his "*Alpha & Omega."* They are: "Prospects in Psychiatric Research" (Elkes 1952), "The ACNP: A Note on its History, and Hopes for the Future" (Elkes 1962) and "Psychopharmacology: Finding One's Way" (Elkes 1995). The latter of which includes photographs of key places and events.

Joel is also an artist from his childhood days, whose talented paintings are on exhibit in a number of institutions of art. They constitute the final theme in the CINP tribute as a collection of 15 paintings from 1988 to 1992. Joel's artistic oeuvre at that time was dominated by somber tones and broad-brush strokes, all black and white, painted in the three years before and a year after the memorial lecture to his much beloved father. A subsequent collection painted at and published by the Fetzer Institute, where he is Founding Fellow and Senior Scholar in Residence, begins to explore the brighter colors of the spectrum (Elkes 2003).

An art critic comments as follows: "In a threatened society Joel Elkes creates beautiful images to lighten the soul. Using a new process, his prints reflect, with magical skill, his original paintings. They are alive with a light that carries us from the beginning of time to a life that will not be destroyed" (Kasle 2003). As in all other areas of his prodigiously productive and long life, this multi-tiered scientist, humanist and scientist continues to evolve, moving beyond the Holocaust to happier times.

Envoi

It remains to better define the nature and origins of Joel Elkes' unique contributions to neuroscience and medicine.

Joel was genetically well endowed by parents who raised him in an environment imbued with intellectual, artistic and moral precepts. His father was a noted physician role model and his

mother a nurturing overseer of his growing years. Inherent insight, empathy and sensitivity were enhanced by a personal analysis begun early and completed later. Scientific principles were implanted by medical and physiology training in both humans and animals. These seedlings bore fruit in mature integrative thinking and behavior.

Joel's intellectual approach possesses all three of the characteristics identified in creative scientists (Blackwell 1971). These are an ability to see analogies, the tendency to seek original solutions and a type of Gestalt thinking that views parts in relation to the whole. These talents are reflected in his prescient grasp of the need to integrate neurochemical and physiological methods of study, the specificity of drugs on different cell populations and the need for a translational approach from animals to humans.

In the clinical arena Joel pioneered the empirical use of double blind controlled study to confirm or refute clinical observations. He stressed this in the early testing of the first psychotropic drugs used in State Mental Hospitals and the VA. Joel influenced the design and scope of these studies at both the national and international level through his work with the NIMH at St. Elizabeth's Hospital in Washington, D.C., and in convening the first international study group on psychopharmacologic agents by the World Health Organization.

After psychiatry in America divorced itself from patient-centered sites to academic medical centers, Joel developed innovative methods to connect psychiatry with medicine including combining M.D. with PhD. training programs, humanizing medical student education and advocating for an integrative biopsychosocial approach to diagnosis and treatment.

The tension Joel Elkes' experienced in mid-life occurred in the context of a changing Zeitgeist and is not uncommon in the career patterns of pioneers in our field as illustrated in the INHN series of biographies. (See Jean Delay, Jose Delgado, John Smythies and Frank Berger). Like Joel each of these eminent scientist-clinicians found late life solace in other talents; literature, art and philosophy.

Joel Elkes' incomparable lifetime accomplishments serve as a beacon to encourage and sustain present and future neuroscientists and psychopharmacologists at a bleak moment in our history, when progress seems sparse and the future uncertain.

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Chapter 4

Beginning with Lithium

Lithium over the ages (Schioldann, Part 1)

Preamble

It is paradoxical that a simple metallic ion, not a manufactured compound, should create so much interest and controversy as the first effectivr drug in the modern history of psychopharmacology. The full story derived from two books published by Australian authors seven years apart.

Chapter 4 by Johan Schioldann is Part 1 of his book: *The History of the Introduction of Lithium into Medicine and Psychiatry* 2009

Chapter 5 follows and deals first with Schioldann's view of the role of the Australian psychiatrist, John Cade in re-discovering the effect of lithium for acute psychotic mania. This is in Part 2 of Schioldann's book; *Birth of Modern Psychopharmacology 1949*

In De Moore & Westmore's book *Finding Sanity Cade. Lithium and the Taming of Bipolar Disorder* 2016. the authors relay a compelling but different story on the controversial role played by Cade.

Finally Chapter 12 tells the story of the Lithium Controversy that broke out in 1968 following Schou's discovery of lithium prophylactic effect in recurrent bipolar disorder.

Lithium over the Ages

I am grateful to Tom Ban and Sam Gershon for drawing my attention to, and inviting me to review, Schioldann's remarkable book, eight years after its publication. Its provenance is as unique and gratifying as its contents. The author is a psychiatrist educated at the University of Copenhagen, interested in medical historical biography, married to an Australian wife, living in Australia since 1984 and now Emeritus Professor of Psychiatry at the University of Adelaide.

What better progenitor to explore the historical role of lithium and the enigma surrounding the Australian, John Cade, who reported the effectiveness of lithium as treatment for acute mania

in 1949, a compound with a long prior history of use in gout and its associated psychiatric manifestations, beginning 90 years earlier in Denmark.

To grasp the premises, scope, nature and validity of this historiographical enterprise, first read the Preface by German Berrios, Chair of Epistemology in Psychiatry at the University of Cambridge, England. Among his observations is a cogent comment that priority questions often raise issues of a nationalistic nature: "The Lange brothers and Schou in Denmark fulfill the same social function as Cade does in Australia. All that a good historian can (and should) do is try and understand why it is so important for countries to have heroes, and why some official stories, however mythological they may be, cannot be changed or replaced."

This should be enough to whet any reader's curiosity as they are about to enter a dense forest of fact, inference and conjecture. The volume opens with a prescient quotation, "All knowledge is cumulative, and dependent on previous discoveries that have been made available to the scientist and to his fellow man" (Keys 1944). An introduction lays out the scope and skeleton of a 390-page volume that aspires to weave, "as far as the source material allows, an in depth, comprehensive and scholarly fabric that extricates, even if not fully possible, the actual events and sequence of the intricate, checkered and quixotic story of lithium."

The Historiographic Method

An amateur historian at best, this is my first exposure to the pleasures and pitfalls of this method. Google informs me it was developed to make history a respected academic discipline and exists in many different forms applied to a wide variety of topics, both cultural and scientific.

In this instance, the author is concerned with identifying the entire world literature encompassing *The History of the Introduction of Lithium into Medicine andPsychiatry: Birth of Modern Psychopharmacology 1949.*

To this end, 1,245 references are cited in many different languages, as far back as the mid-19th century. This unique and massive bibliography is a generous gift to any reader desirous of knowing the breadth and depth of available information on this sometimes controversial topic.

The Text

Each of 30 chapters is scrupulously referenced; there are photographs of the principal protagonists and copious indexes of persons and subjects. The 390-page text is divided into two parts: **Part I**: Birth of Lithium Therapy, 1859, and **Part II:** Renaissance of Lithium Therapy. Birth of Modern Psychopharmacology 1949. There are three appendices: **Appendix I** *Carl Lange: On Periodical Depressions and their Pathogenesis;* **Appendix II** *The many faces of John Cade, by Ann Westmore;* and **Appendix III** *My journey with Lithium, by Mogens Schou.*

Part I: The Birth of Lithium Therapy

Gout is one of the earliest diseases described in the literature, from the time of Sydenham who suffered from and wrote about the condition (Sydenham 1683); it was considered an affection of the nervous system, with melancholia an inseparable companion (Roose 1888). Neurosis was also considered an etiologic factor (Duckworth, 1880). Uric acid was discovered in calculi in 1775 (Scheele 1776) and identified as an etiologic contributor to uric acid diathesis, linked to diet (Parkinson 1805). Mania was also reported to be a manifestation alone (Whytte 1765) or in conjunction with melancholia (Lorry 1789).

The belief that gout, melancholia and mania were co-morbid was widely held throughout the 19th century in America and Europe, endorsed by many of the leading mental health physicians, discussed at international conferences and articles about the subject were published in leading psychiatric journals of the day (Pinel 1809; Esquirol 1838; Trousseau 1868; Reynolds 1877; Rayner 1881).

Naturally enough, treatments proliferated, some from antiquity and others directed mainly towards the presumed uric acid diathesis. Early in the second century AD Soranus of Ephesus recommended alkaline waters for "manic excitement" while Colchicine dated from the sixth century AD (Alexander of Tralles). Deterred by its drastic purgative effects, a spectrum of other remedies flourished, including cautery, moxibustion, acupuncture, blood-letting, non-protein diets and abstemious life styles.

Towards the end of the 19th century, a review of the evidence found the author "completely baffled" and doubtful about etiologic assumptions concerning uric acid that were "more acceptable

to charity than likely to be accepted by psychologists," but it might be satisfactory and agreeable to "lay some of human frailty to the charge of uric acid" (Fothergill 1872).

Lithium in Gout

Lithium enters the stage with its discovery in 1800 by the Brazilian Jose Bonifacio de Andrada e Silva who found it in a pile of rocks in an iron ore mine (Johnson 1985). It was not chemically identified as a metallic ion and named lithium, Greek for stone, until later (Vaquelin 1817). It was first mentioned as a potential therapeutic agent when lithium carbonate was found to be four times better than sodium carbonate as a solvent for uric acid (Lipowitz 1841). Clinical utility was suggested two years later when lithium carbonate was shown to dissolve a human kidney stone *in vitro* (Ure 1844), then first used *in vivo* by Binswanger in 1847 (Sollman 1942).

Lithium's widespread use in gout and addition to *Materia medica* is attributed to Garrod, who also noted a therapeutic effect on co-morbid affective symptoms, "occasionally maniacal symptoms arise which I have myself witnessed." Garrod's work, including therapeutic dosage levels, was disseminated in the English, German and French literature (Garrod 1863). Lithium was first listed in the *British Pharmacopeia* in 1864 and in *Merck's Index,* from its first edition in 1889 until its fifth edition in 1940, after which its use was banned by the FDA due to lethal toxicity in cardiac patients when used as a salt substitute.

During almost a century, between its first use and until its lethal side effect was recognized, lithium was used in various formulations for a variety of conditions in addition to gout. These included lithium bromides in epilepsy (Locock 1857), as a mild tonic (Gibb 1864), as a sedative (Levy 1874) and in America for epilepsy and "general nervousness" (Mitchell 1870).

Lithium in Affective Disorders

The first systematic use of lithium in affective disorders alone occurred at the Bellevue Hospital in New York (Hammond 1871) for "acute mania with exaltation or acute mania with depression" although the compound used was lithium bromide and its effect was attributed to an alleged ability to "diminish the amount of blood in the cerebral vessels causing cerebral congestion." However, Hammond's later publications, from 1882 till 1890, make no further mention of this

use which the author speculates might have been due to lithium toxicity because of the "tremendously high doses he administered.

In 19th century America the rationale and sequence of indications for lithium use were reversed. Hammond made no mention of gout or co-morbidity but in New York Leale took on where Hammond left off. At a conference in London, England (Leale 1881) he resurrected the concept of co-morbidity. "When these gouty functional disturbances are ridiculed or neglected by the physician and the sufferer permitted to long continue in this irritable nervous condition under the pleas that he is hypochondriac and permanent changes are allowed to occur in the cerebral meninges then he may have acute mania, ending in incurable insanity, with the remainder of life spent in a lunatic asylum."

Others followed Leale's lead in what became known as "American Gout" (Da Costa 1881) or "Metabolic Narcoses" (Dana 1886). In such cases the orthopedic manifestations were sometimes minimal ("half gout") and while the mental symptoms were also occasionally mild there were clearly recognizable depressive or manic manifestations of affective disorder, often attributed to "lithaemia, lithiasis or uric acid diathesis." Of interest is the work of John Aulde in Philadelphia who was greatly frustrated by the "unwillingness" of some of his patients "to pursue a course of treatment" and who were only willing "to seek the doctor when trouble overtakes them" (Aulde 1887). An interesting comment on poor compliance, a problem that would not be widely noted or named until more than 90 years later (Blackwell 1997).

Lithium in Denmark

In Denmark, lithium would finally emerge as a treatment for specific mental disorders. Pride of place is accorded the Lange brothers during the last quarter of the 19th century and the first decade of the 20th, (1874-1907), after which its popularity dwindled and was eventually extinguished. Carl Lange (1834-1900) was an academic neuropathologist in private neurology practice and his younger brother, Fritz Lange (1842-1907), was an asylum psychiatrist at Middlefort Lunatic Asylum.

Carl propounded his thesis on "periodic depression" and its response to lithium treatment (Lange 1886). His description of this disorder was later categorized as recurrent unipolar depression (Felber 1987) which Carl Lange distinguished from bipolar disorder because "lack of

spirits and *joie de vivre* is their constant complaint" and also from melancholia due to an absence of delusions and hallucinations. In Carl Lange's experience episodes of "periodic depression" never developed states of mania. If they had occurred, he would have classified them as "cyclical forms of insanity." His theory of etiology included both heritability of "decisive significance," as well as "a constant tendency of the urine to deposit uric acid sediment." About the latter he was ambivalent, "in no way is it certain that uric acid is the cause of periodic depression." Nevertheless, he posited that rational treatment to counteract the underlying diathesis required the "alkaline treatment method," which included lithium salts that had been entered into the Danish *Materia medica* in 1863 (Gazette de Hospitaux 1863), as well as dietary restriction to eliminate sources of uric acid. Significantly, Lange stressed that both of these measures be undertaken, not only during acute episodes of depression but long term and, if possible, lifelong, although this required in both patient and prescriber, "not insignificant amounts of energy." One of his patients (case vignette No, 5) was non-compliant and refused lithium treatment because she did not believe she was ill, but attributed her malaise to existential calamity, "all sin and disaster."

Carl's efforts were devoted more to the nosology of periodic depression and Fritz's more to the etiological theory of "autointoxication" due to the uric acid diathesis. Towards the end of the 19th century criticism came on both fronts from leading contemporary colleagues (Levinson 1893; Pontoppidan 1895; Christiansen 1904). Unfortunately, Carl died in 1900 and Fritz in 1907, three weeks before his attempted rebuttal, "Uratic Insanity," was published (Lange 1908).

With the death of both brothers, interest dwindled and opposition grew until "in a meeting of the Medical Society of Copenhagen in 1911 the Lange's theory of periodic depression was dealt its death blow" (Faber 1911). The proceedings gave short shrift to the alleged disorder and its treatment: "The dilapidated ruins of uric acid diathesis should be removed, partly because it is a hindrance to newer and more correct understandings, partly because it also results in useless or even harmful therapy."

Lithium around the World

Not surprisingly however, the Lange's theories and practice spread to other countries around the turn of the century where they gained criticism and little support from psychiatrists as documented by authors in Great Britain, America, France and Germany. In the last edition of his

book, Henry Maudsley touched on the occasional co-morbidity of gout and mental disorders, downplayed the significance of uric acid and mentioned neither Carl Lange nor lithium (Maudsley 1895).

American views were reflected in the popular opinion that Lithia springs and water were beneficial for a broad spectrum of maladies assumed to be due to uric acid diathesis, a belief endorsed by a long line of Presidents but eventually debunked in the popular press; "The time is now to overthrow the Lithia water fetish the only use of which is to extract annually many thousands of dollars from the pockets of real and imagined sufferers." (Leffmann 1910).

A more scientific source in America noted that "The uric-acid hypothesis is a scrap basket for all improperly diagnosed cases" (Futcher 1903).

In Europe, Kraepelin's final verdict was to dismiss Carl Lange's beliefs about periodic depression; it had not been confirmed by clinical observations and was not consistent with his own experience that only a few patients had co-occurring gout. He viewed the diagnosis as more likely being manic depressive disorder in which the manic phase had been missed, but did not mention lithium in its treatment, although he did use it for epilepsy (Kraepelin 1927).

The author notes that preceding Lange's work a relationship between gout and symptoms of affective disorder, including mania, had been "the darling of French medicine" including authorities such as Pinel, Esquirol, Trousseau and Charcot, but did not include the use of lithium.

The author also adds a more contemporary note by citing a study which showed a correlation between cyclic changes in manic-depressive illness and changes in daily uric acid excretion, particularly in the early stages of remission - whether natural or lithium induced. The authors speculated that lithium interferes with the active transport of organic acids in the kidney and the brain (Anumonye et. al. 1968).

Back to Denmark

In 1927, the same year that Kraepelin issued Europe's dismissive *coup de grace* to Carl Lange's concept of "periodical depression," Hans Jacob Schou, father of Mogens Schou, published a vehement defense of what he described as "one of the most beautiful descriptions, absolutely classical, which can still enrich and instruct readers of our time" (Schou 1927).

Appropriately he delivered this endorsement with caveats: Lange had made the mistake of separating periodic depression from melancholia and periodical mania when, in fact, the mental and physical symptoms he described were "completely analogous to those of melancholy, differing by degree only," coupled with the fact that both mild and severe forms "occur in manic-depressive families" and had a similar natural history. Schou also speculated that Lange had missed many manic episodes because "his patients were exclusively non-hospitalized and they would consult him when depressed but not in their exalted periods." Later in life he modified this view to speculate that what would become unipolar depression might be separate from manic-depressive forms (Schou 1940). He recommended treatments ranging from psychotherapy, opium and barbiturates to "the modern shock treatment" (Schou 1946).

Schou also considered that Lange's etiologic theory of uric acid diathesis was refuted by his own research. He disapproved of Lange's suggestion that work and exercise were prime remedies, but did not mention the Lange brother's interest in alkaline medicinal remedies (including lithium) or any investigations of his own involving lithium (Schou 1938). Since the uric acid diathesis did not exist there was no reason to mention any medicinal remedies for it.

This logical assumption was later mistakenly characterized as the deliberate abandonment of prophylactic lithium treatment by the father of Mogens Schou, (Amdisen 1985) creating a mythical father-son disagreement (Schou 2005).

While Mogens Schou's denial that his father was the indirect source of any knowledge of lithium's potential therapeutic efficacy is definitive the potential role of the Lange's own work is equivocal. In one publication (Schou1996), he conceded the brothers treated many hundreds of patients "with dosages large enough to lead to serum concentrations of the same magnitude as those used today," but two years later (Healy 1998) he dismissed their work for lack of convincing case histories, lacking statistics or double-blind technique.

Nevertheless, the author considers that Schou senior missed the rediscovery of lithium's effect in manic-depressive disorder "by a whisker." Interestingly, he noted the use of "nerve mixtures" in the disorder's treatment, many of which, listed in the Danish Pharmacopoeia in 1907, contained various salts of lithium (Schou 1946). If the Lange brother's ingenious observations had been followed up, that discovery might have come even earlier (Schioldann 2000).

In a helpful synthesis of the massive amount of preceding information the author provides a prologue to Cade's discovery in 1949. The lithium story began with the fallacious uric acid diathesis which invited alkaline remedies as a treatment repertoire for its allegedly protean manifestations, including psychiatric symptoms. Equally fallacious was the premise that because lithium was a preferred remedy based on its superior solvent properties *in vitro* this would transfer to *in vivo* use, an assumption never clinically confirmed. In addition, the earliest use was with lithium bromide- bromide itself having sedative properties.

The first to use lithium in the acute phase of manic-depressive illness was possibly Hammond (1871), while Da Costa (1881) suggested prophylaxis using lithium citrate. In using lithium prophylactically, both Aulde and Fritz Lange were frustrated by patients' unwillingness to commit to systematic treatment. Both Lange brothers were the first to use lithium carbonate for acute treatment and prophylaxis of periodical depression, finding it superior to the bromide salt. Carl's findings were based entirely on outpatients, while Fritz's included some inpatients suffering from bipolar mood swings. Indisputably, the Lange brothers were the "founding fathers of the systematic use of lithium in psychiatry."

In the first decades of the 1900s, the uric acid diathesis was discarded as an erroneous concept by leading Danish psychiatrists (Faber 1911) and lithium was ushered out with it. The Lange's theories experienced brief renaissance two decades later with regard to the nosology of manic depressive disorders, but the "old Danish lithium treatment" was ignored, "only to fall into oblivion" half a century before Cade "rediscovered" its use in acute mania.

Chapter 5

John Cade and the Re-Discovery of Lithium

Birth of Modern Psychopharmacology (Schioldann, Part 2)

John Cade; An Intimate Second Opinion (*Finding Sanity:* De Moore & Westmore)

The detailed story of Cade's rediscovery of lithium for the treatment of acute psychotic mania is told twice in the two separate volumes, first by Schioldann in Part 2 of his book *The Birth of Modern Psychopharmacology* and 9 years later by De Moore and Westmore in *Finding Sanity.*While these accounts share some details they also differ in their sources and conclusions.

The Schioldann Story

Appropriately Schioldann begins with a historiographical analysis of whether Cade's discovery was spontaneous or influenced by what had historically preceded it. In doing so, he cites seven sources beginning with Johnson and Amdisen (1983) whose conclusions are both ambivalent and equivocal. First, they state there had been others "unknown to Cade who had already done so, and indeed, for exactly the same purpose – the control of manic excitement." Later, in the same paper they state: "It hardly seems likely that the various claims which had been put forward for over a hundred years for the therapeutic benefits of lithium in a wide range of disorders, including mental affections, were either totally unknown to Cade or failed to influence his thought, at least in a general way." In another publication, a year later (Johnson, 1984), the author states: "The evidence is difficult to establish, often equivocal and almost always circumstantial." A year later (Amdisen 1984) concurred: "It had escaped Cade's historical research that for as long as 80-90 years before he published his results a presumably not seldom used treatment for mania existed."

Frank Ayd, in a volume on the *Early History of Psychopharmacology* (Ayd 1991) notes that "In his original report on lithium (1949), Cade reviewed the history of lithium as he knew it then, but in time, it became evident that he had, in fact 'rediscovered' the use of lithium… when Cade learned more of the early history of lithium he acknowledged its earlier uses in mania."

But in 1970, when Cade, along with all the other pioneers in the field, presented his story of lithium at a conference on "Discoveries in Biological Psychiatry" neither in the text nor the references is any mention made of an earlier use by others of lithium in psychiatric disorders (Cade 1970).

Having reviewed the early history of lithium treatment Vestergaard (2001) concluded Carl Lange's observations and writings "were probably known to Cade, but there was nothing to indicate he had been influenced by them." Himmelhoch (2001) concluded, "I would guess *(sic)* that Cade himself was well aware of Lange's ideas."

Finally, Callahan and Berrios (2005), in a brief book chapter on *The Story of Lithium* state: "Unknown to him, Cade was retracing the steps of a Danish neurologist, Carl Lange, who had reached the same conclusions 50 years earlier and who had successfully given lithium to patients with affective disorders. However, locked in the Danish language Lange's work was not available to Cade."

The author's conclusion, based on these citations and "a great array of additional source materials," is that it may not be possible to tell the full story to "support an attempt at unravelling the elusive puzzle that is Cade's discovery of lithium." Nevertheless, the chapter ends with a paean of praise for initiating the *third revolution in psychiatry. The biochemical revolution* in 1949, three years before the discovery of chlorpromazine (Fieve 1997).

This story of Cade's discovery predates the publication of a more detailed analysis of the origins of his ideas about the etiology of the major mental disorders (de Moore and Westmore 2016). Essentially, in addition to a childhood living on the grounds of mental hospitals where his father was a psychiatrist and with a demonstrated interest and involvement in research as a medical student and postgraduate, Cade's views were influenced by his experiences as an officer and general medical practitioner in a Japanese prisoner of war camp during World War II. These experiences shaped a conviction about the organic etiology of severe mental illness, coupled with the simplistic idea, derived from thyroid disease that depression might be due to the absence of a centrally mediated metabolite and mania due to an excess akin to myxedema and thyrotoxicosis (Cade 1947). He communicated these ideas to his wife in a letter *en route* home from captivity and

remained loyal to them in his final publication (Cade 1979) where, not for the first time, he expressed his negative views about Freud and psychoanalysis.

Lithium in Guinea Pigs

Cade's search for a toxic substance began logically in collecting fresh, concentrated morning urine from manic patients and controls with other diagnoses. In a primitive laboratory in the pantry of a chronic ward at the Bandoora Hospital, where he was Superintendent, Cade injected these samples into the peritoneal cavity of guinea pigs and reported his finding that "urine from a manic patient often killed much more readily" (Cade 1947). Identifying urea as the culprit, he described its toxic effects, proceeding from ataxia to quadriplegia, myoclonus, tonic convulsions and eventually *status epilepticus* leading to death. Interestingly, he discovered that creatinine produced 25% suppression of convulsions and a 50% reduction in mortality, noting the similarity between its structure and that of the anticonvulsant Dilantin.

Putting aside this distraction, Cade returned to his attempt to find a toxic substance in the urea of manic patients and selected uric acid as a candidate. Confronted by its insolubility in water, he chose the most soluble urate, which happened to be lithium. He now observed the toxicity was far less than expected which he described as the great paradox, "speculating that the lithium ion might be exerting a protective effect" (Cade 1949). Now, using a 0.5% of lithium carbonate, he found this protected all 10 animals injected with an 8% aqueous solution of urea which had previously killed five out of 10 animals. This result of lithium was accompanied by making the animals lethargic and unresponsive for up to two hours before returning to normal. The only extant records of Cade's guinea pig experiments with lithium are in his seminal publication *Lithium Salts in the Treatment of Psychotic Excitement* (Cade 1949), published in the *Medical Journal of Australia,* which became the journal's most cited publication. Close inspection of cards (by the author) describing his experiments in guinea pigs deposited by his wife in the Medical History Museum at the University of Melbourne contain none that describe his experiments with lithium.

Cade's observations on guinea pigs when injected with lithium carbonate have been the object of interpretation and controversy among investigators who attempted to replicate the findings. Schou noted that the apathy and slow reaction might be due to intoxication or a direct action on the brain. Experiments in mice and rats also failed to show any comparable effects.

Schou's eventual conclusion was critical (Schou 1992): "The reasoning behind his animal experiments was far from clear… and it is my conclusion that the lethargy observed in those guinea was in fact caused by over dosage rather than by a specific tranquilizing action of lithium. I have at least not been able to produce such an effect in guinea pigs or rats with anything but strongly toxic doses." A similar conclusion was expressed (Gershon 1968) with the later caveat that despite a faulty interpretation, the observation provided the incentive to administer lithium to patients with remarkable benefits (Soares and Gershon 2000).

In his 1949 paper, Cade's only reference to earlier medical use of lithium was in gout when he mentions Garrod's text (Garrod 1859). About gout's many "manifestations," he makes no reference to depression or mania mentioned by earlier authors. His conclusion about the historical use lithium was unequivocal: …"the uselessness of lithium in most of the conditions for which it was prescribed, and the fact there was other, more efficacious, treatment in the only disease in which it been shown to be of some value, (and so) it is not surprising that lithium salts have fallen into desuetude." Long after his own discovery he was able to write: "So the introduction of the lithium ion into medicine was all a silly mistake. It was perfectly useless for the conditions for which it was prescribed" (Cade 1978). He did, however, note that, "The water of certain wells was considered to have special virtue in the treatment of mental illness … it is very likely that their supposed efficacy was a real efficacy and directly proportional to the lithium content of the waters."

Lithium in Patients

Cade's decision to proceed to clinical use was expedited by two factors: first he experimented on himself to determine the safe dose, correctly arriving at 1200 mgs of citrate thrice daily and 600 mgs of the carbonate; and secondly, "I was able to go my own way, unhindered by advice, criticism or caution. I don't think it could happen these days. One would be suffocated by hospital boards, research committees, ethical committees and head of a department. Instead I was answerable only to my own conscience and personal drive" (Cade 1981).

Despite the total lack of evidence in Cade's own writings that he knew of lithium's prior use in affective disorders, the author advances slender evidence that it might have been otherwise. Cade's immediate predecessor in the Victoria Department of Mental Hygiene, W. Ernest Jones,

had been Medical Superintendent to an asylum in Wales, UK. His successor, after Jones' move to Australia, discovered a half empty large canister of lithium presumed to date from the early 20th century. Brian Davies, immigrant from the Maudsley and first Professor of Psychiatry at Melbourne, discussed this hypothesis with Cunningham Dax, Cade's and Jones's superior, who never heard them discuss the possibility of its use in mania, nor did Jones' own research mention it. Another slender thread in the rumor mill was provided by a psychiatrist who worked at Sunbury Mental Hospital from1947 to 1950, the same hospital where Cade's father was Medical Superintendent in 1932 (Ashburner 1950). When Ashburner heard of Cade's discovery and wanted lithium to prescribe, the pharmacist found a big jar of lithium carbonate, a relic from years earlier when the vogue was to use lithium in the treatment of rheumatism. The final piece of tendentious deductive reasoning was derived from the case card of Cade's first patient with mania which records the prescription of lithium with the added comment that he had "an extremely high blood uric acid." The author states, "This case card is highly indicative of the fact, if not proof, that Cade was fully acquainted with the views of his scientific forbears of a presumed connection between mania (gouty mania) and uric acid." A belief never expressed in any of Cade's writings about his discovery and totally inconsistent with the views about lithium he expressed above.

This issue would remain speculative in the minds of others who wrote about Cade's discovery. Johnson, an ardent and consistent admirer, felt it was "hardly likely" Cade was totally unaware of its use "in a wide range of disorders, including mental affections" (Johnson 1985), but then concluded: "The evidence for this is difficult to establish, often equivocal and almost always circumstantial." An even more remarkable psychoanalytical hypothesis and linguistic analysis was advanced that Cade projected lethargy (a human idiom) onto the guinea pigs while supposedly suppressing prior preconscious knowledge of the historical use of lithium in humans (Reines1991), a tendency ascribed in general to "modern psychopharmacologists (who) either are unaware of or choose to ignore the older clinical literature."

Cade's trial, described in his 1949 paper, included 10 manic patients (three with chronic mania and seven with recurrent episodes), six schizophrenic patients and three with melancholy. Without any control, the results were unequivocal; the manic patients all recovered between a few days and a couple of weeks, relapsing if lithium was discontinued or they were non-compliant. The schizophrenic patients showed a reduction in excitement or restlessness, but no improvement in

the core symptoms, although he later reported two patients diagnosed as schizophrenic who did respond (Cade 1969).

The individual case histories of Cade's sample are provided in more detail elsewhere (de Moore and Westmore, 2016), but the fate of his first patient (W.B.) is spelled out in detail in the chapter, "Cade's first lithium patient: a paradigm of lithium therapy." According to the original medical record (Davies, 1983), which extends from February 24, 1946 (a synopsis of the disorder prior to treatment), and continues until March 3, 1949: "The patient continued well with occasional biliousness." This, however, was not the end of the matter. Johnson (1984) gives a more complete account leading up to the patient's death from lithium toxicity. On March 8, 1950, W.B. was readmitted with lithium toxicity and the drug was discontinued when Cade commented: "Under all circumstances it seems that he would be better off as a care-free restless case of mania rather than the dyspeptic, frail little man he looks on adequate lithium." Two days later, on May 12, 1950, lithium was reinstituted because his manic state worsened. "This state seems as much a menace to life as any possible side effects of lithium." Within a week, by May 19, 1950, lithium was ceased again when he was semi-comatose and had three fits; three days later, on May 22, W.B. was *in extremis* and died the next day. Cade recorded the death as "toxemia due to lithium salts, therapeutically administered," a verdict accepted by the coroner in October 1950.

Cade never publicly admitted the cause of death and, years later, in four publications he portrayed the final outcome as successful (Cade 1967; Cade 1970; Cade 1978; Cade 1979). Mogens Schou and Cade began corresponding in 1963. Subsequently, Cade learned of lithium's potential as a prophylactic agent in recurrent manic-depressive disorders and Schou accurately predicted it would become far more widely used worldwide. Meanwhile, routine plasma monitoring had made it a far safer drug to use by work done in his own backyard (Noack and Trautner 1951), something Cade also never publicly acknowledged. Sam Gershon, a psychiatric resident under Cade, later reported his statement that, "If you are a good clinician you don't need the machine" (Gershon 2007).

Another unexplained mystery is that in 1950 Cade banned the use of lithium at his own hospital. The author notes that based on his own experience Cade was fully aware of lithium's toxic effects and warned his colleagues of precautions to take in its use (Cade 1949). In February

and March 1949 *JAMA* published reports of fatal toxicity in cardiac patients given lithium as a salt substitute in America. This was published in the Medical Journal of Australia in July, two months before Cade's paper was published on September 3rd. In March, Lithium had been banned from all uses in America by the FDA. Nine months later, Cade's first patient, W.B., died of lithium toxicity. This might certainly have been what triggered Cade's decision to ban its use, although this is something to which he never alluded.

Lithium around the Globe

The question arises as to how quickly the use of lithium spread around the globe. A first unpublished account of its use by a British psychiatrist in 1949 was reported as a personal communication years later (Johnson 1984). The first published account after Cade was in Australia (Roberts 1950) of just two cases, one of which, a female with chronic mania, was fatal. The timing of this might well have contributed to Cade's concern even though that might have been ameliorated by a letter to the journal in which Ashburner (1950) claimed to have treated more than 50 patients without toxicity at another Australian mental hospital, safety he attributed to use of lithium carbonate, far safer than the chlorate or citrate Roberts was using.

Measurement of Lithium Levels

Also in 1950, a world authority on gout and uric acid published a paper on lithium as a salt substitute (Talbott 1950) suggesting that monitoring serum levels might stave off toxicity. The idea was picked by a psychiatrist at Mount Park Hospital in Melbourne and a faculty member in the Department of Physiology at Melbourne University (Noack and Trautner 1951). Using a flame photometer, they decided to study Cade's findings in detail, including three fatalities since they were published. They studied more than 100 patients suffering from mental disorders and confirmed Cade's findings without any serious intoxication (Noack and Trautner 1951). By 2004 their paper, like Cade's, was among the 10 most cited articles in the *Medical Journal of Australia.* In a letter written in 1974, Schou congratulated them on a method of primary importance in the development of lithium as a safe and efficient procedure (Goodwin and Ghaemi 1999). Cade, for the reason given above, remained silent (Gershon and Daverson 2006).

Mogens Schou and Prophylaxis

In 1951, Stromgren in Denmark learned of Noack and Trautner's work at a conference in Paris and drew the attention of "his brilliant research assistant, Mogens Schou" to Noack and Trautner's paper (Stromgren 1951). In 1952 and 1953, Schou collaborated with colleagues in Denmark on the use of lithium in 38 manic patients in a double-blind placebo-controlled study, (Schou et. al. 1954) confirming the work of Cade. This might be the point at which lithium could be considered a scientifically-based safe and effective treatment of acute mania.

According to the author, both Stromgren and Schou disavowed any influence of the Lange brothers in their decision to study lithium; Schou also denied hearing his father speak of it. Schou gave the credit entirely to Cade and they soon became close friends, exchanging approximately 40 letters between 1963 and 1970, by which time the scope of lithium began to be vastly inflated by Schou's discovery of its prophylactic effect.

Following his presentation at the 1970 Baltimore Conference on *Discoveries in Biological Psychiatry,* Cade (1970) visited Schou in Denmark where Schou heaped praise on him in a lecture as "the man who introduced lithium into psychiatry and described its anti-manic effect." Cade reciprocated as follows: "I feel rather like woman who as a girl had an illegitimate child and had adopted it out. And now, 20 years later, I am visiting the adoptive parents and finding out what a fine big boy he has grown into, but knowing far less about him than his adoptive parents" (Schou 1983). This apt and colorful quotation coveys a strong and synergistic relationship between the two men and a somewhat humble contribution made by Cade. It was described by Schou as, "The nicest compliment we have ever received" (Schou 1983).

Serendipity or Not?

The author spends 13 pages addressing this somewhat controversial and provocative topic which plays a recurrent theme throughout the discovery of all the earliest treatments in psychopharmacology (Ban 2006). While it is a term sometimes used by the discoverers themselves, others have viewed it as dismissive or even derogatory. The author notes that Cade "was very annoyed that his discovery was considered by many as serendipitous… he never ceased to point out that it was based on a specific hypothesis and experimental observations." And later, "that he was emphatic that the discovery was the result of a continuous and consistent chain of reasoning."

Among the many citations relevant to this issue, ranging over more than half a century and many countries, a pattern emerges. In the earlier years, while Cade was still alive, there are no less than 16 authors worldwide, alone or together, who use the term "serendipitous." In his book, *Serendipity: Accidental Discoveries in Science,* Roberts (1989) singles out lithium's discovery as "the most improbable of all." Rejection of this attribution occurs much later and from fewer sources, often linked to memorial occasions celebrating the discovery and Cade himself in Australia. Two individuals stand out in defense of Cade's own position. Johnson, a psychologist and long-time author and advocate for Cade who, in his obituary (Johnson 1981) notes: "He always strenuously denied that his work with lithium contained any element of serendipity." His most vehement advocate was Mogens Schou who consistently attributed his own knowledge of lithium's anti-manic effect to his friend John Cade. In 1977, he addressed the topic at the *43rd Beattie Smith Lecture* in Melbourne and in 1982, during the *First John Cade Memorial Lecture,* he expressed his distaste for the way in which serendipity was used "in a derogatory sense; arbitrary success, random discovery, sheer luck." Interestingly, Schou's overall views of Cade's work were quite nuanced. He noted: "The hypothesis which started his work was crude. His experimental design was not particularly clear. And his interpretation of the animal data may have been wrong. Those guinea pigs probably did not just show altered behavior, they were presumably quite ill." Nevertheless, placing more emphasis on the revolutionary consequences of the discovery for sufferers of manic-depressive illness, Schou added: "...and this is the marvel of the thing – a spark jumped in John Cade's questing mind and he performed the therapeutic trial which eventually changed life for manic-depressive patient all over the world" (Schou 1996a). Perhaps understandably, Schou conflates Cade's discovery by integrating it with his own.

The author offers no reconciliation or adjudication between these conflicting views of the role or not played by serendipity in Cade's discovery of the effect of lithium in mania.

Cade's Legacy and Role in the Birth of Modern Psychopharmacology

This penultimate chapter begins, appropriately, by singling out America as most tardy in the recognition of lithium for mania. "The magnitude of this discovery is not yet realized in this country (Williamson 1966). This was undoubtedly due to the complete ban placed on lithium in 1950 by the FDA, the year after Cade's discovery, triggered by its lethal toxicity in cardiac patients

when used as a salt substitute. This ban stubbornly persisted until 1970 due largely to the failure of academic psychiatry and the FDA to recognize the fact that toxicity could be avoided by blood monitoring (Noack and Trautner 1951). Paradoxically, the ban on use in mania, but still not for prophylaxis, was lifted in 1970 at exactly the time Cade was invited to present his work for the first time in America (Ayd and Blackwell 1970). Doubtless the ban was also not vigorously opposed because lithium was a basic ion, not a patented or marketed drug, backed by the large pharmaceutical companies busy developing and eventually selling expensive, less effective, "mood stabilizers" with more side effects.

Ironically, in 1949, Sweden had awarded the Nobel Prize to Egaz Monez for frontal lobotomy while lithium, discovered in the same year, went largely unnoticed, although it was "difficult to find a specific drug that is as efficacious in a high percentage of patients of a specific nosological category" (Lindheimer and Schafer 1966).

It was not until after Schou and his colleagues reported lithium's prophylactic effect in recurrent manic-depressive disorder, a far broader indication with wider usage, that in the mid to late 1960s Cade's earlier contribution in mania began to gather widespread recognition with vastly magnified claims to its significance in the entire field and history of psychopharmacology. In America, Nathan Kline's article, *"Lithium Comes into its Own*" (Kline 1968), gave rise to exuberant correspondence in the *American Journal of Psychiatry* triggered by his description of lithium as "The 20-year-old Cinderella of Psychiatry." Hyperbole spread round the globe like the Plague. In an editorial, the *Medical Journal of Australia* (1999) eulogized lithium and the man: "John Cade was among the highest order of scientists whose work on lithium in patients with mania revolutionized their management and facilitated return to society." Another American psychiatrist, in a book for lay public, declared: "Cade's discovery initiated the third revolution in psychiatry" (the first two were Pinel and Freud) (Fieve 1997). In a commemorative article, a lay journalist in Australia described Cade's original paper as, "one of the most revolutionary in medical history" (Haigh, 2004). A trio of psychiatrists expressed the view that "lithium not only had profound effects for patients with affective disorder, but has also launched the pharmaceutical revolution (Watson, Young and Hunter 2001). Others felt that the introduction of lithium by Cade in 1949 can be "considered to have heralded the modern era of psychopharmacology" (Baldessarini, Tondo and Viquera 2002). Last, but certainly not least, was Johnson (1975) in an

early edition of his book, *The History of Lithium Therapy*: "Cade's discovery is considered by many working in the field of psychiatric research to have been one of the most significant in pharmacology."

Appendix I: Carl Lange; on Periodical Depressions.

This is a verbatim translation from Danish into English by the book's author of Lange's speech to the Medical Society of Copenhagen in 1886, the essence of which is discussed in the text.

Appendix II: The Many Faces of John Cade by Ann Westmore

Ann Westmore (2016) is the co-author of the book, *Finding Sanity: John Cade, Lithium and the Taming of Bipolar Disorder.*

She gives a brief synopsis of John Cade's youth and character traits, including his interest in collecting, classifying and experimenting as well as his strange hobby of studying animal footprints and fecal patterns. He also shared an interest in literary skills with a younger brother and journalist although his scientific articles tended toward brevity and had been criticized for that.

After medical training, Cade undertook a post graduate doctoral degree (without thesis), a mirror of the British practice preparing for an academic or research career, and also an approach he urged his colleagues to pursue following his discovery of lithium. In his first Beattie-Smith lecture, Cade said: "Let us never rest content with the present bounds of knowledge, it is up to us to initiate a particular approach to a psychiatric problem and if we have not the necessary knowledge to seek it."

During the span of his career, he fulfilled many teaching assignments, helping to train as many as 300 psychiatric residents, as well as medical students, between 1952 and his retirement in 1977. Like Frank Ayd, he wrote a column for thousands of fellow Catholics on a whole range of medical, psychiatric, ethical and social issues. But he was "equally capable of undermining doctrine," including a witty paper on Masturbational Madness (Cade 1973).

Westmore comes to a modest conclusion: "By teaching curiosity with crude research techniques and the freedom to pursue ideas, John Cade helped to generate an Australian presence in the modern psychopharmacology revolution."

Appendix III: My Journey with Lithium; Mogens Schou

In addition to a synopsis of his own career, Schou provides a profile of his relationship with John Cade. In addition to a long correspondence, they met on three occasions between 1972 and 1975. “He was a mild- mannered modest person who once said of himself 'I am not a scientist – I am only an old prospector who happened to pick up a nugget.'” But, Schou comments: “Prospectors find because the seek.” John Cade was characterized by an insatiable curiosity, keen observation, a willingness to test even absurdly unlikely hypotheses and the courage to risk making a fool of himself.” Schou characterized Cade as an “artist” compared to “myself as the systematic scientist.”

This Reviewer’s Comments

Because I have played a personal and significant role in the controversies swirling around lithium (Blackwell, 2014) and this is the second book I have reviewed on the topic (Blackwell 2017), I have shunned commenting as far as possible in my review of the book itself and have chosen to address five important aspects that play central roles in the enigmatic story of Cade and lithium.

A Histiographic Fallacy?

In my untutored opinion, there seems to be a strong implication that a long ago historical archive would almost inevitably be known to an enlightened investigator even when it was not acknowledged in that person’s publications or evident in collateral information. I will challenge this assumption both with regard to Cade’s biography and personal experience.

Cade’s passage to becoming a psychiatrist was unusual by today’s standards. He did not start out wanting to be one. From 1929 till 1935 he was a medical student and in his final year he attended 12 psychiatric lectures. Following graduation, he spent a year as an intern in medicine and pediatrics ending with a near fatal episode of pneumonia in pre-antibiotic days. After recovering, he decided to follow his father and become a psychiatrist.

In November 1936, he was appointed as a Medical Officer at Beechwood Mental Hospital “having spent a few months studying psychiatry” (de Moore and Westmore 2016). For the next

two years he experienced on the job training in a rich clinical environment and also studied for a post graduate degree in general medicine (M.D.) which he obtained in 1938. Also during this time he became involved in research and had two publications.

In September 1939, Australia joined Britain in declaring World War II against Germany and later, Japan. John Cade enlisted in December 1939 and joined up fulltime in July 1940 to begin training as an army general medical officer; he shipped to Burma in January 1941. What followed was four years as a POW of the Japanese in Changi, a time during which he was bereft of medical journals and literature.

Driven by a strong sense of urgency and creative ideas incubated at Changi, Cade returned to Bandoora Repatriation Hospital in 1946 and almost immediately supplemented his demanding work as Superintendent with his intense solitary search in guinea pigs for a toxic cause of mania. “He was a man in a hurry.” (de Moore and Westmore 2016).

To Cade’s credit, we know that, despite fragmented and distracting formal training at the start of his career, he was a voracious reader of medical texts who annotated them meticulously. After studying this archive, previous reviewers noted: “John Cade, it seems, was completely unaware of these previous endeavors to use lithium in psychiatric illness." By the late 1940s, notions of lithium’s supposed curative properties in all diseases had lost favor and it seems to be included in reference books, almost apologetically, as a testament of past faulty reasoning (de Moore and Westmore 2016).

It is equally unlikely that lithium or uric acid diathesis were mentioned in the curriculum of medical school or postgraduate medical studies.

Even supposing, however unlikely, that Cade did know of the early Danish work decades earlier, why would he fail to acknowledge that in his own work? Most scientists bolster the credibility of novel findings by citing prior work that corroborates their own.

The extent to which early and long-buried knowledge may be overlooked in the discovery process is the subject of an essay on *Adumbration* (Blackwell 2014). This tells the story of the tardy discovery of the sometimes fatal interaction between MAO inhibitors and tyramine containing foods five years after these drugs were introduced for the treatment of tuberculosis and

depression. A compelling archive of information in prominent journals that might have predicted this toxic interaction was unknown to basic scientists and clinicians working for several pharmaceutical companies, as well as academic and journeyman physicians in various disciplines who treated thousands of patients.

Serendipity

In preparing my thoughts on this matter, I consulted the *Oxford English Dictionary* (OED) and was delighted to find that serendipity might be considered a **portmanteau word** that carries the burden of more than one meaning (The example given is **brunch,** for **breakfast** and **lunch**.

A second discovery was an excellent article, the best and most comprehensive I have come across, on the history and role of the word (Ban 2006). Tom traces its origins to a 16th century fairy tale *The Three Princes of Serendip,* a text translated from Persian to Italian and then French over the centuries until Horace Walpole (1717-1797), an English literary genius, in a letter to a friend in June 1754, coins the term "serendipity" which describes the three princes who were "always making discoveries by accident and sagacity of things they were not in search of." In my opening lecture on *The Process of Discovery* (Blackwell 1970), at the Conference where Cade received the *Taylor Manor Award* for this discovery, I related the example which Walpole gives in the letter to his friend, drawn from the original story. One of the princes "deduces a mule is blind in the right eye because the grass was eaten only on the left side of the path." This is clearly an example of deductive reasoning reflective of the prince's sagacity. Note no experimentation was required which might have demanded a scientist's inductive skills.

More than three centuries of usage in three languages have blurred the precise definition of the word serendipity. Ban cites three dictionaries with differing definitions.

1. "Making happy and unexpected discoveries by accident" (OED).
2. "Finding valuable and agreeable things not sought after" (Webster).
3. "Finding one thing while looking for something else" (Stedman).

The essence common to all three is a search in which the outcome is unexpected. In none of them is there any hint that the word might or can be used in a derogatory way which both Schou and Cade assumed to be the case.

Ban systematically and rigorously applies these definitions to nine different psychotropic medications and divides them into four categories: 1) in four drugs, LSD, meprobamate, chlorpromazine and imipramine, “one thing is found while looking for another”; 2) in three drugs, potassium bromide, chloral hydrate and lithium carbonate, the discovery was serendipitous because, “an utterly false rationale led to correct empirical results”; 3) in one drug, iproniazid, “a valuable indication was found that was not initially sought”; and 4) only with chlordiazepoxide was discovery due to “sheer luck.”

In conclusion Ban notes, “Serendipity is one of the many contributing factors in the discovery of most of the psychotropic drugs." Also included is the potential of findings based on knowledge or past experience and cites Goethe’s aphorism , “Discovery needs luck,.invention, intellect – none can do without the other” (Kuhn, 1970) He aslo mention’s Pasteur’s .\well known “Chance favors the prepared mind” – cited in the original French.

Tom Ban’s conclusions about Cade’s discovery concur with the significantmajority of the independent opinions cited by the author of this volume. It does not explain the rationale for Cade and Schou’s opinions that use of the term serendipity was dismissive or derogatory.

.Legacy and Primacy

Schioldann’s assessment of the importance of Cade’s discovery of lithium in 1949 and its impact on the early development of psychopharmacology tilts strongly in a positive direction in a manner not supported by the data. This clearly defines two distinct time periods: from 1949 to 1980 and from then to the present.

Within less than three years of his discovery Cade had banned the use of lithium in the hospital where he was superintendent, a topic about which he remained silent although it coincided with the death of his first patient due to lithium toxicity, followed by the death of another patient at a different hospital and preceded by a total ban on its use in America. During the remainder of this first period Cade’s interests shifted dramatically. He was preoccupied with administrative

manners dictated partly by the arrival of a new administrator recruited from Britain who supervised his work and implemented innovative changes in mental health care, but also by a shift in Cade's clinical interest to schizophrenia and insulin coma. During this time, he was also sent to Britain for six months to study changing trends in mental health care possibly applicable to Melbourne.

It was during the period, from 1958 to 1963, that the CINP was formed and convened its first three international Conferences, none of which Cade participated in nor did any psychiatrist from Australia. The first to do so was Brian Davies, recruited from the Maudsley in Britain to become Professor of Psychiatry at the University of Melbourne, who joined the CINP in 1961. Lithium was not mentioned in the main program in any of the first three meetings in 1958, 1960 and 1962.

It was in 1963 that Schou first wrote to Cade informing him of an interest in prophylaxis, congratulating him on his discovery and initiating a continuous correspondence. It is from this point on that Cade's interest in lithium was vigorously renewed and from this point forward that comments begin to appear in the literature about the positive influence of events in 1949 on the entire history of the field. The flood of positive attributions stems largely from authors with a special interest in lithium, writing 20-30 years after Cade's discovery and at a time when innovation in the field had slowed to a crawl.

In 1970, when Ayd and I planned and convened the Baltimore Conference, we invited 17 of the world's leading researchers and clinical pioneers to participate. All agreed and each received the same Taylor Manor Award. Included were Chauncey Leake, (Amphetamine), Tracy Putman, (anti-convulsants), Alfred Hoffman, (LSD), Frank Berger, (Meprobamate), Irv Cohen, (Benzodiazepines), Hugo Bein, (Reserpine), Pierre Deniker (Neuroleptics), Jorgen Ravin (Thioxanthenes), Nathan Kline, (Iproniazid) Ronald Kuhn, (Imipramine) and John Cade, (Lithium).

This meeting provides a different perspective on events in the field. Three drugs were in use before lithium: LSD, amphetamine and diphenylhydantoin. Joel Elkes, regarded by some as the successor to Thudichum, presented on "Beginning in a New Science" during which he described work on neurochemistry at the Department of Pharmacology and Experimental Psychiatry between 1942 and 1950 when he moved to the NIMH at Saint Elizabeth's Hospital in

Baltimore (Blackwell 2015). Also included was a paper by Irvine Page on "Neurochemistry as I have known it", describing his work in Germany from 1928, his book on *The Chemistry of the Brain* in 1938 and at the Cleveland Clinic after 1945, including the discovery of serotonin.

Frank Ayd gave a concluding talk on the Impact of Biological Psychiatry. There was a friendly sense of collegiality among participants and a shared awareness of being part of a group of pioneers in the field. Lithium was considered one compound among many and no speaker was singled out for special credit or leadership of the field of psychopharmacology.

In 1985, Michael Shepherd asked me to review the latest edition of Johnson's *History of Lithium Therapy*. In doing so I quoted the following paragraph as an expression of concern about how far the book portrayed the biases in the field about lithium: "Lithium is being taken by one person in 2,000 in most civilized countries, possibly more in Denmark. At a stroke the elusive ethereal Freudian psyche was replaced by the polyphasic, physico-chemical system called the brain. Lithium, like no other single event led to psychiatry becoming truly interdisciplinary. Its ubiquitous use suggests a new basis for classification of psychopathological states. It is so cheap and easy to administer that it will transform healthcare in underdeveloped countries whose psychiatric services are otherwise stretched to the limit."

On the 50th anniversary of Cade's discovery, two leading psychiatrists informed the public: "Lithium inaugurated the psychopharmaceutical revolution. Essentially it saved psychiatry as a medical specialty" (Goodwin and Ghaemi 1999}

Plasma Monitoring

This constitutes perhaps the greatest enigma of all: Why did John Cade never speak of the work of Noack, Gershon and Trautner, carried out in Melbourne's own university, when Gershon had been a resident under his care and the biggest aid to lithium's safe and wider use would have been plasma monitoring? The only clue we have is that when Gershon asked Cade he commented that a good clinician didn't require laboratory help. This is consistent with a confident self-image of his own skill as a clinician, based perhaps on having experimented on himself and the early experience he had with the 10 patients he was treating. But after his first patient died with a puzzling mixture of medical deterioration and side effects, and soon after that a patient at another

hospital died on what appeared to be therapeutic dose, why not change his mind and acknowledge plasma monitoring augmented clinical judgment? One can only imagine pride might enter the equation, especially if he had already decided to ban lithium's use. But this hardly seems consistent with a concern for the many other psychiatrists treating patients with lithium unless he simply did not feel an obligation to be involved now that he had decided to ban lithium use and perhaps believed others would disseminate the information. Added to all this is the fact that 20 years later, when he presented his paper in Baltimore, Cade knew of lithium's increasing and widespread use and openly praised Schou for his discovery of prophylaxis, but still could not bring himself to mention Trautner's work. This suggests a deep-seated personal antipathy he was not able to resolve.

National Heroes

I have left this to last because I suspect it may be the most important factor bearing not just on the interpretation of the book under review, but the enigmas of the entire lithium story. It is also a response to the clue Professor Berrios handed us in his prescient forward to the book and the historiographical method. Berrios noted that "priority questions often raised issues of a nationalistic nature which Cade and Schou fulfill in Australia and Denmark and that however mythological these "official" stories are "they cannot be changed or replaced."

In responding to this assertion, a distinction is made between the first and second parts of the book. The massive database of lithium's pre-1949 history is impressive and valuable to all clinicians and research workers interested in lithium. I have only one caveat to assert that however compelling it might be, there is not a shred of evidence, real or circumstantial, from his own or the writing of others, that John Cade knew anything of that. As a matter of fact, neither apparently, did Mogens Schou, who always asserted he learned of lithium when his mentor Stromgren drew his attention to Cade's work in 1951 or 1952 (Appendix III) and not from either Lange's research or his own father. This, apparently, was the bond that created such a powerful synergy between Cade and Schou. There appears to be something of a historiographical bias that if research is well established in the literature, an educated professional must know about it even without evidence to substantiate such an assumption.

In the second part of Johan Schioldann's book we can see how Cade's Hero status is preserved and protected. The voluminous database is somewhat subjectively and selectively mined to favor Cade and Schou's view that the discovery of lithium was not serendipitous, a word they regard as dismissive or derogatory and not the product of deductive reasoning, although Schou does consider Cade to be "artistic" in contrast to himself as a "systematic scientist." The burden of proof tilts in favor of both serendipity and a deductive cognitive style.

Furthermore, Cade's discovery of lithium's value in mania is combined and conflated with Schou's later discovery of serendipity to claim that this body of work formed a foundation for the whole of psychopharmacology as a discipline, an assumption not supported by close scrutiny of the relevant literature. Other concerns a careful reader might raise are doubts about Cade's ban on lithium; failure to acknowledge Trautner and colleagues work, which made lithium safe to use; and concealment of his first patient's death due to lithium toxicity. It is true that the literature assembled does not cast new light on these blemishes, but failure to mention them does serve the purpose of embellishing a perfect Hero image.

Experience informs me that an unfortunate side effect of commenting on a Hero in anything less than affirmative terms may be perceived as an *ad hominem* attack on their persona or integrity. I plead for the reader's indulgence to avoid such an attribution and accept my assurance that Cade and Schou, Trautner and Gershon each deserve a place in any lithium pantheon of pioneers; but as colleagues and peers, diverse and without preferred status.

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John Cade;An Intimate Second Opinion

This biography of John Cade was published 36 years after his death with the intriguing title of *Finding Sanity*. (de Moore and Westmore, 2014). The reader will be beguiled by a balanced, carefully scripted, and well documented account of the benefits and hazards of this simple metallic ion imbedded in a nuanced biography of the enigmatic man who discovered them.

This tale fills gaps in our understanding of events and does justice to a unique accomplishment, told appropriately, by two Australian authors who consider it to be, "without doubt Australia's greatest mental health history." With pride they proclaim "Lithium is the penicillin of mental health … a simple salt of the earth that was a balm for a troubled spirit."

The first author, Greg de Moore, is an academic psychiatrist and historian, already author of an award-winning biography (*Tom Wills*). Greg first became interested in the present topic as a fifth-year medical student when he read John Cade's slim volume *Mending the Mind* (1979). Greg began compiling eight interviews from 1997 to1999, including John's wife Jean, and two of his four sons, Jack and David.

Over ten years later he joined forces with Ann Westmore, a social scientist and medical historian whose Ph.D. thesis acquainted her with John Cade and his accomplishments: *Mind, Mania and Science: Psychiatry and the Culture of Experiment in Twentieth Century Victoria* (2002).

Together, the two authors completed a further 18 interviews from primary sources between 2010 and 2015. They also compiled an impressive bibliography, included in the book, of archival material, conversations with authors, texts, newspaper and journal articles as well as unpublished sources – letters, memorabilia, memoirs and lectures.

The product of these labors is a 324-page volume in five parts, including photographs of the participants and a comprehensive index. It is easily accessible to lay as well as professional readers and will make an elegant addition to any library.

Biographies posted on INHN have variable provenance and different genres. Several are derived, like this one, from an authored biography, some from autobiographical memoirs, others are authored by me. The goal is always to provide a comprehensive portrait including extensive material from the author's text in quotes, supplemented by editorial background material or commentary.

As an aid to lay, and a reminder to professional readers, the book's Prologue sets the historical stage in 1948 with a two-page clinical vignette of a typical person with untreated bipolar disorder. He experiences wide mood swings, delusional thoughts and bizarre behaviors as he wanders along Bondi Beach and onto Sydney Harbor Bridge, contemplating suicide and without hope of an effective remedy

Part 1: Playing ball with Jesus

This part about John Cade's ancestry, youth and early career, also sets the tone of the biography by quoting Emil Kraepelin's definition of the disorder in *Manic Depressive Insanity* (1921) before proceeding to trace the origins of the Cade clan and John's own early years in Australia.

For 150 years in England, the male Cades were nearly all doctors or pharmacists until Frederic Cade, born in 1802, migrated to Australia. By 1842 he was established as a "druggist" in Melbourne, home to future generations. On January 1912 David Cade's first son was endowed with three personal names, John, Frederick and Joseph, in remembrance of his great-great grandfather, great grandfather and grandfather, testament to a proud lineage. David, John Cade's father began as a country general practitioner and his mother was a devout Catholic a "strong

pioneer type woman," also a nurse who became a competent and conscientious Matron, known for a kind and genial manner. David described his infant son as "a strange mixture of gravity and brightness who, quite early, manifested signs of the spirit of investigation and experimentation."

In more general terms, John was seen as "a child with a logical manner; curiosity and persistence impressed observers. John Cade, whatever else his attributes, was born with a tidy, tenacious and inquisitive mind."

When World War I erupted Dr. David Cade enlisted in 1915 leaving behind John, aged three and two younger sons. Aged 40 and a veteran of the Boer War, David spent four "darkened and disturbing years in Gallipoli and France." When he returned home, badly scarred by war, his softer attributes had been stripped away, leaving him "austere and fusty." Suffering from what he called war weariness, almost certainly PTSD, "he sought refuge from the mental anguish of incessant general practice and in 1920 became the resident doctor at the Beechwood Hospital for the Insane."

The family lived in a cottage on the grounds and John, eight-years-old, played with "disturbed men who thought they were Jesus… in these germinal years John's affection for the mentally ill stirred and took root." Two years later his father transferred to Sunbury Asylum for the Insane on the outskirts of Melbourne and, after a short stint, moved on to Mont Park Hospital for the Insane.

"As a boy John was a collector – of stones, of insects, of words. And he was a classifier, carefully placing everything into columns and rows in the same way that a nineteenth century naturalist might, and labelling everything neatly and precisely. John displayed an innate and joyous curiosity, and early on, describer with a love for the natural world. "There was a compulsiveness of it all … a thoroughness he brought to everything he did."

These traits served John well in school where the headmaster singled him out for special tuition in the vain hope of a scholarship. He was also an athlete with good hand-eye co-ordination that served him well at golf and tennis – sports he excelled at lifelong. John also learned to box, taught by an elderly patient who imitated Jack Dempsey.

At age 13 John elected to enter Scot College, an exclusive school favored by the wealthy and with illustrious alumni. It was a Presbyterian school; a choice he made that reflected a stubborn

self-assurance despite the fact he was raised Catholic by his mother. His father was Anglican, who John always called "sir."

Although not a precocious scholar, he was studious and excelled in biology, chemistry and physics, topics congruent with family tradition and his own future. At graduation he enrolled to study medicine at the University of Melbourne.

His fellow students remembered him as meticulous, organized and careful, fascinated with things biological and research minded. In his final year he won the forensic medicine prize. Also, that year, he attended lectures on mental diseases and studied from a psychiatry textbook, *Aids to Psychiatry,* in which "He scrupulously underlined sentences with the steadiest of hands." It seems clear that, based on a childhood spent in asylums, "he saw psychiatry as a subject worthy of serious study."

After graduating as a doctor, John spent his first year as an intern at the flagship Catholic hospital and then moved on to study pediatrics at Children's Hospital. While there he fell desperately ill with pneumococcal pneumonia and, before antibiotics, came close to dying. But during convalescence he was nursed by his future wife, Jean.

"Somewhere along the way, in a moment of epiphany, John abandoned the idea of becoming a pediatrician and decided to take up his father's profession, psychiatry." In 1936, aged 24, he became a Medical Officer at Beechwood Mental Hospital located in one of the prettiest spots in the State of Victoria. John was warmly welcomed by those who remembered his father and the young boy who worked and lived there in the 1920s.

"John settled into this rural retreat of the deranged but was not impressed…the whole place is constructed on the idea that mentally afflicted people are infinitely more dangerous than criminals, with no regard for their comfort." He entered the locked wards to encounter, "the unholy triad of stale urine, tobacco and floor polish. The swilling mix rose like fumes from the stinking bilge of a ship. All the women's clothing was made in the sewing room, they had no underpants, toilet paper was a luxury, female patients crushed geranium petals as rouge and sometimes styled their hair with cooking fat when soap was absent. Aggressive types might be isolated in wooden cubicles, physical restraint was common, some patients trussed up like poultry and released only at feeding times; canvas restraints for men and women, all coarse and stiff, like steel."

None of this deterred John, like a new broom he swept clean, astounding the staff and Matron with, "unorthodox and undoctorly habits." He set about seeing patients daily, examining them and keeping detailed medical records. John Cade encountered patients that matched Kraepelin's original descriptions, especially depressed and manic ones. The causes remained obscure, some assumed a biological cause, others faulty upbringing. "Of course, there were pills and potions, like a mad hatter's apothecary."

In 1937 John married his former nurse Jean who joined him at Beechwood; both participated in patient activities including a monthly dance where John waltzed with his wife and the patients, "a humanizing link between patient and doctor that seems forever lost." Bodily contact with his patients and watching them naked in the communal shower awakened John to the stigmata of nutritional deficiency causing scurvy. News of this discovery was rapidly spread by word of mouth leading to corrective action and the hiring of the first dietician in a Victorian mental hospital, "a turning point in the care of the mentally ill in Australia."

Following the British tradition John completed a postdoctoral degree in medicine. His topic is not mentioned, but he also published three articles in the *Medical Journal of Australia*, on death from arterial spasm (Cade, 1938), a statistical study in 1940 in which he collaborated with McFarlane Burnet, who later won a Nobel Prize in Medicine (Burnet, Cade and Lush 1940), and another statistical study on the onset of primary dementia (Cade 1940). John Cade's research activities marked a deliberate turn from "plush private practice" to the "unrivalled opportunities and wealth of clinical material" in mental hospitals. In 1939 he became a founding member of an association of like-minded Victorian psychiatrists dedicated to clinical studies to improve the lot of Asylum inmates. But the time was not propitious; on September 3rd Britain declared war on Germany.

Part 2: The interminable years.

This is a 50-page saga of John Cade's wartime experiences and how they displayed and molded his persona as a general medical officer, first captain and then major in the 2/9th Field Ambulance. Within a few months of the outbreak of war John enlisted and by mid-1940 had become a fulltime army doctor. Like his father David, he was about to embark on several years of warfare on foreign soil, leaving behind a wife and two children, the oldest not yet 3-years-old.

Shipped first to the Malay Peninsula and then, as the Japanese conquered Burma, he was trapped with tens of thousands of allied troops on the tiny island of Singapore. After their surrender in February 1942 the Japanese force marched their captives to Changi in the southeast corner of the island. It was the ideal place for a prison, bound by the ocean on three sides with no escape possible.

The British, Dutch and Australian prisoners were segregated and semi-autonomous. John found himself caring for patients in the 1000-bed Australian wing of Robert's Hospital where he functioned as a general physician, but also in charge of a small 10-12 bed psychiatric ward that earned him the nickname, "Mad Major."

The authors of *Finding Sanity* paint a detailed portrait of over three years of incarceration until twin atomic bombs forced the Japanese to surrender in August 1945. John Cade's work with the wounded and sick was exemplary and gained the plaudits of his fellow soldiers and officers. Bound together under extreme brutality and privation they provide a crystal-clear picture of the man. All point to "a quiet man, universally liked and with the gift of discretion; compassionate, stern and fair-minded in just the right mix. Decency was the fulcrum around which he based his POW life." A fellow prisoner and physician would say, "I regarded him as one of the best medical officers I had anything to do with. I just found him an honest, decent fellow who was out to do whatever he could do to help people. Most of the doctors were good, John was outstanding." Another fellow prisoner comments, "A great officer. He wasn't a demanding type of person, but had an ability to get things done."

Unlike his father, whose psyche was unraveled by war, John Cade garnered strength from the ordeal. Two major themes are identified. Dealing with both severe physical and mental disorders, "I had ample time to meditate on the possible causes of mental illness." The notion that mental symptoms are somehow anchored in an underlying physical or chemical problem was one John kept coming back to.

As John was aboard ship returning home from Singapore he wrote the following prescient lines to his wife Jean, "I believe this long period of waiting has allowed many of my notions in psychiatry to crystallize and I'm just bursting to put them to the test. If they work out they would

represent a great advance in the knowledge of manic-depressive insanity and primary dementia, (*schizophrenia).*"

A second lasting effect on his persona was ingrained by the barbarity to which he was exposed. "The Jap war machine is the foulest, most soulless thing ever invented by the wickedness of man… it blisters my soul when I dwell on it." The authors suggest this had a lasting impact on John's social demeanor. "He had learned well the survival skill of never allowing emotions to spill over, of not allowing facial expression to betray his thoughts. Controlling one's emotions was a skill needed to stay alive. His deep-seated reserve would confuse some people in the postwar years when trying to assess John Cade."

When John was reunited with Jean and his sons, Jack and David, he was about to turn 34. His wife says, "I could hardly recognize him, he looked dreadful; his knee bones stuck out from the opening in his dressing gown, his nose was just bone and his skin was horrible… he looked as though he'd been starved." Jean reports that, never the less, one of the first things John said was, "I must get busy, I've spent five years away; three and a half as a prisoner of war and I had to look after people with no equipment… I must find something to stop the melancholy."

Part 3: Salt of the Earth

In just over the 80 pages it took to describe John's wartime experience, this part tells the three-year history between Cade's return to work and the publication of his research, *Lithium salts in the treatment of psychotic excitement* (Cade 1949).

The title page sets the tone with two quotations. First, from the 1941 edition of *The Handbook for Mental Health Nurses* stating that prolonged immersion in a warm bath for several days "has a marked effect on maniacal patients." Juxtaposed is John Cade's pithy epigram *On Experimentation*: "For goodness sake don't waste your time elaborating untestable hypotheses. Guessing becomes only a game unless it's a plan of action." (Cade 1951)

With action in mind, John Cade returned to Bundoora Repatriation Hospital, 20 kilometers north of Melbourne, including more than 50 scattered buildings spread over 160 acres and housing 200 repatriated warriors from two world wars.

The family moved into a red brick bungalow for the resident doctor, with a gate through the back fence and a gravel path leading to the hospital. “The doctor’s house was as much a part of the asylum as any of the wards in which the patients lived.”

John’s day was governed by his temperament, manifested in rituals. Two cups of scalding tea for breakfast, mid-morning, lunch, afternoon and dinner, before which he was welcomed home with a glass of sherry, all in parallel with his daily ration of seven cigarettes smoked at strategic intervals. As he strolled the path back and forth from home to hospital he studied the droppings of wildlife, “a self-professed scatological specialist.”

Proximity bred intimacy; patients wandered over to acquaint themselves. “A haphazard trickle of curious and well-meaning men, old and young, offering whatever they thought the young doctor and his family might like.”

In return, “The Cade’s embraced the patients, with all their oddities as an extended family.” The two boys, Jack and David, were especially enamored. “Our friends called Bundoora a loony bin. But to us it was home, the patients our friends. Certainly, we knew they were loopy. But that was certainly in the acceptable range for us.”

In this benevolent environment, “an idea smoldered in John’s broad-gauged mind.” The author’s trace its origin. Cade was a prodigious and punctilious reader who underlined and annotated the books he devoured. First a physician and then a psychiatrist, who kept a stethoscope in his pocket; John’s library was eclectic and included Cameron’s 1945 volume, *Advances in Endocrinology,* (Cameron 1945). Reading about how the thyroid gland’s over and under activity affected body and mind John speculated, “was it possible that an excess of some unknown chemical orbiting your body made you manic – with all its wild elation – and, if so, maybe a deficiency of the same chemical made you depressed.”

“John Cade was a pragmatic man… what could John examine in order to find this imagined substance that caused mania in excess?” There were no modern imaging devices, blood tests were intrusive and hitherto unrewarding, so, like Thudichum years before, John began work with urine.

John set about collecting jars in which to store urine. “We might be able to use them afterwards” he joked with Jean when she protested the cost. Once equipped, John set about

collecting early morning samples from diagnostic cohorts." It was asylum lore, it was the most potent brew… any chemical became concentrated overnight."

Without a laboratory John started work in his garage while he searched for and soon found one in the pantry of a new ward which had hot and cold running water. It became known as "The Shed."

Each patient's urine was decanted into a screw top bottle, numbered and shelved (to Jean's horror) in the family refrigerator. Without any sophisticated equipment to analyze the urine and not knowing what he was looking for John decided to inject the urine into guinea pigs. Some were kept in the Shed, others roamed the house. Son David recalls, "They got a lot of kitchen scraps; I remember Dad, handling one on his left arm and stroking it, they were tame by constant handling. They were good looking, tan, black and white. My favorite was a tan and brown one."

In the Shed "John would gently hold and turn over the guinea pigs and inject the urine into their abdominal cavities… one by one, regardless of diagnosis, they perished and he performed a post mortem on every one." When he had time during the day and each evening after work he returned to the Shed. His wife remembers how secretive, intense and frustrated John became, "He didn't tell me, he didn't tell anyone of us what he was doing. He wanted to work all by himself. He wanted no interruptions at all."

After 18 months John believed that urine from manic patients was more toxic and killed more guinea pigs than from other diagnoses. We now know this was an erroneous conclusion, but it spurred John on to look at both urea and uric acid. When he found that manic urine had no more urea than other diagnoses he turned to uric acid.

John Cade described himself as a "lone wolf" researcher. He was no chemist, but with knowledge gained at Changi and Bundoora, he routinely prepared medications for his patients using basic chemicals. He knew that uric acid was insoluble in water so he added lithium to make lithium urate and also experimented with lithium carbonate. These salts made the guinea pigs restful but alert. Excited he called Jean to share his finding. "These lovable rodents, normally a mass of vibrating muscle and fur, would lie with equanimity on their back, staring with soft eyes at John while he gently prodded them with the stub of his index finger. They seemed alert but they were calm."

After examining John Cade's carefully written records the author's note, "It is virtually impossible to follow his line of reasoning. He was wrong when he concluded that urine from manic patients was more toxic than other urine. He was also probably wrong when he thought the guinea pigs were resting after lithium. It was more likely due to the toxic effects of excessive lithium."

Noting that many of Cade's observations cannot be replicated the authors comment, "so reproducibility, the gold standard for scientific sturdiness is absent." Other mysteries remain, including from where John obtained his lithium, whether relics from an asylum dispensary or a modern drug house. The former seems unlikely since the authors note, "Cade, it seems was completely unaware of these (previous) attempts to use lithium in psychiatric illness." Given that John later experimented with "a Who's Who of the Periodic Table" a modern source is more likely.

Like many curious and creative scientists before him John decided to take lithium (and many other metallic ions) but, "strangely for a man who documented with Swiss precision each injection into his experimental guinea pigs John left no written vestige of the experiments upon himself." What is clear is that these experiments infuriated Jean, fearful of losing a husband and father due to what she saw as "reckless experimentation."

Whatever questions and doubts posterity poses John Cade's experimental enthusiasm and clinical determination made the next step inevitable. "Seemingly without flinching or taking a wavering step he sought out a patient for whom lithium might work its spell."

As the authors note, "John's keen eye did not have to scour the wards to find perspective patients. Manic patients encircled John." His benevolent regard for them is obvious, "For all their eccentricities, their oddness, and the hazy worlds into which they withdrew, John's writing reflects his fondness for them. Not only were they ex-soldiers – an affinity which cut deeper to him than any other – they were men of common, decent cut."

As an aid to lay readers and reminder to mental health professionals of how matters stood in the mid to late 1980s, the authors provide vignettes of four such patients from John Cade's own medical records. This is prelude to an entire nine-page case history of Bill Brand, the first of 10 patients John Cade would treat with lithium. It is a scrupulous, well researched account of Bill's roller coaster of life from late adolescence until his death in May 1950 at the uncertain age of around 45 after just over two years intermittent treatment with lithium, begun in March 1948.

Bill's recorded saga begins at age 19 when, in 1915, he volunteered for service in the First World War, passed as medically fit, and the following year was shipped to England. On board he developed a puzzling illness diagnosed as "cerebrospinal fever," manifesting as "periods of permanent excitement… lacks comprehension… does not remember at all." Bill's months in England were characterized by "a mishmash" of detention in various hospitals… and of "disorganized and petty criminal behavior." Bill was shipped back to Australia in mid-1917 where his mental state was an enigma to doctors who variously labelled him as suffering from dementia, concussion, shell shock (he never served in battle), epilepsy or malingering. He was finally discharged as, "medically unfit and 100 percent disabled" which began a lifetime struggle to obtain an adequate military pension that was perennially frustrated by, "military custom, misplaced medical certitude and the inertia of indifference."

None the less Bill managed to eke out a living and in 1923, at age 27, he married Pearl, a nurturant working class girl, but "despite marriage Bill was a mess." Pearl's best efforts to obtain an adequate pension or tolerate Bill's strange behaviors lasted seven years before she fled.

In the early days of the Second World War, severely depressed and probably delusional, Bill was admitted briefly to the Military Repatriation Hospital where he was diagnosed as "a constitutional psychopath… treatment useless." Not surprisingly, he absconded. The Army's blind and cruel manner of dealing with Bill had not altered one jot over 25 years.

In 1943, in his early 40s, ranting and raving at his parents, the police were called and took him to the Army General Hospital. Obviously manic, he was heavily sedated, diagnosed as a "lunatic" and transferred to Bandoora where he came under John Cade's care. "Bill Brand was a scoundrel in the asylum. He was notorious among the nurses and attendants, and regarded as the most grubby and pesty of patients. They nicknamed him Monkey."

John's oldest sons, Jack and David, developed a close and regular relationship with Monkey and describe him as follows, "He talked quickly, loudly, lots of jokes and puns. He was happy to be with us; we weren't frightened one bit. He talked at times to non-existent people and did so fluently."

Their father's notes record his clinical impressions, "His mental state has remained unchanged over the last two years; excitable, restless and has no power of concentration whatsoever, so

lacking even momentary attention that questions fail to interrupt his flight of ideas. He is dirty and destructive, noisy day and night. A rubbish gatherer and petty pilferer."

John Cade decided to try ECT, in 1946 a primitive and frightening procedure, without anesthesia or muscle relaxants, described in painful detail for lay readers. After nine treatments John wrote, "Remarkable improvement. He is now quiet, clean and tidy in his appearance, well behaved and an excellent and willing worker."

Bill's mental state remained normal for several months and he went home on leave, but quickly relapsed and was readmitted in a manic state. This time he failed to benefit from ECT.

By the start of 1948 Bill Brand had been in and out of a state of mania for close to five years. The remnant of a debilitated human being, Bill was a wreck by the time John Cade resorted to lithium. "There was no hand of convenience to thwart him, nor was there a whiff of an ethics committee to question his wisdom. Nothing could stop John except his conscience. And this, he felt, he had answered."

On March 6, 1948, he noted that Bill's uric acid was extremely high. "John believed from his guinea pig experiments, that he had found evidence implicating uric acid in the state of mania, evidence we now know was false. And, in his mind, he felt that administering lithium to Bill might induce the state of tranquility he had observed in guinea pigs."

In mid-March John, "like a military leader," condensed his thought about Bill as follows, "Bill Brand, age 51, chronic mania of about five years duration. Fair but temporary improvement after ECT two years ago. Since November '46 has completely reverted to his usual state – noisy, restless, untidy and mischievous."

A few days later he went into the Shed to make up a precise solution of lithium citrate to be administered three times daily. He gradually increased the dose, but when, after a few days, Bill commenced vomiting and bed wetting he switched to lithium carbonate and reduced the dose. By the fourth day of treatment Bill was a little quieter and John cautioned Jean not to talk to anyone. In late April Bill was sufficiently improved to move to a less restrictive environment. Within 10 days John was able to write, "Now has appeared perfectly normal to my observation and that of his relatives for over a week. Continues on lithium carbonate 5 grains twice a day."

Bill's metamorphosis was as unpredicted as it was exhilarating. "By the last day of June, Bill Brand, as sane as any man on earth, was allowed brief temporary leave from the asylum. The symptoms that tormented him for over three decades all simply dissolved into the air."

Bill was discharged on "indefinite trial leave on July 9th 1948." This was just under five years after he was admitted to Bundoora and after five weeks of lithium therapy. "Bill, with a stiff breeze at his back unfurled his spinnaker and set sail from the asylum harbor, relieved of his burden of 30 years." He returned to see John in two weeks and continued to do so for the next few months.

Meanwhile John Cade set about treating other long-term mania patients. "All improved to some degree on this fabulous lithium solution and gave satisfaction to John Cade."

Around Christmas 1948 Bill became "excitable and argumentative" after stopping his lithium, unbeknown to John, and on January 30, 1949, he was readmitted to Bundoora as manic as ever. "It was the most bitter disappointment of my life." Bill had remained well on lithium for almost six months and relapsed within a few days or weeks of stopping it. Like so many future patients Bill had been troubled by physical complaints he attributed to the medicine, frustrated and unknowing about the need for compliance, a concept and word that was years away.

Bill was restarted on lithium and returned back to normal in three weeks. He had brief relapses over the next three months after which he "remained well for six months, pottering about the hospital grounds."

John Cade worked alone and in complete isolation on his lithium experiments from 1946 to 1949. He sought no help or advice and wanted no interference. It seems likely that in 1948 he may have mentioned his fledgling work to colleagues at meetings and this may have triggered curiosity and suspicion about his experimental activities. According to his wife he rebuffed all enquiries with a brusque, "I'll let you know when I know."

Early in 1949 John recognized the significance and scope of his discovery and was ready to share it. His historic paper was published in the *Medical Journal of Australia* on September 3, 1949 (Cade, 1949), ironically the 10th anniversary of the outbreak of World War 11 which had long delayed Cade's return to psychiatric practice. The authors of *Finding Sanity* describe its style, content and impact as follows, "It is a four-page wonder. It's scope – of life and death –- is

operatic… it doesn't fall over itself trying to impress; there are no incomprehensible statistics, just simple numbers any primary school student would understand. Cade records the lithium treatment of ten manic patients, each one a story." In time this paper "became celebrated as the journal's most cited paper and for changing the way we think about mental illness."

Within weeks the word spread, letters from colleagues endorsed his findings with reports of their own and his fellow psychiatrists "circled *en masse*." Jean was displeased; "Every status-craving psychiatrist sniffed at John's door to snatch their unearned lot." John himself remained, "never susceptible to the false charms."

Meanwhile, Bill Brand remained at Bundoora throughout 1949 until October, the month after publication, when he began to complain of vomiting, "his temper and testing, arguing with John about taking his lithium." A fractious relationship lasted for several months until John gave in, hoping Bill might remain less manic, but free of physical distress. Within two weeks Bill's relapse was complete, back to "his best manic manner and old quarrelsome self." John responded by restoring lithium in ever increasing amounts until, "By late November, Bill was taking 40 grains thrice daily – what we now know, nearly 70 years later, was a massive dose." When Bill showed no improvement John surmised, "He is either not taking it or quietly rejecting his mixture." At this point John is "the closest we get to seeing John lose control of his meticulously pried-back emotions." Both John Cade and Bill Brand "seem exhausted, and a bit fed up with one another."

Bill was obviously at a maximum dose, not tolerating it well. "His hand shuddered when he raised a cup to his lips and he wobbled as he walked." Bill began refusing food, was despondent and wept. John reluctantly reduced the dose and by the middle of December Bill was much improved and able to leave the hospital, this time not to his parents, who had become alienated after his antics over 30 years, but to a new community placement. After a few weeks he returned to Bandoora in early February, 1950. Later that month John reduced the dose to mitigate side effects and, once again, Bill deteriorated. John noted, sadly philosophical, "under all the circumstances it seems that Bill would be better off as a carefree restless case of mania rather than the dyspeptic little man he looks on adequate lithium." John concludes and underlines his notes, <u>Lithium discontinued.</u>

Between the end of March and mid-May 1950 Bill's mental state deteriorated further and John vacillates, "His state seems as much a menace to life as any possible toxic effects of lithium." On May 12 he prescribes lithium again, ushering in the final act of a year-long tragedy. It made little difference to his mental state and Bill's physical condition deteriorated. "Bill ate almost nothing and his flesh fell away. In his half-demented state, he picked at his skin; infected sores sprang up in crops on his body. His bony wrists and ankles – mere spindles, poking out from beneath his sheet – were wrapped in bandages." Bill sank into a still state, lithium was stopped. Deep into that night he wafted into lost consciousness. Two partial seizures presaged his whole body into a prolonged epileptic convulsion. John, present at Bill's bedside, drew up a syringe of phenobarbitone and injected the contents into whatever meaty spot he could find on Bill's body. The convulsion stilled. In a final attempt to resurrect Bill a feeding tube was inserted into his nostrils and threaded down his gullet. Badly needed nutrition was poured in.

Bill lingered on for 10 days between life and death "until, late in the evening on May 23, 1950, when all trace of life leached away." With tragic irony the Repatriation Board met the month before he died and awarded Bill the maximum pension he spent his life seeking.

A coroner's inquest was held 5 months later on October 26, 1950. "John responded to cross examination with a curt one-page synopsis of Bill Brand's medical history – concise and without any hint of deception." The coroner's report acquitted John of blame concluding, "Death was from bronchopneumonia following lithium poisoning, consequent on treatment with lithium salts, which the state of the deceased warranted."

The author's note, "John, in all of his subsequent writings, never penned a further word about the death of the first man he treated with lithium." None the less the author's note that "Australia's vast land mass supported fewer than a hundred psychiatrists. Like juicy gossip in a small town, news of death from an experimental treatment didn't take long to sweep through to every psychiatrist."

Post hoc word of mouth came too late to avoid two other lithium related deaths due to lithium toxicity before Bill died that "John must have known of." Each psychiatrist had read John's paper and followed the treatment protocol and list of side effects he published. One was a female patient in her late 50s who had developed side effects within a day of starting treatment. "Lithium was

stopped and 2 days later she died following seizures and coma." The other death occurred at a hospital whose Superintendent was a close friend and alumni colleague of Cade. One of his psychiatrists, who was an avid prescriber of lithium, had a male patient with a 15-year history of mania who, "Initially did well on lithium but then developed the classical symptoms of toxicity and died."

Part 4: After the face, the hands reveal the most.

This part, of equal 80-page length, places John Cade, the person, and the lithium ion in the broader context of a life's work including his clinical, administrative and educational accomplishments, as well as his Catholic faith and opinions about psychoanalysis. It also describes research by others that would make lithium safer to use as well as the impact of the discovery of lithium for prophylaxis, stifling repetitive episodes of bipolar disorder. Both of these events would vastly expand the scope and significance of lithium, drawing Cade back to center stage in the lithium saga.

Each of these facets add color and dimension to the portrait the authors paint of Cade and his persona, casting further light on ancient enigmas.

John's discovery garnered tangible recognition and rewards, paradoxically shifting his focus from lithium and research to clinical and administrative matters. In 1950, the year after his discovery, John was promoted to become Superintendent of Bundoora Mental Hospital. He was also invited to give the twin Beattie Smith lectures, "An outstanding distinction for a young psychiatrist, placing his name before the general public. From that point onward, the name of John Cade was a staple in the Melbourne media."

Demonstrating his legendary "equanimity under pressure" – the Osler ideal – John stifled any nervous qualms about the lectures, "never a gossip or blabbermouth" as Jean described him. To the surprise and displeasure of Melbourne's psychoanalytic establishment John launched into announcing his belief that, "Freudian psychology has cast a blight upon the minds of men that will last perhaps fifty years." Then, after disparaging the idea that schizophrenia was caused by faulty upbringing, he taunted his smug colleagues by adding, "I may remark in passing that the offspring of psychiatrists and psychologists have not yet achieved a reputation for outstanding stability."

Years later Russell Meares, an eminent Professor of Psychiatry, recalled how his father, also a psychiatrist, heard and remembered John's speech. "The psychoanalysts in the audience looked upwards towards the ceiling embarrassed, they groaned and smirked a bit and covered their mouths with their hands, as if somehow trying to expel their distaste of the criticism of Freud. My father put it down to Cade's Catholicism."

Catholicism was indeed a deeply ingrained and silently protected creed from childhood on at a time, in the 1950s, when the Church was "ill at ease with psychiatry; uneasy that psychiatry had no need for sin or to call for a higher power and fear that Freudian ideas might undermine and usurp the Catholic way of understanding humanity." Deeply religious, "John attended Church on Sunday with the precision of an atomic clock." "John's idea that mental illness should be seen as a branch of medicine with a chemical basis" was far more acceptable than "some jiggery-pokery world of Freudian fantasies."

Alongside this bold assertion of faith was John's humility about his research ability. "I might kindly describe myself as an enthusiastic amateur, full of curiosity, with a fair determination, golden opportunities, inadequate knowledge and woeful technique. But even a small boy, fishing after school in a muddy pond with a string and a bent pin, occasionally hauls forth a handsome fish." To this delightful metaphor Jean, his most ardent supporter, added her caustic opinion that "John was not even a researcher's bootlace."

Overall John's discovery and public approval of his lectures led rapidly to further promotion. In 1952 he was appointed Superintendent of Royal Park Mental Hospital in the heart of Melbourne, the city's only receiving house for newly diagnosed mentally ill men and women. "It was a dramatic elevation in status and profile."

The timing and circumstances of John' transition from Bundoora to Royal Park brought pain and challenges. Some of the inmates at Bundoora were men of the 2/9th Field Ambulance and many others survivors of two world wars. Jean recalls, "He loved his men at Bundoora. He really loved them and they loved him. They were all ex-servicemen."

Five days before he took up his new job in July 1952 another death from lithium toxicity occurred. The psychiatrist's report to the inquest noted "She was given not more than the dose (of

lithium) found to have been safe in many hundreds of patients who have been treated in many mental hospitals."

But larger concerns were abroad during the prelude to John's new job. "Melbourne was a political and social powder keg in the early 1950's. Discord was rife within psychiatry, just as within the universities and political parties… in 1948 and again in 1950 major reports slammed the administration and poor conditions of Victoria's mental hospitals." John's psychiatric mentor, also a devout Catholic, had been scapegoated and the consequence of this upheaval was the recruitment of a brilliant and innovative psychiatrist from Britain as Chairman of a newly created Mental Hygiene Authority to clean up the mess.

Eric Cunningham Dax, had pioneered work on ECT and lobotomy in the 1930's and early 40s before studying the relationship between art and psychosis at the Maudsley Hospital in London and then moving on to become Superintendent in 1946 of Netherne Asylum in Surrey where he pioneered art therapy in mental illness, assembling one of the largest collections of patient art in the world. It is now housed at the Dax Center in Parkville, Victoria, dedicated to the study of the mind, mental well-being, mental illness and trauma.

In Australia Dax pioneered the development of community mental health centers and lobbied successfully to create the first Chair of Psychiatry at Melbourne University in 1963. From 1969 to 1978 he was Co-coordinator of Community Health Services in Tasmania and on retirement became a Senior Associate in Medical History at the University of Melbourne until dying at the age of 100 in 2006.

The authors record Dax's impact on Australian psychiatry and his relationship with John Cade. "He was an imposing man of supreme erudition and lofty manner, who confessed on occasion, to being overbearing to get the task done. A princely Dax arrived in Melbourne in December 1951… with gusto he set about the task of reforming a malnourished medical service ...he brought a banquet of new ideas with which he was about to enrich Melbourne."

When Dax turned his attention to John Cade's new domain he considered Melbourne's premier psychiatric hospital to be "no better than a second class boarding house, quite unfit to receive early cases of the mentally ill."

At this point in Australian history, citizens proud of their accomplishments had a thin-skinned sensitivity to talent from overseas and John, who had a humane and impeccable record at Bandoora must have felt justifiably upset, so it is not surprising that "after a respectful beginning this was a rocky relationship."

"Saturated with clinical and administrative duties he had little time for medical research." Insulin coma was in vogue for schizophrenia and John understandably banned the use of lithium, concerned about his own experience with Bill and continuing reports of deaths due to toxicity using the protocol he had devised. Coincidentally in 1950, the year after Cade published his findings, lithium was banned by the FDA in America as a "toxic poison" due to deaths among patients with heart disease who took lithium as a salt substitute.

As befits his obsessional personality John "emphasized regular routines and the highest of clinical standards" and he was probably a better than average administrator although he expressed "a disdain of bureaucracy for the minutiae of administration and its bloated constipated rituals."

It is a gift to posterity and our understanding of events concerning lithium that the authors interrupt the story of Cade's career at this point to introduce the accomplishments of Eduard Michel Trautner, an unusual and remarkable character "who changed everything and kept afloat John Cade's discovery… it is quite possible that lithium treatments would have died a natural death if it hadn't been for this exotic figure… 'Trautie' is the forgotten hero of the lithium story."

Catholic by birth but an atheist by choice, Trautner served in the German Army during the First World War before studying medicine in Berlin with a particular interest in homosexuality. "Detesting Hitler and fearing fascism" he escaped to Spain and then to England where he was rounded up as an "enemy alien and potential spy". At Winston Churchill's instigation Trautner and 2,000 other men, "a hotchpotch of England's rejects were forced aboard the liner *Dunera* and shipped to Sydney Australia in mid-1940 in much the same way as convicts in the first half of the 19th century."

Aged 50 he was placed in an internment camp from where he was rescued by a Professor of Physiology at Melbourne University who "had a talent for collecting strays with scientific talent." Within weeks of reading Cade's 1949 paper Trautner joined forces with a psychiatrist, Charlie Noack, and began a systematic study of lithium effects and toxicity developing a method to

measure blood levels in patients at Mont Park Hospital. “John Cade had little to do with this paper. Trautner did communicate with John but their relationship was a difficult one.”

In 1952, Trautner and Noack were joined by Sam Gershon, a refugee from Poland and a second-year resident in psychiatry who had also read Cade’s paper as a student. Encouraged by his supervisor at Prince Alfred Hospital he transferred to Royal Park hoping to work with lithium in John Cade’s department. He was disappointed. There is no written record by Cade, but “there is a sense that he was, from the start, irritated by the youthful bustle of Gershon. On the one hand, Gershon was an outgoing, overtly ambitious man on the rise; John was a man of formality and reserve.” Gershon’s own reflection affirms this picture, “we had a highly formal and slightly hostile relationship… John didn’t want anything to do with lithium; he’d banned it, he didn’t want to hear about it.” The authors found confirmation for Cade’s behavior at this time from two independent sources. A junior doctor at Royal Park and roommate for Sam, as well as a lecture at the University of Melbourne by the professor who recruited Trautner and sponsored his work. He recalled that “Cade had dropped lithium like a hot potato.” Cade’s oldest son, Jack, also supports this conclusion, “He was a busy clinician and administrator… I don’t think he felt a need to be at the front. He felt he had done what he could and left the rest to others with more research skill. He was always curious about what caused schizophrenia. He left lithium for a while looking for something similar in schizophrenia.”

On this matter there is no direct evidence from Cade himself or any other historian, but “there can be little genuine doubt that John was troubled by lithium. The real question is did he lose faith in it altogether?”

Fortunately for the future of lithium Sam Gershon was undeterred by Cade’s demeanor and decision to ban its use. He turned instead to Trautner with whom he formed “a close professional and personal relationship.” Sam’s wife, Lisl, paints a vivid picture of their friend. “He was his own person; he didn’t care about convention or what people thought of him. He was a jovial person, a bon vivant. Very European, cosmopolitan. He was devoted to science but also devoted to living… and he looked like Yoda from Star Wars.”

One can imagine how such a person might be anathema to a button-downed formal person like Cade, more akin to the Melbourne stereotype in the 50s described by Lisl as "very British, very white, very pink, very WASP, it was so boring." (Except John was a Catholic).

Trautner, "rose like a comet that lit up the Melbourne skies. His thick, heavily accented voice exposed with every syllable his Germanic background, in a Country reeling with post-war Teutonic sensitivities about the enemy." So Trautner, in defense, anglicized his name from Eduard to Edward. This might not have inured John Cade from his opinion of this extroverted atheist, a libertine, exported from England as a suspected Nazi sympathizer. John who hated war and what it had done to his father and his beloved comrades in the 2/9th Field Ambulance might be forgiven a xenophobic thought or two toward the Trautner-Gershon team he never expressed publicly, but who others viewed as "an odd pairing – a non-Jewish German radical and a Polish born Jewish Australian."

This "mentor and acolyte labored on lithium's mysteries during the 1950s… by the end of 1952 Gershon had left Royal Park and was working at Ballarat Mental Hospital." Sam describes his work there, "Ballarat was a hospital of near 1000 patients. There was one psychiatric Superintendent who spent all his time locked in his office… the hospital was like a Gulag… I could do what I liked up there… I'd take the samples of blood for testing lithium levels down to Melbourne." In 1952 and early 1953 there were three deaths at Ballarat that coroner's certified as due to lithium toxicity. Sam does not remember the details, but the authors believe John Cade "would have known immediately about those deaths." The impact of John's views about lithium and the team working on it is not known, but he was painfully distracted at this time by a life-threatening illness to his 14-year-old son Jack, a sequel to an earlier death of an infant daughter Mary. Mercifully Jack recovered fully, possibly due to the discovery of a new drug, cortisone.

As 1954 dawned John was faced with a new challenge. In January Dax planned for him to make a six-month paid tour of Britain to study current psychiatric practices in several leading mental hospitals, including Netherne and the Maudsley. Dax made all the arrangements and agreed John could take his wife, "but you'll have to pay for her yourself."

The couple were housed in a hotel south of London from where John commuted by bus, first to Netherne to absorb Dax's accomplishments and then to the Maudsley, the epicenter of European

excellence under the leadership of Aubrey Lewis and Michael Shepherd. There is no written record of John's impressions of the Maudsley. Aubrey Lewis did his doctoral thesis on Aboriginal culture (Goldberg and Blackwell 2014), and John's son Peter describes his father's interest in an Aboriginal community close to their vacation home as well as his hobby of making boomerangs. Whether they discussed lithium is unknown, but the authors cite Aubrey's belief, presumably expressed in the 1960s, that lithium was "dangerous nonsense."

John fell sick with pneumonia in May 1952, was hospitalized, and he and Jean returned home soon afterwards. John discovered meanwhile that Dax had begun instituting significant changes towards modernizing mental health care throughout the state of Victoria, including Royal Park, its flagship hospital. Among them were "a new occupational health center, an entertainment center and laboratories to conduct research. Strait jackets were given short-shrift and disappeared into a museum."

No doubt Dax and Cade shared the goals and ideals underpinning these "massive changes," but while both men liked to be in command their styles differed and temperaments clashed. "John's admirers called him formal, his detractor's rigid."

Dax's opinion tilted towards the latter as his recorded observations indicate. "Cade ran Royal Park in the same way things were done in the army. He'd come in at 8 am. I'm sure he expected everyone to stand at attention… Cade turned up at the right time. He was always at meetings. He had his notes and his reports… I'd put the buildings there and left him to manage them. I was overbearing perhaps; Cade had to fall in with it… well he was rather rigid… a person who had high standards and very good Catholic principles… he worked conscientiously around the day. He could always be relied upon… he was a very good rigid administrator."

As John labored to transform Royal Park, research on lithium continued elsewhere. Gershon confirmed John's clinical findings that lithium curbed mania and Trautner's brilliant work using flame spectrophotometry defined the effective and toxic blood levels. "It was the vital breakthrough lithium needed." (Trautner et al.1955).

The use of lithium was reinstituted at Royal Park. The hospital's prescription book from mid-1956 to late 1957 records "eight different doctors writing 27 prescriptions for lithium carbonate over a six-month period… the last recorded lithium death in Victoria was in 1953."

The duo that made these discoveries did not linger in Melbourne. “The enigmatic Trautner remained until the end of the decade, when, like some furtive bush marsupial, he slipped away into the night as mysteriously as he had arrived. The ambitious Sam Gershon, who had a close, almost filial relationship with Trautner, relinquished Australian citizenship and migrated to the United States. He would have more to do with lithium there, and became an evangelist, preaching its virtues to the non-believers until the Americans eventually re-entered the fray – like their entry into both world wars – late.”

In further attempts to define Cade’s persona the authors explored his reading habits and *modus operandi.* They discovered John’s lifelong preoccupation with Conan Doyle’s character Sherlock Holmes and described how he, “unashamedly replicated the methods of Sherlock Holmes in his daily psychiatric work.” In his lectures to medical students he emphasized “The necessity for scrupulous observation” amplified in his publication on *“Physical Signs in Clinical Psychiatry”* (Cade, 1961). He states, giving examples, “After the face the hands reveal most.” To the students these were, “The best lectures on offer,” which Dax “gently deprecated… he taught things in black and white… lectures they would remember for the rest of their lives.”

Testimony to John as a role model is that two of his four sons became medical students. But in contrast to his entertaining pedagogic style, John’s work habits, home and recreational pursuits remained routine and sometimes rigid with fixed rituals. When he dined at his club, “He never bothered with a menu. He knew exactly what he wanted. It was always a dozen oysters and a beer for the doctor.” Before he ate them, he counted them to make sure there were a dozen, “like a boy counting out his marbles on the playground.” If short changed he remonstrated with the waiter. “Everything had a value and honesty, even in the smallest things in life, was a moral to live by.”

The flaws in Cade’s distinctive style of reasoning are revealed in some of the ideas he developed. Characterized by the authors as “elastic curiosity” were his belief that mongolism (Down’s syndrome) was caused by a lack of manganese in the diet of pregnant women because he observed they often stopped drinking tea (Cade 1958). He also proposed that eating fruit with pits (cherries, peaches and apricots) might offer protection against developing schizophrenia (Cade 1956). The authors propose that this is “the same broad-gauged idiosyncratic thinking that led John to lithium.” Cade advocated this alternative to conservative medical research “that played along

lines that were unimaginative and did not strike out to pursue new ideas… this timidity would never lead to new discoveries."

The final chapter in Part 4 deals with Schou's discovery of the prophylactic value of lithium in recurrent bipolar disorder. John was alerted to this by a letter from Schou in late 1963. It was an "intensely personal communication" well in advance of the published research. This became a regular correspondence that blossomed into a relationship "of great warmth", which "rejuvenated John's passion for lithium." "After 15 years of little experimental activity… he looked upon this special metal with refreshed curiosity."

The authors now identify two reasons this vastly expanded indication for lithium use had such a delayed impact on broader use worldwide. The first stumbling block was the United States ban, imposed by the FDA in 1950, which had still not been lifted despite Trautner and Gershon's research. Getting the FDA to rescind this ban "would be a critical step in Lithium's acceptance worldwide."

Secondly, compounding this obstacle was criticism of Schou's published findings "from the well-respected Mausdley Hospital in England… the authors regarded lithium as a misplaced infatuation with an unproven and dangerous treatment." In the vigorous debate that ensued, "Scientific civility, always a slender thread in world research was now worn thin." (Blackwell 2014).

In exploring this evolution in events, the authors cite two distinguished Australian psychiatrists who trained at the Maudsley. Russell Meares, a resident from 1964 on, notes "It was a curious atmosphere; it was very, very critical and they were very good at ripping people to shreds. People were very careful not to say anything that could be criticized… it was a tightly controlled atmosphere. Aubrey Lewis, of course, was very clever. He'd start asking questions to expose the first deceit if you were presenting to him; it brought some trainees to tears. It was a strangled rigidity and the atmosphere could be one of cruel humiliation."

Brian Davies, the first Professor of Psychiatry appointed to the Chair at Melbourne initiated by Dax states, "They (the Maudsley critics), never used it (lithium) on a patient and followed through and saw the family, they didn't have any clinical experience with lithium. You only have

to do it to one patient and family and it (bipolar disorder) stops. You don't need any bloody clinical trials."

To John Cade this scientific dispute was "all blister and bullshit; he never had much time for British condescension. We imagine he saw this as Changi all over again; the Brits want to take charge and bulldoze lithium. John simply ignored then and their criticisms."

As John waited patiently "further research vindicated him" and John, "with the killer instinct of a prize fighter" wrote to Mogens Schou commenting that he had "K-oed them (the opposition) in the final round… your contribution has been proven so convincingly that the whole world must be persuaded."

"All that was needed now was for the FDA to lift their 24-year ban on lithium. At the end of the 1960s John was living a comfortable middle-class life. He had his family, the well-worn routine of the hospital and was respected within and outside psychiatry. Lithium was increasingly accepted around the world and was helping revolutionize mental health care. John expected, indeed wanted, little else."

Part 5: Even the Dogs were Barking Lithium

On July 4, 1969, John Cade received a letter from the United States to learn he had been awarded *The Taylor Manor Psychiatric Award* and was invited to tell the story of lithium discovery at a Baltimore symposium in April 1970. "More than a dozen eminent scientists and clinicians, including John, would have the opportunity to tell their stories of discovery in their own words. If there was a single moment when John Cade was catapulted form obscure doctor, who looked like a suburban bank manager, to world fame it was this moment."

John Cade became the object of instantaneous media and public interest, invited to provide his opinions about the treatment of mental illness and his discovery of lithium. In an interview with *Women's Weekly* he told the story of Bill Brand, his first patient, who, the magazine reported, "remained normal the rest of his life." In order to explain this falsehood, the authors entertain a

variety of possibilities. Perhaps "reluctance to tarnish a glowing story or to detract from the American award. Perhaps he was never asked what happened to Bill or the journalist glossed over his fate. John felt the evidence was now so overwhelming in favor of lithium it might do more harm than good to elaborate. So, as has happened before, and would do so in the future, the fate of John's first patient was never revealed in a public interview."

John had apparently been told that President Nixon might attend the award ceremony, but this failed to occur for a bizarre and ironic reason. The contemporary Apollo 13 mission, returning from the moon, experienced an explosion in a liquid oxygen tank and, "the impotent spacecraft dangled in space. The astronauts and the mission were saved when canisters of lithium hydroxide converted the rising toxic levels of carbon dioxide to lithium carbonate."

As John delivered his speech *Time Magazine* announced that the FDA had approved lithium for treatment of the manic phase of bipolar disorder. After the conference the Pope's delegate to the United States hosted the Award ceremony and presented John with his award. "This must have been the sweetest of sounds to the ears of John Cade, the Catholic."

After the Baltimore conference John flew to Denmark to meet Schou. Four years later, in 1974 they shared the Kittay Award, "the world's richest prize in psychiatry." Two years later John received the *Order of Australia* "a newly minted award that replaced the antiquated British Honors system."

"John had grown more comfortable with his celebrity and now enjoyed every lick of it." He was inundated with letters from grateful patients, strangers who had benefited from lithium and accolades from colleagues and former students."

In 1977, at age 75, he retired after a quarter century as Superintendent of Park Royal Hospital. He would live in placid contented retirement for another five years until his health deteriorated rapidly beginning in March, 1980.

In quick succession, starting with cataract surgery, he suffered a ruptured appendix, time in intensive care and then a hemi-colectomy for cancer. In early September he was diagnosed with cancer of the esophagus, too disseminated for surgery.

"Undaunted by mortality, John set about the task of dying as he had lived: organized and not fussing, tidying up what needed tidying." In mid-November, eight short months after his first illness, he was admitted to intensive care and died the next day.

Commentary

This review covers much material in which I was personally involved. During the author's elegant telling I have refrained from commentary, letting John Cade's life tell its own unique and scientifically significant tale. My involvement and opinions are offered in four short reflections.

Melbourne, the Maudsley and Money

A covert but understandable animus towards the Maudsley is discernable in *Finding Sanity* to which I feel compelled to loyally respond. I confine these remarks to personal matters, but urge readers to seek further enlightenment from three sources: a full biography of Sir Aubrey Lewis (Goldberg, Blackwell and Taylor 2015), a brief account of his contributions to psychopharmacology (Blackwell and Goldberg 2015) and a lengthy historical review of the entire Lithium controversy (Blackwell 2014). recapitulated in Chapter 12.

Brian Davies was senior registrar in 1962 on my first rotation at the Bethlem Royal Hospital. He was a benevolent supervisor of my flawed beginnings as a psychiatrist, supportive of my early work on the MAOI and cheese interaction and coach for my first presentation to Aubrey Lewis – a woman with myoclonus epilepsy, misdiagnosed as hysteria. Inevitably Aubrey's first question hit the bull's eye, "Had I read the recent Japanese literature?" Of course not!

So, the next day I went to see Miss Marshal, Aubery's guardian at the gate to his inner sanctum, and retrieved the Japanese journal he had taken from the library so Brian and I could cite the article in the paper we wrote on the psychiatric aspects of myoclonus epilepsy (Blackwell and Davies 1964). By the time it was published I believe Brian must have been in Melbourne.

Russell Meares, who was two years behind me as a registrar at the Maudsley, was certainly present at the Saturday morning Journal Club when a fellow Australian delivered a highly unusual come-uppance to his inquisitor. George Palmai was a rough-hewn Aussie, a former wrestling

champion at the national level and former research fellow on an Antarctic expedition where he studied diurnal rhythms. My fellow resident David Taylor and I befriended George, a lonely bachelor, and welcomed him into our homes, catering to a gargantuan omnivorous appetite. In return, George invited me to co-author two articles we published. One was on the diurnal rhythm in salivary secretion which was reversed in melancholia and reverted to normal after ECT (Palmai and Blackwell 1967). The second reported on the centennial of Bleuler's Burgholzi Clinic in Zurich (Palmai and Blackwell 1966).

The Burgholzli Centenial was the topic of George's journal club, about which George was palpably anxious. Facing his interrogator George finally got to the point where he spoke about Bleuler's feelings on this prestigious occasion. Aubrey Lewis pounced. "How could you possibly know how Bleuler felt?" George hesitated before he explained; he had flown to Zurich at his own expense and personally interviewed Bleuler in German, a language George was fluent in. Of course, this speaks to the other side of the coin – the lengths to which trainees sometimes went to gain the heights they were expected to achieve and the skills they hoped to learn.

George's innovative method of measuring salivary flow demonstrated how a diurnal biological rhythm was reversed in melancholia and could be returned to normal by a physical treatment. Later in my career I would use this methodology to study the anticholinergic effects of different tricyclic antidepressants (Blackwell et al. 1972) and also to demonstrate that their benefit in enuresis was due to the immediate anticholinergic effect of the first dose and not to a delayed antidepressant action. Sadly, George Palmai never knew of this or received credit. He had returned to Australia where he ended his own life for reasons unknown to me.

It is true, as Russell Meare's suggests, Aubrey Lewis set the bar high and his teaching style was demanding and rigorous, as befit the premier training institution in Europe at that time. But it is a travesty to imply that these standards were intended to demean or humiliate trainees rather than create expectations appropriate to the goal of graduating psychiatrists with the knowledge and skills, sufficiently mature and self-possessed, to take their place as Chairs of academic departments, outstanding clinicians and leading researchers. This Aubrey accomplished and for that earned a knighthood.

When I completed my time with Lindford Rees and Brian Davies at the Bethlem Royal Hospital I was promoted to the Professorial Unit at the Maudsley, doomed to wear a white coat for six months under the eagle eye of Sir Aubrey. I found him an empathic and inspiring mentor, teaching a Meyerian approach to care that included social, psychological and biological components within an empirical framework. When first seen as outpatients, people were required to bring a relative or significant other with them who was interviewed separately to provide a broad perspective.

Aubrey had an encyclopedic knowledge of the literature. After I published my first report of interactions between cheese and MAOI antidepressants he drew me aside to say that "he thought Hippocrates had something to say about cheese." I found a book about Greek medicine in the library (Brock 1929) and, on page 49 read Hippocrates doubts about cheese; "*It is not enough to know that cheese is a bad article of food in that it gives pain to anyone eating it in excess, but what sort of pain, and why, and with what principle in man it disagrees."* This became the preface to my doctoral thesis at Cambridge University, itself the product of Aubrey Lewis inviting me to take a two-year training fellowship in pharmacology under Ted Marley.

On the question of lithium, suffice to say Shepherd, Lewis and lowly Blackwell were indeed skeptical, themselves entirely innocent of any use of the metallic ion and especially the unique and novel concept of prophylaxis. But psychiatry was susceptible to therapeutic myths that the Maudsley was willing and equipped to skewer. There is no better example than the international delusion that insulin coma sometimes cured schizophrenia, until Maudsley research showed it didn't. And chlorpromazine arrived.

Brian Davies was correct. The efficacy of lithium, like all the first psychotropic drugs, was immediately apparent to skilled clinicians, without the need for statistics. But by mid-century a world weary of placebos, panaceas, snake oil and thalidomide was wary of enthusiastic endorsements and serious side effects, demanding scientific proof of safety and efficacy.

Often this delayed approval. In the case of lithium and mania, it meant an anguished ban imposed by Cade on a toxic element even though it could be accurately measured. With Schou and prophylaxis it meant a three-year hiatus until four UK hospitals proved the case with a double blind placebo controlled trial Schou had deemed unethical (Coppen et al. 1971).

Nothing, however, excuses the quarter century delay by the FDA in approving lithium, first for acute mania and then prophylaxis of recurrent mania. However, they remained obdurate in approving prophylaxis in recurrent bipolar disorder including depressive episodes. This was enabled by the fact lithium, a natural substance, was not patentable and therefore unprofitable. Instead a creative pharmaceutical industry synthesized lucrative alternative and marketed them as "mood stabilizers," never tested against lithium. Clearly the FDA was complicit in delaying approval of lithium and protecting the lucrative endeavors of the industry it was legislated to oversee (Ch.19).

More recently objectivity was further impaired by Congress passing the *Prescriber User Fee Act* requiring the FDA to charge drug companies fees for marketing approval, amounting to half the FDA's annual budget (Angel 2004). The fox was now guarding the hen house (Blackwell 2016).

Experience suggests that increasing amounts of mood stabilizers are being prescribed and that the appropriate and safe use of lithium is declining (Shorter 2009).

Cade, Shepherd, Sherlock Holmes and Freud

Five years after Cade's death and shortly before his own, Michael Shepherd, nicknamed *The Hammer of Psychoanalysis,* published a slim 30-page volume with the title, *Sherlock Holmes and the Case of Dr. Freud* (Shepherd 1985).

I was intrigued; John Cade had hated Freud but worshipped Sherlock Holmes. At the Baltimore Conference where Cade presented the account of his discovery I gave an opening talk on *The Process of Discovery* (Blackwell 1970), an up-to- date review of the world literature which included research on the cognitive styles of scientists who made discoveries. I didn't think Cade fit the profile and wondered if Shepherd's book might cast light.

Both Sherlock and Sigmund had a similar deductive style: the elicitation of sparse facts to prove a general statement. This contrasts with the scientific inductive style where a general law is inferred from many particular instances produced by systematic research, testing a hypothesis.

A review (Koch, 2016), explains the deductive style that Shepherd identifies in both Holmes and Freud. "It compares the pseudo-logic deductive method of drawing sweeping conclusions from

tiny and trivial clues of Sherlock Holmes to Sigmund Freud's analytical method of inferring something about the patient's motivations from slips of the tongue, dreams and other refuse of the mind. What Holmes decries as "absurdly simple" is "simply absurd.

"Shepherd argues that the enormous success of both the fictitious detective and the very real doctor are mythological representations of human archetypes."

I realized that the deductive style of reasoning that John taught to students was what led him to his strange, unlikely and unproven hypotheses about the etiology of Down's syndrome and Schizophrenia. What Shepherd does not discuss is the possibility that one person might be capable of using each style to meet different needs.

From childhood John had been a collector and classifier of things, a trait which might be the seedbed of inductive reasoning. But did this lead to a creative insight and a general law? I felt John gave no evidence of this. Rather he was firmly embedded, lifelong, in rigid obsessional behaviors and ways of thinking.

How then to explain his discovery? I speculate that the answer may lie in a conjunction of Pasteur's aphorism that "chance favors the prepared mind" (Vallery-Radot 1924) and John's compulsivity. The latter endowed him with the determination and energy to pursue his single-minded goal despite errors of observation and inference that no one could replicate.

This may be the best example of serendipity in the literature; finally discovering one thing by chance while looking with great determination for another.

Ayd, Cade, FDA, the President and the Pope.

In 1970 Frank Ayd became both my friend and mentor when I worked briefly for Merrell Pharmaceutical Company before returning to academia. Together we planned a conference at the Taylor Manor Hospital in Baltimore where Frank worked, on *Discoveries in Biological Psychiatry* to honor and award all the pioneers who made the original discovery in each category of psychotropic medication. Through his international connections in the CINP Frank knew each of them personally. Included was John Cade, who Frank knew both through his discovery of lithium and because they were both devout Catholics. Frank was father to 12 children and had spent time at the Vatican as a guest of Pope Pius XII who he advised on medical and ethical issues, as well

as speaking on Vatican Radio. Frank persuaded the Pope to give an opening address to the First International Congress of CINP, held in Rome in September 1958. The opening was chaired by Aubrey Lewis and Michael Shepherd was present. There was no one from Australia although Brian Davies became the first member after he moved from the Maudsley to the Chair in Melbourne.

Lithium was not on the program and did not appear until 1970, but Mogens Schou was present in 1958 and made the following prescient statement during a general discussion towards the end: "On the therapeutic environment lithium is one of the smaller stars and, until now, it may not even be noticed by all psychiatrists. But its light appears unmistakable, and it may turn out to be steadier than several others of the celestial bodies which shine now so brightly" (Schou, 1998).

In Baltimore Cade gave a polished talk about his own work, mentioned the work of Schou with enthusiasm, but made no mention of Trautner, Noack or Gershon and their research making lithium safe. In my opening talk on discovery I had cited the literature and given examples of younger colleagues denied credit by a dominant senior which Robert Merton called "The Mathew Effect" after a verse in the bible. Cade's talk was next to last on the agenda. He includes brief discussion of his first 10 patients with results he calls "gratifying." He mentions no serious side effects and no deaths. A brief synopsis of Bill Brand is truncated with no mention of his death and ends thus, "A month later he is recorded as completely well, and ready to return to work" (Cade 1970).

The account of the Baltimore Conference in *Finding Sanity* differs from my recollection in one important way. As co-convener with Frank Ayd I never knew of President Nixon's alleged plan to attend the award presentation which was presided over by the Pope's representative. I sense Frank's involvement – the Pope in 1970 was Paul VI – convener of the last three sessions of Vatican 2 and very involved in psychological matters affecting the Church. Given Frank's organizing role and the presence of John Cade, another devout Catholic receiving an award, Nixon might have seen some political value in participating, but requested secrecy. It is true, however, that he did not attend and the reason he gave as attending the Apollo space craft landing does coincide in time.

It is also accurate that the FDA did meet to discuss lithium in April 1970 shortly before the conference. They agreed to approve use of lithium in acute mania, but not prophylaxis for recurrent episodes despite strong advocacy from Gerry Klerman (Shorter 2009).

Themis and Hippocrates

Let us imagine that Themis, Greek Goddess of Justice, blindfolded and holding aloft her scales, with Hippocrates, Father of Medicine, have met to assign credit to the humans who discovered how lithium, one of the earth's three primeval ions might mitigate human suffering.

Themis and Hippocrates, seated on thrones, after diligently studying the evidence, deliver their verdict to a waiting world:

> "*First, we determine the Australians take precedence over Denmark. Evidence suggests that Schou was inspired by Cade, not by his own ancestors, although he deserves credit for prophylaxis, a far broader and significant indication. (If only the British would not disparage it and the Americans would give it full credit and demonstrate its superiority to more expensive 'mood stabilizers.)*
>
> *"Among the Australians, Cade, Trautner and Gershon we yield to the principle and precedent of 'first do no harm'. Cade troubles us for two reasons. First, he never gave credit to Trautner and Gershon for reasons buried in his psyche, but, more seriously, he concealed the deaths due to toxicity, including his first patient. Evidence indicates he 'dropped lithium like a hot potato' when its toxicity threatened his reputation and only picked it up again when safety was ensured and its indications expanded.*
>
> *"Between Trautner and Gershon our choice is hard. Trautner was the true innovator, but left before the story was fully told. Gershon on the other hand became a persistent, lifelong, advocate for lithium in America and certainly deserves equal or greater credit.*
>
> *"Taking all this into consideration we believe Trautner and Gershon equally deserve primary credit for the safety and utility of lithium overall while Cade*

and Schou deserve separate credit for discovering the primary use of lithium in acute mania and prophylaxis in recurrent mania and bipolar disorder."

Having delivered their verdict, the judges relinquished their thrones, turned towards Mount Olympus, and headed for home. Themis removed her blindfold and glanced towards Hippocrates who was clearly distressed. Enquiring for the cause he reveals a preference for Schou over Cade because he believes the Scandinavian to be a superior scientist and better man.

The two pause to consider and discuss this turn of events. Themis reminds Hippocrates that, in matters of science, justice is blind to issues of creed, culture and character. The verdict is just and must stand. Hippocrates concedes without demur and the couple resumes their journey. Themis places a consoling hand on Hippocrates shoulder as they slowly disappear into the clouds that shroud Mount Olympus.

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Chapter 6

Chlorpromazine Arrives

Jean Delay

Jean Delay is perhaps best remembered for the discovery of Chlorpromazine, the first effective drug for the treatment resistant psychotic men and women who filled the world's asylums up until the mid twentieth century. Compared to Delay's other scientific and literary accomplishments, as told in Driss Moussai's biography below, his role in this discovery was largely conceptual and clinically modest, but as was customary in hierarchical French academia, Delay's name came first on scientific publications.

The clinical work was conducted by Pierre Deniker and an intern in his department, J.M. Harl, who died prematurely in a mountain climbing accident. Deniker described the early work in detail (Deniker, 1970) when he received the Taylor Manor Award for the discovery and presented his paper, "*Introduction of Neuroleptic Chemotherapy."*

"Logically a new drug was tried in cases resistant to all existing therapies. We had scarcely treated 10 patients - with all due respect to fervent adherents of statistics - when our conviction proved correct. It was supported by the sudden, great interest of nursing personnel, who had always been reserved about innovations."

When the first paper was presented to the French Medico-Psychological Society at a meeting on shock or sleep therapy the effect was described as "neuroleptic" – effecting the neuron - in cases of "manic excitation, and more generally, psychotic patients who were often resistant to shock or sleep therapy." The specific effects were noted on "agitation, aggressiveness and delusive conditions of schizophrenia which improved. Contact with patients could be re-established, but deficiency symptoms did not change markedly."

When six definitive papers were published between May and June 1952 these observations had been made on only 38 patients without any attempt at controlled design (Delay, Deniker and Harl 1952). The first controlled trial was by Joel Elkes in England (Ch.3). Within five years the drug was in use worldwide with the exception of America, where psychoanalysis still held sway. The phenomenon of "deinstitutionalization" had not yet taken place, but its relative failure might

have been predicted by Deniker's prescient observation that these drugs "failed to benefit deficiency symptoms," those most necessary for survival in community.

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A Biography of Jean Delay byDriss Moussaoui

Excerpta Medica Publications, a division of Elsevier Science, 2002

This short volume of 112 pages plus references, eight illustrations and index is high in impact and contemporary relevance. It was authored by Driss Moussaoui, Chairman of the Rushd University Centre in Casablanca, Morocco, whilst he was Secretary for Meetings of the World Psychiatric Association (WPA) from 1996 to 2002. Its stated purpose is threefold: first, to eulogize outstanding pioneers of the WPA, this is the initial volume in a proposed series; secondly, to pay tribute to the man who for 27 years was in charge of Psychiatry at the University of Paris, a close collaborator of Pierre Pichot and Pierre Deniker who mentored Driss as a young foreign medical graduate studying psychiatry in France; and finally, as a tribute to Jean Delay's unique contribution in founding a world renowned academic program that played a leading role in French and international psychiatry and initiated a worldwide neuropsychopharmacology revolution with the discovery of chlorpromazine in 1952. Dr. Moussaoui's devotion to this task is further illustrated by his initiation of the Jean Delay Prize (the largest in psychiatry) for work that "best helps to bridge the gap between biological and psychosocial aspects of psychiatry," a goal that reflects its namesake's devotion to integrating all aspects of our field.

From this reviewer's perspective, an added virtue of this biography is that describing the persona, life challenges and career accomplishments of this remarkable man may serve as an inspiring role model for neuroscientists of all disciplines and cultures, at a difficult time in the evolution of neuropsychopharmacology.

This book has a novel and creative format; its nine chapters are thematic rather than strictly chronological. They portray the professional and personal man with his associations and accomplishments in both the medical and literary domains, including his family, friends, and colleagues, other sectors of psychiatry, as well as major societies and organizations. This mosaic creates a cohesive whole, which the author describes as "a rambling harvest" and, while there are occasional repetitions, these are never redundant.

An overarching metaphor, presented by Delay in the book's prefatory quotation and limned by Juan Jose Lopez-Ibor (President of the WPA) in a preamble, is the mythological two-faced image of Janus; integrating science and literature across a palate that blends the social, psychological and biological components of psychiatry, in both its academic and community settings.

The text begins by describing Delay's origins in the medieval Basque city of Bayonne, born of a father who was a successful surgeon, and who, eager for the son to follow in his footsteps, disparaged Jean's fledgling literary talents and ignored his innate clumsiness. Delay's mother, on the other hand, was a nurturing, sensitive, and affirmative influence on her only child.

All Jean's early pursuits and games were intellectual; he had an exceptional memory, was academically precocious and gained a baccalaureate in philosophy at age 14 with a thesis on "The relationship between the physical and moral." The following year, he entered the faculty of medicine in Paris and aced the competitive exam to become a hospital clerk, at age 18. His choice of psychiatry as a specialty deviated from the norm among top interns (as it does today), while his rejection of surgery (reinforced by hating the sight of blood) upset his father. Instead, leaning to the distaff side of his heritage, he also chose to study aesthetics at the Sorbonne along with his medical, neurological and psychiatric programs. When he graduated with the highest grade in philosophy, his thesis supervisor advised him to "leave medicine and devote yourself to aesthetics." Rejecting this advice, he nevertheless, began to write and publish short stories at the age of 20, while an intern at the Salpetriere hospital, under the pseudonym Jean Faurel, a decision based on advice that being recognized as a writer might diminish his reputation as a scientist. But in his personal diary Jean wrote: "My true life, literature; my profession, psychiatry."

At age 31, Jean Delay obtained a Professorship of General Medicine at the Paris faculty and developed an interest in the new field of the EEG. Soon after, in the middle of World War II, he obtained a doctorate in literature, with a thesis on "The Dissolutions of Memory," which Pierre Janet lauded as "a work that reconciles psychiatry and medicine."

In 1942 Jean made his final professional move to become Professor of Medicine (the youngest in France) at the Saint-Anne Hospital and joined the Clinic of Mental Illness and the Brain (CMME). He became Chair in 1946 (age 39) and remained until his retirement from medicine in 1970, at age 63. This timetable and Delay's accomplishments in Paris closely mirror Aubrey Lewis's in London (Ch. 11).including acommittment to aclinical model integrating the socil, psychological and biological components. This was the environment in which he created his major goals, beginning with a hospital which was still a virtual asylum, and turning it, over the next 24 years, into a multi-disciplinary academic team and program with laboratories in all the disciplines related to psychiatry, unique and exceptional in France. The CMME became a magnet for the best young doctors from around the world (foreign assistants) many of whom (like Driss Moussaoui) went on to found academic departments in their home countries.

Delay's major colleagues during this period were Pierre Pichot, Pierre Deniker, Raymond Sadoun and Therese Lemperiere. Pichot had dual training in mathematics and psychology, pioneering quantitative psychopathology and behavioral psychotherapy, while co-editing two text books with Jean Delay on Psychology and Psychometric Tests. Pierre Deniker did Trojan work during the war with the French Red Cross, eventually joining the Free French fighting forces and receiving the Croix de Guerre. Subsequently, he participated in the discovery of chlorpromazine and co-edited a textbook with Delay on New Medications in Psychiatry. Therese Lemperiere was the woman on Delay's team, devoting most of her time on a women's unit and her special interest in hysteria. Raymond Sadoun was a prominent member of the team in the mid and later years, an expert in epidemiology, who worked closely with WHO.

During his scientific career, Jean Delay published more than 40 books, as well as more than 700 medical articles on every aspect of psychiatry, distributed across national and international journals. Confronted with this massive oeuvre, Driss acknowledges the impossibility of an in-depth review and opts instead to identify Jean Delay's most outstanding contributions.

The first, chronologically, is the First World Congress of Psychiatry in Paris on September 19, 1950. This event is placed in the context of earlier international congresses, dating from 1850, as well as the devastation following the end of the war in 1945. Its multi-national nature is emphasized, with 52 different countries and 35 societies involved, including a planning process that took three years.

Second, in time, but prime in scientific and humanitarian impact, was the discovery of chlorpromazine with Pierre Deniker and J-M Harl, announced to the world in May 1952. The biography presents a compelling portrait of the clinical principles underlying the team's use of the drug and identification of its properties. It was not to potentiate other sedatives for "hibernation," but used alone, it modified cognition, affect and behavior in unique ways when given continuously by mouth or injection, to produce a prolonged action in individually variable amounts (as low as 75 mgs daily) that took several weeks to secure full benefit. The dramatic changes the drug produced in asylum care are elegantly portrayed; from a lifetime of often bedridden squalor, including strait jackets, forced feeding, violent and frequently ineffective "treatments," to the possibility of returning to life in the community. The international network of psychiatrists assembled for the First World Congress (1950) ensured swift dissemination of chlorpromazine's promise and potential to other countries by the time of the Second World Congress (1957), with the notable exception of America, where psychoanalytic hegemony over academic psychiatry still considered drugs as mere adjuncts to psychodynamic therapy.

Jean Delay's third important and most pervasive influence was his conceptual and integrative way of thinking and problem solving that included a bio-psychosocial approach combining all the available knowledge into one paradigm – long before George Engel introduced the model in America.

In summing up Jean Delay's scientific accomplishments, Driss Moussaoui engages in intriguing speculation about why Jean never received the Nobel Prize or Lasker Award for his seminal discovery. True, Deniker, a member of Delay's team did receive the Lasker Award in 1957, shared with Laborit, the French military surgeon who first recognized the unique properties of 4560 RP in pre-operative sedation, ("lytic cocktails") and Heinz Lehmann who introduced chlorpromazine into Canada after his wife translated the French articles. In the 1980s, Driss asked

Deniker which team member was most responsible for the discovery; without hesitation he named Delay.

The Nobel Committee's rationale for failure to award the prize was an alleged lack of an underlying hypothesis to support the mechanism of action of the discovery. However, the Delay team had already postulated that a chemical substance could therapeutically benefit a mental illness with earlier work on isoniazid (INH) and depression, five years before Nathan Kline demonstrated that iproniazid benefited depression through a postulated action on monoamine oxidase – for which he also receive a Lasker Award. Furthermore, Delay's decade long work on the therapeutic action of chemical "shocks" to the diencephalon-hypophyseal system with drugs, including insulin and cardiazole, contrasted with the limited effects of lesser sedative drugs on psychotic patients, supporting Laborit's claim that chlorpromazine was doing something unique and beneficial. Interestingly, Delay spoke of this as not so much a "discovery", but as a "find" -- a nuanced distinction between serendipity (looking for one thing but finding another, as with Cade and lithium), compared to recognizing what is needed and anticipated (as in Pasteur's aphorism; "chance favors the prepared mind").

Moussaoui speculates that the Nobel Committee's real reluctance was due to the "problem of paternity." Too many potential conflicting squabbles for priority, of the kind well- documented in the literature and demonstrated by controversy over Kline's Lasker award for the MAOI discovery.

Due to the success of Jean Delay's entire program during its "Camelot" years, Driss comments: "He reigned supreme over the academic sector in France… his slightest gestures were observed, analyzed, dissected, and interpreted." Undoubtedly, this was facilitated by Jean's multidisciplinary interests and the relationships he developed with key figures in other fields and related programs.

Prime among these was collaboration with the public sector and its uncontested leader, Henry Ey, who never held an academic position, but was head doctor of the Bonneval asylum from 1933 until retirement 37 years later, in 1970. The relationship between these two men was a model of academic-public sector collaboration, each of them prominent and productive in their own domain, both authors of influential textbooks and adherents to a bio-psycho-social model. This

collaboration was still remarkable, given their contrasting personalities. Ey was an extrovert, "go-ahead rarely bothering about protocol," while Delay was an introverted diplomat, "an aristocrat who kissed ladies' hands." But what they also shared was an insatiable desire to serve psychiatry, demonstrated by their crowning accomplishment as joint organizers of the First World Congress of Psychiatry, and subsequently, the World Psychiatric Association.

Delay's relationship with psychoanalysis was more ambiguous and nuanced, "he handled the concepts with great dexterity but he refused all dogmatic excesses and said so in plain language." He included psychoanalysts in his team, but selected those "he knew would serve the patients well." Jacques Lacan was a seminal example. Jean's attempts to synthesize the organic with the dynamic inevitably elicited complaints from both sides of the fence, but he remained determined to integrate complex theoretical positions and take the best from each, remaining undeterred.

Also contributing to Jean Delay's place in the scientific and public limelight was his involvement in various scientific societies. He was the first person to serve twice as President of the WPA (1950, 1957). Other organizations he served as President were the French language Congress of Neurology and Psychiatry (1954), the Societie Medico-Psychologique (1960) and the International Congress of Psychosomatic Medicine (1960). Delay was a founding member of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) and later served as its President (1966). In 1955, he was elected to the National Academy of Medicine at the unusually young age of 48. He attended all its sessions, until 1968, but after turmoil terminated his scientific career, his allegiance shifted to his first love, the *Academie Francaise.*

It was in May 1968 that dramatic events occurred, "a sudden thunderstorm in a clouded sky," ushering in the end of Jean Delay's brilliant career as a clinician, scientist and educator, and with it, the golden era he had created. A national Trotskyist movement erupted, paralyzing France with widespread strikes, student protests, and blocked public transport. Its ideology was anti-authoritarian and profoundly anti-psychiatric. Psychotic and delusional patients were not mentally ill but only "victims of the system," an echo of contemporary Scientology sentiment and radical libertarian ideology. Delay became the prototype of an alleged "contemptible order of mandarins" and 500 people invaded his department, occupied his office and lecture hall, ridiculing his teaching. The students demanded the separation of psychiatry from medicine and its complete

removal from the medical field. Within two years, some of these changes had been implemented and Delay decided to retire, due partly to ill health, but driven by a deep desire to devote himself entirely to his first love, literature.

Whatever relief removal of the scientific burden offered, it should not detract from Jean Delay's remarkable literary accomplishments before, as well as after his retirement. He became a member of the elite *Academie Francaise* in 1959, at the age of 52, when his scientific endeavors were at their peak. The *Academie* is composed of only 40 "immortals," so named as they serve until death. It was founded in 1635 by King Louis XIII and out of 700 members elected since its creation, Jean Delay was the first, and only, psychiatrist to be admitted, but only after an arduous induction ritual, in which each potential candidate must defend his right to fill the vacant seat created by death of the owner, before the surviving 39 members, who take a secret vote based on the humanitarian, personal, and literary talents of the candidate. On election, Jean took the seat once occupied by Louis Pasteur and, upon his own death, it was taken by Jacques Yves Cousteau who, in his acceptance speech, talked of replacing someone who seemed to have been "a phenomenon somewhat like Leonardo da Vinci." By the time Delay was admitted to the *Academie,* he had relinquished his pen name, comfortable that his considerable literary works would not detract from his scientific reputation.

In the biography, Driss Moussaoui offers a detailed dissection of Jean Delay's entire scientific and literary oeuvre (Chapter 7). The two scientific works he highlights are *"Les dereglements de l'humeur"* (Mood Disturbances) and *"Introduction a la medicine psychosomatique* (Introduction to Psychosomatic Medicine). The literary work most contributory to election into the *Academie* was probably his psycho-biography of Andre Gide, *"La jeunessed'Andre Gide."* Out of his total 14 literary books, perhaps the major work, written after his retirement, was *"Avant Memoire,"* a socio-biography of nine generations of a Parisian family, which included his mother, covering three centuries of French society.

Apart from charting Jean Delay's scientific career, Driss also creates a portrait of the person within, reading between the lines of what he wrote, cataloging his considerable literary output, talking with colleagues, family, and friends.

What emerges is a man who created his own success the hard way, in a well-ordered manner, rising at 4 am every day ("20% inspiration, 80% perspiration"). Jean was a humanist, eager to care for and cure his patients, who viewed medicine as both science and art. He possessed a remarkable power of observation, with integrative thinking far ahead of his time and dedicated to bridge-building between people and organizations. Those who knew him best sensed an inner fragility, reserved, anxious and timid, at times, traits partially tamed by an addiction to nicotine and concealed beneath a majestic appearance; haughty on occasion, but devoid of exhibitionism. Jean was also discrete, secretive and uncritical of others in public; a good listener and accomplished communicator, with well-chosen spoken and written words, "A sentence sculptor, he was also a purist who sought perfection in everything." Finally, Jean disliked confrontation, crowds, noise and agitation, as well as driving a car. His cardinal features were a search for synthesis and balance, of justice and service to others.

Those who counted most in Jean Delay's life were four women: his mother, spouse and two daughters, one a psychoanalyst and author, the other with a brilliant career in literature, the first woman in history to follow her father as a member of the *Academie Francaise*.

Apart from family, Delay had many admirers, but few close friends, all carefully chosen and cherished. Most were older and all, even the physicians, had a strong literary bent. His three closest literary friends were all Nobel Laureates in Literature: Roger Martin Du Gard (1937), Francois Mauriac (1952) and Andre Gide (1957). On the medical side, Pierre Janet was also a professor of philosophy (and 50 years older) and Jean Bernard was an essayist and poet, a member of both the Academy of Sciences and *Academie Francaise*.

A reader on the threshold or early stages of a career in neuroscience might reflect on the personal qualities, scientific modus operandi, support systems and research philosophy of Jean Delay. Above all, on his capacity for hard work, integration and collaboration. On a sadder note, it is well to acknowledge the role that a sudden change in the social or scientific zeitgeist can play in shaping and terminating a brilliant career.

In placing all this before his readers in a brief, succinct and enjoyable manner, Driss Moussaoui provides a service to our field and a worthy acknowledgment to his mentors

Chapter 7

Chlorpromazine and Imipramine in Canada

Heinz Lehmann Biography

While chlorpromazine spread around the world it was largely ignored by academic psychiatry in America in thrall with psychoanalysis, a myopia that lasted more than another decade. Instead, it took root and flourished in the State Asylums and Veterans Administration hospitals.

In Canada the drug attracted the interest of Heinz Lehmann, a refugee from Nazi Germany in 1937. Heinz, like Joel Elkes in Britain, educated himself in an asylum setting living on the grounds with his wife, a nurse, and his young son at Verdun Protestant Hospital where he became Medical Director in 1947. He quickly established a reputation in biological research and in 1953 he read a paper in French about chlorpromazine. The following year, with a young colleague, he published the findings, the first in the English language, which earned him the Lasker Award in 1957.

Like the French before him, Heinz was convinced by chlorpromazine's effects on agitated psychotic patients, but he did not introduce the word "anti-psychotic" until three years later. Impressed though he was, Lehmann, like Delay, rejected a simplistic view that drugs alone were adequate treatment, a viewpoint confirmed in the 1960s by the modest results for life in the community after what became known as deinstitutionalization.

In 1961, Lehmann's work attracted the attention of the NIMH in America and he became a lead member of the Early Clinical Drug Evaluation Units (ECDEU) funded by the Federal Government and largely composed of State Hospital and VA Hospital programs. He was joined by Tom Ban, a newly arrived migrant from Communist Hungary and together they embarked on a highly productive collaboration lasting 18 years, publishing 211 scientific articles on almost all of the new drugs discovered by the pharmaceutical industry in the pioneer era.

In 1964, Heinz attended a meeting in Europe where he heard Roland Kuhn describe his discovery of the antidepressant effects of imipramine, the first of the tricyclic compounds that

would replace the monoamine oxidase inhibitors. Proud of his clinical judgement and clear cut results Kuhn shunned doing a controlled study. Returning to Canada and reading the results in German, Heinz fulfilled that need and, as with chlorpromazine, published the first results in North America.

Like Delay, Lehmann experienced a Marxist anti-psychiatric movement in Montreal during the early 1970s, contemporary with the Scientologists in America, which, unlike Delay, he adroitly managed and survived. He continued his productive career until mandatory retirement in 1976 after which he continued to work voluntarily until he became Deputy Commissioner for Research in Mental Health for New York City. Responsible for a budget of $30 million and two research units he was paid a dollar a year, work he continued until his death, mourned by colleagues throughout Canada and the United States.

Heinz Edgar Lehmann's Biography

Heinz Lehmann is the third member of a triumvirate of pioneers whose early work with chlorpromazine set the world stage for an end to centuries of asylum care of people suffering severe and persistent mental illness. In France, Jean Delay's team reported its beneficial effects in *"des etats d'excitation et d'agitation"* (Delay, Deniker and Harl 1952). This effect was confirmed in Britain two years later by Joel Elkes and his wife in an early controlled double blind study on *"chronically active psychotic patients*" (Elkes and Elkes 1954). Canadian psychiatrist Heinz Lehmann provided the first independent confirmation in North America as "*a new inhibiting agent for psychomotor excitation and manic states."* (Lehmann and Hanrahan 1954).

This brief biography of Heinz Lehmann, compiled from multiple personal and published sources, sets the stage by describing the beginnings of the revolution in psychopharmacology, followed by an account of Heinz's early life and persona, leading to an overview of his entire life and career accomplishments as a clinician, educator, researcher and a reluctant but talented administrator.

In the beginning …

In 1937, at age 26, a refugee from Nazi Germany, Heinz Lehmann spent a year at the Montreal Children's Hospital, Canada where he perfected his English before becoming a junior

psychiatrist at Verdun Protestant Hospital in Montreal, Canada on the eve of World War II; one of four fellow physicians who provided the medical, surgical and psychiatric care to 1500 patients, on call every third night. In 1947, he became Clinical Director and by 1954, he had a well-established reputation in biological research with over twenty publications in leading medical and psychiatric journals.

Throughout this time, he lived on the grounds of the hospital, in close proximity to his patients, with his wife Annette, a nurse at the hospital and their young son, François, born in 1944. The only treatments available were largely ineffective; François, in first grade and on his way to school, could look toward the women's pavilion where naked and disturbed patients cavorted in large poorly furnished rooms, walls smeared with feces.

Heinz kept up to date with the research literature by reading journals on Sundays in his hot bathtub; one Sunday, his interest was attracted by a paper in French, dropped off at his office by a pharmaceutical drug representative. It described the effects of a new drug on excited and agitated mental hospital patients. Already a cautious scientist, he noted that pre-clinical animal work by Rhone Poulenc pharmacologists reported a calming effect without excessive sedation and wondered if this is what translated to patients. Reading his journal pages above the water line, this was definitely not an Archimedes-like "*Eureka"* moment.

On Monday morning, he asked his resident, Hanrahan, "Do you want to try this fancy new drug? It seems to be incredible, what they claim for it." (Lehmann 1994). Receiving an affirmative reply, Heinz obtained free samples from Rhone Poulenc. First, he confirmed chlorpromazine's unique dissociation between a calming effect and deeper sedation by giving it to eight volunteer nurses before beginning an uncontrolled trial in a heterogeneous group of 72 agitated psychotic patients with twelve different diagnoses that included schizophrenics, depressed, manic and organic states. It did not do well in the organic states and nor did it help anxious patients. Later in life, he described his skeptical reaction to the dramatic results in the following way; "Within days, some of the patients had stopped hallucinating and within two weeks a few were in remission and ready to leave the hospital. I assumed we were seeing flukes, perhaps resulting from an extremely strange selection in the sample. It seemed almost as improbable as winning one million dollars twice in a lottery. Much as I wanted to believe what I was seeing, I didn't for a long time… we thought it might be a new modification of some sedating and inhibiting action, but we did not label

the drugs antipsychotic. In 1956, when I was addressing the Canadian Medical Association, I introduced the term 'antipsychotic' apologetically, and more as a metaphor than a designation" (Lehmann 1993).

Heinz also noted the circumstances surrounding his discovery, "No IRB's, no informed consent, no Food and Drug Administration (FDA) regulations, nothing; also, no money whatsoever" (Lehmann 1994). Nor was it easy to publish the results. He submitted them in August to *The Archives of Neurology and Psychiatry*. "Since I hadn't heard anything by December, it seemed that something was fishy. So, I wrote them that I wanted the paper back, and I'll get it to somewhere else. Then, they immediately published it. It came out in March of next year (Lehmann and Hanrahan 1954). I think what happened is that we were in Canada, and the Americans that were working with it, I think Winkelman, wanted to be first one out. His paper came a month later. He had worked with chlorpromazine in neurotic patients."

Viewed through the eyes of 11-year-old François, things looked better and simpler. Three months after his father's experiment, François recalls seeing the same woman's pavilion, quiet, clean and orderly, now populated by fully clothed patients (personal communication).

History rightly records these events as revolutionary, but to those who experienced them, they may have seemed evolutionary and improbable at the time.

Early Life and Persona

Heinz Edgar Lehmann was born under the sign of Cancer on July 17, 1911 in the Mitte district of East Berlin, a place he would revisit with François in the 1970's shortly before the fall of the Berlin Wall. He was descended from a line of physicians, his father a surgeon and ENT physician was Jewish and his mother a Christian.

Heinz's childhood was disrupted at age 14 when, around puberty, he lost the capacity to concentrate on the rigorous demands of the Gymnasium to study Greek, Latin and Mathematics. Teachers told his parents he would never be able to graduate: "I just wasn't made for it and I should learn a trade." Heinz's mother "didn't believe it and used her good judgment to get me a tutor" (Lehmann 1994). Later in life, he would self-diagnose this as a childhood depression, a condition not recognized at the time and which lasted about nine months, the natural history for an untreated

episode. His tutor came daily, recognized his disability and did all his homework for him. Interested in psychology, the tutor also gave him Freud's works and, by age 15, Heinz had read them all, at which time he made up his mind to become a psychiatrist (Cahn 2015).

Fully recovered, he graduated from the Gymnasium and began his medical training in the German fashion, attending "as many universities as your father could afford." First was Freiburg, his father's alma mater, followed by Marburg, where he studied Kretschmer's work, then Vienna to meet Julius Wagner-Jauregg, at that time the only psychiatrist to win a Nobel Prize. Reminiscing about his time as a medical student, "he remembered more about existentialism and Heidegger than any courses in medicine." (Ban 2015a). Eventually, he received his M.D, from the University of Berlin in 1935, at age 24.

Heinz's father "chafed at his son's choice of medical field". Heinz himself recalled that psychiatry "in 1930 was a rather derelict career. People only went there if they couldn't do anything else – or were alcoholic." (Tone 2004).

After graduating, Heinz did a customary rotating internship in medicine, surgery and neurology at the Martin Luther Hospital and the outpatient clinic of the Jewish Hospital in Berlin.

Life was not all work and no play. By the time Heinz was 18, he was an accomplished cross-country skier; with friends he would traverse one mountain top after another in the Alps. On one such occasion, a less expert skier became too exhausted to continue so Heinz volunteered to stay behind until others returned the next day with help. Conditions were so harsh and bleak the companion froze to death in his arms during the night (François, personal communication).

In understanding the young man that Heinz became, it is important to remember that his growing up years were during the Weimar Republic (1919-1933), a time of political freedom and cultural creativity he enjoyed from ages 8 to 22. A photo at this time shows a handsome young man with blond hair, twinkling blue eyes, sporting a pipe.

By the time Heinz was a fully-fledged physician, the "Weimer Republic had been wiped out by Hitler and the Nuremburg Law was in effect for the protection of German blood." Germany was no longer a place where Heinz Lehmann could live or thrive. But, like so many Jewish citizens, the Gestapo did not want Heinz to leave and America did not want to welcome him. Faced with

this dilemma, he arranged for a Canadian friend to invite him for a short ski vacation, arriving in Halifax on New Year's Day, 1937. All he possessed was a camera and a suitcase packed with personal belongings underneath a complete magician's set of tricks. A puzzled Customs Officer asked, "Why the hell does a skier need all this?" Heinz, who then hardly spoke any English replied, "A man's got to have a hobby" (Ban 2015a).

Whatever other traits Heinz Lehmann brought with him to Canada, they clearly included "intrepid," fearless and adventurous. Later on, his father would also escape Nazi Germany to practice in America as an ENT physician for many years but his mother remained behind, dying just before the end of the War.

Clinician and Teacher

Like all refugees, Heinz had to report regularly to the Royal Canadian Mounted Police but he was able to obtain a temporary medical license and worked for 12 months at the Montreal Children's Hospital. He would not become a naturalized citizen until 1948 but, once acclimatized to the culture and mastering English, he moved on to join the staff at Verdun Protestant Hospital on the City outskirts (later renamed the Douglas Hospital). It was a 1,500-bed inpatient facility affiliated with McGill University. Heinz would work there for the remaining 62 years of his life; a tenure he proudly claimed outlasted any other psychiatrist in the nation (Cahn 2015).

As Heinz explains it, there was no formal postgraduate training in psychiatry but in any case, he had not time or money to afford it. His role models were Jaspers and Kraepelin, so there was "no particular person I could consider a mentor" (Cahn 2015). Later in life, he would explain that instead "I learned it the right way, working from 8.30 in the morning until about 12.30 at night. I had up to 600 patients during the war. We didn't have interns; we didn't have residents. I had one trained nurse, the others were untrained attendants. So, I did learn a lot. I taught myself and the patients taught me." Asked if he read, Heinz replied, "That's what I did after 11 o'clock in the hospital library." He also courted his future wife Annette, who told him of a rumor circulating among the staff suggesting he was "probably a heroin addict because nobody would walk around the hospital library at 3 o'clock in the morning" (Lehmann 1994). Heinz's assimilation into the culture and marriage to a French-Canadian wife ensured he was fluent in English, French and German, enabling him to read scientific articles in their original language.

His intense immersion in patient care and diligent reading convinced Heinz that "psychoses such as schizophrenia and the affective disorders had some sort of a very strong physical component." So, he began to try large doses of caffeine and chemicals to induce changes in plasma pH, "hoping and dreaming about some drug that would eventually do something about the psychoses" (Lehmann 1994).

Here was a psychiatrist who also, "read history, philosophy and theology, played chess and cards with the patients and believed empathy was as important as neuroscience to the practice of psychiatry" (Tone 2004). Spending time with patients was crucial and he lived in close proximity to them on the grounds of the hospital. Every Christmas, Heinz and François would tour the entire facility, greeting and wishing each patient well (eight miles, measured with a pedometer). Historian Andrea Tone also credits Heinz with recording these events and preserving mementoes of his patients in the International Archives of Neuropsychopharmacology (IANP) at Vanderbilt University. The collection includes letters, postcards, watercolor paintings, poems and a silk tapestry. One patient scribbled, "I am sorry for the way I am" around the rudimentary sketch of a hand drawn horse (Tone 2004).

This is the portrait of a man who was not a single minded or avid biological psychiatrist. Underlying his empathic approach to patients was an intellectual conviction that pharmacological treatment needed to be "supplemented with psychotherapy and social support." In his comprehensive approach to psychiatry, he combined the best of American and European traditions. With his lifelong preference for evidence over experience, however, he was also constantly striving to replace old beliefs with verified knowledge about mental illness." (Ban 2015b).

This nuanced view of the causes and treatment of mental illness meant that while he experienced the futility of psychoanalytic treatment for psychosis, he espoused the essential need for psychiatric trainees to understand the workings of the human mind. This mindset is illustrated in the anecdote of an event occurring two years before Heinz's acquaintance with chlorpromazine. "In 1952, during one of his rounds at Verdun, Lehmann and a group of students were looking at two schizophrenic patients who were gesturing excitedly toward the ceiling from where they were hearing frightening voices. Concerned about what he saw, one of the students asked: "will we ever get a pill to help these people?" Lehmann smiled and replied: "unfortunately, it would never be as simple as a pill" (Ban 2015b).

In 1948, Heinz Lehmann obtained his Teaching License from the College of Physicians and Surgeons of Quebec and became a Lecturer in Psychiatry at McGill University, supervising residents and medical students on their clinical rotations at the Douglas Hospital, work he continued for a lifetime, long after official retirement, until shortly before his death. As Heinz's career and reputation expanded, he moved rapidly up the academic ladder achieving Full Professor of Psychiatry at McGill in 1965.

His clinical and teaching skills were soon in high demand throughout North America, where he had forged relationships and friendships with other pioneers; among them, Nate Kline in New York, Frank Ayd in Baltimore and Doug Goldman in Cincinnati. In the early days of psychopharmacology, he was in great demand as a speaker and visiting lecturer, occasionally even teaching by telephone.

Back home at the Douglas hospital, the academic affiliation with McGill, 10 kilometers away, continued to flourish. In 1970-71, 25 residents rotated though the hospital, along with medical students and postgraduate students from around the world attending a diploma course. As if this was not enough, his teaching and clinical skills earned him a part-time consultant role at three other Canadian hospitals (two in Montreal).

Research

Heinz Lehmann's prolific research contributions are recorded in 382 journal publications between 1939 and 1986 (see INHN Archives). He was first or only author on 50% of these articles and also edited six books (five with Tom Ban and one with Nathan Kline), and eight book chapters (seven as single author and one with Nathan Kline). His research productivity can be divided into three periods.

1. Pre-chlorpromazine: 1938-1954

Most, if not all, of this early research was carried out as part of his job as a clinician without external support. Throughout his life, he was "a fervent adept of what he called "bootstrap research"; unpretentious clinical research carried out with limited means without publicity and usually by small numbers of like-minded collaborators. Late in life, he was puzzled by the large numbers of co-authors (as many as 30) one sees on neuroscience papers today" (Dongier 1999).

Research in this beginning era includes 23 publications on a wide range of topics including therapeutic, diagnostic and clinical issues, often as the only author, sometimes with colleagues.

Therapy included: Metrazole convulsions in psychoses (Dancey and Lehmann 1939); Nicotinic acid in confusional states (Lehmann 1944); Niacin therapy in psychotic states (Lehmann 1952a); Nitrous oxide treatment in depression (Lehmann and Bos 1947); a new preparation for sedation in organic brain disease (Lehmann 1949); and Electroshock therapy (Lehmann 1954).

Diagnostic issues included: Psychoses with somatic disease (Lehmann 1946); a device for the objective measurement of the negative after image phenomenon (Lehmann 1950); stress dynamics in psychiatric perspective (Lehmann 1952b); the clinical application of the Verdun projective battery (Lehmann and Dorkin 1952); and the use of finger paintings in the clinical evaluation of psychotic conditions (Lehmann and Risquez 1953).

Other clinical issues included: the iron content of CSF in psychoses (Lehmann and Kral 1951), Kral and Lehmann 1952); the eosinophil level in psychiatric conditions (Mann and Lehmann 1952); and socio-psychiatric observations on displaced persons (Lehmann 1953).

For someone with no formal training in research, carrying an enormous clinical and educational load, this is a remarkably productive and diverse output over a 15-year time span, well before psychiatry was viewed as a scientific domain within medicine.

2. Start of a New Era: 1954- 1961

This seven-year period began with Lehmann and Hanrahan's seminal article on chlorpromazine and moved on to include 23 publications on new experimental drugs, other therapeutic procedures, evaluative topics and drug reviews.

The drugs included: Chlorpromazine: new inhibiting drug for psychomotor excitement and manic states (Lehmann and Hanrahan1954); therapeutic results with chlorpromazine (Lehmann 1955); neurophysiologic activity of chlorpromazine (Lehmann 1956a); a dynamic concept of the action of chlorpromazine at physiological and psychological levels (Lehmann 1956b); a therapeutic trial of Marsilid in depressed and apathetic patients (DeVerteuil and Lehmann 1958); psychophysiological testing with a new phrenotropic drug (trifluperazine) (Lehmann and Knight1958); the treatment of depressive conditions with imipramine (Lehmann, Cahn and

DeVerteuil 1958); and combined pharmaco-fever treatment with imipramine and typhoid vaccine in the management of depressive conditions (Lehmann 1960c).

Other therapeutic procedures were: experimental sleep deprivation in schizophrenic patients (Koranyi and Lehmann 1960); and placebo proneness and placebo resistance of different psychological functions (Lehmann and Knight 1960).

Evaluative topics were: the problems of evaluating psychotic art at three levels, objective, interpretive and intuitive (Lehmann 1957); differential screening of phrenotypic agents in man (Lehmann and Csank 1957); developmental norms on four psychophysiological measures in the evaluation of psychotic disorders (Csank and Lehmann 1958); methods of evaluation of drug effects on the human nervous system (Lehmann 1959a); Ccncepts, Rationale and Research (Lehmann 1959b); psychotropic drugs and their influence on the dynamics of workingcapacity. (Lehmann 1960b); The place and purpose of objective methods in psychopharmacology (Lehmann 1960a); and Measurement of changes in human behavior under the effects of psychotropic drugs (Lehmann and Knight 1961).

Drug reviews were: tranquilizers and other psychotropic drugs in clinical practice (Lehmann 1958); psychiatric concepts of depression (Lehmann 1959c); and new drugs in psychiatric therapy (Lehmann 1961).

This body of work is informative in several ways. Early on, Heinz was involved in evaluating several of the newly appearing categories of drugs, the first MAO inhibitor antidepressant, the newly appearing antipsychotics, trifluoperazine and perphenazine and, most importantly, imipramine, in 1958. In 1957, Heinz attended the second International Congress of Psychiatry in Zurich, Switzerland. The Swiss psychiatrist, Roland Kuhn presented a paper on a new drug, supposedly with antidepressant properties, tested in 40 patients with "vital" (endogenous) depression (Kuhn 1957). So skeptical were the conference attendees that "barely a dozen" attended the presentation (Kuhn 1971). Heinz Lehmann was not among them but read the paper in its original German on the flight back to America. Impressed by the results, he contacted Geigy for supplies of imipramine and, with two colleagues, embarked on a controlled study in an 8-week trial of 84 patients, of whom 60% recovered or were much improved (Lehmann, Cahn and

DeVerteuil 1958). This study replicated the earlier chlorpromazine one – it was the first controlled and confirmatory work published on a novel drug.

The initial publication in this new era, on chlorpromazine, was the first in the English language but was also published in German, Heinz's native language. It attracted immediate attention in North America and throughout the English-speaking world, resulting in the prestigious Lasker Award to Heinz Lehmann in 1957, America's leading prize for medical research. The citation accompanying the award states, *"In his first publication on this subject, Dr. Lehmann was able to outline the clinical guidelines so clearly, describe the results so accurately and evaluate the dangers so frankly that with this paper alone, any other psychiatrist was in a position to apply this medication with confidence and safety."* It might also be said that this singular research provided a solid foothold for psychiatry as a medical discipline, initiating a category of psychotropic medications that would become widely used by physicians of all disciplines over the coming decades.

The other publications during this seven-year period further illustrate the broad scope of Heinz's research interests, both in treatment and innovative methods of evaluation, backed up by the psychophysiological laboratory he set up and the Verdun projective battery he co-developed with psychologist Herbert Dorkin. He also worked with occupational therapist Mary Cato to develop a method of scoring finger painting to measure progress in treatment.

Finally, it is interesting to note his use of the term *"phrenotropic"* (Lehmann and Csank 1957), describing the chlorpromazine like agents, even though he had coined the term "antipsychotic" two years earlier. Derived from Greek roots, this innovative nomenclature implies stimulating the mind but it never caught on and, after 1958, Heinz reverted to the earlier and still current term "antipsychotic."

The Lehmann-Ban Era: 1961- 1977

This highly productive period of collaboration between Tom and Heinz lasted 16 years, and their friendship a lifetime. Its roots lay in several connections that generated ample resources and abundant talent to create a program second to none in North America, located at the Douglas Hospital and affiliated academically with McGill University.

A newly arrived immigrant from Hungary, Tom Ban met Heinz Lehmann on July 1st 1958, the first day of Tom's first year of residency. "He took me together with the other new residents around the hospital that day and, while walking through the wards, he pointed out a few patients posturing, some roaming around naked, and one happily fishing for his stool in the toilet bowl. When he talked about chlorpromazine he referred to it as a 'tranquilizer.' We understood that with the introduction of the new drugs a major change for the better had taken place in hospitals like Verdun" (Ban 2015b).

A few months later, Tom was invited to assist Lehmann in a project on Sernyl (phencyclidine), the outcome of which would become their first published collaboration, with Ban as first author (Ban, Lorenz and Lehmann 1961).

Between 1958 and 1960, Tom assisted Heinz in a number of projects but the most unusual and memorable were studies on the effect of early psychotropics on the enzymes and biological systems of plants, predominantly the ubiquitous dandelion weed, with its unique survival capacity. Heinz presented these findings at the 10th Symposium of the Galesburg State Research Hospital in 1960, explaining that there was a plenitude of animal research on these new drugs but none on more primitive life forms devoid of a brain. Harold Himwich commented favorably on this novel evolutionary approach.

The next major step solidifying the Lehmann-Ban collaboration was serendipitous, a product of the Zeitgeist. All of the early research by Lehmann was conducted entirely without financial support, absorbed by existing salaries and service operations at Verdun. Simultaneously, in the United States, there was growing concern that psychopharmacology studies were sparsely funded by industry, poorly designed and conducted in often ill-equipped mental hospitals. The Psychopharmacology Research Center (PRC), under the direction of Johnathan Cole, developed Federal funding to support a dozen centers of excellence, the Early Clinical Drug Evaluation Units (ECDEU).

In 1961, the year Tom Ban completed his residency, the Verdun Project received a major grant from the U.S. Public Health Service to become a founding member and later a lead component of this consortium. ECDEU went on to develop common procedures in validated rating scales and trial design to allow comparison and consolidation of results between the programs.

Heinz Lehmann and Tom Ban became Co-Principal Investigators at Verdun and published their first report of its activities in 1964 (Lehmann and Ban 1964 a, b). Together, they also recorded the startup of the entire ECDEU network (Lehmann 2013). The history of the ECDEU (later NCDEU) until its demise in 1976 is recorded by Tom (Ban 2015c).

Additional funding for the Verdun Unit came from the Canadian Medical Research Council for conditioning studies on psychotropics, a particular interest of Ban's. The scope, quality and volume of their research also invited unrestricted support from the pharmaceutical industry, without strings attached to specific projects or outcomes. This combined economic endowment also enabled the recruitment of WHO fellows as well as support for residents and post-doctoral fellows from McGill.

The prodigious output of ideas and research generated by this level of support and the experience, energy and organizational skills of Ban and Lehmann is difficult to summarize. In less than two decades, the Verdun Project studied a total of 70 compounds, including marketed drugs in early development, experimental drugs (with code numbers), along with methyldopa, thyrotropic releasing hormone, anabolic agents and placebos. These were studied alone or in combination in every category of severe psychiatric disorder, including depression, schizophrenia, bipolar disorder, alcoholism, memory loss, Parkinson's disease, epilepsy, geriatrics and psychiatric emergencies.

In addition to clinical outcomes and rating scales were conditioning and reflex responses, psychophysiological and psychophysical measures, rapid eye movement, blood levels, dexamethasone suppression, sexual function and gender differences.

Numerous side effects were recorded and described, some for the first time, including skin pigmentation, adynamic ileus, EKG abnormalities, toxic psychoses, extrapyramidal effects, jaundice, urinary incontinence, leukopenia, teratogenicity and systemic lupus.

These were documented in 211 articles over 18 years, reaching an apogee in a two-year period, when together they collaborated with other team members in publishing 34 scientific papers in 1970 and 23 in 1971. As they accumulated this data, they analyzed and disseminated the knowledge and wisdom it yielded to practicing psychiatrists worldwide, in reviews, books, book

chapters and conference presentations. A selected few of these, based on their general relevance to the field, are cited below and fully referenced at the end.

Together, Tom and Heinz published their notes from the log-book of the Verdun Research Unit (Lehmann and Ban 1964a, b); Heinz summarized their experience with the placebo response in double-blind studies (Lehmann 1964) on the pharmacotherapy of depression, (Lehmann 1965), schizophrenia (Lehmann 1966), and the psychotic geriatric patient (Lehmann and Ban 1967); as well as their overall experience with psychotropic drugs (Lehmann 1967a). The 1967 *Textbook of Psychiatry* (Freedman and Kaplan) contained three chapters by Lehmann on aspects of schizophrenia (Lehmann 1967 b, c, d). Heinz also worked on side effects of lithium (Vacaflor, Lehmann, Ban 1970) and prophylactic use (Vacaflor et al. 1973).

During this time period, Heinz Lehmann also carried out a major task with wide societal implications. He was appointed by the Canadian Government Commission of Enquiry into *Non-Medical Use of Drugs* to work with two other scientists on the role of Cannabis (Le Dain, Lehmann and Stein 1972). Their major prescient conclusion was that while law enforcement should prohibit trafficking, simple possession should not be a crime.

Changing Circumstances

This decade of research collaboration overlapped with the so-called *"Quiet Revolution"* in Quebec (1960-1970). It began when an elected Liberal provincial government usurped control from the Roman Catholic Church in health care and education, establishing Ministries of Health and Education and triggering a period of intense social, political and cultural change that essentially secularized society and created a welfare state. The civil service was unionized, electricity production was nationalized and a province-wide pension plan set up.

These events had a profound impact on McGill University and its affiliated hospitals. "There was a lot of unrest and a lot of psychiatrists and university teachers were leaving …the department was almost falling apart at that time." The Dean of the School of Medicine, clearly seeking a calm and highly respected clinician, teacher and researcher, offered Heinz the Chairmanship of the Department of Psychiatry. "I didn't want to have anything to do with administration. I hated anything to do with administration. I told the Dean I needed it like a hole

in the head." But the Dean was insistent and, in 1970, Heinz reluctantly acquiesced; "Because I was from there and I knew about holding things together." (Lehmann 1994)

But political unrest persisted after 1970; emboldened by the existing changes and a visit by General De Gaulle, who gave a speech in Montreal proclaiming, "*Vive le Quebec libre!"* A small Marxist faction began a push for political sovereignty. Part of that agenda must have included a more general assault on the alleged evils of totalitarian government that infected and radicalized youth, including a psychiatric resident or two, protesting the use of medications as "mind control" in schizophrenia. This fed into a broader North American movement in the mid 1970's led by the Scientologists, including psychiatrist Peter Breggin, stirred up by public concerns over the CIA's MK ULTRA funded research program with alleged human abuses by several eminent psychiatric researchers, including Ewen Cameron, Heinz's early predecessor as Chairman at McGill. In 1972 and 1973, the President of the *Citizens Commission on Mental Health* toured 70 major psychiatric facilities in Canada, allegedly interviewed thousands of patients and compiled a catalogue of harmful psychotropic drug side effects. These findings were published in the Scientology magazine, *Freedom,* including a photo on its front page of Verdun Hospital with the caption, "Some of Lehmann's experiments at Verdun (now Douglas) hospital were fatal, yet have gone virtually without comment."

These allegations, long since discredited, are still posted on Google (www. Freedommag.org/English/vol134ilO8.htm). Heinz Lehmann's response came in the form of a public debate when the distinguished philosopher Herbert Marcuse spoke for the motion, *"Psychiatry is an Agent of the Establishment"* while Heinz spoke against. Heinz probably relished the encounter. Marcuse, who must have been in his late 70's at the time, was a German Jew who, like Heinz, studied at Freiburg, graduated from Berlin University and fled Nazi Germany before World War II. Fiercely opposed to totalitarian regimes, his early work combined theories of Marx and Freud; in America, he taught political theory at several major universities, including Harvard and Brandeis and became known as the "The Father of the New Left." He believed that many aspects of the modern state, particularly technology, amounted to social control of the individual. Presumably this ideology fit with the notion that use of psychotropic drugs was repressive or abusive and, although his writings do not proclaim this, it may account for why he was invited to defend the motion. It was a position Heinz was well equipped to negate. So, while getting the

better of the argument, Heinz was attacked by a psychiatric resident who came prepared with a spray can and covered the professor in whipped cream. Without missing a beat Heinz calmly wiped the foam from his face and continued the debate, widely viewed by the audience as the winner (Personal communications, Francois Lehmann and Thomas Ban 2015).

During his brief chairmanship (1970-1974), Heinz continued work on the Douglas Unit in collaboration with Tom Ban, producing another 50 publications. After stepping down as Chair, he became Director of the Division of Psychopharmacology at McGill until mandatory retirement at age 65, in 1976, producing another 80 publications until, in that same year, Tom Ban moved to Vanderbilt University to become Professor of Psychiatry and Director of the Clinical Research Service at the Tennessee Neuropsychiatric Unit. This ended their collaboration at McGill but Heinz and Tom remained friends for the remainder of Heinz's life and published their last paper together in 1997, when Heinz was 88. It is a 20-page review of the History of Psychopharmacology of Schizophrenia with 120 references (Lehmann and Ban 1997).

Work without Pay

Heinz Lehman was a person for whom material things mattered little. Retirement was an arbitrary concept that terminated work he could be paid for but not what he chose to do. That was determined by philosophical and moral imperatives. "Retirement is a bureaucratic arrangement, not a state of mind" (Ban 2015a).

By the time Heinz was required to retire, what he had always known to be true became abundantly clear. A pill was not enough; people with severe mental illness were everywhere homeless on the streets. Both the first and second generation antipsychotic drugs (Chlorpromazine, Clozaril and their analogues) stifled the hallucinations, delusions, paranoia and excitement that had mandated asylum care for the insane but they did little to improve the intellectual, social, motivational or psychological deficits that deprived them of work, shelter and economic wellbeing living in community. The remedy for this lay beyond medication alone and resided in social policy, economics, research and politics, all the domain of administration, "The thing I've always hated in my life" (Lehman 1994).

Perhaps, above all else in life, Heinz had always responded to a desire to be useful to others with little regard for his own needs. So, in 1981, Heinz Lehmann decided to donate two days each

week to become the Deputy Commissioner of Research for the New York State Office of Mental Health in return for the nominal salary of one dollar a year, which he never received. He had many psychiatric friends in New York and commuted back and forth to Montreal where he continued to teach residents and medical students at Douglas and McGill until the very end of his life. His bibliography of research publications ends in 1986 at age 75 but the demands of his new administrative position were considerable.

He had a budget of $37 million and administered two research institutes, one of them named after his friend, former colleague and co-author, the Nathan Kline Institute. "I have to sign off on all research protocols; I have to make sure every IRB is working all right. I have to deal with all the political infighting about the various jobs in the various hospitals and research institutes. I have to fight about budgets and try to outwit people, get around and manipulate people… I do all the things administrators do" (Lehmann 1994). And clearly Heinz Lehmann did them all well, even enjoying what he once despised.

Accomplishments, Accolades and Awards

Heinz Lehmann had accomplishments other than clinician, educator, researcher and administrator. In addition to serving as President of the world's two leading psychopharmacology organizations, the ACNP (1965) and the CINP (1970), Heinz was a Life Member of the American Psychiatric Association, a Fellow of the American Association for the Advancement of Science and a Foundation Member of the Royal College of Psychiatrists. He was also a Member of the American Psychopathological Association, Association des Médecins de Langue Française du Canada, the Canadian Psychiatric Association, the Quebec Psychiatric Association, the Canadian Medical Association and the Montreal Medico-Chirurgical Society. He was an honorary member of psychopharmacology organizations in Turkey and Germany.

In 1976, Heinz Lehmann was made an Officer of the Order of Canada; in 1970, he became a Fellow of the Royal Society of Canada; and in 1988, he was inducted into the Canadian Medical Hall of Fame in the distinguished company of William Osler and Norman Bethune. "*He was a humble and affable man who made the world a better place."*

Heinz was a member of four editorial boards: The Canadian Psychiatry Association, L'Encéphale; Revue de Psychiatrie Biologique et Thérapeutique, the Executive Editorial board of Progress in Neuropsychopharmacology and Focus on Psychiatric Practice.

Over a lifetime, Heinz Lehmann garnered many awards, none sought after. His early work earned him four awards: from the Newspaper Guild of New York (Page One Award, 1956), the Albert Lasker Award (1957), the Annual Award of Merit of the Canadian Mental Health Association (1957) and the Stratton Award from the American Psychopathological Association (1962).

His research during the Lehmann-Ban era earned him three McNeil Awards from the Canadian Psychiatric Association (1969, 1970 and 1974) and contributed to receiving the Taylor Manor Award (1970).

His lifetime accomplishments include the Psychiatric Outpatient-Centers of America Award (1980), the Leonard Cammer Memorial Award (1981), the Silvano Arieti Award from the American Academy of Psychoanalysis (1988), the Outstanding Citizen Award from Montreal Citizen Council (1991), the Van Gieson Award from the New York Psychiatric Institute and the Prix de L'Oeuvre Scientifique from L'Association des Médecins de Langue Française du Canada (1992). At the 21st Congress of the CINP in Glasgow, he received the Pioneer in Psychopharmacology Award (1998).

Heinz Lehmann's teaching skills made him the first recipient of the McGill Psychiatry Resident's Association Award for Outstanding Teaching (1985) and the Distinguished Scholar Award from the Harlem Valley Psychiatric Center (1998).

For an educator and researcher there is no greater honor that to have an endowed award named in your honor and to be its first recipient. They are the Heinz Lehmann Award for Excellence in Psychiatry by the Quebec Psychiatric Association (1986), the Heinz E Lehmann Research Award by the New York State office of Mental Health and the Heinz Lehmann Award for outstanding contributions by a single individual in the field of research in Neuropsychopharmacology by the Canadian College of Neuropsychopharmacology (1999).

Portrait of the person

A remarkably consistent portrait of Heinz Lehmann emerges from multiple sources, mostly substantiating what one has learned from his early upbringing and professional life, only occasionally surprising.

Tom Ban, who knew him for just over 40 years, as student, colleague and friend has much to say. Even into his eighties, Heinz was full of youthful vitality and energy, whose curiosity and probing mind extended to all different aspects of life. He had compassion, insight and charm, coupled with a fair minded and even-handed approach. This must have endeared him to patients and students but it also was an important cohesive force as an administrator and committee member.

Despite his preference for evidence over experience, Heinz was not unduly enamored by rapidly changing theories of neurochemical etiology and felt that some of the millions of dollars spent on neuroscience might be better used preventing emotional and mental problems in children by teaching parents on how to raise children or by addressing the problems of homelessness in people with mental illness. Heinz pioneered and taught a psychiatry that paid attention to the biology of illness integrated with the psychology and social situation of the person (Ban 2015 b). His clearest enunciation of this ideology was among his last lectures titled, *Psychotherapy's empathy and intuition versus modern drug strategies and brain investigation technology*. (Lehmann 1995).

His ultimate hope for mankind was that a "psychological revolution" would transform society from "money and power" to "constructive social action." (Cahn 2015).

A former student and colleague noted he was a man of strong opinions who never shirked a challenge and knew exactly where he stood. In addition, he was a great idealist and inspiring teacher, innovative and open to new ideas, while questioning traditional wisdom (Paris 1999).

Heinz's domestic life was overseen in tranquility by his wife Annette, a kind and older spouse, who took good care of him, exhibiting benevolent judgment and wisdom, epitomizing "encadrer," as the French say. Only after her death, did the family learn her secret: she had altered her birth certificate to conceal the fact that she was 13 years older than Heinz.

Heinz was a medical and moral role model for his son François, who became a family physician and also an ordained deacon - their only disputes were over religion where perhaps faith contested with the skepticism and empiricism that governed his father's ideology as an agnostic.

Heinz never again experienced the kind of major depressive illness that marred his childhood but he underwent less severe self-limiting episodes of sadness with which he mostly coped without disruption to his working life.

Personal life had its pleasures and pastimes. The family skied together and François' parents were among the first to frequent the slopes of Mount Gabriel, from the days when they were too poor to visit the Lodge or buy a drink, until their 50th wedding anniversary was celebrated there in bountiful manner among family and friends.

Among his many skills, Heinz Lehmann was an accomplished amateur magician to the delight of his grandchildren, Hugo and Joel. He had a childlike sense of fun and playfulness that Tom Ban recalls in interactions with his own son, Christopher.

Heinz was also a scuba diver and a strong and vigorous swimmer, even off the New Brunswick coast where there were powerful tides and undertows but no life guards. On more than one occasion he rescued unwise and less powerful swimmers.

His main hobby was star gazing through a large telescope on the balcony of his home, an avocation reminiscent of his British contemporary's recall of Emmanuel Kant's words that inspired his fellow pioneer, "*Two things continue to astonish the mind, the more it dwells on them. One is the starry sky above me and the other is the moral law within me"* (Elkes 1997). Heinz also collected precious and semi-precious stones wherever he went, polished and cut them, so his wife could set them for friends and family. He had the unusual habit of fondling an emerald, the symbol of love, while listening to lectures at conferences (Ban 2015a).

Heinz owned a car in Germany but never drove one in Canada, where he had a lifelong preference for his bicycle. On longer trips, he used a Taxi and in later life had a driver, preferring work in the back seat to driving. Although he told friends this was his choice and they attributed it to his modest habits, François believes his father was forbidden to own a car after early on driving his mother into a ditch on more than one occasion! It is a little-known fact that Heinz's aversion

to driving was shared by his famous contemporaries in Britain (Aubrey Lewis) and France (Jean Delay).

Altogether, family life was convivial and calm with many shared activities and memorable annual holidays on Cape Cod, along with François and his wife Ghislaine, whom Heinz adored, and his two grandsons, Hugo and Joël.

Exiting Center Stage

Heinz Lehmann died on April 7th 1999, suffering from a sickness not named in any of numerous obituaries. But Tom Ban presents a clear picture (Ban 2015a). In October 1998, they had been together when Heinz was inducted into the Canadian Medical Hall of Fame and he appeared well. In December, he attended the Eleventh Annual New York State Office of Mental Health Research Conference and presented the annual awards "with his usual wit and humor." Following this, they both attended the usual mid-December meeting of the ACNP in Puerto Rico.

He was now "visibly weak but attended sessions and enjoyed discussing what he learned. As usual he had his emerald in his hand while listening, but unlike before, when he got bored he just left the room." Although he was unsteady, was having memory problems, had no appetite and had lost weight, his only complaint was difficulty sleeping, for which none of the usual hypnotics had helped. Characteristically, he walked around the poster session, carefully reviewed every one that dealt with insomnia and "brought to the exhibitor's attention the need for a different kind of hypnotic." Together, Tom and Heinz visited the beach and Tom enjoyed watching him swim and the pleasure it gave Heinz, followed by a good sleep in the afternoon. That night they enjoyed a cocktail, ate dinner together and shared a main course.

Over the next three months, they were in frequent phone contact and Tom visited Heinz three days before his death. Heinz dwelt on his insomnia and relentless search for relief. A couple of nights before he was admitted to hospital for the last time, "he had a good sleep after taking a small dose of olanzapine and his restlessness had gone." This drug is an anti-psychotic, not normally used for insomnia. Heinz felt this should be looked into to help others with the same problem. Tom notes, "I did not look into it but he did." Heinz experimented on himself to find out if the drug really worked or if it might be a placebo response. After stopping the drug, "All his symptoms recurred and promptly remitted with the resumption of olanzapine in a small dose."

This must have been among their last conversations. Heinz, the incurable scientist, took the results of his final experiment with him, leaving behind a grieving family, his lifelong friend Tom and a worldwide audience of bereft fellow psychiatrists.

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Chapter 8

The Monoamine Oxidase Inhibitors

Nathan ("Nate") Kline

Of the many pioneers in psychopharmacology Nate Kline deserved but has been denied the services of a professional biographer to document his intriguing life and its accomplishments. Nor was he interviewed by one of his peers for the ACNP's Oral History of Neuropsychopharmacology (OHP) due to his tragic premature death in 1983 at the age of 66 during heart surgery (Gruson 1983)

As a result, there are gaps in our knowledge of his early life and career at the same time that his contribution to the genesis of the discipline is under rated.

Born in 1917, Nate was 35 in 1952, the year chlorpromazine was discovered when the American population of asylum patients was near the half million mark with no effective treatment in sight. By that time he was already Director of Rockland State Psychiatric Hospital and had a busy private practice in New York City. We know nothing of his early life or when and where he trained as a psychiatrist, but he was a graduate of New York University School of Medicine with some background also in psychology.

In 1970 Nate received the Taylor Manor Award in Baltimore and presented a talk titled, *"Monoamine Oxidase Inhibitors. An Unfinished Picaresque Tale."* (Ayd and Blackwell 1970). Nate took this opportunity to speak by first explaining his introduction to psychopharmacology in general. Always an entrepreneur Nate had seized on the discovery of chlorpromazine to set up a Research Institute at Rockland State and, in the spring of 1953 began to seek pharmaceutical company support for laboratory equipment. Informed that such support was only given for promising product development Nate "scratched around to find such a potential new product" (Kline 1970).

Reading recent British and American literature he learned about *Rauwolfia Serpentina*, the 2000-year-old Ayurevedic drug used to effectively treat hypertension with a long history as a panacea in many other conditions. Nate requested a small grant to study its effects in psychiatric

patients at exactly the time Ciba isolated the active ingredient *reserpine.* The company agreed to fund the work and Nate completed a placebo controlled study in 710 patients with schizophrenia, achieving similar results to chlorpromazine. The findings were presented to the New York Academy of Sciences in February 1954 (Kline 1954).

As a consequence, chlorpromazine and reserpine were clinically approved and available for use that year. In 1957 Nate would receive the Lasker Award for discovering reserpine by which time its side effects, including akathisia and depression, would soon lead to chlorpromazine becoming the treatment of choice.

Nate tells the story of his collaboration with Mortimer Ostow, an analyst, describing the effects of both reserpine and chlorpromazine "in everything from neurophysiological to psychoanalytic terms" This theoretical exercise led them to postulate "the existence of drugs that would function as antidepressants." This included their hypothesized benefits in simple and melancholic depression.

These speculations were made in early 1956 at a presentation to the American Psychoanalytic Association. In April 1956 Nate lectured on reserpine at Warner Laboratories and was invited to view experiments in animals given iproniazid prior to reserpine. Instead of being sedated they became hyperactive, results similar to those obtained by Pletscher in Brodie's lab. at NIMH. The following month Nate was visited by the Medical Director of Hoffman La Roche who had begun a search for an antidepressant drug. This resulted in Nate hiring John Saunders, a basic scientist from Ciba, to begin considering the possible clinical applications of iproniazid in patients at Rockland State.

In November 1956 Saunders launched a trial of iproniazid in 17 patients with dementia praecox at Rockland State while Nate and two colleagues began to prescribe it to depressed patients in private practice. By February 1957 "it was obvious we were on to something exciting" (Kline 1958).

Because iproniazid was already approved and marketed for tuberculosis its use in depression spread dramatically and, in the year following, FDA records showed 400,000 patients had received the drug. Invariably side effects occurred including jaundice and eventually iproniazid was

withdrawn. But meanwhile Saunders had identified its mechanism of action as an MAOI and other companies were quick to follow with drugs of their own.

In 1964 Nate Kline would receive his second Lasker Award this time for the discovery of the first antidepressant drug. It was an honor that became mired in controversy over priority, ending in a court case in favor of Nate's colleague with whom he was required to share the award.

Throughout these early years Nate was active in lobbying Congress to support the new science of psychopharmacology. In 1955 he testified about reserpine that led to approval of the Mental Health Studies Act which eventually funded the new Psychopharmacology Service Center. Nate received $2 million for research on reserpine and throughout the 1960s the Rockland State Research Institute blossomed, adding 300 more staff to become an ECDEU program under the direction of George Simpson and attracting biomedical researchers from around the world. In 1968, again with Federal support, he pioneered the computerization of the Institute with many improvements in the clinical and administrative services.

During the 1950s and 1960s Nate played important roles in the evolution of psychopharmacology nationally and internationally. He was one of 33 founding members of the CINP in 1957 and an active participant in its First Congress in Rome the following year. His ACNP membership began in 1961. He was not a member of the six-person organizing committee but became the 6th President of the organization in 1967. Although not active in further leadership he attended the Annual December Conventions in warm places accompanied by a bevy of acolytes, attractive companions and a public relations person.

In 1958 Nate founded and directed the International Committee against Mental Illness, active in developing countries, predominantly Haiti and Sub Saharan Africa where they established health care facilities and distributed psychotropic drugs donated by industry.

Throughout his career Nate published almost 500 articles in scientific and lay journals and was author of the best-selling book, *From Sad to Glad.*

A Personal Reflection

I first met Nate as his co-host with Frank Ayd at the Baltimore Conference in 1970 where he received the Taylor Manor Award for his discovery of the first anti-depressant. I was puzzled by

the title chosen for his talk and looked up the meaning of *Picaresque* in my dictionary. According to OED it is "An episodic style of fiction dealing with the adventures of a rough and dishonest but appealing hero." From the French *picaro* for rogue.

It was unclear if Nate knew the true definition of the word he used and whether the adjective described the discovery or the discoverer. But he helped clarify the matter when he launched into the talk. Its first few paragraphs, reproduced below, are self-revelatory and may also cast light on the exuberance experienced by other pioneers when they observed the benefits of the first effective drugs on previously untreatable conditions (Kline 1970).

> "*Research Scientists are wide-eyed manipulators. When an observant brat discovers for the first time that he can push buttons, turn faucets, open doors, dial phone numbers and exploit his parents, he is astonished and delighted at his ability to uncover and control the physical and social environment. Some of us never recover.*
>
> *"Until fairly recent times, the researcher was paid substantially less than those earning an honest living. In many cases this was because he felt guilty taking any money at all for doing something he so much enjoyed. This position is not as ridiculous as it sounds since the Royal Society in England was formed by wealthy gentlemen for the sheer pleasure of carrying out experiments. We are not only granted these extra-ordinary prerogatives, but equipment and supplies are provided plus a salary to boot.*
>
> *"Few joys equal the realization of fantasies in which a successful researcher indulges, few joys equal the fantasies themselves. Imagine being able to spend a whole lifetime poking around to see what will happen. The fact that the questioning and answering is sophisticated and according to certain rules doesn't change the basic activity. For those of a mechanical bent it is possible not only to keep on purchasing the most intriguing Erector Sets but even to have one built to specifications.*
>
> *"If you like to sleep late and work in the evening, no one really objects and, if the work gets a bit dull, it's always justified to visit a laboratory (located in some*

seasonal climate) that is doing the same sort of activity. If you climb high enough up the hierarchy, you can then direct others to carry out all sorts of interesting things you don't have time to do yourself. One of the sweetest smells in the world, that of fresh galley proofs, is an added attraction; the absolute power to, subtract from, and alter an article that is to become part of the world's 'permanent' literature guarantees permanent immortality.

"The apogee of the whole voyage occurs when something New reveals itself to you (whether it later proves to be incorrect or not is irrelevant). You have found a missing piece in the jigsaw puzzle! You have forged a passkey which might open innumerable closed doors! I will never forget the picture of Linus Pauling in a meeting at McGill describing the creative process. He rubbed his hands in pure sensual satisfaction and his baby-blue eyes positively glittered: "Just think", he said, "I know something that no one else in the world knows- and they won't know it until I tell them."

"A hundred years from now our names will be impersonally listed in a book or in a memory bank of a computer or perhaps erased completely. Yet medicine and science will be Just That Much Different because we have lived; treatment and understanding of illness will forever be altered even though the alteration is no longer perceptible, and in our own way we will persist for all time in that small contribution we have made toward the Human Venture."

Use of the collective pronoun in the final paragraph suggests Nate might have believed he was speaking on behalf of the 16 other pioneers being honored. I do not recall any comments made by them nor did I, as a very junior participant, speak up. But a few months later I did have an opportunity to challenge Nate when he published a review paper in the Journal of the American Psychiatric Association about lithium, calling it "The 20-year Cinderella of Psychopharmacology." In a letter to the editor I chided Nate, suggesting that the title was appropriate for a topic which had begun to resemble a Fairy Tale. This sparked an entertaining correspondence in which no egos were badly damaged. I was 36-years-old at the time.

Forty years later, in 2010, at the age of 76, I was working with Tom Ban on the OHP and edited Volume 7 which I decided to dedicate to Nate Klein. The reasons I gave to the reader, in addition to the accomplishments described above, were as follows: "*There is nobody who better personifies the pioneering spirit that initiated the field of psychopharmacology. Nate was intensely energetic, creative, curious, challenging, provocative and entrepreneurial."* He fulfilled many roles: *"a researcher, administrator, busy practitioner, author, publicist, politician and world traveler."*

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Chapter 9

Women Pioneers

None of the major biographies in this volume were about women. Out of the 57 mini-bios (*dramatic personae)* I wrote for the OHP prior to publication in 2011 only 10 were women, nine of whom had careers that fell within the pioneer period 1949-1980. Perhaps due to inate mysogny in the field women's productivity spanned both the pioneer and modern eras. All nine were educated during the pioneer period and while only two (Fisher & Scholer) were highly productive in this time all nine remained active and contibutory well into the twentieth century.

Putting aside differences in detail and length, the 10 male and nine female biographies can be considered a comparison group with regard to major career accomplishments.

Whatever cultural factors determined disparity in numbers between genders, competence and clinical diversity were not among them.

The women included basic science attributes and clinical accomplishments across the spectrum of child and adult life. Five women held Ph.D. degrees in a variety of disciplines including statistics; neuroanatomy; epidemiology; psychology and social work; and they made contributions in social function, suicide and relapse prevention, quality of life, interpersonal psychotherapy and multiple factors in schizophrenia, including the interaction of psychosocial factors with drug therapy. Four women were physicians working on clinical aspects, drug responses and outcomes of depression, bereavement, eating disorders, schizophrenia and a variety of childhood disorders.

By any measure of career accomplishment women performed with distinction equal to male peers, including grants awarded from government; foundations and industry; volume and impact of original contributions; and scientific publications, mentorship, leadership roles at NIMH or professional organizations, work as journal reviewers or task force members at the FDA or APA, including development of DSM diagnostic criteria.

These career accomplishments were recognized by prestigious professional and lifetime achievement awards to women simultaneously fulfilling traditional child rearing and spousal roles. Two of the pioneers also received recognition as outstanding female and scientific role models.

Dramatis Personae

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 10 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 would 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 20 years (1988-2007) the team has published almost 100 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 10-20 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 20 clinical and basic science journals. Finally, she is a member and often chairperson to many study sections and review committees that influence and fund the future direction of brain research.

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 to 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 likeminded faculty that included Sam Guze, George Winokur and Eli's wife, Lee Robins. Almost unique in 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 10 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 $300,000 to $11 million.

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 more than 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."

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 18, 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 *Textbook of Comprehensive Psychiatry*, published in 1980. These included 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 100 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 150 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 50 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).

Fifteen years after the start of her academic career in 1970 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.”

Katherine Halmi is the self-styled “grandmother of the eating disorder field,” a title she earned by devoting more than 30 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 four 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 30-bed inpatient unit. In 1979 she moved to Cornell Medical Center (Westchester Division) 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 more than 20 years research supported by more than $3 million 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 (cooperate 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 lead 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 100 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 more than 40 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.

Nina R. Schooler is a pioneer in two senses; born in New York in 1934 she was a member of the first class of women (1951), admitted to the general study programs at the College of the City of New York (CCNY). She was also one of three women elected to the ACNP in 1975, doubling the total number of female members to six. Only three of 47 ACNP Presidents have been women, the first in 1988 (Eva Killam), 27 years after the ACNP was founded by an all-male organizing committee.

Scientifically Nina has been a participant in almost all of the important research on schizophrenia over the last 37 years, beginning when Sol Goldberg recruited her as his part-time research assistant at the newly formed Psychopharmacology Service Center (PSC) set up by Jonathon Cole at NIMH (1963).

Nina's undergraduate degree was in anthropology (1955), supported by a New York State Regent's Scholarship and the Tremaine Scholarship from CCNY. Her graduate work in Social Psychology at Columbia University began in 1956 and continued part time for 13 years until her PhD. in 1961 on language patterns in schizophrenia, based on the patient population in the first NIMH 9 hospital collaborative study of chlorpromazine and placebo, coordinated by Sol Goldberg and Nina.

When that study began Nina "didn't know anything about psychopharmacology" and she describes her feminine role, at a time of cultural "modest expectations," with a quote borrowed from George Bernard Shaw's description of women preachers: "It's like a dog walking on hind legs. You admire the fact that it does it and don't comment on the quality." But Nina was good at what she did; prior to NIMH she worked in market research, co-coordinating researchers and their data, "a task I've been doing ever since … but in other areas."

Surrounded by a cadre of the best psychopharmacologists in the field and with excellent mentoring from the likes of Cole, Klerman and Goldberg, Nina quickly gained skills, credibility and responsibility. Armed with her new found title as "Dr.," she attended her first ACNP meeting in 1970, joined Sol's study group on "Prediction of Response in Schizophrenia" and from then on (1971-1988) she helped design and co-ordinate the NIMH sponsored series of drug studies in schizophrenia which set the benchmarks for future clinical practice. Nina notes, "I'm a really good collaborator and mentor," talents predicted by a grade school report that, "she works well with others."

The interview with Tom Ban in 2001 relates the sequential studies completed over 17 years, defining the short and long term effects of phenothiazines, optimal treatment regimens, relapse rates, compliance and placebo response and, ultimately, with Jerry Hogarty, the interaction of drug with psychosocial treatment.

Dr. Schooler retired from the NIMH in 1988 to become a full time academic at the University of Pittsburgh (1988-1997) where she was appointed Professor of Psychiatry (1992) and Professor of Psychology (1994) with the title of Director of Psychosis Research. She remained involved in bringing the NIMH studies to completion but also set up her own independent Special Studies Center at Mayview State Hospital where her research focused on treatment in both first episodes of schizophrenia and chronic refractory cases. In collaboration with industry she also began a series of studies on clozapine, and then other "second generation" anti-psychotics.

In 1997 Dr.Schooler moved to New York to join John Kane and became Director of Psychiatry Research at Zucker Hillside Hospital (1997-2003). In those five years she continued her work with second generation antipsychotics comparing clozapine with haloperidol and risperidone with olanzapine. She also worked with NMDA agonists in treatment, focusing on negative symptoms.

After New York, Dr.Schooler moved her base of operations to the VA Medical Center in Washington DC to become Senior Research Psychologist (2004-Present) with academic appointments as Professor of Psychiatry at SUNY and Adjunct Professor of Psychiatry and Senior Psychiatric Neuroscientist at Georgetown University School of Medicine (2004-Present). Consistent with her lifelong pattern of collaboration and continuity she maintains academic and collaborative relationships in both Pittsburg and New York.

Throughout her independent (post NIMH) career Dr. Schooler's research has been supported by 14 NIMH grants (two current) and 16 industry projects (two current).

The full measure of what Nina would make of her encompassing experiences and unique career were not clear at the time her interview took place in 2001. The subsequent decade (2001 – present) has been a period of remarkable productivity and expanding influence during which Nina remains fully active at an age when many colleagues and contemporaries have long since retired. Comparing the first half of her career (1966-1983) with the second (1984-present) the number of her scientific publications has quadrupled (26 to 104) and book chapters have tripled (8 to 22). The topics in this literature cover her personal involvement in virtually every aspect of schizophrenia, its treatment and outcome.

In the last 10 years Dr. Schooler has been active in sharing and disseminating her extraordinary knowledge of the field. In addition to teaching medical students, psychiatric residents and psychology interns in her hospital and university settings she has been a guest lecturer or visiting professor in 18 foreign countries (Europe, Asia, Africa, South America and Scandinavia) and 23 states in America.

In addition to research, teaching and her continuing collaborations Dr. Schooler participates actively in the professional arena. She is a Fellow and Past President (2000) of the American Psychopathological Association; Fellow and Past President (1991-1993) of the Association for Clinical Psychosocial Research; Fellow and Council Member (2004-2010) of the CINP and she has been a member of 8 ACNP Committees over 30 years (1979-2010).

Nina has served on the Editorial Boards of five journals and is a reviewer for many more; she is active in NAMI and NARSAD and an advisor to the APA DSM task forces on tardive dyskinesia, psychotic disorders and schizophrenia. She has been a consultant and member of work groups, research and advisory panels, review committees and study sections for the NIMH, VA and FDA.

At the end of his interview in 2001 Tom Ban's final comment is, "you seem to intend to keep on going." Never were truer words spoken!

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 migrated 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, “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, long since discarded.

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 Medical 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; and 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 more than 150 articles and book chapters published in just over 30 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 15 journals.

Judith Rapport*'s* lifetime leadership role in child psychiatry began with an NIMH postdoctoral fellowship 47 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 300 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. Rapaport 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 40 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 22 languages, sold more than 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.

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 18 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 30-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 22 articles in scientific journals of which she was the first or only author on 15. 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.

Chapter 10

Early Optimism and Ambiguity

Frank Berger; Chemistry and affect

Jose Delgado biography; Brain stimulation

John Smythies biography; Transmethylation hypothesis

As Psychopharmacology evolved from mid-century to the early 1960's contemporary attitudes and beliefs about the state of the field were often divergent. For some, hopes of solving the mysteries of the brain and its function were optimistic, sometimes lapsing into ambiguity while others began and remained cautious and skeptical. Chapter 10 offers three examples of the former followed by Chapter 11, expressing the latter viewpoint.

Frank Berger

Frank Berger's posthumously assembled book of short writings, *A Man of Understanding* (Berger, 2013) is a lifetime's treasure trove of wisdom; of truth in action. As he states in its "Personal Views" section, "I have only one prejudice: that there is nothing beyond the inquiry of science. The notion that there is any truth we are not allowed to know is abhorrent to me." See also Frank Berger's contribution to the *Anxiety Enigma* (Ch.13).

Readers should realize the how and why of the way in which this unusual and unexpected book came to exist. Frank was an eminent member of the half-dozen or so true pioneers who made the breakthrough discoveries in psychopharmacology in the mid-twentieth century. The drugs they discovered released thousands of patients from asylums into more humane (but still inadequate) community care. Frank Berger's particular contribution was to develop, beginning with research in animals, the first effective drug for the treatment of anxiety: Meprobamate or "Miltown." This and other so-called "minor tranquilizers" rapidly became among the most widely used drugs in America, prescribed by physicians of all stripes including family physicians and psychiatrists. In

one short year, 1995-1996, Frank's discovery increased Wallace Laboratories'' annual revenue from $80,000 to $200 million.

The milestones of Frank's scientific career spelled out at the beginning of his book appear in more detail in *The Oral History of Neuropsychopharmacology* (ACNP 2011).

Frank's entry into medical school in Prague was pre-determined by an interest in research and he made his first discovery at age 22 while still a student, a drug treatment for cystitis he sold to a pharmaceutical company. Frank's long and productive life ended at age 94 in 2008. Throughout this time, he kept detailed notes that reflected his philosophical views on life, quite separate from his scientific work. In "*Why Write the Book?"* he says, "What I have learned is much more important than what I have contributed… it is not original and has been taken over intentionally and unintentionally from others. And: "In my immodesty I want to offer a recipe for happiness and success."

Dr. Berger clearly intended to eventually publish his material with a working title borrowed from Maimonides, Judaism's medieval physician-philosopher: *A Guide for the Perplexed,* which is retained as the title of the book's introduction. After his death that task fell to his widow, Christine Berger who brought the book to press with its current title and Dr. Berger as posthumous author.

Why Frank Berger's only book for the general public should be about his philosophy of life and not his scientific discovery is revealed by the only allusion he makes to this paradox, quoted on the back cover, *"There are misunderstandings about tranquilizers, about what they can do, who should use them, when and how to use them. They may make you feel normal again, able to cope again, but are no substitute for philosophy."*

This honest appraisal is striking and key to understanding Frank's purpose for his book. In 1970, three years before he retired from industry (but not research); Frank was honored with an award and presented the story of his discovery at a conference in Baltimore that I helped convene with Frank Ayd. The lecture was published in the book we co-edited, *Discoveries in Biological Psychiatry* (1970). By that time Miltown had been overtaken by the benzodiazepines, Librium and Valium, and controversy was raging in Europe and America over the appropriate and inappropriate use of minor tranquilizers; whether they were panaceas for the vicissitudes of daily life or were

more effective treatments for a biological brain disorder. Frank Berger's position was crystal clear; following a scholarly review of anxiety and its treatment he concluded they were useful for the latter and not the former. With the passage of time his reason for this became clearer and more widely acknowledged: drugs can stifle anxious thoughts, feelings and behaviors but cannot change them; they re-emerge once treatment ends. New improved responses to anxiety-provoking stimuli only arise when learning occurs, based on life experiences and sometimes facilitated by talk therapy.

This is made explicit in the Introduction where Frank describes the book as "an attempt to share some of the things life has taught me." Further, that they "are not concerned with medicine or science but with "an approach to day-to-day living that has helped me deal more successfully with life's most vexing problems." A life-changing experience produced one of those lessons: escaping from his Czech homeland two days after Hitler invaded, being denied passage to America at the last minute and crossing to Britain instead with his wife, no money and unable to find work or speak the language. "There was good reason, one might say, for me to be depressed or downhearted." So, Frank's response was to "set about doing the best I could in the face of great difficulties".

This epiphany is translated into four cardinal components of his philosophy that liberate action: tolerating uncertainty and being content with small victories; accepting life's cultural and spiritual realities while rejecting comforting but ineffectual religious, scientific or philosophical dogma; letting go of unconscious beliefs or fallacies and establishing new beliefs. This last point is driven home by a quotation from Buddha; "The man of understanding makes for himself an island that no flood can overwhelm." This is prelude to Frank's benediction: "May this book help you see that it is possible to build such an island without leaving the mainland."

In the main body of the book Frank Berger's insights, merged with those of independent philosophers, scientists, authors, politicians and others are stockpiled in alphabetical order in 60 categories the reader can delve among.

Finally, Frank the scientist and empiricist might pose the question, "To what end?" As a philosopher he would be wise enough to know that the answer is beyond the reach of our often crude and error-prone "outcome measures." It will be up to the reader to seek whatever insights fit

their existential predicaments or angst, testing them in real life and sharing them with friends, family, lovers or fellow workers and, perhaps, with a therapist or two. It remains only to quote Anglo-Saxon folk wisdom: "*The proof of the pudding will be in the eating thereof."*

Jose Manuel Rodriguez Delgardo

Sometimes the personality of a scientist, his chosen field of enquiry and a changing social or scientific zeitgeist can collude to create unanticipated and career changing controversy. There may be no better example of this than what befell Jose Delgado during the half century of a distinguished career. I first learned of this while writing his obituary for *Neuropsychopharmacology* (Blackwell 2012a) I became so intrigued that my research eventually produced a10,000-word biography published in my memoir titled, *"Science, Hubris, Nemesis and Redemption"* (Blackwell 2012b).

Jose Delgado was born in Ronda Spain in 1915, a founding member of the ACNP and lifelong Fellow he died at age 96, three months before ACNP celebrated its fiftieth anniversary.

Jose intended to emulate his father, an ophthalmologist, but fell under the spell of Santiago Ramon y Cajal often considered the "Father of Neuroscience," Nobel Laureate in 1906.

Jose enrolled in Madrid Medical School in 1933 to study both medicine and physiology. In 1936 the Spanish civil war erupted, his mentor Juan Negri fled the country and Jose joined the Republican side as a medical corpsman. After the fascist victory he spent five months in a concentration camp before obtaining his M.D. and Doctorate of Science, both *cum laude.*

From 1942 to 1950 he began research in neurophysiology on selective brain ablation and electrical stimulation in animals, published 14 articles and won several prizes. In 2005, at age 90, he was interviewed for the ACNP's Oral History of Neuropsychopharmacology where he tells how he went to Africa to buy primates for research, bonded with a gorilla and, unable to operate on his "new friend," donated the animal to a zoo.

In 1950 Delgado won a scholarship to Yale University in the Department of Physiology under the direction of John Fulton whose pioneer work on pre-frontal lobotomy in chimpanzees encouraged the Portuguese psychiatrist Egas Moniz to perform the operation in schizophrenic patients, for which he received the Noble Prize in 1949.

Delgado flourished at Yale; rising to Professor of both Physiology and Psychiatry he eventually succeeded Fulton as Director of Research. Described as "a technological wizard" he invented the "stimoceiver"; implanted electrodes which established two-way communications with the brain in mobile animals allowing Jose to stimulate different regions, producing changes in affect and behavior. Encouraged by these results, and Moniz example, Delgado extended his research to patients with chronic refractory epilepsy and schizophrenia.

This ground-breaking research was published in 1952 anticipating similar work by Bob Heath at Tulane University. 1952 was a watershed year in neuroscience, when chlorpromazine was being given to patients with schizophrenia, spawning the neuropsychopharmacology revolution.

Delgado positioned himself between growing disapproval of mutilating brain surgery and his own belief that electrical stimulation of specific brain areas was scientifically superior to oral administration of drugs whose effects were mitigated by liver metabolism, the blood brain barrier and uncertain distribution. at multiple sites with variable effects.

Events proved Jose wrong; the effects of electrical stimulation were imprecise, poorly replicated and yielded no useful therapeutic outcomes. Conversely neuropsychopharmacology thrived. Drugs were developed for every type of psychiatric disorder, deinstitutionalization occurred and, in 1970, the Nobel Prize went to Julius Axelrod and colleagues for discoveries about humoral transmitters at nerve endings that supported the catecholamine hypothesis of depression.

Nevertheless, in two decades (1950-1970) Delgado authored 134 scientific publications on electrical stimulation in cats, monkeys and patients, psychotic and non-psychotic. In 1963 he performed an experiment that attracted worldwide attention, including a front-page article in the New York Times. After implanting his stimoceiver in the caudate nucleus of a fighting bull Jose stood facing the bull waving a red cape before stopping the animal in its tracks by activating the electrodes.

Soon after this Delgado was invited to contribute a volume to a series on *"World Perspectives."* Its editorial board comprised twelve of the world's most distinguished leaders in ethics, sociology, economics, spirituality and science, including three Nobel Laureates. The series editor was a renowned philosopher whose life was devoted to inviting leading scientists and

thinkers to speculate on the societal and philosophical implications of their narrow fields; to "extrapolate an idea in relation to life."

Jose chose a provocative title for his volume, *"Physical Control of the Mind: Towards a Psychocivilized Society."* The text and tone were equally challenging. While Jose's discussion of his scientific findings was modest and objective the philosophical speculations were grandiose and went beyond the data. None the less his intent was benevolent; to encourage the development of "a future psychocivilized human being; a less cruel, happier and better man." In essence he was proposing that science might accomplish what two millennia of religion failed to do!

Unfortunately, this rhetoric and hyperbole clashed with a changing scientific, political and social Zeitgeist, engulfing Delgado in controversy that would end his career in America. Without distinguishing between science and philosophy Jose's research and ideas were attacked and denigrated on two fronts.

In 1972 Congress held hearings in response to efforts to end funding for this type of brain surgery. Testimony was given by a libertarian psychiatrist, a scientologist at the time, who disparaged drugs, ECT and biological psychiatry. This included a collage of selective, out of context, quotations from Delgado and other neuropsychiatrists.

Coincidentally public and political outrage surfaced over covert CIA "mind control" experiments, designed to combat communism, initiated in the McCarthy era and extending into the mid-1960s (MK-ULTRA).

These twin forces manifested a plethora of websites fed by conspiracy theorists and alleged victims of psychosurgery that disseminated innuendo and largely unsubstantiated accusations for four decades. Delgado's name and book figure prominently along with other well-known psychiatrists from among 43 Universities and Colleges alleged to have been involved.

Mired in controversy Delgado accepted an offer to become Chair of Physiological Science at a new medical School in Madrid and moved there in 1974.

For the next quarter century Jose continued to publish his research and philosophical ideas, achieving a lifetime total of over 500 articles and six books. His final book, in 1989, was titled "Happiness" and went through 14 editions.

In the last years of his life Jose and his wife returned to America and lived in San Diego where he died unheralded. Unjustly treated and harshly judged by segments of the public and his profession Jose Delgado's ground-breaking research, benevolent philosophy and memory deserved better. His career trajectory may provide budding scientists with a cautionary note about the pitfalls of mingling science with philosophy and the perils inherent in a changing social, political and scientific landscape.

.John and Vanna Smythies

It was a pleasure and privilege to review the Smythies' memoir. (Smythies & Smythies, 2005). Its 113 pages are divided between John's life story and that of Vanna, his wife of 65 years. While their stories and styles differ, they share a talent for colorful prose tinged with humor that portrays people, places, culture and life's predicaments in what is also a travelogue of International work and play in England, Canada, Australia, Scotland, Bermuda, Italy and throughout the rest of Europe.

There are now many memoirs of distinguished neuroscientists on the INHN website in the Biography Program I edit. They vary in length, style and format but all convey a lifelong passion for the clinical and scientific rewards of careers in neuropsychopharmacology enabled by strong supportive partners and domestic tranquility. Reviewing them has been easy and enviable task with the sole caveat that this occasionally requires me to rescue the authors from overly modest reticence about their own accomplishments. Such is the case here.

John Smythies' scientific oeuvre extends from 1952 till the present (at age 92), created in several of the world's leading academic environments and many published in major journals. This body of work includes the first modern neurochemical theory of schizophrenia (the transmethylation hypothesis), a balanced approach to the role of vitamins in prevention and treatment of disease (orthomolecular theory) and philosophical speculation concerning the ancient enigma of putative mind-brain relationships. The book includes a Bibliography of the 16 books he has published and a modest selection of 25 scientific papers (from more than 200 published).

John begins the story with an exploration of his genealogy. Like many ancient English stock the family name is toponomic; derived from the Yorkshire moors where small pits (smythies) contained iron ore, limestone and charcoal from which blacksmith's smelt and fashioned tools.

Henry VIII hung six subjects of that name for treason in 1528! John's direct male lineage traces back to forbears who graduated from Cambridge University in unbroken succession through nine generations from 1617 until John matriculated in 1940. Sifting through the occupations and accomplishments of his genome there is much to admire and live up to. John's father won philately's highest award, his brother was a leading ornithologist and more distant cousins included the ethologist Richard Dawkins and the author Graham Greene. He describes his ancient ancestors; "The family portraits of the Divines, all dressed in black with their little white puritan collars, all display the well-fed confidence as pillars of the Establishment … they were mainly friendly but cool, reserved rather than affable, and devoted to the concept of duty. My father's last words were to ask if he had done his duty." John sums up the ethos of his ancestors as, "Thus the Smythies family for over three centuries have been marked by the sturdy values of Puritan theology and the Enlightenment."

John's matriarchal heritage is more nuanced and laced with wry humor. His mother traced her descent from the "Celtic Princes of North Wales and the time of Owen Glendower" (1349-1415, date added). John's maternal grandfather Percy owned a fine manor house large enough to raise his seven children and directed the company that founded and dominated the marble exporting business in Carrera, Italy. Percy was rumored to be the illegitimate offspring of a "certain member of the nobility"; he came to an enigmatic and tragic end, dying from a penetrating knife wound which the family blamed on an accidental fall onto "an open pair of scissors." More probable is that, "He was stabbed by a jealous Italian husband." To deal with their social stigma the maternal side of John's family developed a myth that an ancestor was awarded a coat of arms by a medieval King for bravery. Later in life, on a visit to the College of Heralds in London, John learned the shield was bogus and that, "The story was typical of the attempts many Victorian families of dubious origin made to add a little glamour to their humdrum lives."

John Raymond Smythies was born on November 30, 1922 in the Indian Hill Station of Naini Tal. His father and grandfather broke from their clerical lineage to work as Forest Officers in the days of the British Raj; his mother described her own experiences in two memoirs, "*Tiger Lady"* and *"Ten Thousand Miles on Elephants."* John's early upbringing was typical of the time and place. The family owned thirty servants and his parents "Spent all summer in a whirl of tennis parties, yacht races round the little lake, golf matches, fancy dress balls and so on." John saw little

of them and was cared for by an Indian Ayah, a male bearer and a groom who looked after his pony. “When I passed my seventh birthday this paradise abruptly vanished. I was taken back to England and deposited in a boarding school … the shock was severe.” John contrasts the “warm colorful world of India where I had been the center of affectionate attention of my little Indian team” with the new environment he likens to, “a modern-day version of Dotheboy’s Hall.” He describes it as, “cold, grey, austere, impersonal, totally lacking in affection, sparkle, culture and wit, or any semblance of anything human except discipline, repression, Latin, compulsory games and compulsory chapel.”

After suffering for a year John was rescued and removed to live with a maternal aunt and her three children while he attended a day school where his English master was the famous poet, Cecil Day-Lewis. This influence blossomed late in John’s life when, at age 80, he published his own book of *“Poems from the Edge of Time.”*

How often and long John was separated from his parents in India is unclear but his need and appreciation for affection is everywhere apparent. During summer he spent time with his grandfather in Devon. After his spouse died he married the housekeeper, much to the dismay of the family. “Aunt Dorothy was warm and affectionate, unlike most of my own relations, who believed that discipline, not coddling was the thing. So, I much preferred her to them. I wept bitter tears on the country bus taking me back from Dolton to school. Every childhood deserves at least one place that one weeps on leaving.”

At age 13 John’s life took a predestined turn. Like his male ancestors for 200 years he had been enrolled since birth as a future pupil at Rugby, in the top echelon of archetypal English “Public Schools.” John describes his ambivalence to the new environment in elegant prose. It was a place of “Spartan discipline tempered by muscular Christianity They also provided a superb academic education. But they failed to focus on the need to develop the finer aspects of personality.” To his chagrin “The only way to achieve prestige was to be good at games … The system was not designed for sensitive and imaginative Athenians, such as myself, who did not excel at sports.” He quotes Evelyn Waugh in *“Decline and Fall”* … “anyone who has been to an English public school will always feel comparatively at home in prison.” How would an adolescent youth compensate for such a lack of affection and prestige? It was certainly not in “muscular Christianity.” John notes: “Their system of religious instruction was particularly disastrous …

based largely on compulsory chapel." Hopefully, John took the matter into his own hands, "inspired by Darwin and modern science I told the Headmaster that I would prefer not to attend chapel." More "in sorrow than anger" he was told, "Boys who refused to attend chapel were expelled."

John struggles to rationalize the unhappiness inherent in his boarding school experience, noting that his school days "Coincided with the Great Depression ... At least we were not compelled to join the Hitler Youth or the Young Communist League." The near impossibility of this task reveals itself; "We should have put up cheerfully with the enormous rats that lived under the floors in the School House, dormitories so cold that ice formed on the jugs of washing water left overnight, and food that even the rats found unpalatable … we should have shown more understanding in our rejection of the continual attempt to make us fit for a world that a few years later ceased entirely to exist."

Fortunately, the winter holidays provided a respite and a reward. They were spent in Switzerland where, "I became a competent skier, the only sport I was ever good at." Occasionally (he does not say how often) he was joined by his parents from India. Summer vacations were spent in Cornwall where another aunt had discovered an idyllic sandy beach on the Lizard peninsula. Noteworthy and prescient, John spent one spring holiday with an uncle in Carrera where he was entranced by a friendly Italian niece. "The way that the English girls I knew moved was honed by many hours playing hockey and by many hours astride the saddle – Italian girls did not play hockey. They flow and do not jerk. Every gesture seemed destined to end in a caress. I must have tucked that away in my unconscious mind."

As John matures his thoughts and plans turn towards medicine. He does not attribute this to psychological influences but to a forced choice in the Rugby curriculum between mathematics and biology. After failing at the former he found "biology endlessly fascinating." This led naturally to medical school and he was accepted at Christ's College in Cambridge University in 1940. "Cambridge in wartime was a shadow of its former self. A skeleton staff, a meagre social life, very little fuel and not much food. However, I cared not a whit for these … I found anatomy, physiology and biochemistry endlessly fascinating." The following year he did well enough in the exam to be elected an Exhibitioner of the College. "I was content to spend all my time in my rooms totally

immersed in the marvels of science." This was despite the icy Cambridge winters and a totally disinterested (though famous) tutor, C.P. Snow.

In 1942 Cambridge was followed by University College Hospital in London for clinical studies. Interestingly the focus switches abruptly form study to social life. John shares a flat in Soho with a Cambridge friend, next to the "best restaurant in London." His room-mate's father was a famous film actor and his mother a leading gynecologist both "steeped in the avant-garde culture of Bloomsbury … familiar with the writings of Freud and Marx and close friends with Bertrand Russell." John contrasts "The world of socialist politics, psychoanalysis, art, music and writers … to my own world of Empire, the Army and Church."

This convivial social atmosphere pervaded the medical school as well. "It was the tradition in those far off and distant days for medical student to live rakehelly lives … our language would have made a bargee blush. One was expected to get drunk at respectable intervals and girls were there merely to be chased." One of John's class mates wrote the famous *Doctor in the House* books under the pen name Richard Gordon. John joined in, "I discovered that glamorous young starlets can take innocent young men on a giddy ride." John also did his bit as a firefighter when German rockets were pouring down on London during which he saved a Ward Sister "from a sticky end."

There is little mention of the serious side of medical training, perhaps due in part to the fact that teaching was dilatory, "The Consultants were God Almighty and the whole system was run by them and for them." Most made their money in Harley Street private practice and hospital work was for charity, a system that would change drastically when the National Health Service was introduced in 1948.

In 1943 all medical students were sent to hospitals in the Midlands to tend the D Day casualties from Normandy and John was among the first to use Penicillin. In 1945 he took and passed his final exams and "became a full-fledged Doctor of Medicine at the absurd age of 23." Following graduation family connections with an Admiral secured John a plum draft posting as a Temporary Acting Surgeon-Lieutenant assigned as a ship's doctor to a frigate of the West Indies Squadron based in Bermuda. John describes a convivial congenial life on board at a time when the island was, "literally a paradise on earth" and one of his daily jobs was to "supervise the issue of rum to the sailors" in the timeworn naval tradition. On shore he became familiar with wealthy

American land owners and, again, his impression was prescient, “How pleasant I thought they were, how open and friendly, how free of so many layers of hidden and sarcastic meanings was their speech.”

On completing his two-year draft and returning to England John “started in the wrong direction”, taking a job as a trainee surgeon at Addenbrooke’s Hospital in Cambridge where he discovered, “I have jumpy nerves, a vivid imagination, fingers that are all thumbs and my knots show a distressing tendency to become unraveled.” John accepted an interim position at Charing Cross hospital in London and “started packing his bags.”

During this last week in Cambridge John experienced two juxtaposed events that were life changing. At a time when he was “feeling very low” because his career had stalled and he had just been jilted he lay awake one night “ground between the millstones of regret and remorse.” What then transpired was a transforming religious conversion of the kind described by William James in *Varieties of Religious Experience.* Immediately John awoke he visited a bookstore in Cambridge and “without hesitation went to a bookshelf and took down the first book I saw. It was Albert Schweitzer’s *Civilization and Ethics.*” Back home he spent the day reading and underlining key phrases, coming to the twofold conviction he had experienced an “instantaneous enlightenment and would model his future life on Schweitzer’s example.”

This revelatory experience bridges John Raymond Smythies’ past with his future. John’s brilliance as a Cambridge scholar echoed the promise of his forebear’s talents and accomplishments but had not blossomed in Medical School or the British Navy, overshadowed by age related social preoccupations. It is likely that deeply felt *noblesse oblige* (privilege dictates responsibility) also helped trigger John’s spiritual awakening and ensuing commitment to employ his intellect and energy in the service of others. From this point forward, his life trajectory becomes purpose driven and quickly bears fruit, fulfilling Pasteur’s aphorism that “chance favors the prepared mind.” He would soon discover his life’s theme and meet the person whose presence and persona would anchor their lives going forward.

In John’s own words he would emulate Schweitzer; “I would get a thorough professional grounding in medicine, philosophy and ethics as he did, as well as psychology and the science of the brain. I would also look for a branch of medicine for my practice more suited to my overall

plan than surgery." John would follow this commitment rigorously and faithfully for the remainder of his life.

Paradoxically, while he planned this course of action, the interim position he accepted required that he fulfill an obligation to "mainly taking out tonsils … I got quite adept at it." Meanwhile he spent his spare time at the public library reading voraciously on topics relevant to his real plans. On Christmas Eve he attended a hospital party crowded with house officers in white coats and imported Irish nurses. "I caught sight of a remarkably beautiful girl standing by herself." The rest is described in elegant prose ending with, "I fell in love at first sight." This was his future wife Vanna and the outcome of that epiphany is told by her in the second half of their memoir.

"Still fizzing slightly from my religious experience … deeply in love and loved in return", John took turns working in the hospital's emergency room where he encountered psychiatric patients he worked up enthusiastically, following them to the psychiatric clinic. In this milieu he also treated a professional hypnotist and clairvoyant who so impressed John with his gift that he joined the Society for Psychical Research, beginning a lifelong interest and developing many friendships.

In April 1950 John Smythies' future career began to crystallize when he started work as a psychiatric registrar (resident) at Saint George's Hospital in central London. The three Consultants he worked under were all distinguished and competent Harley Street psychiatrists but none had any interest in research or transcendental metaphysics. However, the senior registrar, Humphrey Osmond, had a "keen intelligence and remarkable range of interests." He also wrote plays.

Six weeks into his first psychiatric rotation events would unfold that forever linked the names of Osmond and Smythies in jointly proposing the first neurochemical theory of schizophrenia, attracting worldwide attention. In pursuing an interest in hallucinations John had come across a French book describing visions from eating peyote. The author, Rouhier, identified the active principle as mescaline and published the chemical formula. Working with John a medical student on the psychiatric rotation, Julian Redmill, identified it as adrenaline. "So perhaps schizophrenia was due to a defect in the metabolism of adrenaline, leading to the production in the body of a substance chemically akin to mescaline?"

Visiting a friend in Cambridge John was introduced to an organic chemist, John Harley-Mason, who worked out a possible metabolic route by which a methyl group could be added to adrenaline to produce a substance like mescaline (M- substance). The trans-methylation theory of schizophrenia was published in the Journal of Mental Science – precursor to the British Journal of Psychiatry – in 1952 (Osmond and Smythies, 1952). This was the same year that Jean Delay and his team in France discovered chlorpromazine, the first effective treatment for schizophrenia. But "The Consultants at Saint George's did not show any interest in our theories" and Humphrey Osmond soon left England to take up a position as Deputy Director of a psychiatric hospital in Saskatchewan, Canada where he continued work on his theory with Abram Hoffer.

In mid-1950, as John's scientific career was about to flourish, he experienced a profound personal setback. He took Vanna to Ireland to meet his parents but the trip was not a success. "To marry a nurse was bad enough – to marry an Italian as well was insupportable." His mother's sights were set on an upper crust marriage to the British aristocracy. Temporarily derailed, John began to have doubts of his own until Vanna was stricken and hospitalized with a mysterious fever; "I dashed to the hospital and proposed at once at her bedside. After that it was all plain sailing." John's appraisal of his parent's opinions provides a stringent vignette of his own feelings, "They were racist beyond belief, snobbish beyond reason and xenophobic to a ridiculous degree." As John and Vanna travelled the world, settling in different cultures, John's comparative dislike for the English class system became a recurring theme.

The marriage of John and Vanna took place in December 1950 followed by an extended honeymoon in Europe visiting Vanna's relatives and friends, described in lyrical language. On return to London John continued to fulfill his career plans by an appointment in the EEG Department at Queen Square – the epicenter of European neurology and neurophysiology. Here he established significant contacts with leaders and mentors in the field as well as elaborating his own theories concerning the brain and consciousness.

After completing his appointment but finding that the British Medical Research Council showed no interest in the trans-methylation hypothesis John's thoughts turned to Canada and the prospect of joining Osmond and Hoffer who was both a psychiatrist and biochemist, Head of Psychiatric Research in Saskatchewan. Their interests had shifted from a theoretical M-substance to a known oxidation product of adrenaline, adrenochrome, which produced a florid psychosis

when taken orally. John's research during this time is described more fully in the scientific literature (Smythies 1998).

Before John moved to Canada he visited Carl Jung in Zurich where they shared their common interest in the observation that mescaline visions were unrelated to the personality of the subject experiencing them but, instead, induced scenes "all of a transcendental beauty and depth of meaning … Jung and I agreed that the collective unconscious must indeed be a strange and marvelous place – similar to the Bardo so clearly described in Tibetan Buddhist tradition."

John joined Osmond at Weyburn Hospital after he had assumed the role of Director and began transforming the asylum from a snake pit into the most improved hospital in North America. John describes one "horrific ward" he helped oversee before this improvement occurred. "It housed some eighty severely retarded male patients … There was no furniture in the ward and the patients had no clothes. There were no toilet facilities other than a hole in the floor that led to the drains. Every morning the attendants would hose down the patients and the floor with powerful jets of water."

After a year John was invited to join the Neurological Research Team at the University of British Columbia (UBC) in Vancouver where he spent a highly productive two-year period. This included mapping the intricate pattern of brain synapses under the microscope, work that earned him a Doctoral degree from Cambridge University. Simultaneously he took a second degree from UBC in philosophy and cultural anthropology to help fulfill his "Schweitzerian program."

While all this was going on interest in the adrenochrome theory attracted the attention of the Rockefeller Foundation, granting Hoffer and Osmond six years of support after the Foundation had grown weary of supporting "Ivy League universities to establish Chairs of psychoanalysis … money that had been wasted" (Hoffer 1998).

John took a different tack, continuing to broaden his interests and knowledge base. Throughout his career he was committed to remaining a generalist to "make sense of the whole picture … in an era of ever increasing specialization and the accumulation of enormous amounts of information" (Smythies 1998). To pursue this goal, he sought further training in neurophysiology and was attracted to the work of Sir John Eccles, a Nobel laureate in Canberra, Australia, who, like John, was a modern-day mind-body dualist committed "to the older tradition

that people have minds or souls as well as bodies." To accomplish this, he needed financial support. His work on mescaline had attracted the interest of Heinrich Kluver the German scientist, now working in Chicago, who used his influence with Sir Aubrey Lewis, "the king of British Psychiatry" in obtaining support for a two-year Nuffield Fellowship in Medicine. Sir Aubrey may well have been influenced by his Australian origins as an anthropologist and similar support he received from the Rockefeller Foundation to broaden his own training that helped him become a quintessential generalist in the field of psychiatry (Goldberg and Blackwell 2015).

Sadly, these well laid plans were dashed. Six months before the Smythies left Vancouver for Canberra their daughter Nicola was born. From birth she was increasingly fretful with problems in motor development. On the ship to Australia her symptoms worsened and on arrival in Sydney a neurologist diagnosed severe cerebral palsy with total paralysis of voluntary movements. It became clear they would have to return to England where Nicola died two years later.

John's fellowship was transferred to work in the Psychological laboratory at Cambridge University under Oliver Zangwill. Here he spent two productive years on research into the hallucinations generated by flickering light (stroboscopic patterns). As usual this research was connected to his broader interests. "I thought this might offer a way of tackling the unsolved problem of how brain processes generated conscious experiences." The research resulted in three long papers in the British Journal of Psychology and also contributed to his first book, *The Analysis of Perception"* (Smythies 1956). Simultaneously John continued his philosophical enquiries by joining the Moral Sciences Club "where Wittgenstein had once terrorized his opponents" and where he presented a paper of his own.

After completing the fellowship in Cambridge there were no attractive openings congruent with John's career plans in Britain so he decided to spend almost two years in America (1958-1959) dividing his time between two centers of excellence. During this epoch of psychoanalytic dominance both these biological enterprises were located in the State Hospital system. First was the Galesburg Laboratory at the State Hospital in Illinois where the research space was named Thudichum after the "Father of Neurochemistry." Harold Himwich was the head of research involving basic animal and human experiments across a broad spectrum of neurochemical and neurophysiological projects. (Vanna later tells the story of how Himwich served the colleagues and guests at his parties cocktails spiked with raw alcohol!).

Research was supplemented by weekly seminars in clinical and basic topics by invited experts from America and round the world. Its reputation was further advanced when the team was joined by Ermino Costa who arrived "like a cyclone" in 1956 (White 1998). John's involvement was relatively modest. He completed work on stroboscopic patterns and participated in ongoing clinical trials with the new antidepressant, imipramine. His principal learning must have come from immersion in a vibrant epicenter of innovative research conducted by world leaders in their fields.

Following this John spent a second year at the Worcester Foundation in Shrewsbury, Massachusetts transformed from one of the earliest asylums in America into a distinguished center of biological research under Hudson Hoagland (Calloway 2013).(see Ch.2) Here John worked with a Swiss scientist studying the effects of serotonin on reflexes and mescaline on the electrical activity of the brain.

As was his custom John also spent time in America pursuing contacts with the Parapsychology Foundation and its Irish President, who garnered her fame from predicting the disaster of the British airship R101. Reminiscent of John's time in Bermuda the Smythies fell in love with America and its people. "Here the people accepted us for what we were. They were not in the least arrogant, condescending or infatuated with their own self-importance. They were direct, generous, friendly and kind. We loved it."

John's sojourn in America ended, perhaps for two reasons. However impressive his degrees and credentials, to practice medicine in America would require him to repeat his clinical training and pass the requisite exams. In addition, outside the centers of excellence he visited, academic psychiatry was in the stranglehold of psychoanalysis. Psychopharmacology was still in its infancy and located largely in the V.A. and asylums. The American College of Neuropsychopharmacology (ACNP) was not founded until 1961 and John would not become a member until 1981.

Nevertheless, John promised Vanna they would one day return to live in America when "I have reached the top of the tree." And so, they did!

The Smythies return to England in 1959 coincided with John's realization that to move up the academic ladder in Britain, "it was time to complete my training in clinical psychiatry; and the only place to do that was the Maudsley Hospital which was the center of the web of influence and

patronage." John's impressive career path, research accomplishments and publications as well as the advocacy of powerful supporters like Heinrich Kluver and Lord Brain assured his appointment as a senior registrar at the Maudsley, beginning in October 1959. John's impressions of the training environment under the eye of Aubrey Lewis are cited in a recent biography (Goldberg, Blackwell and Taylor 2015) and John Smythies' contributions to psychopharmacology are mentioned in a commentary on Aubrey Lewis' generative contributions to that field, (Blackwell and Goldberg 2015).

As John's time at the Maudsley drew to a close in 1962 (the same year I began as a registrar), the Smythies' fourth child, a son Robert, was born with the same disorder as Nicola (after two normal boys). He died six months later and John describes a two-year period of grief and mourning that clouded their lives.

Perhaps it was attenuated to some degree for John by accepting a new job as Senior Lecturer and later Reader in Psychiatry at the University of Edinburgh. The family also took an idyllic trip through Europe in the hiatus between jobs. John and Vanna enjoyed Scotland's wild countryside and welcoming folks. "We found the Scots to be refreshingly free from the class consciousness that sours life in England. All Scots people, like the Americans and the Irish, have an inbound sense of their own worth, not conceit but derived from a firm grip on old-fashioned values."

The new job involved giving lectures, running a small clinic and doing research funded by a grant from the Medical Research Council to continue work on mescaline. Collaborating with chemists, the team synthesized congeners and tested them in a rat model of psychosis. During his twelve years in Edinburgh (1962-1974) John's teaching activities are reflected in the publication of four textbooks dealing with the biochemistry of schizophrenia, the neurological basis of psychiatry and biological psychiatry, all cited in the memoir's Bibliography (Smythies 2015).

John's literary account of life in Scotland is evocative and colorful with interesting characters and enjoyable pastimes. He developed an interest in lapidary and Vanna turned the agates he found into fashionable jewelry. Leisure included summer camping trips throughout Europe and Arctic skiing adventures in the Cairngorns.

Meanwhile John's academic career and reputation prospered. He was elected President of the International Society of Psychoneuroendocrinology and a Fellow of the Royal College of Physicians. In 1968 he spent six months as a Fellow in Neuroscience at MIT, including time with Seymour Kety. For several years John was a Consultant in psychopharmacology to the World Health Organization, attending WHO sponsored meetings around the globe. In the penultimate year of his time in Edinburgh he spent a sabbatical year in Alabama at the University that opened the door to the future and the remainder of his long career.

But between Edinburgh and Alabama John's memoir includes three pages, titled "Storm Clouds" that tell a story of the vicissitudes that can influence and afflict a scientific career. In his words, "A new and sinister development took place." But these were events kindled years before that burned with a slow fuse. John's account is in agreement with and supplemented by the updated Wikipedia Encyclopedia entry that includes 81 citations from scientific, philosophical and religious sources. (Wikipedia 2014).

In 1952 when Osmond and Smythies published their ground-breaking paper, *"Schizophrenia a New Approach"* work with mescaline immediately attracted the attention of the American author Aldous Huxley who offered himself as an experimental subject. Soon afterwards Osmond and Huxley met in Los Angeles at the annual meeting of the American Psychiatric Association after which Osmond visited Huxley in his home and administered mescaline, producing an eight-hour psychedelic experience. Huxley and his wife then took a 5,000-mile car tour of all the American National Parks following which Huxley wrote "*The Doors of Perception"* composed in a month and published in 1954. The title is taken from William Blake's poem, "*The Marriage of Heaven and Hell."*

"If the doors of perception were cleaned everything would appear to man as it is, Infinite.

For man has closed himself up, till he sees all things thro' narrow chinks of his cavern."

Huxley's public tone concerning hallucinogens was restrained and discrete. For the next decade Osmond and Huxley restricted their experiments to a "carefully selected group of academics – psychologists and philosophers." (Wikipedia 2014). John did likewise, all three sharing the view that mescaline's purpose was to acquaint professionals with "something they needed to know about their subject – i.e. the theory of mind." The initial psychiatric response in

1954 was constrained and consistent with this. William Sargent reviewed *"The Doors of Perception"* for the British Medical Journal hoping it would stimulate "physiological rather than psychological theories". . Despite the Centuries long history of the use of hallucinogens in faith-based rituals the philosophical and religious opinions tended to be ambivalent viewing it as a "flight from reality" (Buber 1965) or "an artificial interference with consciousness" and nothing to do with the Christian "Beatific Vision" (Richards 2005).

Perhaps inevitably, in the 1960's, the tide began to turn from psychiatric and philosophical speculation to the popular use of hallucinogens as part of the emerging hippie drug culture abetted by misguided advocacy from the likes of the Harvard psychologist Timothy Leary (Leary 1968). As John Smythies notes, "The lid was off Pandora's Box" with deleterious effects on psychiatric research and its funding. "Mescaline from being a possible key to unlock the secrets of schizophrenia became a pest that had to be stamped out at any cost."

During John's tenure in Edinburgh there were additional setbacks affecting his chosen areas of interest. Abram Hoffer had continued his work on adrenochrome but ran afoul of Julius Axelrod's Nobel Prize winning catecholamine research, backed by Seymour Kety's influence that failed to confirm the role of adrenochrome in the metabolism of schizophrenia. Meanwhile 6Hoffer and Osmond's research led to conclusions that supported Linus Pauling's controversial orthomolecular theories concerning the prevention and treatment of various diseases and the role of vitamins in maintenance of optimal body function. These provoked allegations from the medical establishment of quackery due to failure to confirm the claims in traditional double blind studies.

John's final paragraph rightly asserts these storm clouds would eventually dissipate when more modern findings cast them in a better light but in 1971 the future for his ideas, research and funding in Britain must have seemed bleak and he might rationally have been seeking greener pastures.

Ron Bradley, John's friend, colleague and fellow Journal editor had already quit Edinburgh to settle at the University of Alabama in Birmingham (UAB) as Director of a new Neuroscience Program. Here John accepted an invitation to spend his sabbatical year and, after returning to Edinburgh, the philanthropic Irish family offered to endow a named Chair for him at UAB - *The*

Charles Byron Ireland Chair of Psychiatric Research. He accepted and would remain in that post for the next 16 years until mandatory retirement.

In Birmingham the Smythies adjusted rapidly to a congenial antebellum environment that included many families of Anglo-Saxon ancestry. John's research and writing prospered, backed by tenured security and the resources of an endowed chair in a parent Department of Psychiatry with a supportive Chair, "A slot that often attracts the power hungry, cunning and unscrupulous – at least in England."

During this epoch John's team identified two enzymes in the brain defective in schizophrenia, MAT and SHMT. He was able to continue research on mescaline and he facilitated the recruitment of Humphrey Osmond from Canada to work at the State Psychiatric Hospital in Tuscaloosa. John's imaginative and inventive brain also lured him into a novel enterprise; stimulated by Linus Pauling's CPK plastic models of neurotransmitters, "My subconscious, tuned to my work in anatomy immediately took to these examples of microanatomy. I wondered if it might be possible to use them to build up models of receptor molecules in the brain on which neurotransmitters act." John spent several years on the Research Advisory Board of a California research and development company seeking for novel drugs capitalizing on this new paradigm but with little success. "Like many scientific hypotheses my model did not turn out to be right in detail, but it was useful."

This honest and modest observation may reflect insight derived from the painful experience of witnessing three of his major contributions mired in controversy that prefaced his migration from Britain to America. It might also underpin what, for such a fertile mind, was a relatively fallow period during which he chose to use his talents in different arenas. A bibliography of books and selected scientific papers at the end of the memoir reveals a hiatus in publications during his sixteen years at UAB (1972-1988). He cites no scientific papers between 1969 and 1994 and only three books (two authored, one edited) all in the early years (1973-1978).

However, John remained an active participant in international neuroscience. During this entire period, he spent three months each year travelling to numerous scientific meetings often combined with family vacations in Europe and the West Indies, during which he regularly attended the annual December ACNP meetings in Puerto Rico or Hawaii. He describes the people he met

and the places visited in elegant and occasionally astringent prose. In 1972, early in his time at UAB, he was one of only five scientists from the West invited by the Academy of Medial Sciences of the USSR to attend a conference on schizophrenia. “I was impressed by the warm and genuine friendliness of our Russian hosts. I was also impressed by their complete inability to organize anything efficiently and by the dismally low standards of their research.” The Professor who organized the conference was chief architect of the “infamous policy of throwing dissidents into psychiatric hospitals with the diagnosis of a non-existent disease called ‘sluggish schizophrenia’ he had invented himself.” Not much had changed in Russia since Aubrey Lewis visited there in 1938 on his Rockefeller Foundation tour. (See Goldberg, Blackwell and Taylor 2015).

John Smythies dealt with retirement in 1988 in a manner to be expected from someone of his intellect and temperament. He sought an environment that was domestically tranquil but intellectually vibrant. So, the Smythies returned to England where John obtained an honorary appointment at Queen Square in the Psychiatry Department and the family moved to a country cottage on the Sussex-Hampshire border.

Whether John was intellectually satisfied is unmentioned but the domestic debacle is described in a colorful portrait of their dismal life in an uncomfortable rural setting plagued by English plumbing, weeks of wet weather and social ostracism. “You have to live in an English village for at least ten years before the locals will take any notice of you.” The only ameliorating aspect was proximity to the English Channel providing the opportunity for regular escapades to France with its attractive bed and breakfast “gites” where they were “welcomed into the inner life of the family.”

It took only two years to decide that “life in the country is strictly for the birds.” They sought refuge in the North Country, birth place of the Smythies dynasty, and purchased a Victorian terraced house next door to their son and daughter in law in York, “the best medieval city in Britain, one visit to the Minster charges one’s spiritual batteries for a month.” Meanwhile when a former friend at MIT described San Diego as the new center of gravity for neuroscience in America the Smythies decided to sample its ambience. Finding the atmosphere ‘gemutlich’ and the climate perfect they began a commuter life between the cities of York and La Jolla.

John's intellectual pursuits began to flourish again at the University of California at San Diego (UCSD). He "spent the first few years at UCSD catching up with the great advances that had taken place in neuroscience. I also learned to manage a computer." Inevitably the domestic and intellectual charms of California won out. "Every year our visits to La Jolla grew longer and our time in England grew shorter." Finally, the family relocated fulltime in America; their son and daughter in law in Alabama and the parents to La Jolla where they moved into an idyllic mansion looking out over the Pacific Ocean.

John Smythies' memoir tells its own story of a remarkable renaissance in intellectual productivity beginning in the mid-1990s (at age 72) and continuing to the present (at age 93). This work has revisited and updated two of his lifelong interests in mind-brain dualism and antioxidants as well as a novel interest to integrate "the vast amounts of information being churned out about biochemical mechanisms involved in synaptic plasticity of the brain." This late life burst of creativity also produced a volume of poetry (Smythies 2002).

Most impressive about John's return to the adrenochrome (Smythies and Galzigna 1998; Smythies 2002) and megavitamin-antioxidant controversies (Smythies 1998) is that John sets the record straight with impeccable science devoid of hyperbole. His new views on synaptic plasticity are set forth in *The Dynamic Neuron* (Smythies 2002) with theories that may have significance in Alzheimer's and Parkinson's disease as well as schizophrenia. Perhaps John's most controversial contributions are in mind-brain dualism both because of its spiritual implications as well as the highly sophisticated, complex conceptual relationship it theorizes between the physico-chemical structure and function of the anatomical brain and our sensations, images, feelings, memories, thoughts or experiences.

John first presented these ideas in his book *"The Walls of Plato's Cave"* (Smythies 1994) and later elaborates on them in an article, *Brain Consciousness: The Ghost in the Machine*, (Smythies 2009). Whether or not mind is merely a function of the brain, possibly unique to humans, has been a central issue throughout the history of philosophy with three prevailing schools of thought, materialism (identical and interdependent functions), dualism (separate and independent functions) and idealism (mental functions only). The new school of thought proposed by John, "Substance Dualism" (Smythies 2009) and its significance may be difficult for most lay and many empirical scientific readers to grasp. The theory requires "a paradigm shift in our

concepts of time and space" in which we need to replace a four-dimensional model with a higher dimensional structure in which phenomenal space, with its contents, (mind or soul) and a physical space, with its contents, (brain) are different cross sections (branes) of a higher dimensional space (the bulk).

The abstract level of reasoning and semantics are a rarity but, John suggests, a comforting one, which can "explain the facts discovered by parapsychologists … and it can present a plausible account of a human soul in 'next world'."

The final paragraph of John's contribution to this shared memoir reminds the reader that his saga began with a commitment to emulate Albert Schweitzer. He makes the categorical statement, "I do not accept the current dogma that science has abolished the soul. Of course, neither has it been demonstrated by scientific methods that it exists. This question is still wide open." John notes that to adopt such an ambivalent position is ethically sound based on "a rational religion such as the gentle faith of "Quakers, Buddhism and Hinduism shorn of minor polytheistic components." In this he seems to be following in the footsteps of Thomas Jefferson.

The space between the male and distaff side of the Love Story is taken up by John's tribute to his wife in the form of a poem. Vanna's tale is told in fewer pages but with equal eloquence and colorful prose spiced with humor and psychological insights.

Vanna was born in Trieste in 1928, a city founded by the Romans, incorporated into the Austro- Hungarian Empire and rebuilt in the 18th century in Viennese style. The population is multi-ethnic and polyglot. All her family are fluent in Italian, German, French and English while her father, from an ancient line of ship owners, also spoke Rumanian, Spanish and Arabic.

Vanna grew up in "bitter-sweet culture" and lived in a large and beautiful house, bought by her grandfather when she was four, looking out over the old city and sea beyond. This served as the compound for a fragmented and dysfunctional family. It housed her father, "who always saw the end of the world around every corner" her uncle Alfredo, "a cheerful playboy" and her Aunt Titty, "a tyrannical monster of the blackest arrogance and malice" into whose care she was committed by parents who led a 'marriage of convenience' and a mother who "found her pleasures elsewhere." It was a time and culture where "children had to fit into the straight jacket that had been prepared for them and do what they were told – no matter what."

This ideology set the framework for a bleak childhood as the victim of her aunt's verbal and physical abuse. She was forced to eat foods she hated, received "stinging blows to the face" and was repeatedly locked in a dark coal cellar for hours on end due to minor infractions her aunt deemed "wicked resistance." After years of such torment Vanna was labelled "incorrigible" and packed off to a nearby Convent boarding school to be cared for by nuns where her "heart would ache and long for home."

While John and Vanna's childhoods shared parental neglect and early banishment to boarding school their reaction and coping strategies differed. While John eventually found refuge sheltered in a prestigious all male public school Vanna responded with exuberant escapism, sustained by "a cheerful, resilient and optimistic nature." Aided by a close friend, Beatrice, Vanna found ways to evade school and home, "So I limped along from childhood to youth sustained by my many friends … Italian, Greek and Jewish of happily mixed parentage. I lived an intense, happy and varied life with all these gifted, beautiful, witty and charming young people." These friends, both male and female, included a group of talented musicians and with them she "went sailing, swimming, walking, window shopping and dancing."

As Vanna reached puberty and early adolescence (not long after John visited Carrera) the Nazi's occupied Trieste ushering in "years of near starvation, misery and fear." In 1947, aged 17, Vanna and her friends welcomed the victorious New Zealand army, later joined by the British Navy and American troops.

Liberation brought "a whirl of swimming parties, balls, all sorts of get-togethers and social activities that went on day after day." Allied officers distributed largesse in ample supplies of food; "after years of little more than boiled onions and stale bread soup, this was bliss for us."

A year later, aged 18, and on the cusp of adulthood, Vanna decided it was time to leave home, escape from her relatives and "find something worthwhile to do." When a friend offered to help her find work as an *au pair* in England she leapt at the chance. With an idealized view of the English she pictured a new life ahead. "Stimulated by the novels of Agatha Christie that I had read, I dreamt of a large country house filled with gracious people, looked after by friendly servants I could gossip with, and possibly with a Rolls Royce outside the door. Here I could put on my nice

clothes, stretch out my legs, flirt with a tall, slender and handsome heir to the estate and look after a bunch of blond and blue-eyed children."

The reality that greeted her in suburban London was to find herself, "a skivvy in an awful house amid awful people." She was dealing with a "small fat and ugly woman … with a greasy little girl in tow." The father and husband refused to pay her the agreed stipend, she hardly had any time off and had to defend herself from his attempts to fondle her and invade her barricaded bedroom door at night.

In England the post-war law for immigrant workers left Vanna with only one choice apart from domestic work, which was nursing. At random she picked Charing Cross Hospital in central London and enrolled in a three-year nursing program, a wise but arduous decision. The profession was still entrenched in the Florence Nightingale ethos of servitude. Twelve hour shifts with dormitory accommodation several miles and a crowded Underground train away from work. "I was always cold and my nose was red, my hands were chapped and my feet felt like pancakes."

But there were compensations, "I loved my work and was good at it. I relished the challenge of helping sick people. I found I could talk easily to patients, smile at them and then cheer them up – and they liked to tell me their problems. All my life I've been a good listener." The job paid enough for annual visits to friends in Trieste and Vanna realized that, overall, she had earned her freedom, responsibility to make decisions and how to look after herself.

Meanwhile she was accommodating to the English way of life and becoming aware of differences in her two cultures. Invited to the homes of fellow nurses she was shocked to have to share a bed; "the semi-detached houses were mean, draughty and damp. We sat huddled in front of a small gas fire. Our cheeks were roasted whereas our rears remained icy."

Despite the hard work and long hours there were opportunities for fun, dancing and dating. Vanna began to see an ardent medical student suitor until he invited her to, "Meet his Parents (shades of Jane Austen!)." Things did not go well: "I felt it in my bones that I was not cut out to be a nice proper wife of a nice proper lower middle class churchy doctor and spend the rest of my life in a semi-detached, passing around tea and sandwiches. As a parting gift he gave me a Missal."

Vanna's concluding comment in this section (Escape) ushers in the next (The Coins meet). "I was soon to find the very right person in (almost) every way."

In December 1949, Vanna, now aged 21, is on night duty (her favorite) and catches a glimpse of the new house surgeon on an adjacent ENT ward. "He appeared promising, tall, blond also slender." They met formally at the annual Christmas Eve party and John became her partner at a reciprocal Nurse's New Year Ball. They quickly fell in love and Vanna runs through her checklist for a suitable mate. John passes with flying colors save the exception of 'Elegant' where she bemoans the difference between "Englishmen who have no inborn dress sense and our dandified Italian men." She is ambivalent about the fairness of this distinction; pages later in a final analysis of "How things look now", Vanna enthuses about the marriage because, "He would always come with me to buy my clothes and I always relied on his excellent taste."

Early on Vanna was most impressed by John's "extraordinary ability to do several things at once. This was a sign of his quick intelligence. He always seemed to be two steps ahead of everyone else." Her final prenuptial opinion was, "on the whole, affectionate and friendly as he was he would do – with a bit of give and take."

The truth of this caveat was quickly revealed when, once again, a ritual meeting with her lover's parents went awry. But this time it was Vanna who felt rejected. The meeting took place in his parent's imposing castle in Ireland. John's mother, the self-styled 'Tiger Lady', weighed up the candidate to become her daughter in law against her aristocratic ambitions and found Vanna wanting; "Her first glance raked me from stem to stern." As previously told by John their relationship weathered this storm but they now confronted the archaic obstacle that she must obtain permission from the general Nursing Council to marry contingent on completing her training. Grudgingly granted, newly married student nurses were routinely assigned to night duty and posted to suburban locations that restricted contact with their spouse to once weekly.

Safely married this, "sensitive and high-spirited couple with lots of personality" needed room to express themselves and adapt to differences in cultural background that Vanna identifies. John's "stiff upper lip," emotional reticence and polite, uncritical, understated manners contrasted with Trieste's ebullient tendency to poke fun, exaggerate everything and "scatter their feelings all over the place."

Later on, some of John's lifelong traits became more apparent: a tendency to introspection, note taking, forgetting social commitments and taking solitary walks. To this reader it sounds somewhat like the stereotype of an "absent-minded English Professor." Once again Vanna adapts; she learns to assertively and effectively manage their travel plans and domestic environment. If walks are indicated she takes the entire family with her. "So, there were lots of differences to be ironed out. But with perseverance we managed to do so quickly."

In less than 20 pages and two sections, "Off around the world"' and "Edinburgh and after," Vanna describes their travels and adaptation to differing work environments John chose in his lifelong career crusade. Conforming to English upper class social traditions their two sons Adrian and Christopher were enrolled at birth to follow in the Smythies' tradition as pupils at Rugby public school, now gender integrated. Vanna agreed it was best "but I gritted my teeth, hid my tears and missed them every day."

In the midst of the turmoil of many moves and different cultures, illustrated by a cornucopia of interesting and amusing anecdotes, Vanna notes, "I preserved my balance by focusing at times on my own values, needs and talents." She lists them: running a restaurant with a friend, making jewelry, buying or selling antiques, knitting, dressmaking, professional flower arranging and embroidery. And regular visits to Italy were "a means of recharging my batteries."

Vanna sums it all up: "Life on this basis was usually fun … or if not … interesting." Together the Smythies struck a balance "between John treading on the accelerator and my reaching for the brake."

The final paragraph in the memoir reflects Vanna's sense of lifelong contentment and achievement, culminating in a family reunion at La Jolla attended by all their children and grandchildren. Her husband a content accomplished academic; their sons happily married, one the Vice-President of a bank, the other a neurosurgeon. Trevi Fountain fulfilled its promise!

The INHN website is intended to lay bare the lessons of history for posterity and the future of our field. What can be learned from "Two Coins in the Fountain?" Posed as a love story it invokes the role of marriage and its influence on a creative scientific career. In an essay "*Physician Lifestyle and Medical Marriages"* (Blackwell 1984) I reviewed what the medical literature had to offer and in a later talk to graduating residents in psychiatry (Blackwell 2012) I suggested, "choose

a life partner who is psychologically minded, who is at least as intelligent as you are, and who has a strong sense of humor. Above all do not marry a real or metaphorical patient."

The marriage of John and Vanna Smythies epitomizes these ideals and echo's the advice of Henri Nouwen that, "Man and woman do not have to cling to each other but can move graciously in and out of the others circle." Each of the memoirs on our website paints a similar -but less detailed portrait of marital harmony and titrated interdependence.

John Smythies career span and trajectory is impressive, stretching from the earliest biochemical theories of schizophrenia to the contemporary hiatus in drug development. Following a conversion experience John's rigorous pursuit of the best training necessary to fulfill his 'Schweitzerian' ideals lasted 16 years from graduation as a physician in 1945 to his first academic appointment at Edinburgh in 1961. This was indeed a "purpose driven" life further illustrated by the tenacity demonstrated pursuing his chosen areas of interest.

The fact that these were cutting edge issues exposed him to risk and controversy that effected his career in a manner reminiscent of Jose Delgado's need to relinquish his mid-career tenure at Yale for an endowed chair in his native Spain (Blackwell 2014). Delgado's life span (1915-2011) is only a few years different from John Smythies and although a changing social and scientific Zeitgeist influenced both careers John's reputation remains untarnished. He never made the mistake of confusing science with philosophy, acknowledging the difference between proof and speculation, a distinction Delgado blurred in his pioneer work on brain stimulation. -Both men remained active into their ninth decade but John's creativity continues to flourish, ----------further informing novel areas and clarifying issues that became controversial since their conception earlier in his career. Since the publication of the memoir John has remained productive in new fields of neuroscience, generating twelve papers including the function of the claustrum, adding to the unfinished work of Crick and Koch (Smythies, Edelstein and Ramachandran 2014a), as well as new molecular mechanisms in information processing of the brain (Edelstein, Smythies and Noble 2014b). His work on exosomes has implications in several key areas including Lamarkian inheritance, the function of telocytes and cancer neogenesis. John Smythies' burst of late life productivity certainly makes one wonder yet agian about the wisdom of Sir William Osler's conviction concerning "the comparative uselessness of men above forty years of age" (Osler 1932).

There is an interesting resonance between Osmond and Smythies interaction with Aldous Huxley over mescaline and Frank Berger's experience concerning meprobamate, the first 'minor tranquilizer' he had discovered. In 1956 Frank invited Huxley to give a keynote address to a national conference celebrating the science and success of his discovery. Huxley's enthusiastic endorsement coupled with his book *Brave New World* and its panacea "soma" may have helped ignite the subsequent heated debate about the wisdom of widespread prescribing and potential abuse of minor tranquilizers (Blackwell 2014). However, like Smythies, Berger drew careful distinctions between his scientific work and his philosophical speculations published by his widow after his death (Blackwell 2015).

I hope that students of neuroscience will read the Smythies' memoir in full as well as the other biographies and memoirs in this book and published on the INHN website. They may cast light on the potential challenges, training, trajectory and success of their chosen career.

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Chapter 11

Caution and Skepticism

Preamble

Sir Aubrey Lewis: Lifetime Accomplishments

Aubrey Lewis: Psychopharmacology Accomplishments

Adumbration; a learning lesson

Patient Compliance and the Therapeutic Alliance

Preamble

The full Biography of Aubrey Lewis, the Maudsley Hospital and Institute of Psychiatry's Director, explores the origins and impact of an epistemological and critical mindset which was drilled into all of its graduates.

In 1938, just prior to World War Two, Aubrey engaged in an exhaustive tour of European Psychiatry on behalf of the Rockefeller Foundation in America, interested to know more about the state of psychiatry to help govern its philanthropic research grants. This provided the seed bed of Aubrey Lewis's own beliefs, implemented by his scrupulous and rigorous personality.

In his scientific paper, *Between Guesswork and Certainty in Psychiatry,* Aubrey expresses his philosophy in elegant style: "It is the common state of reflective and enquiring minds to be somewhere between untrammeled guesswork and certainty. It would be discreditable if psychiatrists were to be huddled at either extreme, wholly engaged in guessing or ignorantly certain."

Often regarded as nihilistic towards novel treatments in general and drugs in particular, the second brief biography records his generative influence on psychopharmacology ending with a quotation from his 1963 article on *Medicines and Afflictions of the Mind* which is a pithy and remarkably prescient comment relatively early in our odyssey: "Psychiatric advances have been less dramatic and less conclusive than in other therapeutic fields." Few probably felt this was true in 1963 but it certainly is today.

The final essay, *Adumbration,* is a personal reflection on the historical, scientific and ethical lessons learned from research on a discovery of my own that Aubrey Lewis facilitated and watched over with a critical eye and benign indulgence.

-Sir Aubrey Lewis: Lifetime Accomplishments

By

Sir David Goldberg, Barry Blackwell and David Taylor

Although he described himself, aged nine, in an essay while in primary school as "an Australian, and my essay is from an Australian point of view" (Shepherd 1986). Aubrey Lewis became the foremost psychiatrist in the United Kingdom of the 20th Century. He transformed psychiatry in Great Britain and produced a generation of academic psychiatrists; and he was directly responsible both for shaping the Maudsley Hospital from its early beginnings, and bringing about the existence of the Institute of Psychiatry as part of the University of London. He combined an encyclopedic knowledge of world psychiatry with an exacting standard of scholarship. He did his utmost to ensure that each of his trainees achieved the highest standard of both clinical care and the results of their research. This paper will describe how he came to work at the Maudsley, and finally will outline some of his major achievements.

Early Life and Training

Aubrey Lewis was born in Adelaide in 1900. His father earned a living in the 1890s in a small watch-making and repairing business and his mother was a prize-winning local teacher of elocution. In view of his later achievements it is of interest that he could not read until he was seven, nor was it financially possible for his parents to send him to the school of their choice. It is possible that his development was delayed because his parents would have been advised that he should avoid eye-strain following an attack of measles. Once he started his reading, there was clearly no stopping him. He was educated at the Catholic Christian Brothers College in Adelaide, where he soon attracted the attention of his teachers. In competition at the age of 14 the judge specially complimented "Master Aubrey Lewis, who, without notes of any kind, discussed Shakespeare and his works with agreeable delivery and wonderful fluency." In the following year, his teachers recorded the prophetic words that his discourse on the origin and history of words "exhibited a remarkable grasp of philology" (Shepherd 1986). His earliest interests were in literature, history and languages, so much so that the school teachers in his home town of Adelaide,

Australia, predicted a distinguished career in the humanities (Jones 2003). However, his early education formed a secure and lasting foundation for all his subsequent achievements.

During his years as a medical student at Adelaide Medical School he was a prominent member of the Medical Students' Society: “Mr. A. J. Lewis read his paper on 'Quacks', which proved to be one of the finest ever heard by the Medical Students' Society. His quick touches of humor, quiet sarcasm, balanced judgment, and above all, the brilliant style in which it was written, only go to show how great has been Medicine's gain, and I hope this will not prove to be literature's loss” (Shepherd 1986).

After house jobs in Adelaide his first piece of research was an anthropological study of the aborigines of South Australia which included their physical measurements, their implements, songs, vocabulary and psychological observations. Later that year he was awarded a Rockefeller medical research travelling fellowship for “study in psychological medicine and nervous diseases, with the special object of training the holder for studying the mental traits of the Australian aboriginee.” He spent the next two years in North America working with Adolf Meyer at Baltimore; in London at Queens Square with Gordon Holmes; in Germany, at Heidelberg, with Karl Beringer; and at the Charité in Berlin with Karl Bonhoeffer. On a brief return visit to Australia it became clear that there were no appropriate opportunities for him at home and the Rockefeller Foundation allowed him to change from psychology to psychiatry and return to London.

After a brief spell at the National Hospital for Nervous Diseases in Queen Square in 1928, he applied for a job as a sleep researcher at the Maudsley Hospital, which had opened in 1923 under the direction of Dr. Edward Mapother. A British University Hospital had been the dream of Henry Maudsley, who had hoped to create a university psychiatric hospital similar to -that founded by Emil Kraepelin in Munich. Mapother had served in the British Army in the First World War and Lewis expected from what he had been told that at the Maudsley he might have to re-adjust his modes of thought to a somewhat insular, rigid materialistic and old-fashioned model, of which Mapother would be the exponent. In fact, he found it quite otherwise (Lewis 1969).

Mapother was concerned that research in the UK was carried out by clinicians in their spare time. This led to an unduly optimistic outlook and prevented “the laborious observation-and experiment that forms the basis of every progressive science.” He avoided a rigid adherence to any

school of thought and firmly believed in the advance of knowledge through empirical research. He believed in the importance of hard facts, and disapproved of cross-discipline speculation about causation and the meaning of symptoms. He had a skeptical attitude to new treatments, thinking that a doctor's first duty was to do no harm, and distrusting new treatments for whose efficacy there was insufficient evidence. This aspect of psychological medicine was regarded as "spookery" and thought not to be an appropriate activity for psychiatrists.

Mental phenomena, or the immediate products of perception, were the only objects of knowledge. Where classification was concerned, manic-depressive psychosis was designated a provisional group of heterogeneous disorders, the neurotic-psychotic dichotomy was dismissed as meretricious; and the links between depression and such feeling-states as anxiety and phobias were admitted. Whilst Aubrey obviously felt at home and compatible with Mapother's views, he also brought to the subject additional dimensions of benevolence, creativity, innovation and calculated risk taking. That opinion is shaped partly by personal experience of one of us (BB):

> *"Lewis moved me from the B to the A stream, kept me under surveillance for 6 months and then gave me the opportunity of a lifetime, to work under Ted Marley with the only provision so that I was not to engage in psychoanalysis! While the Medical Director of SKF described the cheese idea as 'unscientific and premature,' Aubrey reminded me that Hippocrates 'had said something about cheese.' The quotation I found about why 'cheese was a bad article of food' became the prelude to my Cambridge M.D. thesis."*

Shortly after Lewis was appointed, Mapother was sent on a tour of major centers in the USA by the Rockefeller Foundation and, like Lewis before him, was impressed by the psycho-biology of Adolf Meyer at the Johns Hopkins Hospital in Baltimore (Jones 2003). Meyer insisted on thoroughness in history taking, in probing the family and social background, and Aubrey clearly agreed with him.

At the time of his arrival the Maudsley Hospital was small scale, so that the entire clinical and scientific staff could sit round a small table for lunch. However, by 1931 staff numbers had risen to 152 (including 17 permanent doctors), looking after 207 beds (Jones 2003). Lewis became a consultant in 1932 and Clinical Director of the Maudsley by 1936 – the same year that Mapother

was appointed the first Professor of Psychiatry at the Maudsley. During the 1930s the Maudsley hospital trained many of those who became well known later, such as Eliot Slater, Maxwell Jones, John Bowlby, William Sargant, Denis Hill, John Sutherland and Wilfred Bion.

In 1938, on the eve of World War II, Aubrey Lewis was commissioned by the Rockefeller Foundation to undertake a review of European psychiatry. He embarked on a six-month journey during which he visited 13 countries, 45 cities and interviewed 234 individual clinicians and research workers in a wide variety of settings; clinics, Institutes, hospitals, asylums, laboratories and prisons.

From this he produced a tour de force that was 90 pages long (Lewis 2003). The report was archived unedited by the Foundation and not published until 65 years later when it was reviewed in an accompanying article (Angell 2003) which comments "while Lewis was sent to the Continent to gain the perspectives and knowledge that would help to make the Maudsley a more impressive candidate for Rockefeller patronage, his disappointments and criticisms perhaps indicate a desire on his part to take Continental psychiatry down a peg or two and dispel what certainly Lewis deemed a myth of excellence. Of course, it may simply be that Lewis' criticisms reflect the character traits that later led to his reputation as someone who spoke the truth, regardless of the views of others or the inconvenience it might cause. What Lewis' report very neatly reflects is a discipline in flux, whose membership was being worked out in a way that would shape the field's development. It was lucky that Lewis, a notoriously frank man, shared the Foundation's fundamental orientation and skepticism over certain branches of the field."

Lewis concluded his report with a four-page summary of his impressions. He starts by noting that most of the good things he found were in related branches of medicine, neurology, physiology and biochemistry. "Psychiatry seemed everywhere a rather stagnant subject." Research activity was "flawed by conflicting results, weak technique, idea-less repetition, excess of speculation or – probably most important of all – failure to see problems that are at once fruitful and attackable. Certainly, the fruits of psychiatric research seem very meager in relation to the volume, it is depressingly less alive and (intellectually if not practically) less exciting than some other branches of medicine." In addition, psychiatry remained "outside the mainstream of medicine" while "the predominance of neurology and the extravagances of some psychotherapists seemed to have an almost equal share in delaying the social and psychological side of psychiatry."

To the recent reviewers this synopsis was "rather like a torchlight beam illuminating a previously dark corner" (Jones 2003).

He also addressed the way young psychiatrists were being taught: "little clinical acumen was displayed in assessing the outcome of treatment, the research possibilities were generally ignored and there was a risk that, as with psychotherapy, over-enthusiasm might in time provoke an excessive disillusionment." He found that the standard of clinical work and knowledge was perceptibly lower in psychiatry than in neurology. *"People often had a very detailed knowledge of the literature and difficulties of some tiny problem that they had worked on for a dissertation or article, but they had a poor grasp of clinical psychiatry as a whole; partly, I think, because they had not time to examine all their cases thoroughly, and because they were unduly satisfied with text-book accounts and needlessly conversant with bygone controversies….they were a little right and a little wrong: names of people and of categories and quarrels usurped the place of immediate experience"* (italics added). Lewis was to return to these problems in his work as an educator after the end of the war. One can also see in these comments where his own future efforts might lie; with the application of stringent empiricism in carefully crafted studies on fruitful topics coupled with a devotion to strengthening psychiatry's ties to medicine and the inclusion of psychological and social influences on outcome.

The Maudsley Hospital was moved out of London in 1939 because of the Blitz from the Luftwaffe, thus providing Lewis with a respite to contemplate the lessons learned from his 1938 European trip and to integrate them with his own bent toward social psychiatry. He became Director of the Mill Hill Emergency Hospital treating servicemen, especially those with "effort syndrome." This led to the first psychosocial treatment for this debilitating condition, from which Maxwell Jones developed into his concept of the "therapeutic community."

Mapother had launched an appeal for an Institute of Psychiatry to be attached to the University of London in 1931, but never lived to see it come about, as he died in 1940.

The Contributions of Aubrey Lewis

In 1946 Lewis was appointed as Professor of Psychiatry at the Maudsley Hospital, but opted not to combine this with medical superintendent of the hospital, but to confine himself to teaching and research and to be in charge of a professorial unit admitting its own patients. With

the arrival of the NHS in 1948, the Maudsley was united with the Bethlem Royal Hospital, giving access to its rich endowment funds, and greatly expanding the number of beds available to what became the Joint Hospitals. He finally persuaded the University of London to adopt the Institute of Psychiatry (IoP) as part of the University of London in 1948, so that Henry Maudsley's dream became a reality. He also obtained funds from the Medical Research Council to support what became the MRC Social Psychiatry Research Unit, with Lewis as its Director. In addition to the psycho-pharmacologists mentioned in our companion article (Blackwell and Goldberg 2015), he ensured that the staff of the Institute included neurophysiologists, neuropathologists, biometricians, clinical psychologists.

Lewis as an educator of a generation of future academic psychiatrists

At the Maudsley Hospital, Lewis ensured that the psychotherapy department contained a wide range of approaches to psychological treatments and did not become dominated by one particular school. On one's first day, one was advised not to read a textbook, but to confine one's reading to scientific papers – an echo of Aubrey's pre-war complaint about European psychiatry.

As a clinical teacher, Lewis insisted on a carefully taken, detailed clinical history, and he was well known for interrupting junior doctors if they asserted something which they could not justify. "Are you sure that you asked the right question?" he might ask, and begin to drum his fingers on the desk. As a result, many found his manner intimidating, and all his trainees would agree with Anthony Storr's comment "that once you had presented a case to him, no other public encounter, be it with a large audience, in a TV studio or a lecture platform could hold any terrors for you." Although he did not intend to terrify us, he most certainly did so.

In one anxiety filled journal club presentation by an Australian registrar on the Burgholzli Centenary, Lewis asked him "how he could possibly know what Bleuler was thinking?", only to discover that the registrar had flown to Zurich at his own expense and spoken with Bleuler in fluent German! This illustrates the lengths residents sometimes went to meet his expectations, their caliber and the climate that he created while still allowing us to talk back.

Nor was the Journal Club the only ordeal; the Friday Case demonstration also inspired anxiety in the trainees:

> "His teaching methods were rigorous in the extreme. All the registrars had to be present while one of them presented his case to the Professor. This had to be done from memory without recourse to case notes. After this the wretched registrar was subjected to a searching cross-examination, spiced with sarcasm and devastating wit. Sir Aubrey clearly believed that in order to keep his students on their toes, it was best to ensure they were trembling in their boots. For all that he was an inspiring teacher" (Blackwell and Goldberg 2015).

Dr. D.L. Davies, who served as the Dean, wrote that "training at the Maudsley had connotations that were partly positive and partly negative. It is not a place that is dominated by too many psychoanalytical or cognate speculations or theories. People recognize this characteristic and regard it therefore in a sense as hard-headed, perhaps hypercritical, perhaps skeptical, but not pie-in-the-sky or ethereal. On the positive side I should think empirical methods strengthened by the results of research which enable theory to be formulated and eventually applied to practice. But I think it's chiefly in the balance that is observed in Maudsley psychiatry" (Shepherd 1986). There were definitely aspects of the Maudsley that irritated and alienated reputable voices elsewhere in world psychiatry with misunderstandings that persist even today. An example would be controversies over lithium (Blackwell and Shepherd 1968), (Blackwell 2015).

In his paper on the Education of Psychiatrists (Lewis 1947), Lewis argues strongly for an all-purpose psychiatrist. "When he is asked to treat a child, to report on a criminal, to explain the origins of a strange symptom, to supervise a course of insulin, to diagnose a high-grade defective, or to avail himself of the results of psychological tests, he should not have to choose whether he will excuse himself …. the psychiatrist, like other specialists, must acquire knowledge, some technical skill and an attitude for what he has to do…. He may, it is true, become an administrator, or a psychoanalyst, or a forensic expert, or even a professor – very diverse activities, but all requiring a broad training." He saw the primary task in psychiatric education being to train a future generation of teachers.

Until about 1980, it remained true that most of those appointed to the proliferating Chairs of Psychiatry in the years following WWII had trained at the Maudsley. The teaching of Psychiatry to medical students was thus indirectly due to Lewis and this also due to the new generation of consultant psychiatrists coming from the Maudsley to British Medical Schools. These teachers had

themselves been taught a disciplined discourse rather than been left to create their own from reading and observation. Even into the late 1950s medical student experience was of visits to various "Lunatic Asylums" where "residents" were shown on stage while a garbled account of their problematic behaviors was given by the resident doctor. Such displays, naturally, alienated students who might otherwise be drawn to the subject.

Research in social psychiatry

In 1935, Lewis had published a paper in the Lancet on neurosis and unemployment (Lewis 1935) which argued that these men were social as much as medical problems and one should aim at occupational as well as social interventions. He returned to this theme in 1944 from his position at Mill Hill (Lewis 1944).

After becoming Director of the MRC Unit in social psychiatry, he was responsible for the pre-eminent position of the United Kingdom in this field for the next 30 years or so, until new technology directed attention to genetics and neuro-imaging. Men such as Jack Tizard, Neil O'Connor, John Wing, Michael Rutter, Kenneth Rawnsley, Morris Carstairs and Peter Venables worked for him at the MRC Unit. John Wing and George Brown also worked on the Unit, and made important contributions to the substantial body of knowledge that emerged from these important formative years. Lewis's contribution was to ensure that research findings were factual, used reproducible methods of assessment and included social measures.

The high-water mark of these especially productive years was the book on Institutionalism and Schizophrenia (Wing and Brown 1978), which was the first formal demonstration that the phenomena of schizophrenia were not the immutable manifestations of some inner disease process, but were partly a product of the mental hospital environment.

The value of his papers on various subjects

On the occasion of Aubrey Lewis' retirement in 1966, the members of the Junior Common Room undertook to gather together and edit a selection of his papers. In their introduction, they say "For his past students, now scattered throughout the world, these essays will, we hope, be something more: refreshing reminders of their training. For athletes training involves not only a gain in muscular strength, but a loss of excess fat. For psychiatrists Professor Lewis provided its intellectual equivalent. It has been through his teaching, with its challenging mixture of scholarship

and common sense, that his influence has been most widely felt, and it is this which we, his present students, gratefully commemorate" (Lewis 1967a,b). In his review of the collected papers the writer says 'Sir Aubrey wears his scholarship lightly, never writes like a pedant, never descends to jargon yet is never far from that perceptive wit which always lay beneath the surface of his quite remarkable mind even in its most earnest deliberations' (Times Literary Supplement (1967). Lewis' commitment to empiricism was essential and profound - he took an unsentimental (but not overtly unkind) view of how to determine the truth and conveyed this in perspicacious, pithy, elegant prose. In addition, he was not (at least in his later years) preoccupied with his own reputation - either enhancing it or placing it in hazard by speaking the truth as he saw it.

We will here give examples of some of Lewis' more important papers. His early papers on melancholia (Lewis 1934, 1936) report an exhaustive descriptive study of 61 patients with depression. Lewis states that his findings have "compelled divergence from the accepted views, as expressed in textbooks and monographs" and the validity of (what were) accepted views on the classification of depression. Lewis describes paranoid features, the patient's attitude to his environment, the various manifestations of retardation, anxiety and compulsive phenomena in depression. In these papers Lewis shows his almost encyclopedic knowledge of the history of psychiatry – undoubtedly helped by his ability to read papers in both French and German in the original language. He fails to confirm the various groupings described by his predecessors, and takes the view that there are no independent disease entities, but rather an overlapping set of clinical phenomena which defy easy grouping, but are affected by the patient's personality and social adjustment.

His views are best expressed in the section on Psychological Medicine in Price's Textbook of Medicine (Lewis 1956). In this he compresses the whole of psychiatry into less than 60,000 words of clear, pithy prose, in an attempt to influence a generation of medical students. He gives his own views about the classification of affective disorders, asserting that there are three forms, each existing in a major and a minor form: manic excitement and hypomania; melancholia and "neurasthenic" depression; and agitated depression and anxiety state. There are no rigid distinctions between each major and minor form, and in the third form he denies that there are clear distinctions to be made between depressive and anxiety states.

Having excited the interest of a medical student reading his section, the thoughtful student might go on to some of his more profound general papers, from which we will select only two. In "Health as a Social Concept" (Lewis 1953) he argues that health is a single concept: it is not possible to set up essentially different criteria for physical and mental health. We commonly assume a continuum between health and ill-health, for which there is no counterpart in the phenomena but which we cannot yet replace by a continuum since we lack the means of measuring some of the necessary dimensions. There are three criteria for any medical illness: the patient feels ill, a general, subjective datum; he has some abnormality of a part-function, a restricted objective datum; and he has symptoms which conform to a recognizable clinical pattern, a typological datum. Social criteria play no part. The criterion of health is the adequate performance of functions, physiological and psychological. While our estimate of the efficiency with which functions work must take account of the social environment which supplies stimuli and satisfies needs, the criteria for health are not primarily social: "it is misconceived to equate ill-health with social deviation or maladjustment."

In "Between Guesswork and Certainty in Psychiatry" (Lewis 1958), Lewis argues that "it is the common state of reflective and enquiring minds to be somewhere between untrammeled guesswork and certainty. It would be discreditable if psychiatrists were to be huddled at either extreme, wholly engaged in guessing, or ignorantly certain." He goes on to consider why psychiatrists have been suspected of luxuriant speculation or invincible faith in our tenets. At the time one of us (DPG) was reading widely round the subject, and was finding a huge discrepancy between some of the wilder psychological explanations of symptoms I found in psycho-analytic books, and the dogmatic assertions of my undergraduate teachers at St Thomas Hospital. I found great comfort in this article, and decided that if there were brains like these writing in psychiatry; I had better leave my teaching hospital and relocate to the Maudsley. I found to my surprise on my arrival that there were more junior doctors from St Thomas than from all other London teaching hospitals combined. Perhaps this reflects William Sargant's enthusiasm for the subject, suggesting to his students that mental disorders were very similar to physical illnesses, and all responded easily to energetic physical treatment.

We knew Professor Lewis in the closing years of his life, when early Parkinson's disease was making his face a mask, and his voice a monotonous whisper. The death of his wife had been

a devastating blow and he shrank visibly after that. The oratorical feats of his early life were no longer possible for him, but his mind was still razor-sharp, and his knowledge of the subject detailed and precise. He had encouraged his colleagues at the Institute to undertake research in metabolic aspects of psychiatry, in genetics using twin studies, in the common mental disorders encountered in primary care, and as we mention in our companion article, in psychopharmacology — but he did not carry out research in these areas himself. Above all, the "remarkable grasp of philology" noticed by his school teachers never deserted him – he was easily the most scholarly psychiatrist that we have ever encountered.

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Editor's Note:

All three authors began psychiatric training at the Maudsley Hospital and Institute of Psychiatry in 1962 as registrars (residents). All went on to fill department chairs in Britain and America. Sir David Goldberg became Director of the Institute and like his predecessor was knighted by the Queen. They have remained friends and colleagues since, now all retired.

Aubrey Lewis's Contributions to Psychopharmacology

By

Barry Blackwell & David Goldberg

Aubrey Lewis was born into a new millennium (November 1900) in Australia and died in London at age 74 in 1975. After anthropology research in Australia and clinical work in America, Britain and Germany he joined the staff of the Maudsley Hospital in London in 1929 and was named inaugural Chair in 1946 when it also became the Institute of Psychiatry at London

University. Knighted by the Queen in 1959 Sir Aubrey is recognized as having raised the profile and respect of Psychiatry in Britain and worldwide both through his own contributions and those of the Faculty and trainees he recruited and mentored. His major biographer notes (Shepherd 1986) that Lewis had a "formidable and disciplined mind" coupled with an empirical clinical approach that did much to dispel the then prevailing view that, compared to other branches of medicine, Psychiatry's "pretensions were greatest and its foundations least secure."

Far from being a psychopharmacologist himself, Aubrey had his finger on the pulse of the discipline when, in 1957, he became a founding member of the Collegium Internationale Neuro-Psychopharmacologicum (CINP), one of only three psychiatrists from the U.K among 33 worldwide. All three clinicians were from the Maudsley, Aubrey Lewis, Michael Shepherd (Ibid) and Linford Rees (early work on imipramine in depression). The following year Aubrey Lewis chaired the opening ceremonies of the First International Congress of the CINP (Rome 1958).

Sir Aubrey's later contribution to psychopharmacology was not 'hands on' but generative, due largely to the atmosphere and environment he created. He built the Institute of Psychiatry with five full University of London departments including neuropathology, biochemistry, biometrics, physiology and psychology, coupled with a large emergency room and clinical units at the Maudsley and Bethlem Royal Hospitals. Trainees from Britain and around the world rotated through these programs and were exposed to an environment where the major impact was the "internalization of a high standard of critical capacity."

Combined with a requirement for a research Dissertation (later M.Phil.) this created a seedbed for graduates who went on to populate many of the world's leading academic institutions. Among them was a cadre of psychopharmacologists who became pioneers in the field. Included were, John Smythies (Hallucinogens and mechanism of drug action), Philip Connell (Amphetamine psychosis), Eugene Paykel (Depression), Malcolm Lader (Benzodiazepines), Trevor Silverstone (Bipolar Disorder), Ted Marley (Basic neuroscience), Alex Coppen (MAOI) and Barry Blackwell (MAOI and Tyramine and Lithium Prophylaxis).

Sir Aubrey's views on the contribution of new drugs to the field of psychiatry were modestly stated in his paper, *"Medicines and the Afflictions of the Mind."* (Lewis 1963).

"We are not living through a period that marks a new epoch; there is no Darwin, no Harvey or Newton in psychiatry and psychology, nor to put our aspirations on a more realistic plain, have there been discoveries during the last twenty years comparable to those that have signaled the growth of therapeutics and surgery in other fields. Psychiatric advances have been less dramatic and less conclusive. Still, to those who have taken part in them, they have given the satisfaction and excited the hopes out of which enthusiasm is generated."

At the time this was written, in the heyday of new drug discoveries for every psychiatric disorder, the comment was viewed as skeptical, perhaps pessimistic. Today, as we wallow in the doldrums of scanty new drug development the words sound prescient.

Had Aubrey Lewis' own work on the nosology and natural history of mental disorders been better known and understood by psychopharmacologists and clinicians five or more decades of frustrated optimism might have been abbreviated. His doctoral dissertation on melancholia recorded the putative biological components evident in this condition; anhedonia, early morning awakening, diurnal variation in mood, loss of libido, amenorrhea, loss of weight and appetite, and suicidal ideation. These peculiarities became lost in the DSM fog of "Major Depression" or worse still in the ignorant and indolent category, "Depression NOS". Specificity of outcome was diluted and disappeared in a flood of antidepressants allegedly differing in biochemical profiles but yielding undifferentiated outcomes.

Perhaps Sir Aubrey's most prescient and potentially game-changing contribution on the relationship between drug use and psychopathology is contained in a short but sadly overlooked article he wrote in the mid nineteen sixties (Lewis 1967). This is emblematic of his intellectual and literary style and concerns the use of the term "anxiety" in the psychiatric literature at exactly that time when the "minor tranquilizers" were on their way to becoming among the most widely used drugs in medical practice (Blackwell 2015). Although the timing of Sir Aubrey's article and its concerns may have been triggered by these unfolding events, Sir Aubrey discretely avoids mentioning the role of medication use and the pharmaceutical industry in influencing psychopathology.

The article begins by defining the historical usage of the term “anxiety” first in France and Germany, then in Britain. He is careful to note this excludes literature from Russia, Scandinavia, Japan, Holland and other countries. He also notes anxiety’s tardy and sparse appearance in England despite the affects growing theoretical significance in Freud’s emerging psychological theories.

Concentrating on Anglo-American literature Sir Aubrey notes the “far from subtle or precise use” of the term anxiety which appears across a lexicon of emotional states that includes “insomnia, fears, phobias, apprehensiveness and depression as well as cognitive symptoms and social behaviors.” He dissects the ubiquitous use of the term in the psychosomatic and stress domains, the relationship of fear with anxiety and the use of the term, “unconscious anxiety” in psychoanalytic jargon which he dismisses as “a contradiction in terms.”

Sir Aubrey next refers to psychological attempts to define anxiety as a physiological conditioned response or a symptom on rating scales. “Critics emphasize that the scales measure and define only manifest anxiety. Other workers stress the need to recognize ‘unconscious anxiety’ but do not define it.”

Finally, he notes attempts to identify and define anxiety in children by educational psychologists; “in regard to which there is much written but little clearly established.”

Sir Aubrey’s conclusions based on his review of the literature are characteristic of his pithy, frank and perceptive style. “Evidently while many voices proclaim that anxiety is the alpha and omega of psychopathology and that it permeates every sort of mental disorder, there are even more voices insisting that anxiety means what they choose it to mean.” Having reached this conclusion Sir Aubrey proceeds to provide his own succinct seven-item definition of the term ‘anxiety’ and its manifestations.

1. It may be “normal” or pathological.
2. Mild or severe.
3. Detrimental to thought or action or, in some respect, advantageous.
4. Episodic or persistent.
5. Due to physical disease or not; of psychogenic disorder.

6. Accompany other mental disorders or alone.

7. An attack may or may not affect perception and memory.

This honest but highly ambiguous itemization leads Sir Aubrey to pose a final question about use of the term ‘anxiety’: “Should we do away with it?”

His conclusion and its timing are prescient: “The prospect of killing the term is slender, as is the prospect of a successful convention devoted to making the concept and word scientifically successful.”

More than half a century later we can state, in retrospect, that the burgeoning use of drugs to stifle anxiety in its many manifestations succeeded in reifying the concept of “anxiety” and that while DSM nosology defined some of its manifestations the questions so elegantly posed by Sir Aubrey remain largely unanswered (Blackwell 2015).

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“Adumbration”; a History Lesson

The research described, which established my own career in psychopharmacology, is presented here for two purposes – in appreciation for Aubrey Lewis’s benevolent oversight and endorsement but also for the lessons it offers in relation to the field of psychopharmacology.

"History is more or less bunk. It's tradition. We want to live in the present and the only history that is worth a tinker's damn is the history we make today" (Henry Ford: Chicago Tribune, 1916) **Or***"What is past is prologue"*

(Shakespeare: The Tempest, 1610)

More than three centuries apart, these oft cited quotations set the boundary markers of a ubiquitous dichotomy of viewpoints over the benefit of exploring or ignoring the past to explain the present.

"Adumbration" is an ideal semantic companion to this dispute between the man who invented the Edsel and the world's most famous poet and playwright. It is a fickle portmanteau word plagued by ambiguous meanings and variable usage. It derives (OED) from the Latin, *"umbrare"* – **shadow** coupled to *"an"* – ***fore.*** Hence it is defined both as "foreshadowing" or "overshadowing" an idea or a discovery, faintly predicting or disparaging the event.

In manifold writings Robert Merton created a subspecialty of sociological enquiry surrounding scientific discoveries, the behavior of scientists and the dubious role of adumbration in that process. (Merton, 1967, 1968 a, 1968 b, 1969). Within this framework I will examine one scientific discovery in which I played a key role and discuss its relevance to contemporary psychopharmacology. A full description of this process is available (Blackwell et al 1967) and its relationship to the process of discovery is described elsewhere (Ayd and Blackwell 1971).

This essay will set the stage with a barebones outline of the discovery itself before an historical dissection of the manner in which it was foretold in the literature accompanied by reflections about adumbration and other contemporary implications.

In 1962, aged 28, I began as a first-year registrar (resident) at the Institute of Psychiatry (Maudsley Hospital) in London. I had completed my medical training at Guy's Hospital as a House Officer followed by a six-month neurology rotation at the Whittington Hospital in North London. I had already published several articles showing an interest in research but, devoid of the desired Membership in the Royal College of Physicians (MRCP), I was relegated to the "B stream" on Lindford Rees' Unit at the Bethlem Royal Hospital. Lindford was a founding member of the CINP and had engaged in early research on the tricyclic antidepressants which were just beginning to

compete with the MAO inhibitors. Iproniazid (Marsilid) had been marketed since 1958 but was quickly overtaken by tranylcypromine (Parnate) from 1960, popular both alone and with a small dose of Stelazine as Parstelin.

During neurology training I worked under a senior registrar who had published a letter to the *Lancet* about a patient who suffered a subarachnoid hemorrhage when taking Parnate; eliciting a drug history in every patient admitted in such cases was mandatory but unproductive. Until, several months later when I was eating lunch in the Maudsley cafeteria and overheard registrars at the next table discussing a young woman who had just suffered a subarachnoid bleed. Had she been taking Parnate I asked? She had! Soon afterwards, chatting with my G.P. he told me of two similar cases seen in a matter of weeks. Eager to "publish or perish" I fired off a letter to the Lancet suggesting this serious, potentially fatal side effect, might be commoner than appeared. (Blackwell 1963). There had been six similar letters in the previous 20 months describing a syndrome of hypertension associated with a pounding occipital headache and, more rarely, a subarachnoid hemorrhage.

Two weeks later I received a letter from a hospital pharmacist in Nottingham, G.E.F. Rowe, who had read the *Lancet* and recognized the symptoms as identical to those his wife had experienced twice after eating cheese. He described the episodes in detail in a letter that concluded:

"Could there be a link between the effects and the amino acids of cheese? No effects are caused by butter or milk. Although treatment has continued, no further episodes have occurred. If cheese is indeed the factor it could perhaps explain the sporadic nature of the incidence of the side effect. I hope my comment will be of some use to you in your investigations."

My first response to this remarkably prescient description was skepticism tinged with humor, until I shared the letter with the manufacturer's representative, Gerald Samuels, of *Smith Kline and French.* He had heard of similar reports including one in a patient taking tryptophan and tranylcypromine in a research study. Perhaps I should look into the composition of cheese? Instead, together with a fellow female resident, we took Parnate for a week before eating cheddar cheese from the cafeteria and measuring our blood pressure. Nothing happened. But when I checked the hospital menu for the night the Maudsley patient had suffered her hemorrhage I discovered she had eaten a cheese quiche for supper.

Not sure what to do next, *chance favored the prepared mind* (Louis Pasteur). Moonlighting for a local family practitioner (the commanding officer of my reserve army field ambulance) I received a call one evening from a distraught husband whose wife was experiencing a sudden severe occipital headache. She was taking Parnate and had eaten a cheese sandwich for supper. I jumped into my car to do a home visit and found her in the middle of a hypertensive crisis which subsided without treatment while I took her blood pressure. Determined to gather further cases I was unsure of where to look. But not long afterwards, working late at the Maudsley, I ran into the duty registrar (Bob Kendall) on his way to the psychotherapy unit. He had been called to see two women in adjacent beds both taking Parnate, suffering from sudden severe headaches, having returned from the cafeteria after eating cheese.

Convinced now of the relationship between eating cheese and suffering a hypertensive crisis I wondered why we had not experienced this in our self-experimentation with Parnate. Perhaps the interaction was due to some propensity peculiar to patients? Boldly, and by today's standards perhaps unethically, I asked a female inpatient taking Parnate (Mrs. Borrett) and her husband if she would be willing to eat cheese while I took her blood pressure. After I explained the risks and steps I would take to counter any major increase in blood pressure they agreed. She ate cheese and I sat by her bedside for two hours uneventfully before leaving to see patients on another ward. Within ten minutes my pager went off: the nurse caring for my patient asked, "Could she give her aspirin for headache?" I rushed back to the unit, found her in the midst of a hypertensive crisis that subsided without complications or treatment within 45 minutes.

Within nine months of my original letter to the *Lancet* I had collected 12 patients taking an MAOI, mostly Parnate, of whom eight had eaten cheese prior to the event. The publication in the *Lancet* (Blackwell 1963) included a graph of the blood pressure recordings in my volunteer patient. The article produced a rapid response. A patient wrote to say she had known of the association for some time but "doctors laughed at the idea". The Medical Director of *Smith, Kline & French* dismissed my findings as "unscientific and premature". Another doctor had treated hundreds of patients with an MAOI and never seen a severe headache although headache occurs at least once weekly in a third of the population. This spectrum of responses illustrates the dual meanings of adumbration; from faintly predicting to critical disparagement.

It is not uncommon for a serious side effect to be discovered several years after a drug is approved for marketing. In this instance it was unusually long. Eight years elapsed between the first use of an MAOI to treat depression and discovery of the tyramine interactions during which time 40 fatal cases occurred. This hiatus is generally attributable to the inadequacy of short term double blind studies needed to obtain FDA approval. Sample sizes are small and populations highly selected with treatment lasting only long enough to determine statistical significance compared to placebo but inadequate to reveal rare or unusual side effects. It is interesting to note however that among the earliest studies of iproniazid, (Marsilid) in the treatment of tuberculosis (Ogilvie 1955) four out of 42 patients suffered hypertension and headache but a cause was never pursued.

There were other reasons why recognition of the causative factor was delayed. It is a truism that "everyone eats cheese." Eating cheese is common but the side effect was rare while even those who suffered an attack ate cheese again with impunity serving to obscure a cause and effect relationship. An analogy can be made to sex and pregnancy. The first is common but the second is relatively rare; there are many intervening variables between the act and the outcome.

Doubt, disparagement and skepticism were short lived after the publication of the *Lancet* article. Within weeks a team of researchers at a London teaching hospital ate Gorgonzola cheese and identified tyramine with spectroscopy in their body fluids. (Asatoor, Levi and Milne 1963).

It would soon become my responsibility to identify other factors producing a variable response to eating cheese while taking an MAOI. Suddenly in the limelight, I was promoted to the Professorial Unit at the Maudsley and came under the eagle eye of Sir Aubrey Lewis. After observing my work for several months, he took me aside and asked was I "by any chance in psychoanalysis?" Approving of my denial he offered me the chance to learn about research in a pharmacology fellowship under the mentorship of Ted Marley. For two years I worked in a World War II Nissan hut on the margins of the campus surrounded by cages of cats, rats and baby chicks until I completed the work necessary to explain the mechanism of action of the interaction between MAO inhibitors and tyramine containing foods.

Not long after starting my research Sir Aubrey, who was multilingual and a Greek scholar told me he "thought Hippocrates had something to say about cheese." I found a book on Greek

Medicine (Brock 1929) to discover the doubts Hippocrates expressed; "*It is not enough to know that cheese is a bad article of food in that it gives pain to anyone eating it in excess, but what sort of pain, and why, and with what principle in man it disagrees…"* This quotation became an apt prologue to the Doctoral dissertation presented at Cambridge University at the conclusion of research answering those questions (Blackwell 1966).

Working with the National Institute for Research in Dairying we learned that the tyramine content of cheese varies considerably depending on the amino acid composition and the abundance or activity of decarboxylating bacteria that convert tyrosine to tyramine. A myth developed that mostly mature and "smelly" cheeses were at fault but our research on multiple samples of identically appearing cheddar cheese (including several that had caused hypertension) varied widely in tyramine content; pieces of cheddar cheese were like cans of garbage – identical on the outside but differing in their content. (Blackwell and Mabbitt 1965). Excavating the literature revealed that tyrosine was first identified in cheese and named after the Greek word for it, *tyros* (Liebig 1846). Later on, tyramine was also discovered in cheese and in the early 20th century physiologists discovered it was a hypertensive agent (Dale and Dixon 1909).

Two years later an internist developing the sphygmomanometer injected tyramine into adults and children to calibrate the instrument (Findlay 1911). In the process he expressed concern that rapid rises in blood pressure might cause a cerebral hemorrhage.

Observations on patients taking an MAOI and suffering food induced hypertension revealed several factors determining the outcome. Development of severe throbbing occipital headache occurs when there is a large rapid increase in blood pressure (approximately 50 mm or more in less than 10 minutes). Ingestion and absorption of small amounts of tyramine produced less dramatic increases in blood pressure and were asymptomatic. Even if headache occurred the blood pressure usually returned to normal within 45 minutes without treatment. These factors are responsible for the unlikelihood that most people experiencing the symptoms of a hypertensive crisis would be seen by a physician.

Another factor influencing the occurrence and severity of an interaction was the MAOI prescribed its dosage, and the regimen. Although cases were reported with all the MAOI Parnate was by far the most common drug incriminated and early on it was known as "Parnate headache."

In part this may have been contributed to by the fact that in a study on Maudsley outpatients (Blackwell and Taylor 1967) it was the most often prescribed and most effective of the MAOI before the discovery of the tyramine interaction. This was probably due to the drug's therapeutic index and pharmacologic properties. The starting therapeutic dose produced sufficient inhibition of intestinal MAO to allow ingress of tyramine while the drug's amphetamine like structure and effects likely contributed a release of stored nor-epinephrine, augmenting the effect of tyramine. Metabolic studies on a patient taking a less potent MAOI, phenelzine (Nardil) revealed that blood pressure responses to graduated amounts of tyramine in Marmite were influenced by dosage, duration of treatment and proximity to an antecedent dose of the drug. (Blackwell, Marley, Price and Taylor 1967).

Monoamine oxidase was named tyramine oxidase after its first know substrate (Hare 1928) and then renamed monoamine oxidase. Its distribution and purpose in the gut was first described by Blaschko to include the denial of access to the circulation of amines present in foods (Blaschko 1952). This knowledge and speculation was made only three years before an MAO was first used to alter the brain chemistry of patients suffering from depression.

The fear that toxic substances absorbed from the gut might cause serious and unpleasant symptoms has a long history up to the present preoccupation with probiotics and colonic "regularity" (Blackwell 1966). In the late 19th century the German scientist Metchnikoff suggested the colon was a "putrefying sac" from which toxic amines in foods might be absorbed into the bloodstream. Queen Victoria's surgeon, Sir Arbuthnot Lane, subscribed to this belief and made a fortune removing the colon for constipation. In 1906 Bernard Shaw wrote the play, "*The Doctor's Dilemma",* which parodied this practice with a character named Sir Colenso Ridgeon who rem oved an offending imaginatice organ . thr nuciform sac. The controversy surrounding this topic became the subject of a conference convened by the TRoyal Society of Medicine in 1923 during which headaches among other offending symptoms and chesse a potential foodstuff.These events were contemporaneous with the discovery of the hypertensive properties of tyramine and its associated dangers discussed earlier.

If, as this case study suggests, scientific discovery can be predicted or disparaged (adumbration) it is not surprising that controversy can arise over related aspects of the process. Robert Merton writes about several (Merton 1968a, b). These include conflicts over priority (who

made the original or major contribution?), the tendency of scientists to deny an interest in claiming priority (Freud included), the willingness of leading scientists to accept prestigious awards overlooking the contribution of junior colleagues (the "Mathew effect") all of which are abetted by selective forgetting ("cryptomnesia").

Two examples in the modern history of neuropsychopharmacology are the 1964 Lasker Award to Nathan Kline for the introduction of MAOI into psychiatry and the 1978 Lasker Award to Sol Snyder and others for discovery of opiate receptors. In both cases junior colleagues claimed their contributions were overlooked.

The cheese story is not immune from such problems. Two people had reasons to feel slighted. GEF Rowe deserves full credit for the first documented mention of a link between cheese and sudden severe headache while taking an MAOI. My first article describing this interaction (Blackwell 1963) did not make attribution but every subsequent publication has done so. My recollection is that I also sent him copies of all papers we published at the conclusion of the research but this is contested.

The second person, Gerald Samuels, complained vociferously and continuously. Three years after we first met and he encouraged me to pursue the contents of cheese, we met again when he visited me in his role as the pharmaceutical representative for Smith Kline & French. I learned how bitter he was for not being acknowledged in any of our publications. Feeling his resentment was justified and wishing to make amends I suggested we write a joint article describing his role and contribution. This was published with Gerald as first author in the *Journal of Hospital Medicine* (Samuels and Blackwell 1968). Shortly afterwards he came to dinner in my home and presented me with a cheese board engraved with the words, *"Everyone Eats Cheese."* I assumed we were reconciled but about 15 years later he published an angry letter in the *British Journal of Psychiatry* again complaining bitterly. He had contacted Mr. Rowe and alleged he was also aggrieved and had never heard from me. I decided not to respond, feeling that there was nothing further I could do to assuage such deep seated and long-lasting emotions.

Carefully construed there are a plethora of allies to whom I am grateful in the discovery process. In this instance to mentors and colleagues who assisted or encouraged my enquiries; Lindford Rees, Gerald Russell who welcomed me onto his Metabolic Unit and David Taylor,

fellow registrar and lifelong friend. To Sir Aubrey Lewis who opened the door to research. To Ted Marley who endured my clumsy efforts at animal research and pled my ability for doctoral work to Cambridge University. To the female colleague and two women patients who volunteered to be experimental subjects. To the microbiologist who analyzed cheese and educated us in food science. To the scientists at another hospital who identified tyramine in cheese and gave the story credibility.

Still, in addition to adumbration, perhaps there are other ways to think about the lessons learned from the MAOI-tyramine story. Was the field of psychiatry well served by the discovery? Certainly, lives were saved – perhaps five or so patients a year at the peak of MAOI prescribing. But we had learned how to deal with this side effect by avoiding tyramine containing foods; perhaps too many and indiscriminately as recently suggested (McCabe et al. 2006). But still the drugs were too useful to be quickly abandoned. Parnate use declined abruptly, followed over a few years by almost no significant prescribing of MAOIs after the SSRI antidepressants appeared. Eager for the field to move on this transition occurred before we had fully defined the features of patients who benefitted. The vague term "atypical depression" was proposed and included increased sleep and appetite perhaps combined with features of apathy, lack of motivation, decreased libido and self- blame. These sound like the same features that for many years were treated by outpatient use of amphetamines, properties that tranylcypromine shared but for which a comparison was never made.

What might the pharmaceutical industry learn from this story? Industry is always eager to identify a putative "mechanism of action" as part of persuasive advertising. Interfering with an enzyme, receptor system or neuro-transmitter should always raise the question of where else that entity exists in the body, what function it fulfills and the likely consequences of tampering with it. Manifestly this was not so, judged by the speed with which the first article was brushed aside. But the information was all there in plain sight on the pages of credible scientific journals, waiting to be read.

Based on this history of adumbration it would be reasonable to assume that a competent and ethical pharmaceutical company would search the literature to find all the known possible pharmacological effects that might result from the drug they planned to promote including

preclinical research in animals and cautious Phase 1 studies in humans followed by specific anticipatory data collection relevant to the risks in Phase 2.

"Those who cannot remember the past are condemned to repeat it"

(George Santayana 1863-1952)

In 1998 Celebrex (celecoxib) was marketed by Pfizer close on the heels of Vioxx (rofecoxib) already on its way to being a blockbuster. Both drugs belonged in the category of non-steroidal ant-inflammatory drugs (NSAIDs) for the treatment of pain and inflammation in arthritis. Both claimed to be safer and more effective than earlier drugs in the same widely used category. They share a mechanism of action on the enzyme cycloxygenase-2 (Cox-2). Like monoamine oxidase the enzyme exists in two forms, is widely distributed throughout the body with manifold functions.

Sales of Celebrex reached $3.1 billion in 2001 and around that time my joints and spine began to ache and groan from the burden imposed by 20 years of playing rugby and pushing in the scrum. A hip replacement seemed inevitable, but in the honeymoon of this new drug my internist thought it was worth a try.

One week after starting treatment my face erupted in exfoliative dermatitis but, unaware this was a side effect, I continued until a few days later I suddenly became breathless while climbing the stairs at home. Alarmed, though not in pain, my wife drove me to an emergency room where my blood pressure was 210/170 mm Hg. Normotensive throughout my sixty-five years I was on the verge of left ventricular failure. After inserting an I/V and a dose of mild sedative the blood pressure fell to near normal over two hours. It has remained mildly elevated since, responding to conservative treatment. The package insert made no mention of cardiovascular complications so I informed the FDA and the manufacturer. The FDA was silent but Pfizer, knowing I was a physician, mailed several reassuring publications implying the absence of any similar problems.

I was naturally struck by the similarity between this drug reaction, without the headache, and my experience almost forty years earlier with the MAOI tyramine story. I even toyed with the idea of self- experimentation to test the hypothesis but wisely declined. I only had to wait 3 more years for the truth to unfold.

In 2004 Merck withdrew rofecoxbid (Vioxx) from the market. The story is told by NPR on the internet (Prakash and Valentine 2007).

In 1999 Merck, concerned that Vioxx, like other NSAIDs, might cause gastrointestinal bleeding, launched an 8,000-patient study comparing Vioxx to Naproxen, the Vioxx Gastrointestinal Outcomes Research Study (VIGOR). The company appointed a Data and Safety Monitoring Board (DSMB) chaired by Michael Weinblatt (Brigham & Women's Hospital) who owned $73,000 in Merck stock and earned $5,000 a day as a consultant.

During 2000 the results of VIGOR were submitted to the FDA and published in the *NEJM,* but the journal article omitted three cases of heart attack along with other cardiovascular events. Reanalysis of the data by independent researchers cast doubt on the VIGOR conclusion that the increase in cardiovascular risk might be due to Naproxen protecting the heart rather than Vioxx damaging it. Between 2002 and 2004 further epidemiological studies confirmed Vioxx's increased cardiovascular risk.

In September 2004 Merck withdrew Vioxx from the market after it had been used by an estimated 20 million Americans. Subsequent research in the *Lancet* estimated that 88,000 Americans had heart attacks while taking the drug and more than 8,000 died.

Further FDA analysis of the data on Vioxx revealed that cardiovascular events began shortly after starting the drug and remained long after the drug was stopped.

In 2007 Merck agreed to pay $4.85 billion to end thousands of law suits coupled with a statement that it did not admit fault.

After Vioxx was withdrawn Pfizer benefited from an increase in its sales cut short by further bad data and an FDA "black box" warning in 2005 that all NSAIDs shared comparable cardiovascular risks. For a two-year period, they suspended direct advertising to the public but resumed in magazines in 2006 and television in 2007 where their "*For a Body in Motion*" commercials continue to run frequently, casting a "quality of life" glow and drowning out dire mandatory warnings with distracting happy visual images.

In 2009 Scott Reuben (Chief of acute pain at Bayside Medical Center, Springfield, Mass) revealed that 21 studies he conducted on Celebrex and other NSAIDs were fabricated to exaggerate analgesic effects.

The current package labelling for Celebrex conveys the following information: "*As with all NSAIDs, Celebrex can lead to the onset of new hypertension or worsening of previous hypertension, either of which may contribute to the increased incidence of cardiovascular events. Blood pressure should be closely monitored with all the NSAIDs."*

With the wisdom of hindsight, history and adumbration it seems paradoxical that one drug which provoked hypertension for which the cause was removed, should almost perish while another still thrives making $2 billion or more a year while its risks remain intact. Worse still, it feels unjust and unscientific!

The word "unscientific" is used advisedly, providing yet another lesson. The difference between the Parnate and Celebrex stories is that between commerce and science and the conflicts of interest this creates. Both involved unanticipated and potentially lethal cardiovascular effects caused by drugs in widespread use for several years. By reason of how each was discovered Parnate fell into the academic domain of medicine, Celebrex into the commercial. Academic motivations involve both personal and social/ethical goals; publishing scientific papers, obtaining advanced degrees, promotion or tenure, and recognition within one's field. Traditionally also, doctors are sworn to doing good with minimal harm to patients. The target of my investigations was to explain the mechanism of action involved to the benefit of my career as well as making MAOI safer to use and even, perhaps, saving a few lives.

In the case of Parnate, once tyramine was identified the truth was out. Ted Marley and I were invited to SKF headquarters to meet their pharmacologist. We made an agreement to publish the results of our animal research on the mechanism of action simultaneously. Some months later the editor of the *Lancet* informed us that SKF had reneged and submitted their results unilaterally. We were given a month to submit our own research; working day and night we met the deadline and both papers were published back to back (Blackwell and Marley 1964; Natoff 1964).

With Celebrex the story was different. No attempt was made to study or explain the mechanism of action. But like SKF's initial response Pfizer's entire effort was devoted to denying

and then minimizing the problem. The unanticipated nature of the side effect, its severity and frequency, created liability and provoked litigation. To the extent physicians were involved one falsely exaggerated the drug's efficacy while another participated in minimizing its risk; both benefited financially.

Once serious side effects are recognized by the FDA and 'black box' warnings mandated companies use their vast profits to stifle law suits without admitting culpability. Industry views this as "the cost of doing business" which is built into the high price of the drug in question. The only evidence of penitence or accountability on the part of Pfizer was a brief hiatus in advertising directly to the consumer, soon resumed with gusto; observing the letter of FDA law but skirting its spirit. Now that all the official warnings are in place Pfizer no longer has culpability for the drug it sells. Side effects become the responsibility of the physician who prescribes the drug and the patient who is beguiled or bemused into taking it.

Note: For a more complete discussion of "Conflict of interest" see the "Controversies" program on the INHN.Org website.

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Chapter 12

The Lithium Controversy; an Historical Autopsy

Risk and Relevance of Lithium Usage

Preamble

Chapters 4 and 5 provided a detailed account of the use of lithium in medicine and psychiatry throughout the 19th and 20th centuries leading up to its re-discovery by the Australian psychiatrist John Cade in 1949 for the treatment of psychotic episodes of acute mania. The following year its use was banned by the FDA in America due to deaths caused by lithium's use as a salt substitute in cardiac conditions, a ban that was not lifted until 1970. For a brief while Cade, concerned about several deaths following its use in acute mania, recommended against its use in Australia and banned its use in his own hospital. Once its safety was assured with plasma monitoring (never approved or mentioned by Cade), its use spread rapidly around the world, including Scandinavia where Mogens Schou learned of Cade's work and began to use lithium for the prevention of recurrent episodes of manic-depressive illness.

Chapter 12 picks up the story in 1967 when Mogens Schou and his colleague Baastrup published their results in the Lancet concerning its prophylactic effects. Working at the Maudsley Hospital as a research assistant with Michael Shepherd, we published a provocative rebuttal of that claim, also in the Lancet, alleging it was "Another Therapeutic Myth." Baastrup and Schou responded vehemently and the topic assumed the dimensions of a major controversy.

The Lithium Controversy: An Historical Autopsy

It is now more than half a century since Michael Shepherd and I published our article *"Prophylactic Lithium; Another Therapeutic Myth?"* in the Lancet, which commented on and critiqued a previously published study by Mogens Schou and his colleague in the Archives of General Psychiatry (Baastrup and Schou 1967), making the claim that lithium had a unique effect in preventing future episodes of manic depressive disorder. Their riposte to our critique appeared later the following year (Baastrup and Schou 1968).

If history has anything to offer today then such past events deserve to be dissected. As possibly the sole remaining protagonist in the fierce debate these two papers generated, I offer this autopsy, personally performed, and invite INHN members to comment.

This essay is in three parts: reciting the facts themselves; an analysis and interpretation of the scientific zeitgeist prevailing at the time; commenting on the emotions aroused; and, finally, the possible relevance of such matters today.

I completed five years of psychiatric training at the London University Institute of Psychiatry and Maudsley Hospital, including a two-year fellowship in animal research leading to my doctoral degree in Pharmacology from Cambridge University. Following this, I completed a two-year research fellowship with Michael Shepherd. At his suggestion, I undertook to analyze and critique Schou's data claiming that continuous administration of lithium prevented future episodes of manic depression. There was no control substance since other "mood stabilizers" were far in the future and Schou rejected placebo as unethical based on his clinical experience and convictions of efficacy. So, there was no double blind procedure to protect against potential observer bias, although a placebo control was included in the definitive studies that confirmed his beliefs many years in the future (see below). The possibility of bias existed both due to the study design and because Schou was quite open to admitting enthusiasm for his hypothesis, derived from a family member's benefit after all else had failed to stifle recurrences. At this time, prophylaxis was such a unique and unexpected claim it might have evoked a "too good to be true" skepticism, which heightened our concern about potential bias in an uncontrolled study.

There was no established method, at this time, with which to evaluate such a unique claim; Schou's series included a heterogeneous collection of subjects broadly interpreted as suffering from manic depressive disorders but with varying affective manifestations, of differing duration, frequency and severity. This created concerns about the specificity of the claim as well as statistical issues, primarily concerned with regression to the mean – spontaneous remission from a high baseline in a fluctuating disorder. Other statistical concerns were displayed and discussed in sophisticated terms in a paper read to an NIMH/VA study group and subsequently published in Frank Ayd's newsletter (Blackwell 1969). Similar statistical and methodological criticisms were made by Malcolm Lader in the Lancet (1968). The essence of these concerns focused on the impossibility of distinguishing dependency on a medication, or spontaneous remission from

prophylaxis, a problem I dubbed the "panacea paradigm." The scientific caveats evoked sharp rebuttals from clinicians who knew better, including Nate Kline in America (Kline 1968) and Sargent in Britain (Sargant 1968). Sargant's comments are especially illustrative of the tone and angst aroused in this debate. He appealed for the abandonment of "crude statistics" and "valueless double blind sampling" in favor of "bedside observations for the sake of England's treatment reputation in world psychiatry."

Seldom noted or commented on is that in addition to concerns about methodology we applied Schou's statistical technique to a convenience sample of 13 manic-depressive patients from the Maudsley data base treated with imipramine and found results comparable to lithium.

` It is important to place these events in their broader historical perspective and consider how this colored the controversy. Until the Flexner revolution in the early 20th century, medicine was an apprentice profession whose *materia medica* included many panaceas, nostrums and placebos, the popularity of which depended largely on the status of the apothecaries, physicians or barber surgeons who dispensed and endorsed them. As medicine became more scientific and moved from the community into academic medical centers, its remedies became potentially more effective. Trial methodology and statistical analyses developed to rigorously evaluate therapeutic claims. Eventually, the double blind controlled study became the gold standard. Psychiatry lagged behind in this regard; chloral hydrate, barbiturates, paraldehyde and amphetamines were synthesized and well established with regard to effectiveness and shortcomings but nothing new or potentially more effective existed to compare them against.

Lithium had a persisting role in this evolution. A naturally occurring metallic ion with no commercial potential or synthetic rivals, it was introduced into medical practice, in 1859, as a bone fide treatment for gout but then increasingly as a panacea with Lithia tablets used for a wide variety of ailments, despite absence of benefit and occurrence of side effects. In the earlier days of scientific medicine, it was used as a salt substitute in cardiac disease until the absence of a method for measuring blood levels led to cases of fatal toxicity. It was withdrawn from medical practice, in 1950 in America, shortly after Cade reported its therapeutic effect in psychotic manic patients.

Many pioneers in psychopharmacology consider the two decades from 1950 to 1970 as the seedbed for all the original treatments in every category of psychiatric disorder. Lithium provides

twin bookends for this exciting epoch, beginning with Cade's discovery of lithium for acute mania and ending with Schou's discovery of prophylaxis- both enabled by discovery of a method for measuring lithium levels in the blood. In an account of his own discovery, Cade recognizes Schou as "The person who has done most to achieve this recognition."

The trajectory of lithium's ascendancy as a prophylactic agent during these two decades is best told by Schou himself (Schou 1998) and Paul Grof, with whom he collaborated (Grof 1998) and who wrote Schou's obituary at the time of his death in 2005 at age 87 (Grof 2006). The obituary is an appropriate paean of praise for a colleague who was twice nominated for the Nobel Prize in medicine and physiology. Grof traces Schou's dedication to our field from vivid childhood memories of depressed patients in the asylum where his father was medical director, "wandering in the hospital park with drooping heads and melancholic faces waiting for the depression to pass and fearing future recurrences." This impressed on Mogens the need for a sustained prevention of depression "at the time when maintenance ECT was clearly not the ideal."

When Cade published his findings on lithium, in 1949, it attracted Schou's attention although Cade himself had only demonstrated an acute effect in manic psychosis and found that "in three chronically depressed patients, lithium produced neither aggravation nor alleviation of their symptoms" (Cade 1971). Despite this fact, Schou's interest was piqued by his concern that since age 25, his brother had experienced "yearly episodes of depression. In spite of ECT, drug treatment and hospitalization the depressive attacks came again and again" (Schou 1998). During the decade 1950-1960 that Cade vigorously pursued his interest and research on lithium, imipramine was probably not available until towards the end of the decade and it is likely that during this interlude, Schou prescribed his brother lithium, which "changed his life and the lives of his wife and children." This leads me to wonder if, in fact, his brother manifested a Type 2 bipolar disorder, in which mild hypomania went unremarked. Grof notes that late in his career, Schou developed a special interest in "hidden bipolars" – patients with depression who had unrecognized bipolar disorders. Schou's last scientific presentation, shortly before his death, was on this topic and a new study he was proposing (Grof 2006).

Schou was not a founding member of the CINP but participated in the first Congress in Rome, in 1958, when he contributed to the final session a "General Discussion." He recalls his comment that "On the chemotherapeutic firmament lithium is one of the smaller stars" (Schou

1998). Baastrup and Schou's seminal publication in the Lancet (Baastrup and Schou 1968) had been underway for seven years, begun probably in 1961. The above facts help explain why imipramine was not included as a comparative drug, even though the population included both unipolar and bipolar depressed patients. Later on, as his familiarity with imipramine grew, he used the term "normothymics" to include both lithium and imipramine (Schou 1963).

These events resonate with the concerns raised in our paper criticizing Baastrup and Schou's methodology and conclusions (Blackwell and Shepherd 1968) regarding the uncertain specificity of lithium and the absence of a control comparison. To be fair, Schou and Grof draw attention to the problem of using a placebo control based on the high suicide rate in untreated affective disorder. Schou eventually resolved this obstacle with a novel trial design in which sequential analysis of paired placebo and lithium patients was coupled with an immediate switch to open treatment for any recurrence (Schou 1998).

Because the *ad hominem* aspects of this debate still linger, I will quote a few laudatory comments made by his friend and colleague Paul Grof in the obituary. Schou was "a caring man with great humility," with a "love and compassion for people" and also a "highly meticulous" researcher who "never left a task undone."

In 1970, two years after I immigrated to America, my mentor Frank Ayd and I conceived the idea to invite all the scientists and clinicians who had discovered the original therapeutic compounds in each disorder to tell their own story at a conference in Baltimore. These first-person accounts were published the following year in our edited book, *"Discoveries in Biological Psychiatry"* (Ayd and Blackwell 1971). They included Albert Hoffman *(Hallucinogens*), Frank Berger *(Meprobamate),* Irv Cohen *(Benzodiazepines),* Pierre Deniker *(Neuroleptics),* Nate Kline (*MAO Inhibitors),* Roland Kuhn *(Imipramine),* John Cade *(Lithium),* Paul Janssen *(butyrophenones),* and Jorgen Ravn *(Thioxanthenes).* I contributed a chapter on *The Process of Discovery,* using the interaction of cheese and the MAOI as a template and Frank Ayd concluded with a summary on *The Impact of Biological Psychiatry.*

Noteworthy now, but not discussed at the time, was that Frank did not include Schou. Perhaps, speculatively, this might have been for two reasons: first, Schou's contribution was derivative to Cade's and more adaptive than original; secondly, because the benefits of all these

"serendipitous" discoveries had been confirmed in well controlled clinical studies. The methodological difficulty of proving prophylaxis and the specificity of lithium in doing so, would linger experimentally (but not in practice) for almost 20 years, until the definitive studies, in 1984, by the Medical Research Council in Britain (Glen et al. 1984) and the NIMH study group in the USA (Prien et al. 1984). This latter study, larger of the two, involved a two-year follow-up of 117 bipolar and 150 unipolar patients given lithium, imipramine, both drugs or placebo. It reached three major conclusions:

> (1) Imipramine is preferable to lithium for long term prevention following recovery from an acute episode of unipolar depression.
>
> (2) For both bipolar and unipolar disorders, the preventative effects of both lithium and imipramine parallel their effects in acute episodes.
>
> (3) Even when lithium and imipramine are effective, they are not panaceas. Only a quarter to a third of patients with either bipolar or unipolar disease were treatment successes.

Eighteen years after Schou's original study, the issues of diagnostic specificity, comparative and specific benefits for lithium or imipramine and their magnitude were scientifically defined in the absence of potential observer bias and statistical flaws.

In retrospect, some of the angst directed to Shepherd and I might have emanated from various attributions: methodological puritanism, unjust allegations of bias or of potential therapeutic nihilism - for which the Maudsley was rather unjustly credited. Nevertheless, it was a contemporary and colleague of mine from the Maudsley who, in comments on events in the 1960s made the satirical observation that, "Writing from the Olympian heights of the Institute of Psychiatry Barry Blackwell and Michael Shepherd airily dismissed Schou's evidence" (Silverstone 1998). But we were all scientific babes in the wood when it came to prophylaxis, bias must always be assumed unless it is eliminated and, while the atmosphere at the Institute was decidedly empirical, it was also benevolent to developments in psychopharmacology. The 1998 book, *"The Rise of Psychopharmacology and the Story of the CINP,"* lists the 33 Founders of the organization. 27 were clinicians but only three were from Britain: Sir Aubrey Lewis, Michael Shepherd and Lindford Rees. Sir Aubrey was an active participant in the first CINP Congress.

My first rotation at the Maudsley as a resident, in 1962, was under Lindford Rees, a dedicated psychopharmacologist who carried out early studies on imipramine; my second rotation was on the Professorial Unit, where Aubrey Lewis took me under his wing and, once he was sure I was not interested in psychoanalysis, arranged and endorsed my psychopharmacology training. True, Michael Shepherd was a sceptic and scientific purist, but, lest he be blamed for any perceived disrespect towards Schou, I must make clear that I was first author on our Lancet paper, chose its title and was responsible for the data analysis and conclusions reached.

Nor were either of us wedded uncritically to double blind methodology. We were well aware of its shortcomings. Immediately before our paper on lithium, Shepherd and I worked on a drug study for a pharmaceutical company which went nowhere because of rigid, impractical and unrepresentative criteria for recruiting subjects. We published our conclusions on contemporary trial methodology in the Lancet (Blackwell and Shepherd 1967). During my psychopharmacology research in animals, I collaborated with a colleague evaluating and recording the outpatient use of MAO Inhibitors by all the consultants and residents at the Maudsley. This must have been among the first "effectiveness" studies to look beyond the boundaries of conventional controlled clinical trials at what happens in real life (Blackwell and Taylor 1967). The results were unusual and revealing. One intriguing finding was how the interaction between prescriber and drug influenced outcome, precisely what the double blind study is designed to stifle or eliminate. The most powerful effect on outcome, above diagnostic and demographic variables, was prescriber behavior. Those who used MAOI's a lot, as "first choice" drugs," had better outcomes than those who used them more reluctantly, as "second choice" drugs. The reasons appear self-evident. First choice prescribers reaped the benefits of their enthusiasm, the placebo response, spontaneous remission and perhaps a willingness to tolerate side effects. The "second choice" population contained more treatment resistant and side-effect sensitive patients alert to the physician's skepticism. Needless to say, these outcomes were likely to reinforce physician attitudes and behaviors. Pharmaceutical reps soon learned to capitalize on this phenomenon by offering physicians a stipend in return for using their new drug in "the next few patients you see."

Another finding was the intriguing comment one enthusiastic prescriber made in the chart, "Although this patient never looked depressed before, she looks less depressed now." Perhaps drug outcomes sometimes influence diagnostic habits. So, in retrospect, one wonders if Schou's

late-life interest in "hidden bipolars" was evoked by his extensive experience and enthusiasm for lithium. Perhaps he was curious to find if there were subtle and covert clinical indicators of hypomania in some recurrent unipolar patients who, like his brother, unexpectedly benefited from lithium.

Also relevant to the prophylaxis debate was our finding that 18% of that population remained on an MAOI for three years after recovering from an initial episode of "atypical" depression and relapsing on attempts at withdrawal, a finding we attributed to "dependence" but identical to the 11 out of 60 patients (18%) who took lithium for three years and where "prophylaxis" was the explanation (Baastrup and Schou 1967). Further complexity is added by noting that, independent of diagnosis or treatment method, about 80% of all outpatients at the Maudsley stopped treatment within three months, while the remaining 20% remained, sometimes for years. What then is the difference between "dependency" and "prophylaxis"? This raises semantic, philosophical and clinical issues and attempts to discriminate by stopping treatment introduce an ethical dimension of potential harm. Perhaps this introduces an "eye of the beholder" component concerning which semantic meaning one applies and is this, in turn, partly based on the physician's temperament?

I am ambivalent; my heart tells me one thing and my head another. Am I a neutral researcher, seeker after truth, or a benevolent healer following the Hippocratic ideal of "first do no harm"? Is what I see "prophylaxis" or "dependence," perhaps some of each?

The issue of potential clinical bias is nuanced; an intimate interaction between clinician and patient, particularly a friend or relative, can sow the seed of a new idea, worthy of further investigation.

The issue at stake is also a matter of semantics and timing. The word "bias" has a pejorative connotation, especially when applied retrospectively, to allege an investigator's potential faulty judgment in an uncontrolled study. The term then assumes an unpleasant but perhaps unintended *ad hominem* element. Contrast this with the prospective benign intent of a controlled study - to protect an investigator from his or her laudable compassion and therapeutic enthusiasm. On which side of this semantic fence one sits, at a given moment or on a specific issue, may be influenced by other factors, including the reputation and fame of the investigator and one's acquaintance with

them or sympathy with their claims or ideas. There is no better example than Linus Pauling's orthomolecular beliefs and zeal in promulgating them. He was the only scientist to have won two unshared Nobel Prizes: Chemistry, in1954, and the Peace Prize, in 1962. No person on the planet had better scientific and humanistic credentials. But following the onset of Bright's disease, he developed a strong belief that physical and mental illness might be alleviated by manipulating vitamin levels. In 1968, he published an article in Science on *"Orthomolecular Psychiatry."* Pauling, himself, took 3 grams of Vitamin C daily to prevent the common cold and collaborated with a British cancer surgeon on its use in prolonging life. These claims were not disproved until more than 10 years later by controlled research at the Mayo Clinic. A physician critic, in an article in *The Atlantic* (Offit 2013), commented that although Pauling was "spectacularly right" in his early scientific career, his late career orthomolecular assertions were "so spectacularly wrong that he was arguably the world's greatest quack." Putting this cautionary tale aside, it is only just to remark that Schou was certainly right, while Pauling was unequivocally wrong.

By the time Schou was attempting to demonstrate the prophylactic potential of lithium in Scandinavia, the Congress in the United States had enacted the Harris-Kefauver legislation mandating that drug manufacturers prove their products were effective as well as safe. In 1968 I migrated to America to become the Director of Psychotropic Drug Research for the Merrell Company, in Cincinnati. The company was just recovering from the stigma of having marketed thalidomide for insomnia and the market place was cluttered with compounds in search of a credible rationale or proof they were more effective than a placebo. Merrell had two such products in the psychotropic domain and I had the daunting task of proving they could pass muster. One was "Alertonic" a cunningly named reddish-brown liquid popular in nursing homes for the elderly that contained small amounts of alcohol, B vitamins and an amphetamine like stimulant. A substantial placebo response in an elderly population eager for attention made the task of proving efficacy impossible.

A still more dubious drug was Frenquel with the marketing claim that it stifled hallucinations whatever the diagnosis and the odd characteristic that the intravenous dose was higher than the oral one. Since no other drug had a similar claim, this was a niche product and the threat of withdrawal produced a flood of protests from patients and clinicians who "could not live without it." The FDA was unimpressed and impervious to testimonials, but I decided to visit one

of the more credible supplicants to better define what was going on. The following account appears in my memoir in the piece on *"The Pharmaceutical Industry"* as a Bit titled *"Snake Oil"* (Blackwell 2012):

> "I had a trip planned for New York and decided to call on one of the Frenquel seekers. The office where the cab let me off in Greenwich Village was next to a homeless drop in center. The doorbell was answered by a polite, casually dressed, older physician who greeted me and ushered me into a room in the basement furnished more like a family doctor's office than a psychiatrist's den. In the center of the room stood an examining table rather than a reclining couch with an attached shiny aluminum tray on which lay a large syringe containing a colorless liquid I assumed was Frenquel. Sitting on the table, legs dangling and wearing a brightly colored, mildly revealing dress was an attractive young woman. Almost before I could take in the scene, she leapt to the floor, faced me and began to shout, 'So you're the f----ing drug company man that's going to ruin my life!'
>
> "The doctor moved quickly to take her arm, guided her back to the table, and did his best to calm her. She settled down and lay back, still eyeing me furiously, pulling up the sleeve of her dress to expose the veins in the hollow of her arm. This was obviously a well-practiced routine, which the doctor performed often. He inserted the needle and gently pushed the plunger as the patient closed her eyes and appeared to drift into a light sleep. Visibly relieved the doctor removed the needle, lay down the syringe and leaned towards her. 'It's all right, Martha, you can get up now.' Her eyes opened, she smiled at us, and thanked me for coming so far out if my way to help her.
>
> Another surprise awaited me: the doctor suggested the three of us have lunch together. We walked to a nearby bistro, and over a meal paid for by Merrell I spent an hour in the company of two friendly, apparently normal people. Over lunch the doctor explained to me that the alcohol and drug detox clinic adjoining the homeless center used Frenquel often to help 'bring down' people in drug withdrawal.

> On the flight back to Cincinnati, I wrote up my 'trip report' explaining I had found two 'off-label' novel uses for Frenquel: to calm someone who, most likely, had a borderline personality, and to facilitate drug or alcohol withdrawal. I didn't suggest Merrell pursue research into these potential new indications, but perhaps I was wrong. New uses for old drugs are often discovered by chance; looking for one thing and finding another. It's called serendipity. On the other hand, it seemed more likely that everything attributed to Frenquel might be due to suggestion, the placebo response, or spontaneous remission."

I did not state the obvious – that Frenquel clearly had mild sedative and calming properties but certainly not sufficient to justify the rigors of a controlled study in a market already including meprobamate and the first benzodiazepines. Nor were Alertonic and Frenquel a worthy match for lithium in the effort it would take to prove they were effective remedies for a specific problem.

Finally, we come to the saddest part of this tale – the extent to which scientific disagreements can degenerate into strident squabbles. Almost 20 years after our Lancet article, Michael Shepherd asked me to review the book, *"The History of Lithium Therapy"* (Johnson 1984). It was published in *Psychological Medicine* the following year. The author, an academic psychologist, had authored three previous texts on lithium and claimed Schou and Cade as his friends. In unrestrained hyperbole, verging on the ludicrous, he endorses the enthusiasts who see lithium as "the King of drugs" responsible for the "third revolution in psychiatry." The following quotations illustrate the polemical nature of the book:

> Lithium is being taken by "one person in every two thousand in most civilized countries" because "depression (sic) is a crippling condition."

> Lithium alone triggered the chemical revolution in psychiatry; "At a stroke, the elusive ethereal Freudian psyche was replaced as the primary object of attention in psychiatry by the polyphasic, physic-chemical system called the brain."

> Lithium, "like no other single event, led to psychiatry becoming truly interdisciplinary." Its ubiquitous use "suggests a new basis for classification of psychopathological states." And it is so cheap and easy to administer it will "transform health care in underdeveloped countries."

These absurd claims provoked me to satire and to ending my review by suggesting that those who might buy the book would be those who shared the author's view that lithium was the "Cinderella of psychopharmacology" and who wished to have an unabridged version of the fairy tale at their fingertips. These comments were, in part, a reprise of a lively debate between Nate Kline and me in the correspondence columns of the *American Journal of Psychiatry*.

The final irony is that this book was published shortly before the two definitive controlled studies (referred to previously) finally arrived at an accurate scientific demonstration of the specific and fairly modest benefits of lithium and imipramine in preventing recurrences of bipolar and unipolar disorders, respectively.

Some reservations about the impact of unbridled enthusiasm for prophylactic treatment have been expressed from the scientific sector. Paul Grof (1998) notes that the use of prophylactic treatment for "nearly everyone with recurrent affective disorders has led to the point that the natural history of affective disorder the illness is not known anymore. He also notes that with the extensive use of lithium "the concept of affective disorders has dramatically broadened and mood symptoms, rather than comprehensively assessed psychopathology have become the center of psychiatry assessment." It is worth adding that the parsimony of the DSM system has colluded in this outcome.

What can we make of all this today? To begin with, the testing of new psychotropic drugs has passed almost entirely out of the hands of academic clinicians and federally funded projects and into the realm of the pharmaceutical industry and subcontracted commercial companies who, while they adhere to FDA minimal requirements for controlled studies, have adopted other dubious ways to degrade the process and bias the outcomes. We have also learned that even the best of controlled double blind studies may not mirror or predict what happens in real world effectiveness. I would gladly return to the time when experienced dedicated clinicians like Mogens Schou did the very best they could, however imperfectly, to show us what works in real practice. After all, their original study was really an "effectiveness" one and not a controlled scientific evaluation. And Schou was, after all, correct. But perhaps Mogens Schou's legacy is better served by the recognition that his truly innovative contribution was the concept of "prophylaxis" itself and not the agents used to accomplish it. This was the very fact that relentlessly recurrent episodes of

affective disorder could be checked by continuous, rather than episodic treatment, a technique that also suppressed the phenomenon of kindling.

Now we come to the most tantalizing question raised by this autopsy. Suppose that each of us, Schou, Shepherd, Blackwell and Grof, are double blind neuroscientists groping the same elephant. That prophylaxis of recurrent affective disorders is Schou's reality - *the body*, but that lithium is not a panacea for all its forms (Blackwell and Shepherd) - *the tail*, and that more scrupulous analysis of the phenomenology, genetics and neurochemistry might reveal which subtypes respond specifically to lithium, imipramine or valproic acid (Grof) - *the head*. This is a puzzle beyond the capacity of DSM 5 or contemporary trial methodology to solve; worse still, all three compounds are orphan drugs – either un-patentable or generic, so that support for research is unlikely unless the national or federal funding agencies in Britain and America reverse course and revive clinical psychopharmacology research.

At the same time, claims that exceed the level of proof available in efficacy or effectiveness studies should always be challenged and those who exaggerate them beyond belief are free game for Anglo Saxon satire. *Mea culpa!*

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Risk and Relevance of Lithium Usage

In April 2015 I wrote a letter to the Editor of JAMA that read as follows:

"As an octogenarian psychiatrist, previous author and occasional reader of JAMA, I enjoyed with irony two articles juxtaposed in the 2015 March 24/31 issue. In the Clinical Review and Education Section, Mark Olsen reviews work by Hampton et al. on '*Psychiatric Medication Adverse Events in Emergency room Visits ADE ED.'* Among these are an estimated 16.4 per 10,000 outpatient visits (0.16%) due to lithium toxicity. Of these 'roughly one half' (53.6%) resulted in hospitalization, 0.08% of the total. This finding elicits the following comment from Olsen, 'The high frequency and clinical severity of adverse events associated with lithium should be considered amid calls to expand lithium treatment in bipolar disorders.'

"In 'JAMA Revisited' (p.1273), we find a reprinting of '*Why Physicians Err in Diagnosis'* (March 27, 1915), that identifies social and clinical errors, the former of which include what, at the time, were considered 'functional' psychiatric disorders, some that were probably treated with lithium, a panacea at that time.

"Today we recognize that lithium is the only naturally occurring, highly specific, remedy for a particular genetically based psychiatric condition, bipolar disorder, and that it is uniquely safe when adequately monitored by regular plasma levels. This is due to classical, but often overlooked work, by Trautner et al. (1955), which enabled Cade to rescind the ban he had placed on its use. (See Blackwell, B and others in *The Lithium Controversy: A Historical Biopsy* on INHN.Org in *Controversies,* June 19, 2014 and subsequent postings).

"It is a disservice to science, medicine and psychiatry to suggest that sloppy diagnosis or prescribing of a highly specific and effective remedy like lithium for a disabling disorder should become an excuse for limiting its appropriate use." Sincerely yours, Barry Blackwell.

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JAMA Comment on Letter

The above "Letter to the Editor" of JAMA was duly submitted, meeting demands for fewer than 400 words and five references, an arduous process that severely taxed my geriatric computer skills. Several weeks later, I received a formal "Decision Letter" stating: "Considering the opinion of our editorial staff we determined your letter did not receive a high enough priority rating for

publication… we are only able to publish a small fraction of the letters submitted… which means that published letters must have an extremely high rating."

I was invited to "contact the author of the article although we cannot guarantee a response." This roused my professional ire. A scribe of authors (is this the correct collective noun?) delivered their verdict without seeking input from the reviewer or the original authors for comment on the validity of the concerns expressed.

The article on which the reviewer commented is an example of a massive data set that yielded statistically significant results of dubious clinical significance. The reviewer failed to address how to improve prescribing habits, but focused instead on alleged "over-prescribing" without any evidence or mention of how lithium treatment was managed, who the prescribers were (discipline and training) or any details of the patients' diagnosis, natural history or treatment responses.

A scribe of editors judged the reviewer's conclusions and the author's study design did not merit seeking the opinion of either concerning issues raised by my letter. I could contact them myself but not expect an answer. This approach raises serious scientific and ethical concerns about editorial disinterest in the quality of what JAMA chooses to publish and how circling the editorial wagons stifles dissent.

The problem identified by this mega data is not new. It was reported 18 years ago by leading European psychopharmacologists (Kores and Lader 1997), who studied 50 cases of severe lithium toxicity due usually to poor management.

My letter might have suggested a better, more practical solution to this problem compatible with the study design. Every patient admitted with side effects severe enough to warrant admission would be given, at the time of discharge, a brief (one page) outline of ideal management principles and advised to share it with their prescribing physician at a first outpatient visit. This might improve the physician-patient alliance, hopefully viewed by the doctor as prophylaxis for reduced risk of future malpractice litigation.

Of course, such a suggestion might have increased the scribes "priority rating" although adding a sixth reference could have resulted in even more peremptory unthinking rejection.

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Chapter 13

The Anxiety Enigma

Preamble

This chapter, written in 2014 remains true today. Its message is reinforced by the philosophy of Frank Berger (Chapter 10), the work of Karl Rickels (Chapter 14) and most of all the skill and duplicity of the pharmaceutical industry in garnishing the rewards of American infatuation with pills skillfully advertised for new anxiety diagnoses that the DSM system created, (Chapter 19). As I write this preamble *The New York Sunday Times* (December 17, 2017) sits beside me advertising Professor Ronald Siegal's 24 lecture series, "*The Science of Mindfulness: A Research Based Path to Wellbeing."* Founded on work by the Harvard psychology professor (Siegal, 2009) it is promoted for "Its application to a wide range of issues, psychological, social and medical… joining ancient wisdom practices and scientific methodology in forging new possibilities for living." The promise of Mindfulness Meditation is that it is available directly to the public at an affordable cost without the parsimony of the medical insurance companies.

Time alone will tell to what extent "anxiety" is an existential manifestation, a medical disorder or an invention of the drugs that suddenly arrived to treat it

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The Anxiety Enigma

Anxiety has become such a commonplace word in both culture and medicine that it is difficult to view it as "mysterious or puzzling" (*enigma*, Oxford English Dictionary – OED). But viewed through the lens and across the trajectory of my 50-year career the word seems apposite. This essay examines a brief history of the term, its semantics, its nosology and natural history, the evolving and contemporary role for medicine or other forms of therapy and its putative philosophical or existential purpose.

The concepts of "stress" and "anxiety" span mainly from the 20th century into the present. A recent book, *"Emotions and Health"* (Carrera 2013), focuses on the negative dimensions of

feeling described in medicine from the 13th century; melancholy, fear, anger, revenge and sadness are included but not anxiety. Another book, *"The Age of Stress: Science in Search of Stability"* (Jackson 2013), focuses on stress alone and traces this from Hans Selye, who coined the term. Selye was born in 1907, graduated from Prague University as a doctor of medicine and chemistry at age 22 and emigrated to the United States in 1931 where his prolific research and writings laid the basis of psychosomatic medicine. Only six years later in 1937, Frank Berger graduated in medicine from the same university with strong interests and accomplishments in both pharmacology and microbiology, migrating to the United States in 1947 and going on to develop the first modern drug to treat anxiety, replacing the barbiturates. Both these pioneers in work on anxiety may also have been exposed during their training to Freud's theories. By 1896 Freud had abandoned hypnosis and neurology and coined the term psychoanalysis**.** In the 24 volumes of his collected works anxiety is used in the titles for the first time in Volume XX (1925), "*An Autobiographical Study, Inhibitions, Symptoms and Anxiety"* (Strachey 1976), but Pichot (1999) traces Freud's occasional use of the term to beginning in 1895. Freud's treatment and theories were accessible to medical students. In 1901 an internist, Kahane, who joined Freud's Wednesday discussion group with two other medical doctors published "*An Outline of Internal Medicine for Students and Practicing Physicians"* which described Freud's work in positive terms (Rose 1998). A more focused discussion of semantics relevant to anxiety appears later in this essay.

The seven-year hiatus between my matriculation to Cambridge University (1954) and graduation as a physician from Guy's Hospital (1961) formed the serendipitous seedbed for modern psychopharmacology. First chlorpromazine (1952), then meprobamate (1955), iproniazid (1957), imipramine (1958) and chlordiazepoxide (1960), each discovered and introduced for the treatment of psychosis, anxiety and depression. During five years of residency training (1961-1967) lithium was introduced for prophylaxis in bipolar disorder (Blackwell 2014a). Coincident with completion of my training as a psychiatrist, the basic therapeutic repertoire for all the major psychiatric disorders became available. While the number of compounds with similar effects would proliferate they added complexity, expense and novel side effects, but little genuine progress over the ensuing four decades; 1980-present.

Although conceptually and clinically the impact of chlorpromazine on asylum care was dramatic (Callaway 2007; Rickels 2013) it was overshadowed in scope and public attention by an

upsurge of drugs to treat the far more common symptom of anxiety. In her book, *"The Age of Anxiety"* (Basic Books, 2009), medical historian Andrea Tone details the changing tides of clinical, scientific, political, social, cultural and economic fact and opinion from the advent of meprobamate in 1955 to present times. My personal account of unfolding events is synchronized with the broader perspectives in Tone's scrupulously documented account.

Strange as it may seem in retrospect, prior to the release of meprobamate there was no widespread public or professional appetite for such a product. The manufacturer's own Gallup poll of 100 primary care physicians showed no enthusiasm or willingness to prescribe (Berger 2014). Nevertheless, Tone notes that within five years (1955-1960) meprobamate had been prescribed by three quarters of the physicians in America, success attributable to a climate of public approval for a stigma-free adjunct to "enhance the functioning of successful people," an affordable remedy for "the budget conscious and time strapped," readily available from primary care physicians as a tool to stifle the anxiety blamed for "a myriad of medical disorders." So, initially the drug was prescribed by general physicians for benefits perceived as primarily existential and medical, not psychiatric or biologically based.

Enrolled in University, I was oblivious to events occurring in America and, in retrospect, uncertain of their impact on British medicine or any potential import for my planned career. Personal concerns were more pressing; the second year at Cambridge marked a Rubicon and a point of no return was Organic chemistry. I failed this subject in high school and did so again during my first year at university. It was "three strikes and you're out," the major obstacle to becoming a doctor. My final attempt would be in 1955, after I obtained permission from my college tutor to return for the summer session. This was a subject I found incomprehensible and I knew my chances were slender. The tutor greeted me kindly, sat me down and began, "Blackwell I know you failed the exam but there's been a mistake, your name is published in the pass list. I believe you'll make a good physician so I don't plan to say anything" (Blackwell 2012).

This good fortune saved my career and fed an arrogant assumption that chemistry was redundant for medical practice, an opinion bolstered by becoming among the first of my Cambridge peers to receive a doctoral degree – in pharmacology and medicine. In the same month that I obtained my reprieve, April 1955, Frank Berger filed an application with the FDA in America for approval of meprobamate. Born 21 years before me (1913), Frank displayed an unusual

aptitude for basic science in medical school. Concerned that his fellow students might fail pharmacology finals (it was two strikes and you're out in Prague), he set about reading all the pharmacology texts and printed a student guide to the exam which he sold to support his tuition (Berger 2014). Following medical school Frank worked in microbiology research until March 1939 when Hitler invaded Czechoslovakia and he and his wife escaped to Holland, hoping to migrate to America. When their visa was revoked they arrived destitute in England without a medical license, no money, no friends and no job. His wife was pregnant and cared for in a Jewish shelter; Frank slept on park benches and local lock-ups, but eventually found work as a doctor in a refugee camp and then as a microbiologist. He developed a way of extracting penicillin from the liquid it was grown in and his publication in Nature (1944) led to a job at British Drug Houses where he worked on a non-toxic way to preserve penicillin. Among the drugs studied was mephenesin, a muscle relaxant with unusual "tranquilizing" properties in mice (Berger's own term). In 1947 Frank and his wife migrated to America and two years later he was hired as research director for Carter Products (a subsidiary of Wallace Pharmaceuticals), the manufacturer of "Carter's Little Liver Pills." It was their only product. Here Frank worked to develop a longer acting congener of mephenesin. This was meprobamate, marketed as Miltown, named after a small town close to where Frank worked (Berger 2014).

Suffice to say I was ignorant of these events or their impact, immersed in life as a medical student, playing vigorous rugby at the University level, rowing for my college, frequenting the local pubs and on my way to an indifferent Master's degree in Natural Sciences.

At Guy's Hospital in London I captained the oldest rugby team in the world while gradually becoming absorbed in learning the basic skills of my profession in a series of intense three- to six-month student internships. I hardly noticed the unfolding revolution in psychopharmacology and remained blissfully unaware of the events in America which Andrea Tone describes: "The medical management of anxiety had gone mainstream. Miltown encouraged greater acceptance and dependence on lifestyle drugs. It stitched together patients, doctors and pharmaceutical companies in a web of psychotropic drug consumption, setting the stage for the massive expansion of the country's pharmaceutical armory."

Within this widespread approbation Tone documents muted expressions of concern that would later bloom into full blown controversy. In 1956 Berger had convened a national conference

on tranquilizers under the auspices of the New York Academy of Sciences (Berger 1957). Perhaps mistakenly, he invited Aldous Huxley to give the opening speech. Author of *"Brave New World,"* Huxley's novel had showcased "soma," a drug used by a totalitarian state to pacify its citizens "with all the advantages of Christianity and alcohol; none of their defects." Although Huxley subsequently insisted this was "only a literary fiction," he welcomed the arrival of new tranquilizing drugs that were less costly than agents previously used by humans in the search for "self-transcendence and relief from tension." Berger's paper, in contrast, was a scholarly review of the pharmacological differences between major tranquilizers like chlorpromazine and minor tranquilizers like meprobamate in animal and human studies. Throughout his life Frank insisted that his drug was only intended to treat biologically based anxiety disorders and had no capacity to endow "new insights, philosophic wisdom or creative power" (Berger 1970. See Ch.10).

The need to distinguish between Huxley's enthusiastic endorsement of meprobamate and Berger's modest claims obviously struck home to some in the audience. Andrea Tone notes that The New York Academy of Medicine promptly established a Subcommittee on Tranquilizing Drugs whose final prescient report she quotes: "Anxiety and tension seem to abound in our modern culture and the current trend is to escape the unpleasantness of its input. But when has life ever been exempt from stress? In the long run is it desirable that a population be ever freed from this tension? Should there be a pill for every mood or occasion?"

This debate reminds us that human attempts to stifle anxiety and induce a state of tranquility (OED "…*Calm, free from disturbance")* are as old as recorded history including soma, alcohol, marijuana, chloral, bromides, opiates and barbiturates. All of which share the common property of producing an immediate, sought after change in mental state but in many cases associated with dependence, tolerance, addiction and accidental or intended death by overdose. The widespread use and future controversy concerning minor tranquilizers would hinge to a large extent on this equation.

Back in Britain at Guy's Hospital neither the early evolution of psychopharmacology nor the concerns it engendered influenced my choice of psychiatry as a future profession..

After graduating I spent six months as a senior intern in Neurology at the Whittington Hospital in North London where I gained a closer relationship with the new drugs likely to impact

my future career in psychiatry. The neurology service admitted two kinds of patients suffering from the side effects of psychotropic drugs.. Most common were many cases of barbiturate overdose admitted to a neurology bed from the emergency room. Despite the inroads being made by meprobamate and chlordiazepoxide, the barbiturates were still commonly prescribed in primary care to patients with anxiety, insomnia and, I suspect, others with early or covert depression and undetected suicidal thoughts. I chose this as a research project and sat by each patient's bedside injecting brain stem stimulants keeping them alive until recovery.

This study won the hospital's annual research award and the results were published (Blackwell 1964). This colored my view that the newer benzodiazepines were safer and preferable to the barbiturates. Tone notes the massive amount of clinical research conducted on chlordiazepoxide (Librium) prior to its release in 1960, "involving 2000 physicians, more than a dozen leading institutions and upward of 20,000 patients." The studies covered a broad spectrum of clinical conditions and outpatient populations backed up by sophisticated marketing strategies designed to "position Librium as the country's newest ethical blockbuster." Not everyone agreed with this body of information or my own conclusion that chlordiazepoxide represented a genuine step forward. One of the earliest textbooks in the field (Shepherd, Lader and Rodnight 1969) commented: "Although there are interesting differences between chlordiazepoxide and barbiturates, the clinical differences are minimal." Malcolm Lader, my fellow resident and contemporary at the Maudsley who became one of the world leaders in benzodiazepine research, would later admit responsibility for this statement and repudiate it (Lader 1998). By the end of 1960 Librium had captured 20% of the market and doctors were "writing 1.5 million new prescriptions every month."

While it was clear that chlordiazepoxide did not pose a serious overdose problem there was growing concern surrounding possible dependence due to withdrawal effects after rapid cessation. Leo Hollister's work would demonstrate significant problems after high doses of chlordiazepoxide, later replicated with diazepam, raising concerns and controversy about abuse potential (Rickels 1966). See Ch.14.

This was the status quo when I began my residency training in psychiatry. As a neophyte devoid of board certification in medicine, I began at the Bethlem Hospital in the country; the Maudsley at this time was renowned for its descriptive and empirical approach to psychiatry in the

European tradition, decidedly at odds with psychoanalysis. Descriptive implied a commitment to nosology and the natural history of disorders while the empirical approach demanded rigorous scientific evaluation of therapeutic claims. In this regard it is worth noting that while the FDA implementation of the Harris-Kefauver amendments in America had stimulated a large volume of relatively rigorous research on the safety and efficacy of new psychotropic drugs, including the benzodiazepines, anxiety as a medical disorder was an orphan compared to what had been studied and was known about in schizophrenia and melancholia. There was no Kraepelin, Bleuler, Jasper or Leonhard nor did the psychoanalysts' interest in "neurosis" meet empirical standards. In many ways anxiety as a medical disorder was an invention of the drugs that had suddenly arrived to treat it. This created a scientific Catch 22 – it was difficult, perhaps impossible, to study the nosology and natural history of a condition that was already being treated with drugs designed to stifle its symptoms and modify its course.

This is the moment to take a closer look at the semantics of anxiety in order to better understand what exactly might be being treated. Pichot (1999) provides an excellent historical account of the words used to convey anxiety in English, French and German including the differences, ambiguities and overlap in terms. He concludes his essay as follows, "The existing ambiguities, relics of the past histories of the words, are indications of the still incomplete clarity of the corresponding concepts." Pichot does not mention Aubrey Lewis' satirical and almost forgotten dissection of the term anxiety (See Ch. 11). What follows is a more detailed discussion of the current semantic situation in English. Bearing in mind these overlapping and ambiguous synonyms bring to mind Humpty Dumpty's claim that, "When I use a word it means just what I choose it to mean, neither more nor less" (Lewis Carroll in "*Through the Looking Glass".)* All the definitions cited are from the OED.

Anxiety: *A nervous disorder, marked by excessive uneasiness.*

Fear: (1) *An unpleasant emotion caused by threat of danger, pain or harm* or (2) *Feeling anxious on behalf of…*

Anguish: *Severe mental or physical pain or suffering.*

Apprehension: *Anxious or fearful anticipation.*

Dread: *Great fear or apprehension.*

Angst: *A strong feeling of anxiety or dread.*

Panic: *Sudden uncontrollable fear or anxiety*

With the exception of anxiety, panic and anguish the other four definitions combine anxiety and fear as alternate words. Even fear has anxiety as a second definition. Anxiety is qualified by calling it a "disorder" with (presumably) medical implications. Panic is qualified by "sudden" fear or anxiety. Anguish is the only word that combines mental and physical suffering. Pichot (1999) points out that the original Indo-European roots 'ango' or 'anxio' and their derivatives focused mainly on physical discomfort so it is surprising that none of the above, with the exception of anguish, include physical sensations. Even stress (OED: *mental or emotional strain*) omits any mention of bodily concerns. The word 'Panic' was re-introduced into the English speaking medical lexicon in 1962 (Klein and Fink, 1962), but Pichot notes that the first application of the word to a psychiatric symptom was by Henry Maudsley (Maudsley 1879) when he described typical episodes of panic in patients suffering from melancholia.

The question of whether fear and anxiety are separate or synonymous terms is often debated by pharmacologists with the assertion that fear is a reaction to a "real" threat accompanied by a full blown "flight or fight" physiological response contrasted with a lesser form of arousal, anxiety, due to an implied or imagined threat. This dichotomy is not consistent with common usage where the terms "I am afraid of…" and "I am anxious about…" are used interchangeably. Nor is it consistent with the fact that a full-blown panic attack (as seen in emergency rooms) has all the psychic and physiological characteristics of fear absent a "real" threat. Conversely, PTSD arousal is evoked by only the memory of a real event.

Further semantic confusion is added by noting that "anxious" has an entirely contradictory, second OED meaning: "Very eager and concerned to do something or for something to happen." This qualification is added to the verb but not to the noun. Tone notes that this second definition appeals to those who see anxiety as the driving force for ambition or "the seedbed of human and artistic talent." We will see later how these opposing views of the role of anxiety play a part in lay and professional responses to an escalating use of minor tranquilizers in society. Interestingly, the alternate view of anxiety was apparent in the earliest stages of developing drugs to treat it when

the psychoanalytic mainstream that dominated American society believed stifling anxiety would diminish motivation for therapy. Young psychiatrists in the USA, among them some future psychopharmacologists, were admonished that their eagerness to prescribe drugs was either a defense against verbal intimacy or a sadistic counter-transference towards a treatment refractory patient.

In the scholarly debates and discussions during teaching conferences at the Maudsley anxiety was seldom a topic worthy of consideration. My own interest about its ambiguous but pervasive influence arose out of the unusual study described earlier, designed and carried out with my fellow resident and lifelong friend, David Taylor.

A pertinent finding of this study was the way in which availability of antidepressant drugs influenced diagnosis in the interplay of anxiety and depression first noted by our namesake Henry Maudsley 85 years previously. In the triennial compilation of diagnostic statistics at the Maudsley Hospital (Hare 1963) a significant change occurred in diagnostic habits between 1955 and 1957, the meprobamate era, and 1961-1963, the MAOI antidepressant era. In the latter time frame the diagnosis of depression increased by 8.5% while the diagnosis of anxiety disorders (anxiety, hysterical and obsessional neuroses) declined by a corresponding 9%.. Reviewing the chart notes of one enthusiastic and successful prescriber we came across the following case, briefly commented on earlier.

> A 48-year married woman was diagnosed initially as suffering from an anxiety state. The clinician's verbatim comment at that time was, *"The prognosis for such an anxiety state, unless there is an underlying treatable depression, is poor. It is possible however that treatment with an MAOI might benefit her."* After three months treatment the clinician noted, *"Although she never looked depressed before, she looks less depressed now."* (Blackwell and Taylor 1967; Blackwell 1975).

Another finding is relevant: Parstelin, (a combination of tranylcypromine and low dose trifluoperazine), obtained statistically better outcomes than three other MAOI alone and overall the addition of a benzodiazepine improved outcomes from half to two thirds.

At the completion of my psychiatric residency (1967) I had published more than 20 articles on a variety of topics, penned anonymous leading articles and annotations for the Lancet, acquired

a Master's degree in Philosophy and a Doctoral degree from Cambridge in pharmacology and medicine. But I was uncertain about a career in psychiatry. Clumsy from birth, I was not cut out for the fine finger work required for animal research: I shattered expensive glass pipettes and smudged endless smoked drums. Besides, I preferred humans to rodents and felt reluctant to relinquish the breadth of medicine for the narrower scope of psychiatry. The commanding officer of my reserve army Field Ambulance was a close friend and looking for a partner in his suburban London practice. So, I decided to try my hand at family medicine.

It was fortuitous and broadenesd my horizons by exposing me to the mild and early manifestations of affective disorders in primary care, becuase my contemporary and fellow resident, David Goldberg now a Fellow in the Maudsley Social Psychiarty Unit was looking for a site to validate a new survey instrument (The General Health Questionnaire - GHQ) designed to study the prevalence of psychiatric disorders in a primary care setting. Wide disparities in this measure suggested it might be an "eye of the beholder" phenomenon. The fact we were identically trained in psychiatry but I now operated as a family doctor under time constraints and a medical focus created a unique design free of ideological or cognitive biases. The GHQ went on to become one of the first survey instruments for its designed purpose, translated into many different languages and used worldwide.

We published our findings in two articles in the British Medical Journal: the first on *"Psychiatric Interviews in Family Practice*" (Blackwell and Goldberg 1968) and the second on the psychometric properties of this "*New Method of Case Identification"* (Goldberg and Blackwell 1970). In a 200-patient sample, 20% had "conspicuous psychiatric morbidity" the majority were minor affective illnesses, two thirds of which had returned to normal in six months. My discussion noted that patients rarely presented with psychiatric symptoms but used medical terms; feeling "rundown," "fighting off flu," "low blood pressure," often coupled with requests for vitamins, iron tablets or a tonic. These complaints were often metaphors for an underlying mixture of anxiety and depression. For example, a stereotypical patient would be a 30 odd year old mother of children who complained of lack of energy, sleeplessness, irritability with her kids, accompanied by guilt feelings and low sex drive. A study of symptoms in Anxiety States and Depressive Illness (Roth et al. 1972) found that they shared sadness, pessimism, irritability, guilt, agitation and suicidal thoughts.

Unused to seeing people in the earliest stages of affective illness, faced with diagnostic ambiguity and overlap, I chose to prescribe low dosages of a sedative tricyclic antidepressant (75 mgs of amitriptyline, Elavil) to be taken two hours before bedtime with advice that, as sleep improved, coping capacity, patience and sex drive would gradually return to normal. David Goldberg saw this pattern reflected so often in my chart notes he enquired if I believed the practice was Elavil deficient! In an interview by Tom Ban in 1999 for the Oral History of Neuropsychopharmacology (OHP) (Volume 9 ed. Blackwell 2011), Leo Hollister, asked about his classification of depression, replies: "Deniker's group has classified a mixed anxiety depression syndrome. We called it anxious depression. We brought attention to that and it is beginning to be a popular idea. People are beginning to think there is a sort of co-morbidity or, maybe anxiety is part of depression. I remember raising this question with a psychiatrist and he said, 'I can imagine somebody being anxious and not being depressed, but I have trouble imagining somebody being depressed and not being anxious. I thought that was not a bad summary statement.'" Elsewhere, Leo speculates whether the benefit and return to normal with antidepressants is due to improved sleep (*"sleep that knits up the raveled sleeve of care … balm of hurt minds,"* Shakespeare: Macbeth), delayed antidepressant effect, a placebo response or some combination. In his 1998 OHP interview by David Healy, Karl Rickels (Volume 4 ed. Levine 2011) talks about his own work with Covi and Lipman in a series of studies on depressed and anxious patients that "clearly showed that benzodiazepines had only an anxiolytic and no antidepressant properties. In contrast antidepressants had both anti-depressant and anxiolytic properties." This seems to confirm my intuitive use of a sedative antidepressant.

It took me only a year to realize that while I enjoyed some aspects of family medicine it was not the best career for someone with research interests and a need to know each person in depth. There was plenty of psychiatry in medicine and enough medicine in psychiatry.

In September 1968 I migrated to the United States, accepting the position as Director of Psychotropic Drug Research at the Wm. S Merrell pharmaceutical company in Cincinnati, Ohio. Like many others, the company was eager to explore the commercial opportunities in this new field; as Tone notes, by that time Valium (diazepam) had become the "first $100 million brand in the industry."

However, this was hardly the best time to become an industry physician. Merrell had recently marketed thalidomide as a safe drug to treat insomnia in pregnancy only to discover it produced fetal abnormalities of a particularly repugnant kind, phocomelia or deformed limbs. A zealous FDA physician, Frances Kelsey, had detected flaws in Merrrell's new drug application (NDA) to the FDA, leading to criminal indictments. In defense, Merrell "lawyered up" and everything we scientists wanted to do was legally adjudicated with a stifling effect on innovation.

But there were compensatory influences. Merrell had retained one of America's leading psychopharmacologists and a pioneer in the field, Frank Ayd. Frank and I were both involved in teaching our new discipline to public and professional audiences; out of this we developed the idea of bringing together all the scientists in Europe and America who had made original discoveries in our field.

The conference took place in Baltimore and the proceedings were published in 1971 in a book we co-edited, "*Discoveries in Biological Psychiatry"* (Ayd and Blackwell 1971). Among the presenters were Frank Berger, on "*Anxiety and the Tranquilizers,"* and Irv Cohen, on *"The Benzodiazepines."* By this time the latter drugs were capturing the market, pushing meprobamate into the twilight. Less clear at the time, but viewed in retrospect, Berger's presentation was both humble and prescient. His opening statement is worth repeating:

> *"If anything distinguishes man from the animals it is that humans are anxious. Animals react only to real dangers and threat by showing fear. Humans also react to unreal danger, or anticipation of it, by showing anxiety."*

Frank did not present minor tranquilizers as a panacea for all human anxiety; his discussion of anxiety as a potential motivating factor ranged from John Locke, the English philosopher (1689), to Rose's contemporary complimentary view (Rose 1958). He concedes that if this point of view is correct, "*It would be inappropriate to use drugs."* Frank then defines the emotional and behavioral characteristics of anxiety as a discrete disorder based on Cattell and associates development of a rating scale that defined a specific reaction pattern (Cattell and Scheier 1958), including, lack of confidence, a sense of guilt and worthlessness, an unwillingness to venture, a dependency, a readiness to become fatigued, irritable and discouraged, uncertainty about one's self, suspicion of others and a general tenseness." Finally, Frank cites electrophysiological

evidence localizing anxiety to the thalamus, limbic structures and frontal lobes with the suggestion that electrical coagulation or stimulation can evoke or ablate this emotion (Delgado 1969) and concluding with the claim that meprobamate has a *"selective action on those specific areas of the brain that represent the biological substrate of anxiety."*

Frank Berger's conclusions are reflected in the following, sometimes conflicting, comments made at different points in his presentation:

> Anxiety (by which he is alluding to the syndrome outlined above) is "usually one of the symptoms of a disease, such as a neurosis, depression or schizophrenia."
>
> "By showing it is a symptom of disease… anxiety is not present at all, or is only transiently and to a small extent, in normal healthy individuals."
>
> "Considerable evidence shows that anxiety is due to a dysfunction of a part of the brain and that it is a symptom of a disease state. Consequently, it should lend itself to medicinal treatment like many other symptoms of disease."
>
> "Tranquilizers, by attenuating the disruptive influence of anxiety on the mind, open the way to a better and more coordinated use of existing gifts. By doing this they are adding to the happiness, human achievement and the dignity of man."

Berger did not consider phobias and obsessional states to be anxiety disorders. He notes that they respond to cognitive behavior therapy which is "of no value in the treatment of true anxiety states."

In a final paragraph Frank states: "It would be wrong and naïve to expect drugs to endow the mind with new insights, philosophical wisdom or creative power."

Frank Berger's commentary was rendered in the context of DSM 1 and 2 (Pre-1980) diagnostic concepts; some of its conclusions hold water today and others not. Frank was a brilliant pharmacologist in the lab, but rusty clinically and certainly not a nosologist or a practicing physician at this stage in his career. He considers anxiety a symptom, but describes a syndrome of eight or more symptoms that are today scattered among post DSM 3 Axis 1 and Axis 2 disorders. Contemporary evidence for cerebral localization of this aggregation of symptoms is questionable

and some of the historical research dubious (Blackwell 2013). But Frank's insistence that minor tranquilizers were not a panacea and did not confer new skills or attitudes is prescient in view of the alarming increase in their use that was about to occur, blurring the boundary between focused and indiscriminate prescribing. Frank's opinion that the use of such drugs should be limited to attempts to stifle the troubling symptoms of defined disorders and not towards what became known as "problems of everyday living" remains valid and was a point of view to which he clung tenaciously for his entire life. as noted in Chapter 10.

Still, there remains an ambiguous line between Frank's 1970 assertion that drugs, by coordinating existing gifts, add to human kindness and achievement and the implied claim of his postmortem book that philosophy alone and not drugs are a guide to happiness and success. This may be a false dichotomy. Anxiety alone can impair performance and hamper restitution and recovery, while stress is often occasional or intermittent rather than unrelenting. It is possible, indeed likely, that a short, drug-induced respite from anxiety allows a person to recoup their equanimity, reassess their resources and successfully combat future episodes of anxiety. Frank's contention that anxiety is not, or only seldom, an attribute of "normal" people is tendentious and philosophically inaccurate. Anxiety is a ubiquitous companion of the human condition and life without it is an unattainable Utopian ideal.

By the time our book on Discoveries was complete, I realized that, while I had enjoyed and benefited from my time in industry, my self-image and esteem were tied to education and research rather than product development and commerce. Merrell had allowed me one day a week to teach psychopharmacology to medical students and psychiatric residents; this led to an offer to reverse roles, to become a fulltime Professor of Psychiatry and Pharmacology at the University of Cincinnati with one day a week consulting to industry.

My turn to academic life included the opportunity to make piecemeal observations and contributions to the rapidly developing field of anxiety and its treatment. The decade, 1960-1970, gave birth not only to new medications but also to rating scales with which to measure their effects. Initially this mainly took place in the Veterans Administration (VA) collaborative study groups and the Early Clinical Drug Evaluation Units (ECDEU) linking State hospitals and developing Academic centers. The remarkable speed of development and widespread use of these instruments is epitomized by Doug McNair's survey on the use of the Psychiatric Outpatient Mood Scale

(POMS). By 1991 there were 2,000 articles and it had been used in almost every branch of medicine (McNair 1997).

While indispensable to drug studies, rating scales are inevitably reductive (to a numerical score) and reveal little about the individual persona and pattern of response to interventions. Al Raskin notes Jonathon Cole's comment that rating scales are "quick and dirty" (Raskin, 1997). My own approach was obverse -- to attempt to understand each person's unique response to stress and what is generically called anxiety.

I developed and used the following approach with both patients and students, singly and in large groups. This was not a research project but was designed to understand and demonstrate the polymorphous and unique individual cognitive and somatic responses to stress for patients and doctors. It could be considered a "stress biopsy," perhaps especially useful to primary care physicians dealing with somatizing patients (Blackwell 1996). The individual(s) is/are told to choose and imagine a situation in which they typically feel anxious or stressed, such as public speaking, taking a test, arguing with a spouse, confronting the boss etc. Then they are asked to close their eyes and imagine the scene. After a brief pause, the subject is asked to choose one word that best describes the cognitive emotion - stress, tension, fear, worry, apprehension, doubt etc. Still with eyes closed, they are next asked to find a word that best describes any bodily sensation; palpitations, sweating, muscle tension, breathlessness, abdominal cramps, urge to urinate etc. Finally, they are to decide whether the cognitive or somatic response predominates. In classroom demonstrations the diversity of responses is illuminating while the predominance of emotion or bodily sensation tends to split evenly.

Once a person has identified their own pattern of response they are equipped to keep ratings that help to identify linkages between these feelings and everyday hassles as well as the benefit of any treatment.

Teaching psychopharmacology to medical students I also felt it was important they learn about the placebo response, especially as it related to sedative and stimulant drugs. Together with a pharmacology faculty member and a statistician, we designed a class experiment for first-year students explained as a "double-blind comparison of a stimulant and a sedative drug." Students were randomly assigned to receive one or two blue or red capsules and completed a rating scale

later in class to record their responses in mood and side effects. They also worked in pairs to measure pulse rate and blood pressure.

Both the red and blue capsules were placebos containing an inert powder. Based on the existing literature, faculty predicted the nature, size and frequency of the treatment responses and sealed them in an envelope to be opened at the following class after the results had been tabulated and analyzed. When the envelope was opened every prediction was confirmed. A third of the students reported changes in mood; red capsules produced more stimulant responses, including increases in pulse rate and blood pressure; blue capsules were more sedative. Two capsules of either color produced more effects than one. A few students also reported miscellaneous "side effects."

Both faculty and students were surprised and delighted, but the Chair of the department expressed ethical concerns about the deceit involved. The students felt differently and awarded me their "Golden Apple" as the teacher of the year. The article was published in the Lancet (Blackwell, Bloomfield and Buncher 1972) with the title, "*Demonstration to Medical Students of Placebo responses and Non-Drug Factors."* If it was ever replicated I never heard.

In the department of psychiatry, the psychoanalytic Chair, Maury Levine, who had written a book on psychiatry in family medicine, assigned me to run the Psychosomatic Unit (Two West) at Cincinnati General Hospital. This was hallowed ground, previously managed by George Engel, an internist and training analyst who became widely recognized for advocating the "biopsychosocial" model in practice and medical education. Much in vogue at the time was Hans Selye's "Stress" model (a word he coined), modified by psychoanalysts in their customary manner by attempting to link specific personality disorders to particular medical diagnoses.

Although the views of Selye and the analysts were embedded and popular among faculty and residents, I was surprised to find a different viewpoint on the unit where the nursing staff, under my future wife Kathie Eilers, were dealing daily with difficult patient behaviors rather than with their subconscious origins. A creative and talented psychologist, Susan Wooley, whose father pioneered the heart-lung machine, was interested in cognitive behavioral approaches. This began a collaboration that lasted five years, spawning a new and different view of psychosomatic disorders, the roleof anxiety and how to treat them (Wooley, Blackwell and Winget 1978). Selye's

stress model and the prevailing dogma of psychoneurosis focused heavily on anxiety as an etiologic factor in neurotic and psychosomatic disorders; by the mid-1970s many such patients were also being treated, with little success, by minor tranquilizers.

The new treatment we developed evolved from David Mechanic's (1986) concept of "Illness Behavior" and Howard Leventhal's "Health Beliefs" model. We defined illness behavior as "disability disproportionate to detectable disease" and embarked on identifying why some people, unwittingly perhaps, adopted a sick role, what maintained that and how to reverse it. We identified both avoidance behaviors (primary gain) where patients were trapped in anxiety provoking existential predicaments from which the sick role offered relief and positive reinforcement (secondary gain) from the rewards of the sick role – solicitous caretakers, compensation, litigation and entitlement programs. We recognized that anxiety played a co-morbid role in this syndrome but did not accord it major significance nor did we employ minor tranquillizers for a population that used drugs as props for a sick role that encouraged dependency on health care providers and the drugs they dispensed.

The characteristics of our treatment approach are portrayed in the following vignette.

"It Only Hurts When I Cry"

> Lucinda did not look like a clown. She was short, skinny and sad. At her outpatient evaluation the staff was preoccupied with Lucinda's many pains, wheezy chest and ailing heart. Her hobbies hardly seemed relevant.
>
> After she was admitted to the unit, Lucinda's cardiac condition was stable, her pain was chronic and she remained sad and anxious. Lucinda grudgingly agreed that there was nothing fatal or malignant that caused her suffering, yet she was unable to give up her aches or their audience until she glimpsed solace elsewhere.
>
> Lucinda's slow progress speeded up abruptly soon after she told us that four generations of her family were clowns, including men and women, from grandparents to grandchildren. Each clown created his/her own unique face; either White (the provocative French mime), Auguste (the boisterous German bully) or Tramp (a downtrodden American bum). Lucinda was too old to be Mime and too

slender to be Tramp. She chose to be Auguste, a jovial extrovert who jostled the other clowns.

One day, Lucinda brought her clown regalia to the hospital and painted on her face to entertain the other patients. It was a metamorphosis as dramatic as caterpillar to butterfly. Lucinda's crescent lips curved upwards into a smile that spread as far as the crow's feet around her eyes. As she went into her routine Lucinda shed her limp, her shoulders lifted, and her voice lost its weary timbre.

Once clowns are attired they adopt an etiquette. Profanity, smoking and drinking are forbidden. If children rush up to tweak their bulbous nose or tread on their oversize feet, clowns are enjoined to banter back. Irritability and anger are outlawed. Lucinda played the part to such perfection that her aches and anxiety were no longer obvious. Talking about symptoms makes them worse, so in social situations staff and patients are instructed not to complain or enquire. But at morning rounds, when we wear our white coats, we are allowed to ask. Lucinda told us her symptoms were hardly present when she clowned. She sounded surprised, although it was something she had noticed years before but had ignored. Instead, the worse she felt the less she performed, so that even the clowns in her 'ally' left her alone.

When Linda learned she could control her bodily concerns everything else came quickly. She mastered biofeedback, reached her exercise quotas, and slept soundly. When we asked her later what helped the most, she talked about learning to be assertive with her family and no longer letting the kids take advantage. She learned to set limits on their demands and to get her own needs met without needing to suffer or be sick.

Our time on the unit ran out together. My monthly stint as attending physician was over the day Lucinda was discharged. At morning rounds the patients sit in the day room waiting for us to see each of them in turn. As I looked up I saw Lucinda waiting in the wings, ready to walk on stage. She smiled and sat down. The rehearsal was over and the performance was about to begin. I asked how she would

make it in the real world without grease paint. Lucinda laughed and said she thought she could; "now that I can be a clown without letting the kids walk all over me."

Looking after patients on a psychosomatic unit taught me that many of these symptom sensitive worrywarts (aka 'somatizers' or 'hypochondriacs') had suffered abusive or emotionally deprived childhoods during which they failed to develop a rich emotional language – so called 'alexythymia' – no words for feelings. They communicated distress in body language. An extreme example was a man who volunteered for our study, published in the Lancet, on individual response patterns to Transcendental Meditation in patients with hypertension. (Blackwell et al. 1976). We used the "stress biopsy" to develop ratings for each person's unique symptoms. One middle aged married man could only summon up the single word "irked" to describe the spousal tension from which he suffered.

It was during my time in Cincinnati (1970-1974) that a remarkable and exponential increase occurred in the use of diazepam. Thanks to my industry contacts I had access to national prescription data and was able to obtain and analyze the figures for psychotropic drug use in 1972, published in JAMA, *"Psychotropic Drugs in Use Today*: *the Role of Diazepam in Medical Practice"* (Blackwell 1973). The figures were derived from a monthly prescription audit of 400 drug stores throughout the USA.

The three most widely prescribed psychotropic drugs were all minor tranquilizers: diazepam (34%), chlordiazepoxide (15%) and meprobamate (9.3%), followed by phenobarbital (7%). Thus, only four sedative drugs accounted for 65% of all psychotropic prescribing. Diazepam alone amounted to 49 million prescriptions issued by 97% of general practitioners and internists. Trends for an eight-year period (1964-1972) revealed diazepam alone was responsible for this increase. A graph showed its use increasing at a 45-degree angle while the use of antidepressants, major tranquilizers, combinations and the three other sedative drugs was almost flat.

Andrea Tone notes that in 1975 Roche Laboratories spent an estimated $400 million promoting both diazepam and chlordiazepoxide. FDA tests in the 1960s had shown that diazepam was five times more potent as a tranquilizer and muscle relaxant that chlordiazepoxide.

Based on both market research and scientific results from other studies dissection of the prescription data revealed that less than a third of use of minor tranquilizers was for defined

psychiatric disorders while the remainder was for a medley of medical disorders prescribed with other drugs. There was no single explanation for this upsurge in use of diazepam. I speculated on the semantic confusion and symptom overlap in categorizing minor affective disorders in primary care and data suggesting that, at least in the short term, early and mild affective disorders responded well to sedative drugs. In a primary care physician's mind anxiety seemed to be a ubiquitous accompaniment and possible contributing cause to a wide variety of putative psychosomatic disorders. In discussing the widespread popularity of diazepam, I noted it appeared to be more potent than chlordiazepoxide or meprobamate, far safer than barbiturates and perhaps equally effective and safer than tricyclic antidepressants with far fewer side effects. Tongue in cheek, I noted that continuation of the current rate of increase in use of diazepam might result in tranquilization of our entire population within the foreseeable future.

Not surprisingly, the data was already raising the question of whether such widespread usage was proper or the degree to which it concealed widespread overuse, misuse or abuse, (Blackwell 1975). A vigorous debate erupted that had both scientific and moral overtones. Later in life I published a vignette that combined my experience in family practice with these mid-career observations, (Blackwell 1986). Here it is:

Twice in a While

> *"The desire to take medicine is perhaps the greatest feature that distinguishes man from animals."* William Osler, M.D.
>
> "In every age there are medicines of the moment that divide doctors and patients down the middle. In the 18th century it was opium, in the 19th, bromides and in the early 20th century, barbiturates. The 1960s ushered in the benzodiazepines (like Valium) in an era of John Kennedy's Camelot. By George Orwell's 1984 it was clear that some people were more equal than others and that these drugs were prescribed unequally and more often to women, the indigent, the elderly and the maimed.
>
> These new drugs were so safe that they could be used more often and for less reason, raising hackles on segments of the public. Were doctors dabbling in existential predicaments beyond their bailiwick? Were mind tampering drugs being

used to correct a social or a chemical imbalance? Was there a medicine for mother-in-lawness or a pharmacologic lid to Pandora's Box?

These are all appropriate questions to be asked in an age that has amplified 'anxiety' and invented safer 'tranquilizers' to stifle it. But the problem is broader and older than that. It has existed as long as there have been panaceas, physicians to prescribe them and a public eager to seek such comfort. Even if the correct agenda is caretaking and not chemicals, the drugs often help in uncertain ways.

Which drug it is doesn't really matter. But how it happens does. It could be (and has been) various tonics, liver extract, Vitamin B12 shots, iron tablets or thyroid pills. They are given to patients who visit primary care doctors when life events have loaded up on them. Often these are symptom-sensitive people with the amplifier turned up on their autonomic arousal. They voice distress in body language and invite doctors to collude with diagnoses and prescriptions.

After they leave the office, life subsides or the drugs placate them. Next time a spouse leaves, a job ends or a child sickens they return expectantly for more. 'Those pills you gave me really helped,' they say.

Doctors disagree about all this. Prescribers are 'chemophilic hedonists' say the witholders. Withholders are 'pharmacologic Calvinists' say the prescribers. My partner and I sit in friendly disagreement on opposite sides of this chemical fence. She is younger and knows where the benzodiazepine receptors are in the brain. When her patients see me, we talk briefly about their troubles. Some, in a minor way, seem more tranquil. Others sense the skepticism with which I write their refills.

There isn't any harm,' they ask, 'if I just take them once in a while?' 'The only risk,' I reply, 'is twice in a while.'"

In the mid to late 1970s it was difficult to discern the extent to which differences of opinion about the benzodiazepines in general and diazepam in particular were driven by science or ideology. Malcolm Lader (1978) in Britain poured fuel on the fire in a Lancet article titled,

"Benzodiazepines; Opium of the Masses?" His subsequent *mea culpa* (Lader 1998) more than 20 years later, voiced a more temperate opinion, closer to my own: "Short term they are excellent drugs … the problem is preventing short term use from becoming long term."

On the American side of the Atlantic, Karl Rickels, based on his own extensive research as related in his recent memoir (Rickels 2013, Ch.14), took a more nuanced, moderate and data driven stand. Some patients (about half) needed long term treatment, others took benzodiazepines only intermittently and some relinquished them entirely. Karl comments on the underlying "puritanical" beliefs among some primary care practitioners in both Britain and America who refuse to prescribe the drugs and, instead, prescribe high doses of anti-histamines. During the last four years of my career, working in the Wisconsin Correctional System, I commented in depth on this unwise practice (Blackwell 2012). The possibility of dependence on benzodiazepines is a poor excuse for substituting drugs with unpleasant or potentially harmful side effects and are, almost certainly, less effective.

Cultural as well as ideological views can color the extent and method of use of the benzodiazepines. While use fell in Britain and the United States it increased globally. Tone cites France and Japan as examples where use increased but for different reasons. In France physicians shunned the DSM 3 classifications preferring to see anxiety as a co-morbid spectrum disorder. "As benzodiazepine use dropped in the United States it increased in France. One study found that 75% of French users had taken pills regularly for over six months. Indeed, France seems to have realized the greatest fear of American journalists and policy-makers, millions of people for whom long term use was the norm."

The situation in Japan was different: "While the United States and United Kingdom began to experience depression 'epidemics' in the late 1980's Japan, for all appearances remained anxious. Japan did not have a cultural idiom for what in the West would be termed depression. Rather than being muted with medication, a person's capacity to suffer loss was culturally accepted as essential… In Japan where the predominant culture sanctions cohesion, deference and calm, the pharmaceutical containment of anxiety continues to have political and social support."

Concerns about overuse, misuse and abuse produced a social backlash with influences on public policy (Blackwell 1975). The state of South Carolina banned the use of minor tranquilizers

from the Medicaid formulary (Keeler and McCurdy 1972). A comparison of prescribing in the six months before and after the ban showed 35% was replaced by increased use of a sedative phenothiazine (thioridazine), with known cardiac toxicity, a sedative tricyclic antidepressant (amitriptyline) with anti-cholinergic side effect and barbiturates, all three of which drugs are potentially fatal in overdose. No record was made of the outcome of discontinuing treatment in the remaining 65% of the population. In a public service Indian Hospital (Kaufman et al. 1972), vigorous propaganda directed at staff and patients reduced the use of sedative drugs and minor tranquilizers by a third, but the impact was on meprobamate and the barbiturates, not diazepam.

These unfolding events triggered my own curiosity leading to a focused effectiveness study of unusual design. It was accomplished without funding and by a resident under my supervision as senior author (Winstead et al. 1974). The study, *"Diazepam on Demand,"* was published in the Archives of General Psychiatry. The following is a summary of the results:

> "For six months patients admitted to a psychiatric ward were allowed to seek diazepam on demand. Details of 689 requests by 83 patients were recorded. Drug seeking behavior was expressed as a drug seeking index (DSI) based on the ratio of requests to duration of stay. For the whole ward there was an increasing trend in drug use and nurses' attitudes became more favorable."

More than a quarter of the patients never sought drugs and requests were made on an average of only once every three days. The features correlated with DSI were anxiety, being female, white and having an elevated psychasthenia scale on the MMPI. The DSI was not correlated with either psychiatric diagnosis or use of other psychiatric drugs.

Extensive use of antianxiety drugs might be reduced by prescribing then "when necessary" rather than on fixed schedules."

Although not significant, the MMPI subscales that most distinguished high from low users were psychasthenia (bodily preoccupation), hypochondriasis, hysteria and depression.

As the 1970s came to a close a new influence was brought to bear on the term anxiety and its treatment. This was the radical transition to a multi-axial system of descriptive diagnosis. Tone describes this transition as follows: "In DSM 1 anxiety was considered the chief characteristic of

psychoneurotic disorders, how a person handled anxiety denoted the type of reaction. DSM 2 (1968) written by the psychoanalytically dominated APA, expanded the number of listed diagnoses… but maintained the discipline's etiologic emphasis. DSM 3 abandoned the etiologic orientation in favor of diagnostic criteria based on descriptive psychopathology."

This replaced previous attempts to "understand the meaning of the symptoms and undo its psychogenic cause" (Klerman 1984). Anxiety now became ripe for dissection into contiguous disorders or syndromes. Tom Ban (2014) describes the onset of this process as follows: "Donald Klein in the early 1960's identified a population within the anxiety disorders that was characterized by recurrent anxiety attacks. He used the term 'panic disorder' as a label for this population and the term was adopted in DSM 3 as an Axis 1 diagnosis."

Other contiguous disorders followed: anticipatory anxiety, phobias, social anxiety disorder, generalized anxiety disorder and obsessive compulsive disorders, all based on the fact that anxiety was the commonest symptom, although not the defining one.

As Tone comments, the creation of a range of medical disorders was an invitation for industry to develop matching treatments. She quotes Leo Hollister's sage comments, "Making individual brain chemistry rather than social conditions the target for intervention… the new classification of anxiety disorders has vastly broadened the scope of drugs used to treat them."

Tone goes on to chart the way in which public opinion, shaped by pharmaceutical advertising, came to view anxiety as a medical condition for which psychotropic drugs were the most appropriate treatment: "patients increasingly expected and demanded them." Karl Rickels (1998) noted how this "medicalization" was facilitated; although cognitive behavior therapy was effective in some types of anxiety disorder this takes time, therapists are in short supply, is expensive and patients often prefer medication. The modern system of health care insurance is reluctant to finance lengthy treatments. There is no doubt that a "quick fix" has appeal to patients crippled by panic; immediate onset of action is the quintessential attribute of all the drugs used historically to curb anxiety. Tone records how this propensity was manipulated by Upjohn's astute marketing of alprazolam (Xanax) in 1981. Capitalizing on the drugs rapid onset of action and short half-life, the impending end of diazepam's patent and Don Klein's groundbreaking research, the FDA approved alprazolam as "The First and Only Medication Indicated for Panic Disorder"

(Upjohn's promotional advertisement). Although this spurious claim for specificity was soon debunked, Xanax "became a top selling drug accounting for one fourth of Upjohn's global sales." Paradoxically, the drug's metabolic properties contributed both to its early popularity and eventual demise. Its ultra-short half-life, compared to diazepam's long one, made it difficult to wean due to withdrawal symptoms and encouraged dependency. Xanax became known in parody as "The American Express Pill; don't leave home without it."

In contrast, the slower onset of action of the SSRI antidepressants hampered their popularity as anti-anxiety drugs. First introduced in 1987 for depression, they were later approved by the FDA for the treatment of anxiety disorders. Nonetheless, Tone describes how highly skilled and expensive advertising by Glaxo Smith Kline ($92 million in one year) succeeded in establishing a lucrative niche market for their drug paroxetine (Paxil) in social anxiety disorder.

In the ultimate chapter of her book, "Tranquilizers on Trial," Andrea Tone notes that for all the misgivings about the commercialization of minor tranquilizers and their shortcomings, "the number of patients who seek medical advice for anxiety has risen from 13.4 million in 2002 to 16.2 million in 2006. Anxiety is currently the fifteenth most common reason for visiting a doctor, eclipsing consultations for back or joint pain and migraine headaches."

How to summarize this roller coaster overview of anxiety, its manifestations and management? First, a brief historical reprise of the key events, followed by an analysis of their contribution to unravelling the enigma of anxiety.

Anxiety has been the sleeping giant of psychopathology, almost mute through most of history until it erupted on stage in the 20th century. Before then it was a term largely absent from the medical lexicon except for strange physical manifestations. Anxiety's psychological presence was unveiled in Freud's theories of psychoanalysis, on the cusp of the new millennium, and its physical manifestations were explored in Selye's stress model (1930) with "psychosomatic" implications.

At the mid-point of the 20th century, at the beginning of the creative psychopharmacology era (1949-1980), minor tranquillizers entered the picture when meprobamate (1955) followed closely on the heels of chlorpromazine (1952). Following this, there was an astonishing increase in the use of minor tranquillizers to treat anxiety symptoms with a decline of interest in

psychosocial theories of etiology or treatment and a shift towards a descriptive system of classification in DSM 3 (1980), with a biological emphasis on etiology. Anxiety moved from being viewed as a spectrum disorder, co-morbid with other forms of psychopathology to being a group of discrete "disorders."

While this chronology and sequence of events is clear, anxiety has remained an enigma, perhaps more so due to a false dichotomy between etiologic and psychosocial theories on the one hand with descriptive and biological explanations on the other. While there may be some scientific truth in either or both these formulations the fact that tranquillizers effectively stifle anxiety has markedly diminished public interest in psychological alternatives at the same time as increasing industry's zeal to market a new drug for every disorder. Contemporary economic trends have reinforced this ideology with concerns about the rising costs of health care coupled with constraints on psychosocial interventions imposed by managed care companies, government funding sources and private insurance companies.

This dichotomy might be resolved if, philosophically and existentially, anxiety was recognized as a protective warning system attached to the unique human attribute of "prescience," an ability to anticipate the future with both its opportunities or possibilities as well as its threats or pitfalls. This carries with it a person's self- awareness of their ability to achieve or fail these outcomes and with it an introspective accounting of their skills or shortcomings, available or not. To the extent there is a perceived gap between the capabilities and actions needed to meet these challenges and their availability, anxiety is aroused. In plain language: anxiety is the watchdog of the human mind, monitoring its ability to meet life's challenges or match our ambitions; it warns psyche and soma of impending failure in either of these functions. Its manifestations can be stifled by drugs but not its underlying purpose.

The only psychological defense against anxiety once it is aroused is to avoid the challenge or conflict that evokes it; Freud called this "primary gain." Stifling anxiety is the pharmacological equivalent.

Anxiety, like pain and fever, is the harbinger of multiple etiologies. In medical school we learned how to interpret fever charts and to define 10 aspects of the pain experience that hinted at

causes. The microscope, microbiology, X-rays and the surgeon's knife revealed the rest. But the brain keeps its secrets better than the body, blurring cause and effect.

That anxiety arrived among the populace in a rush co-incident with minor tranquilizers stifled not only the symptom but also serious interest in pathogenesis and phenomenology. Yet, clearly, there are different manifestations of "anxiety." In conversion disorders it is allegedly etiologic, but remains silent (*belle indifference*), while in hysterical and borderline personality disorders it is vocal and robust. The bizarre and metaphorical manifestations of anxiety in schizophrenia differ from the unrelenting and more mundane "angst" of melancholia. The sudden onset of both psychic and somatic manifestations in panic disorder and PTSD differs from the pervasive but losing battle to free anxiety from itself by yielding to phobias, obsessions and compulsions.

Whether anxiety is part of a "disorder" *per se* or a co-morbid warning sign that something is wrong in the mind remains a riddle that brain imaging, neuroscience and genetics have yet to solve.

This formulation can be applied to understanding a limitation of the DSM 3 classification of "Anxiety Disorders" that is based on combining syndromes characterized by the predominant and common symptom of anxiety. But this is not always the symptom that is unique to the particular syndrome. These are phobias, obsessions and hysterical conversion, all driven by failed pathological attempts to avoid anxiety. It is noteworthy, but hardly surprising, that minor tranquilizers are not effective or the treatment of choice for these disorders. Instead they respond to cognitive and behavioral strategies that directly confront the anxiety to eliminate it by flooding or desensitization rather than avoidance. Unlike drugs, this can lead to a permanent relief from symptoms. Similarly, conversion disorders are best treated by hypnosis, suggestion, psychotherapy or some combination.

It is in the remaining categories, where anxiety is the only or predominant symptom, that minor tranquilizers play the role of stifling anxiety, often without an attempt to explore its psychological origins or to remediate them. Short term therapy focused on identifying, removing or gaining control over these precipitating factors may remove the need for prolonged tranquilizer

use. Pragmatically, this requires an enthusiastic referral and a willing, psychologically minded patient with the ability to pay for psychotherapy by insurance or out-of-pocket.

The behavioral re-interpretation of many psychosomatic disorders as forms of "illness behavior" is supported by this formulation. Anxiety is not the cause of the physical condition, but avoidance of anxiety due to an existential predicament (primary gain) encourages the patient to seek relief in the sick role while also reaping its rewards, (secondary gain).

This understanding of the role social and psychosocial factors can play in anxiety and psychosomatic disorders is not a repudiation of contributory biochemical factors in etiology or treatment. The very fact that minor tranquilizers stifle anxiety is proof of that. This is compatible with Frank Berger's lifelong assertion that while drugs can attend, short term, to the biology of anxiety, only philosophical or psychological understandings and interventions provide long lasting or permanent relief that ends the need for medication.

The contemporary hiatus due to a lack of psychopharmacologic innovation has re-awakened interest in psychosocial interventions including intensive short term dynamic psychotherapy (ISTDP). A recent review of 13 studies (Coughlin and Katzma 2013) and an editorial (Fawcett 2013) summarizes impressive clinical outcomes in populations relevant to this essay. Eighty per cent of patients were symptom free within six weeks at the relatively low cost of under $1,500 for an average of 13 sessions. In seven studies, including anxiety disorders, chronic headache, treatment resistant depression and personality disorders, 60% of patients ceased taking medication with other significant "medical offsets," including a reduction in hospitalizations, physician visits, emergency room attendance, drug costs and use of ECT. Since it is almost entirely primary care doctors who encounter anxiety disorders driven by "problems of living," it is desirable that this form of therapy referral become accessible to them.

As the ideological pendulum swings, perhaps in the future anxiety and its treatment will seem less "mysterious or puzzling" with more productive outcomes if the short-term use of minor tranquilizers is judiciously used to stifle its immediate symptoms coupled, whenever possible, with psychosocial interventions directed toward removing the precipitants and reducing the costs of long term treatment.

Perhaps the best way to end this essay is with a vignette (Blackwell 1986) that illustrates the intricate interaction of tranquilizer treatment, psychotherapy and social circumstances in the management of a particularly complex case.

Tranquility

"It was a balmy day with warm sand and calm waves lapping along the lakeside. When I teach people to relax, I use these images to graft over the anxious turmoil of their lives. I tucked the thought away. I was here for a respite. Leaving the beach for the swings, I took five-year-old Adam and his friend Christopher, with me. Together we ambled across a wide grassy meadow, its edges in shadow, where pine trees grew and picnic tables sat. In the corner a couple half faced each other. The man was playing a harmonica with expert zest; the woman was strumming a guitar and singing, not in perfect pitch but with a pleasing cadence. Some teen-agers strolling past stopped to applaud, but were ignored. The couple was doing this for themselves.

"Coming closer, I recognized Rosie and Robert. Shortly after I arrived in town Rosie sought me out, describing herself as a 'schizophrenic who nobody would care for.' The diagnosis was doubtful but her ostracism was not. Rosie functioned quite well between episodes of wild psychosis which were triggered by unwise intimacies. In over twenty years she had passed many times through the revolving doors that open unwilling hospitals to inhospitable communities. Now she was barred from inpatient units unable to cure her and shunned by psychiatrists unwilling to treat her for the pittance Medicaid sometimes paid. But Rosie was streetwise and a survivor. She found an agency social worker who understood the metaphor of psychosis and an academic psychiatrist who could afford to take a 'good teaching case.' Hillary interpreted Rosie's struggle with an alien environment and I prescribed 'pills' to buffer her against it.

"Rosie never treated me as more than her medicine man; she came for tranquilizers, not advice. The major tranquilizer she took with a wise reluctance. The brain is a fine-tuned but well protected organ. The doses of drugs that penetrate its barriers

often do damage when they mistake receptors that modify behavior for others that modulate movement. The rhythmic writhing of her lips and tongue testified to that. The minor tranquilizers she took with alacrity. Aimed at the limbic lobes, they brought a rapid respite from anxiety for which she would con me into giving her more with stories of lost scripts and stolen purses.

"We struck a bargain. In return for the drugs she liked, she took the ones I thought she needed. A balance was achieved, between us and within her brain. It was not total tranquility but it was not turmoil and her tongue was still.

"Over the past year Rosie had come to our offices with Robert. He was an older man and a professional musician who served as someone between a friend and a father. The money they made playing the sidewalks and smaller cafes supplemented Rosie's earnings as an occasional organ tuner. Hillary saw them as a couple and helped them titrate their intimacy. She charged them two dollars and each paid half. On medication visits Robert waited patiently outside my office and the State paid.

"Nothing of this prepared me to recognize Robert and Rosie making music in the park. As the distance between us closed, I became aware of my swim shorts, unshaven face and the two noisy ragamuffins in tow. There was still time to turn away, so I did, unsure of whether I was protecting Rosie's integrity or my dignity.

"A few days later I passed Rosie and Robert entertaining on the sidewalk outside the Summerfest grounds. I hid in the crowd and hurried past. Shortly after this second sighting Rosie missed her monthly appointment but called to make another. She sounded cheerful and calm but priorities had changed. She needed my medications less than the money she and Robert were making among the crowds. For Rosie it looked like this might be her first tranquil summer.

"Rosie was a real patient and at the time I was treating her Frank Berger was 73 and well into an active retirement as a consultant to many international drug companies. But he was also a visiting Professor of Psychiatry at the University of Louisville where he, "Had the opportunity to learn some psychiatry and see psychiatric outpatients… My feeling was that most people we saw really had no

psychiatric disorders. They had problems of living' Berger 2014). I wish we could have shared Rosie's story."

After several weeks of creating and mulling over the anxiety enigma essay my subconscious decided it must have the last word. I dreamt I was the presenter at a celestial case conference presided over by Sir Aubrey Lewis. Seated next to one another, we faced an auditorium filled with leading psychopharmacologists from the pioneer era. Among them I recognized Jean Delay from France, Malcolm Lader and Michael Shepherd from Britain and Karl Rickels and Don Klein from America. Sir Aubrey told me to begin. So, I presented Rosie's history ending with my formulation: that after the major tranquilizer had cut short her psychosis and the minor tranquilizer had stifled her existential anxiety, skillful therapy and a vibrant philosophy of living had ushered in her first summer of tranquility.

Questions and comments followed. First up was Michael Shepherd. He expressed wonder and disappointment that, given our work together on the myth of lithium prophylaxis, I could possibly be uncritical enough to think that a single summer of tranquility, following 20 years of relapsing and remitting psychosis, might be anything but a spontaneous remission.

During a vigorous debate Jean Delay, Karl Rickels and Malcom Lader shared their own career contributions and understandings which were closer to my own opinions. The final comment came from Don Klein, justly proud of his pioneer work on panic disorder, he felt my comments about the DSM nosology were too dismissive and he could not see how therapy and philosophy would lead to remission in an illness with such an unrelenting natural history.

As Don sat down I sensed time had run out and turned to face Sir Aubrey. His penetrating gaze met mine and behind his steel framed glasses I sensed the glimmer of a smile. Had I, he enquired, "seen the most recent Japanese literature on this topic?" Checkmated, anxious and crestfallen, I reluctantly admitted my ignorance.

It was not Sir Aubrey's style to do a presenter's work for him: "Stop by Miss Marshall's office in the morning and pick up the journal." I woke up drenched in sweat, relieved it was only a dream. My anxiety abated, quicker than Xanax could stifle a panic attack. If only Frank could have been there. But I was dreaming and he was dead.

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Chapter 14

A pioneer psychopharmacologist; Karl Rickel's biography

Preamble

Karl Rickels' memoir *A Serendipitous Life* (Rickels 2011) is a unique and inspiring account of how a German prisoner of war in America came to love the country and returned after the war ended to become one of our 20th century's leading psychopharmacologists. Karl's moderate voice in the preceding Chapter 13 provided a balanced viewpoint in the contentious debate concerning the meaning of anxiety in both depression and medical disorders as well as promoting a conservative role for the use of minor tranquilizers.

Karl was also known throughout his career for identifying non-specific factors that influenced outcome in drug therapy, particularly the placebo response. He also explored the role that anxiety played in depression and its response to different treatments.

Karl Rickel's Autobiography; A Serendipitous Life.

A Serendipitous Life, is a rich tapestry which weaves together personal and professional life, yielding a satisfying and revealing portrait of both man and scientist.

This slender volume compresses the author's 87 years and a distinguished academic career into 201 pages plus photographs and appendices. Karl dedicates his work to his grandchildren because, "there is much to be learned by looking back," a purpose that applies equally to those neophyte neuroscientists wise and fortunate enough to read the book..

The contents are almost equally divided between personal and family affairs (Chapters 1-4, Chapter10 and three appendices) followed by accounts mainly of work as a clinician and scientist (Chapters 5-9). But this dichotomy is illusory and arbitrary. The seeds of Karl's success, embedded in nature and nurture, blossom into a purpose driven and integrated life, both professional and personal.

For example, Chapter 5, *"The Era of Psychopharmacology,"* is interrupted by two domestic interludes: the adoption of a son in Germany that ends his wife's infertility producing a second son within a year, *"Adding to Our Family",* and introspection about why he has spent his

whole life at Penn eschewing lucrative offers of department chairs in America and Germany, *"Homebody."* These twin tales bookend an intervening piece on *"Research and Discovery."* Throughout the book the warp and weft of family and work mingle with vacations on the Jersey shore and international travel with academic tasks and scientific commentary. Chapter 5 ends with the following passage (Author's italics): *"Serendipity may have provided me with lots of opportunities in life, but it was still up to me to decide which paths to take. I took the ones that were more about people, family and patients, not money."*

Karl Rickels was born in 1924 in Wilhelmshaven, a large North Sea naval port, two years before his parents moved to Berlin where he spent his entire youth. His character and talents owe much to an ancient and distinguished heritage *(Appendix 1: "Family Matters).* On his father's maternal side, he is descended from a priest born in 1487 who became a professor of physics at Wittenberg University where he defended his theological thesis before Martin Luther. On the paternal side, the Rickels name is traced back to the same medieval era when they were farmers in Holstein, near Denmark.

According to family folk lore, young Karl's earliest trait was curiosity and his favorite words were: "What is this?" By age 10 he was academically accomplished enough to be enrolled in the Gymnasium where doctoral level teachers prepared students for university in a multi-ethnic environment. So, he learned French in fifth grade, Latin in seventh and English in ninth. Karl was academically precocious enough to skip the eighth grade. By grade 10 Karl knew he wanted to be a physician and he selected a natural science track; asked to write about what he intended to become he wrote surgeon in German, but was mortified when the teacher admonished him for misspelling the word. Karl was active in long distance running, gymnastics, handball and rowing – the archetypal team sport. He was also an avid reader.

When Karl was eight the Nazis came to power and he was in the ninth grade when World War 2 erupted bringing lost class time and frequent nights in air raid shelters. Throughout childhood Karl thrived in a warm and supportive family environment. Both parents encouraged his educational efforts and accomplishments; his father, Vati, was enamored with books about popular medicine and browbeat the family in correct ways to walk, eat and breathe. In the winter family members had to sit awhile in front of an ultraviolet lamp to absorb vitamin D. Vati was also

an accomplished artist and unpublished author of poetry and plays. He was an eternal optimist, always positive.

In 1941 Karl was 17 and the Russians had switched sides, declaring war on Germany. Vati, convinced Germany would lose, sat Karl down to discuss by whom he would rather be captured, the Russians or the British? The Russian reputation for brutality made the answer obvious. To escape the Russian front and find the British in North Africa he would have to avoid the draft and volunteer so as to select the type of service and where that would be. In addition, he qualified for officer training.

This type of forward (anticipatory) thinking would pass from father to son so, after graduating from gymnasium in 1942, Karl joined the Signal Corps. At boot camp the recruits were arbitrarily divided into two groups: wireless or telephone; Karl was assigned to the first but preferred the latter. Breaking rank for a spurious visit to the bathroom, he marched into the colonel's office, requested and was assigned his choice. More forward thinking! After six months of officer training Karl was required to complete three months of front- line experience as a private first class before being commissioned. In June 1943, aged 18, he joined the Africa Corps serving under Field Marshal Rommel. Both father and son's expectations were prescient; by the time Karl reached the front lines with telephone wires Montgomery had defeated Rommel at El Alamein and the tide of war turned in Britain's favor. In May 1943 the Africa Corps surrendered to the British who turned their prisoners over to the newly arrived American army. This was providential. Karl writes: "We received ice-cold potato salad, the best hot dogs I have ever eaten, and vanilla ice cream… I certainly knew then that the Americans would win the war!" Using an English dictionary his father insisted he take with him Karl spent his free time improving his language skills. In June 1943 he boarded ship for America at the height of the U- Boat war in a convoy attacked by German submarines. "For the first time I prayed for the Americans, not the Germans."

At Camp Swift in Texas Karl's facility with English earned him a job as the hospital interpreter while he "worked hard to replace my book-learned English with American idioms and words." Three months later his belongings, confiscated in Africa, were returned: "…I was once again convinced that America would win the war. Surely this was the most efficient country in the world. This was probably the first time I thought about returning to America after the war."

Karl was not idle. Transferred to another camp he became chief of the ration detail, perfected his English and, with a colleague, became "the ping pong champions of our camp." Later, he also won a chess tournament. Meanwhile he matriculated by mail as a medical student at Berlin University in Germany whilst a POW in America. The camp environment was congenial and relaxed with fraternization between guards and prisoners: "We were all soldiers, not politicians. None of us soldiers started the war. Camaraderie just developed. We all wanted the war to end so we could go home and get on with our lives."

When the war did end in mid-1945 rumors circulated that German prisoners might be shipped as slave labor to France or England. By now Karl had become the interpreter and friend of the officer in charge of selecting prisoners for democratization in an "Anti-Nazi" training program: "I helped him and put my name at the top of the list." Graduates from this program received a certificate stating that they were "Good Germans ready to help the occupying authorities in the rebuilding of Germany." Aboard ship to Europe Karl was leader of 1,500 fellow prisoners, now registered as a German medical student, identified as "the young doctor" and comfortably ensconced in the ship's infirmary. Allowed to choose which occupied zone (American, British or French) he wished to be discharged to he chose British where his mother's relatives lived. Unfortunately, the British authorities, unfamiliar with the American democratization process, were set on sending all healthy prisoners to England to work as farm laborers. Examined by a German doctor for fitness Karl fabricated a history of headaches and dizziness following a motorcycle accident, revealed he was a medical student and was sympathetically declared "unfit for work."

As Karl anticipated medical school at age 22 he reflected on his three years as a POW in America: *"The experience allowed me to grow and mature, to become self-reliant, to learn to fight for things I wanted and not worry about things I could nor change"* (Author's italics). True, but the seeds were planted early in genetic heritage, family upbringing and sage paternal mentoring.

Eager to start medical school immediately Karl faced a final hurdle. At Bonn the Dean of Admissions told him he was too late to enroll and would have to join the winter semester. Instead, Karl travelled 100 kilometers to Muenster, a city 80% destroyed by allied bombs and, once again, was rejected as too late for the summer semester, first by the admissions committee and then by the Dean on appeal. Karl turned to the British university officer, producing his POW democratization certificate. Impressed, the official wrote a formal recommendation on official

stationary, "*His Majesty's Service,*" stating Karl was one of the first students to have applied (from America). Presented with this documentation the Dean "Almost stood to attention, and I was admitted the same day."

In medical school two preclinical years followed by three clinical years in various hospitals were coupled with a doctoral dissertation involving rat research on the nutritional value of essential amino acids. During the last two years Karl met his future first wife, Crista, a PhD student in German and English literature. Post war conditions were arduous, hot water for bathing once weekly, shortage of food (ration coupons provided only 1,200 calories daily), no toilet paper, no student accommodations, living in four or five different rented apartments and poor quality clothing. But Karl also notes the generous clothing and food supplied by many charitable organizations and above all the Marshall Plan: "One of the greatest acts of modern charity, executed by the occupying forces of a victorious nation." Faced with all this and financial hardships marriage was inevitably postponed for four years, until April 1963.

Following graduation from medical school in July 1951 Karl began a 15-month internship in three different settings, an X-Ray Institute, an Institute of Hygiene and the Medical Department of the City hospital in Dortmund. During this time, he published his first scientific paper on blood typing in paternity suits.

After internship Karl's interests turned toward public health, microbiology and pathology. He learned to do autopsies, did lab research on the interaction of antibiotics with bacteria and published three scientific papers. His hope was to apply to Harvard for a job in public health: "At this time, psychiatry was the furthest thing from my mind." Three objectives were foremost: academia, research and America.

In 1954 Karl saw an ad in a German medical journal offering sponsorship to emigrate to the United States subject to spending one year at the Mental Health Institute in Cherokee, Iowa. Crista was now pregnant, but they were both eager to escape the harsh economic conditions in Germany spurred on by Karl's idyllic memories of America. Their flight from Frankfurt landed on American soil on September 1, 1954, and less than two weeks later Karl, now aged 30, began life as a psychiatrist in rural Iowa. Housed in a comfortable apartment on the hospital grounds with

a four-year-old Buick for Karl and a sewing machine for Crista their son Larry was born three months later.

Psychiatry was on the cusp between custodial asylum care and the impending revolution in psychopharmacology (Ch.2 & Ch.16). Karl describes the scene thus: "It was still a time when barbiturates and bromides, the only sedatives available, did not work and straight jackets, cold water baths, electroshock therapy (without anesthesia), insulin coma and trans-orbital lobotomy were treatments to control violent, aggressive but also just unruly patients." Karl takes pains to point out this was "definitely not a snake pit." There were ample support and nursing staff, the psychiatrists were almost entirely well-trained immigrants and although treatment was primitive it was humanely administered. Karl had only been in Cherokee a few months when he was witness, in early 1955, to the effects of the first samples of chlorpromazine and reserpine provided by the pharmaceutical manufacturers. "Suddenly, patients who had been violent and aggressive for many years were quiet and comfortable. They could dress themselves, eat on their own and no longer soiled themselves; the stench that had been pervasive. It was miraculous."

Karl had only been at Cherokee six months when he decided psychiatry was his calling: "I wanted to be involved in this revolutionary development from its beginning and hoped to become an important player in the new field." Knowing he needed further expert training he applied to Harvard, Johns Hopkins and the University of Pennsylvania (Penn). Penn offered an opening subject to an interview that Karl couldn't afford to attend. They agreed to a phone interview perhaps impressed with his three publications. Seeking collateral information, the interviewer called the hospital Superintendent who issued a lukewarm endorsement intended to retain someone he couldn't afford to lose. Asked if they were going to let Karl go and hearing an emphatic denial the astute interviewer saw through the deception and promptly offered Karl a position.

Karl arrived at Penn in late summer 1955 and remains there today, 59 years later. He joined a residency program that was "small and elite" with a salary of $2,800 that matched the first of those adjectives – but it was supplemented by the Chair, Dr. Appel, with additional funds to attend the newly appearing conferences on biological psychiatry that kept them both up to date. At Penn, like almost every academic department in America, psychoanalysis was king. The department headquarters were located at the University hospital but the hub and heart of the program was at the Institute, a large private practice located on "grounds in a palatial setting" where patients from

the “most famous and rich families” were treated by “all the leading psychiatrists and analysts in the city.” Patients lingered for months, some “for their whole lives.”

In this environment Karl was given time for basic research, mentored by the professor of pharmacology under whose direction he did primate work on the effects of anticonvulsants and human studies on the cold pressor test in anxious and non-anxious patients. Results from both were published and the latter would portend a lifetime interest in the anxiety disorders. Karl was also mentored by Dr. Appel after he had seen his last psychotherapy patient at the Institute, often around midnight. He describes two lessons learned in supervision. First, his psychotherapy patient, who was benefiting less and less from a barbiturate, regained the effects after a pink capsule was replaced by a green one containing the identical dose of sedative – a placebo response, one of the nonspecific factors in therapy Karl would later become renowned for studying. The second lesson had generic implications. After Karl failed to connect with a female patient during a 50-minute therapy session Dr. Appel intervened. In a brief 15-minute chat he elicited the missing information while holding constant eye contact, expressing caring and warmth. This “amazed me and served as one of the most important examples of how I wanted to act and treat my patients.” On the hospital consultation service seeing medical patients Karl quickly learned the value of practical, often biological, advice that the surgeons and internists found more helpful than psychoanalytic interpretations.

In 1956, the year after Karl began residency as a second-year fellow, the National Institute of Mental Health (NIMH) established the Psychopharmacology Service Center under the direction of Jonathan Cole with several million dollars of funding from Congress. (Ch.8). The following year, after completing residency, Karl submitted a grant proposal to NIMH to study drug treatment in neurotic outpatients. It was funded on the first attempt. This began a unique half century of continuous NIMH funding lasting from 1959 to 2009 when Karl was 85. His final application required several submissions but Karl persisted as a mentoring example to junior faculty on how to seek and obtain NIMH funding. In 1956, while still a resident, Karl planned and carried out one of the earliest, perhaps the first, double blind placebo controlled study in anxious medical outpatients, collaborating with internists, not psychiatrists. This innovative strategy and population reflected the fact that anxiety is a common symptom in medical conditions for which treatment often reduces medical morbidity. The results were published in the Journal of the American

Medical Association (JAMA) and this strategy was adopted three years later in Britain by David Wheatley co-operating with a large group of family practitioners (also funded as an ECDEU unit by NIMH, Ch.7). Karl's study was prescient of the now well-established fact that primary care physicians prescribe the majority of drugs to treat anxiety and depression. Noteworthy is the fact that Karl's choice of population was also dictated by the reluctance of psychoanalysts in 1956 to prescribe medication for anxiety on the mistaken belief it might reduce motivation for psychotherapy. Despite this fact it was Karl's mentor, Dr. Appel, who encouraged him to go ahead. From this Karl derived the principle of always going to the person in charge for approval because "He or she has more wisdom than the people reporting to them."

In addition to chance and serendipity, synchronicity also played an important role in Karl's career development. He was in the right place at the right time. As other clinicians around the world experienced the same epiphany evoked by witnessing the remarkable reduction in psychotic symptoms due to the first drugs, an impetus to convene and share information evolved. Karl became a prominent participant in three key organizations founded to achieve this end (Chapter 6). The earliest was the *Collegium Internationale Neuro-Psychopharmacologicum* (CINP) in Europe. It was informally convened in Zurich during the Second World Congress on Psychiatry in 1957. Invited members from 13 nations included six basic scientists and 27 clinicians of whom four were from America: three clinicians, (Brill, Denber and Kline) and one basic scientist (Brodie). The CINP held its first Congress in Rome in 1958, addressed by Pope Pius XII, membership was opened and Karl was one of 13 new members from the United States. He presented a paper on the *Methodology of Drug Evaluation in Neurotic Outpatients.* Subsequently Karl published several papers at the Second Congress (Basel 1960) and the Third Congress (Munich 1962) dealing with placebo-controlled drug studies and the role of non-specific factors in treatment outcome. In *"The Story of the CINP*" (Eds Ban, Healey & Shorter, CINP, 1988) Karl's early contributions to the field are cited by several distinguished colleagues.

Perhaps due to the hegemony of psychoanalysis America lagged behind Europe and it was not until 1961 that the *American College of Neuropsychopharmacology* (ACNP) was created and Karl was a member of the charter class of 90 individuals; fewer than 20 still survive among which he must be one of the few still active in the field. He became a Life Fellow in 2002 at which time he received "Special commendation for excellent, outstanding service to the field."

The third organization of which Karl became a founding member was the Early Clinical Drug Evaluation Unit (ECDEU) established and funded by NIMH in 1960 to develop methodology to evaluate the safety and efficacy of new drugs to treat mental illness. A dozen research centers were spread among State hospitals, the Veteran's Administration and a few Academic Medical Centers like Penn where Karl's unit was initially the only one studying outpatients. In the mid-1970s industry became more involved in drug trials, several NIMH funded centers closed and the program changed its name to the New Clinical Drug Evaluation Unit (NCDEU).

Karl was still active in all three organizations when they celebrated their 50th anniversaries; at the NCDEU in 2010 he gave an invited lecture on *"Trial Methodology over Five Decades."*

Five years after completing residency Karl was well established at Penn in a successful career; now a member of the three most prestigious organizations in the heyday of new psychotropic drug development, already an accomplished investigator and confident grant writer. He was domestically settled in a beautiful home, Crista had resumed her graduate studies and their son Larry was a happy seven-year-old doing well in the local elementary school. All of this was when misfortune struck, the antonym of serendipity. Crista developed ovarian cancer in early summer 1962 and died only nine months later. Karl was devastated: "I was a workaholic then (and since), working late hours and even in the evening when I got home. When we were finally settled, and Crista could enjoy a good life, suddenly it was over."

Now a single parent of a young son, deeply engaged and a hard-working scientist, Karl went to Europe for eight weeks as a respite, spent much of the time with Larry and on their return flight discovered how serendipity can accommodate life-changing social encounters as well as profound scientific contributions. During the flight to Philadelphia Karl became engaged with a family returning home to New Jersey after a European vacation. Included was Linda, a student majoring in sociology and elementary education at Salem College. "We talked about my work and I gave Linda my business card asking her to give me a call. Linda must have wondered if I thought she needed to see a psychiatrist." Socially she did! Just over a year later, in June 1964, they were married, a union that produced two sons, lasted 44 years and established another spousal alliance that successfully merged domestic with professional life. (Ch.10)

In his lengthy and prolific career Karl has published almost 600 reviews, articles and book chapters, as well as editing nine books beginning with the classic "*Non Specific Factors in Drug Therapy"* (Rickels 1968) and ending with "*Good Chemistry*" (2004). Chapter 8 of his memoir, *"My Personal Contributions to the Field*," provides details of eight areas of enquiry covered by Karl's literary and research oeuvre. Much of this focused on outpatient treatment of anxiety and, to a lesser extent depression, including pioneer work in family medicine and private psychiatric practice. Karl's findings helped elucidate a strident multinational controversy on the benefits and risks of benzodiazepine (minor tranquilizer) drugs, of which Valium (diazepam) is the prototype, used to treat anxiety. Introduced in 1963, within seven years it became the "most widely prescribed drug in the world." The ensuing debate focused on the appropriateness of treatment, its length and the risks of dependency or abuse (Chapter 13). Much of the concern emanated from Britain where one psychiatrist (Malcolm Lader) called these drugs "the opium of the masses."

Karl brought both experience and expertise to a debate characterized as hedonists versus puritans. He participated in the development of the Hopkins Symptom Checklist, a patient rating scale widely used worldwide; compared the efficacy and side effects of antianxiety and antidepressant drugs in anxious outpatients; demonstrated the influence of physician attitudes and patient expectations on treatment outcome; quantified the frequency and severity of dependence relative to duration of treatment; and, above all, stressed the importance of a "multifaceted, holistic approach to the pharmacological treatment of emotional symptoms." All together Karl believes that antianxiety drugs are appropriately used and that dependence is seldom a severe problem (Rickels 1966). In 2008 he chaired an international symposium at the CINP that reviewed the role of benzodiazepines in the 21st century which concluded: "Benzodiazepines are probably not over-prescribed but under-prescribed."

Karl's academic career as Professor of Psychiatry (1969) and Pharmacology (1976) took a midlife turn when he also became the Stuart and Emily BH Mudd Professor of Human Behavior and Reproduction. The duality of the title reflects his pervasive interests and stems from work with non-psychiatric patients in primary care that led to research on infertility and prevention of adolescent pregnancy. In 1993 he co-authored (with Ellen Freeman) "*Early Childbearing: Perspectives of Black* A*dolescents on Pregnancy, Abortion and Contraception."* Karl also

collaborated with his co-author on the treatment of premenstrual symptoms (PMS) in research continuously supported by NIH for 25 years.

Karl has also spent his abundant energies in many additional directions not mentioned in his memoir (Blackwell 2011a). He is Editor of *Pharmacopsychiatry* (1973-) and serves on the editorial boards of eight other leading journals in research, stress, primary care, and neuropsychopharmacology. He serves on numerous University and Hospital Committees and has been a consultant, committee or task force member to pharmaceutical companies, AMA, NIMH, FDA, NIH, APA and the Academy of Sciences.

The memoir's penultimate chapter (Chapter 9, *Reflections on Psychopharmacology Today*) is a synthesis of the current state of the vineyard in which Karl has toiled for more than half a century. It provides a cautionary tale of troubled times echoing and elaborating on concerns of many of his contemporaries (Blackwell 2011b). Karl's conclusions are followed by reasons and recommendations for remediation: "New drug development … has stalled. Most new drugs are basically 'me too" drugs. Though they typically have a different side effect profile there is still little or no improved efficacy… Our tremendous scientific laboratory advances, such as those made in the fields of molecular science and nanotechnology have, regretfully, at least in psychiatry, not yet lead to treatments via completely new mechanisms… Only side effect profiles and excessive marketing, not efficacy, differentiate the newer from the older compounds." Karl also points out discoveries in the first two decades "were made with much smaller financial investment and fewer researchers than today."

In search of reasons for this impasse Karl includes being "enthralled with the concept of co-morbidity and diagnostic purity" and he indicts consumer marketing and its support by "medical leaders, academics and non-academics alike" who collude in the creation of diagnostic entities to match a drug profile – such as panic disorder and alpazolam (Xanax). He notes that academia is highly represented on lucrative industry speakers' bureaus or advisers to marketing departments, {Ch.19). In an earlier chapter Karl reminds us that he consulted only to research and never to marketing and even there only dealt with the CEO or the Vice president for Research. As a result: "I was able to shoot down many ineffective compounds early in development, saving hundreds of millions of dollars." He is proud of the fact that his appointment to an FDA review committee was approved after he listed all his industry consulting appointments and, in response

to cross questioning, pointed out that all but one of his recommendations to industry was negative. There remains a simplistic assumption today that reciting a list of "conflicts of interest" absolves a researcher from revealing the price paid for his advice and its outcome.

In Chapter 7, a section on "*Thoughts on Methodology*" elaborates on the drug trial methodologies adopted by industry that contribute to the contemporary sterility of the field. It is influenced more by marketing than research departments and suffers from the following shortcomings: many of the newer compounds are inactive or only mildly so; study subjects are often recruited by advertisement and are not true patients in primary care; combined with the previous problem this leads to increased placebo responses contributed to by spontaneous remission and resulting in low drug-placebo discrimination; all this then results in attempts to increase the sample size and number of study sites often including those from developing countries thus increasing variability and unreliability. An overarching problem is that drug trials have moved from academic and private practice settings to drug company owned or sponsored clinical research organizations (CROs) where the primary motivation has shifted from scientific curiosity and academic advancement to financial gain. (Ch.19)

It is difficult not to conclude that in degrading trial methodology the industry has killed the golden goose that lays its eggs. Karl's remedy is to reverse each of the causes he lists.

The final chapter 10, "*Linda*," is a portrait in praise and gratitude to Karl's second wife who died of brain cancer after a long struggle shortly before Christmas 2008. It is followed by three appendices: the first is a family genealogy; the second is the revealing text of a letter Karl wrote to his future mother in law conveying his thoughts and feelings towards her daughter including, in a brief postscript, his philosophy of life and marriage; and the third, titled *"Advice of a Husband and Father to his Children and Grandchildren."* It is a tool kit of desirable behaviors, values and virtues most of which the reader will recognize from the memoir itself. Included are" "Happy and lasting marriage takes two people …divide roles, and once done respect the other's decision… have a positive outlook… learn from your mistakes… be not afraid to make decisions …a job you like and look forward to is more important than making money… always be polite, politeness opens many doors."

In the same year that Linda died Penn awarded Karl the William Osler Patient Oriented Research Award. With gentle irony it is worth recalling what William Osler said about the role of a physician's wife in the 19th century during an address to medical students entitled, "*The Physician's Life."* He states: "What about the wife and babies if you have them? Leave them! Heavy is your responsibility to yourself to the profession and to the public. Your wife will be glad to bear he share in the sacrifice you make." Two centuries later Karl Rickels modernized this antique ideology in his own career with an enlightened and negotiated integration of personal and professional life. He has expressed his gratitude by endowing two chairs of psychiatry at Penn, one in honor of Vati, his father, and the other in honor of Linda, his wife. They testify to the way in which familial influences shaped and supported a unique career devoted, like Osler's, to caring for others. (Ch.10, Smythies)

Karl chose to title his memoir *"A Serendipitous Life*," which is surely an understatement of the forces governing his career. (See Ch.5 for a detailed analysisof this concept). Still, it is this reviewer's opinion that while Karl's contributions may owe something to benevolent chance, much of his unique bequest to the field of psychopharmacology and the patients who benefited was due to curiosity, forward thinking, persistence, creativity, integrity and loyalty.

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Chapter 15

Career role models; vicissitudes and zeitgeists

Ervin Varga

Kanellos Charalampous

Martin Kassell

Preamble

As noted in the Introduction, a significant number of pioneers in American psychopharmacology were immigrants born in the 1920s and 1930s who became victims of ethnic cleansing at the hands of Fascists, Nazis, Communists and often fellow citizens before, during and after the Second World War.

This chapter provides the inspiring biographies of three remarkable individuals, Ervin Varga, Connie Charalampous and Martin Kassell., the first two of whom contributed significant autobiographical material describing their early lives in Hungary and Greece suffering persecution under Nazi, communist and anti-Semitic regimes. The third biography describes the unique contributions of a 100 year old former internist turned psychiatrist at a pivotal time in the evolution of psychopharmacolo

The main purpose of the chapter is to explore how family upbringing, culture and early role models shaped not only a capacity to survive but to thrive, obtain a medical education and begin a career in psychiatry, contributing as pioneers in the evolving psychopharmacology revolution.

Ervin Varga: Family, Culture, Persona and Career.

As the title implies, Ervin Varga's career path has been determined, perhaps more than most, by complex and unusual circumstances. The accomplishments and challenges of his life's work are viewed through the prism of his family origins, the culture he grew up in, the way these shaped his adult persona and responses to the challenges he faced.

Ervin Varga's Own Memoir

Ervin is the scion of a large, industrious and successful Hungarian Jewish family for whom ambition and drive had survival value in an anti-Semitic culture until they became "extras in an immense drama … with a grotesque message; how and why the morally unthinkable became socially acceptable." Ervin comments: "The first half of the twentieth century was, uniquely bloody … marked by pitiless social and radical ideologies." First Fascism and then the "Final Solution" followed by Communism and its totalitarian ethos.

This story is told in *Living and Dying in Hungary: A Jewish Psychiatrist Looks Back* (Varga 2012). Ervin tells the story in lucid and unsentimental prose of how, "Most of my family members were killed before reaching the age of sixty." The events and facts garnered from books, chapters, articles, archives and survivors of the Holocaust took place almost seventy years before he put pen to paper and what begins as a family history also turns into a memoir, published at the age of 87, recording events with photographic clarity that took place between his birth until, at age 20, "We had returned from hell … I was impatient to embark on my medical studies, an untenable dream before."

The account of Ervin's career begins where the memoir ends, initiated in part by Tom Ban's awareness of Ervin's interesting but "under the radar" career, due to their common roots growing up in wartime and post-war Hungary, from which Tom also escaped, but earlier, to Canada. As adolescents, but ten years apart they shared a tutor, Michael, who played a significant role in shaping their world views and personas as well as a mentor, Gyula Nyiro, whose teaching shaped their clinical ideology in profound ways described later.

This biography, like those previously documented on the INHN website in *Biographies,* shares a theme common to that literary mode; an awareness that "The child is father to the man"; that a persona shaped in childhood, adolescence and early adult life invariably influences the choice and shape of a career, especially in confronting the ever changing but challenging and unpredictable scientific, personal and social Zeitgeists.

Ervin's detailed memoir and unusual upbringing are particularly informative in this regard. What follows is a synopsis chosen entirely from Ervin's own words, modestly edited and presented without quotation marks for ease of understanding and flow. This is what he has to say.

He traces his Jewish cultural and genetic roots on both maternal and paternal sides. On the maternal side the Richters were upwardly mobile, well to do and endowed with drive, sheer guts

and common sense. His grandfather was first in the dynasty to graduate from a gymnasium and, eligible for university, he attended a famous seminary to become a Chief Rabbi and Professor at the local gymnasium, teaching divinity and Judaism. His maternal grandmother Emily's kinfolk were the Reichs; she had incredible resources of moral strength and dignity with an aristocratic gift for gentle comments. Deeply religious, so that Ervin concealed his own lack of faith to avoid offending her.

His mother's eldest brother, Uncle Anslem, lacked the Richter's traits but had a keen curiosity and thrived as an antique dealer. In November 1944, aged 60, he was the first relative to die in the Holocaust. Seized by Hungarian fascists, he was force marched towards Vienna. Unable to keep up, he was pushed to the end of the line, shot in the head and buried in a ditch. His daughter, the same age as Ervin, was taken to Ravensbruck concentration camp a month earlier, survived, was liberated in April 1945 but was shot and killed by a Russian soldier a few days later; possibly resisting rape.

Ervin's second uncle Hugo was the most remarkable member of the clan and an important role model. After graduating from gymnasium, he attended Budapest Medical School and graduated *magna cum laude* in 1910, before working in the laboratory of the renowned neuropathologist, Karoly Shaffer, then spent a year in Berlin at the Kaiser Wilhelm Institute and finally worked with Nobel Laureate Wagner Jauregg in Vienna. Returning to Budapest, he was an unpaid Instructor in neuropathology, living in a one room sublet, tutoring medical students to support his mother and her eight children. After serving as an army doctor in World War I, he returned to the University as an Assistant Professor and made discoveries in neurosyphilis, migraine and Pick's dementia. In 1925, he became Chairman of Neurology and Psychiatry at Budapest Jewish Hospital after declining to accept a full Professorship at the University on condition he converted to Catholicism, an offer Ervin and his brother both declined later in the forced labor camps in order to exchange the yellow star worn by Jews for a white one.

In 1929, Hugo was appointed a "private docent", the highest academic rank and in 1939, a year after Kristallnacht, he declined an offer to work in the United States, reluctant to leave his mother and with the false hope Britain would stop Hitler before Hungary entered the war on Germany's side.

Hugo felt Freud was neither a scientist nor a clinician, a skillful writer who reduced complex issues to a sexuality that remained vaguely defined. These opinions did not deter Ervin, encouraged by his tutor, Michael, from devouring all Freud's books, moving on to analyze his classmates in the gymnasium, interpreting dreams right and left, making a strong impression on girls.

For Erwin, Hugo was the silent witness who shaped his choice of medicine, an early influence that encouraged him at age 7 to introduce himself as "Doctor" to friends and visitors. Later on, his view became more nuanced; comparing himself to his idol he says, "Yet I have never felt fully satisfied with myself because of the relentless challenge to live up to his expectations. I got everything, the ambition, the goal, the style but apparently not made of the same fabric." This insight and conviction would later color career decisions Ervin made.

Two of Hugo's female cousins, one Chair of the English Department and the other Professor of Philology at the University of Vienna, were killed by the Nazis as Jews in 1938, although both were lifelong Catholics. Hugo met a more fortunate fate. In 1944, he was placed in a forced labor camp to dig ditches but reprieved; due to political patronage and his reputation, he returned to his post at the Jewish Hospital, now part of the Ghetto. In 1945, after the liberation, he was hit by a Russian truck and died from his injuries shortly after Ervin was able to visit him and bid farewell.

The story of the remaining Richter aunts, uncles and cousins was both colorful and tragic; first under the "White Terror" after World War I when both Jews and Communists were purged in primitive pogroms and then under the burgeoning Nazi regime. The sole survivor, Uncle Mauricio migrated to Mexico and thrived, dying at the age of 90, socially and financially successful but plagued by feelings of inferiority.

Ervin's paternal ancestors were the Weiszes. His grandparents lived in semi-feudal rural surroundings, dwelling in a relatively decent cottage but without sanitation. His grandfather managed a distillery on the estate of the local Count, while his grandmother tended a family menagerie of fowl, cows, horses and water buffalo. Both were murdered at Auschwitz in 1944.

Ervin's father served in the Austro-Hungarian army in World War I, was captured by the Russians, escaped and travelled home on foot through the war-torn countryside without knowing the language or having a penny in his pocket. He was a soft, sensitive and loving man, a travelling salesman, married to a strong wife, who edited, corrected and proofread him like a never ending story.

From these grandparents and parents Ervin learned the lessons of life. He was expected to "behave like a man"; it was fine to seek advice or help but totally unacceptable to solicit sympathy, dramatize accomplishments or feel sorry for yourself. With hindsight and psychiatric training, Ervin realized how systematically he was encouraged to develop inhibitions, repress basic urges and feelings, to pretend strength and suppress anxieties. He rationalizes these as self- regulatory techniques essential to civilized, disciplined behavior.

One other Weisz, Uncle Andor, became a physician. He graduated from Budapest, married, set up a rural medical practice and converted to Catholicism. Despite this, he was taken with his wife and daughter to the ghetto and then to the gas chambers at Auschwitz, among the first Hungarians to die there. Before they were murdered, they were forced to send a handwritten postcard home, "We are all well and in a nice resort."

Ervin Weisz was born February 20th 1925 on Jozsef Boulevard in Budapest, four years after his older brother Feri. It was a comfortable home, presided over by his grandmother and mother while his father was often on trips as a salesman to bring home the family bread. The family kept Kosher and observed traditional Jewish rituals. Included was the annual Yom Kippur sacrifice of live chickens, first held over the adults' heads as they danced around the room, while Ervin and Feri hid beneath the table, from where they viewed the chickens, beheaded by a ritual butcher, running around headless and gushing geysers of blood. Ervin developed a lifelong aversion to eating the flesh of fowls and at age 9, suffered his first real panic attack.

Ervin traces his educational and emotional evolution through childhood and the teen years, during which the family was upwardly mobile. He moved from a parochial elementary school to a private Jewish institution with a strict impartial teacher, who demanded discipline and gave 6praise only when deserved. Pupils learned not only how to read and write but how to behave. They sat with hands clasped behind straight backs, developed the smallest genteel manners, including to eat slowly in small bites, to end meals while still hungry and wait till it went away.

At age nine, Ervin began Cub Scouts, where they were taught larger morals, collective responsibility, sharing and more discipline; it was praiseworthy to be strong, tough and do good to others. During this pre-adolescent phase, Ervin was sensitive and naïve, exposed to sexual innuendo and bullying by older boys and girls, which leads him to reflect on how, over a lifetime, he has been controlled by people, institutions, principle and duty.

At age ten, Ervin entered the rigorous eight year-long academic environment of the gymnasium, where they learned Latin daily. It was also rife with anti-Semitism and patriotic heroism, expressed by teachers eager for national revenge over the two thirds of territory lost from Hungary due to the Trianon Peace Treaty after World War I. At age 12, Ervin and his brother enrolled in the Jewish Gymnasium, a simple move that created a new look on life. It was among the best schools in Hungary, a spectacular modern building letting in light everywhere, a metaphor for an enlightened curriculum in science and arts, staffed by above average teachers, including some brilliant former university professors. Exposed to a socio-political climate of anti-Semitic hatred, the pupils felt propelled to academic excellence. His mother hired Michael as a tutor to reinforce the academic and moral climate. Under his guidance, Ervin read Hebrew, the verse of the English Poets, devoured Freud and the German philosophers. He kept a literary diary and was viewed by the family as modestly superior - knowledgeable but not a show off. After work was over, Ervin attended Boy Scouts, played tennis, ice skated and swam – sports he enjoyed but never excelled at.

On the eve of his Bar Mitzvah, on March 12, 1938 at age 13, Ervin learned that Hitler had annexed Austria and German troops had occupied Vienna. People knew the fascists were coming and felt the winds of hatred but ignored the coming storm. In the summer of 1939, Ervin hiked with a friend in the Carpathian Mountains –a gift to Hungary from Hitler for implementing a restrictive "Jewish Law", which included the *numerus clausus* rule, limiting university admission for Jews. Among the victims, Ervin's brother Feri was forced to become a skilled laborer and then drafted to a notorious labor camp.

At age 16, in the bloom of adolescence, Ervin joined a Zionist group preparing its members to live on a Kibbutz in Israel, a phase that only lasted until his provocative dissensions led to his departure, taking with him a lovable girl Anna. Together they eagerly turned adolescent romance into adult love, living in fragile denial that passive compliance with fascism might divert persecution. But, in 1941, one of the brightest and bravest students at school was arrested by the Hungarian Political Police, taken away and disappeared; soon after an anti-Semitic crowd broke the schools widows with rocks.

Ervin and Anna continued in a Romeo and Juliet state of bliss that sustained the element of denial until he graduated from gymnasium in spring of 1943. Now all Jews were banned from

university and Ervin and his friends were anticipating the forced labor camps. His application to medical school was denied unless he converted to Christianity, even though Uncle Hugo (who had rejected the same offer) knew the President and advocated on his behalf.

News that the German Army had stalled and was facing defeat in Russia bred a brief false optimism but also fueled Hitler's determination to complete the Final Solution. In March 1944, Germany invaded and occupied Hungary, its erstwhile ally, after the interim government attempted to broker an armistice with Britain and Russia. Two weeks later, the Americans started to bomb Budapest. A new pro-fascist government took over and the civilian population felt empowered to escalate its latent anti-Semitic ethos in support of the Nazis. All Jews were required to wear a yellow star over their heart. Anna's father was taken away and the Gestapo sealed their house but not before Anna escaped to take refuge in a tenement where Ervin was able to visit her. In less than a month, all Jews were herded into internment camps, a gateway to concentration camps and the gas chamber. On June 5 1944, Ervin was commanded to report to the forced labor camp at Felsohangony. What started as a six month period in military style housing with enforced hygiene and adequate food, soon deteriorated into an increasingly rabid anti-Semitic environment administered by guards delivering senseless cruelty, blind hatred and officially sanctioned sadism. Treated as objects of intense abhorrence, the prisoners struggled to survive as decent human beings, an irrational hope.

In mid-July, Ervin's unit was taken to a camp in the Carpathian Mountains to build an airfield, where they worked for three months like slaves, 6 days a week for 12 hours daily. In October, at two hours' notice, they began a month long forced march to the town of Kassa, where they were loaded and locked into boxcars, 80 or more at a time. They travelled this way for uncounted days, stopping intermittently to be given soup with a small piece of bread and to carry the dead into the surrounding fields.

On New Year's Eve 1945, they arrived at Hidegseg (Hungarian for coldness) and crowded 50 or more into sheds with frozen mud floors covered with a few reeds. A voice from outside the shed demanded silence: "This is a death camp. If you speak loudly you will be shot. If you are sick you will be killed. If you don't obey fast enough you will be beaten to death." This was delivered without anger or empathy in a voice ice-cold, clear and factual.

Over the next three months, ending on March 29, 1945, this proved an accurate description of unimaginable cruelty and barbarity which Ervin witnessed and endured. Instructed to dig trenches to obstruct Russian tanks, equipped with shovels and axes they could hardly lift, they struck at frozen earth. In the evening, they were fed soup made of potato and carrot peelings boiled in unsalted water, with a slice of bread every three days. People died of starvation, exhaustion, beating, shootings and freezing. Typhoid, dysentery and lice were endemic. The living undressed the dead and distributed the clothes to those unable to move. Those who survived buried the dead.

In February, on Ervin's birthday, the survivors were ordered to stand in a large circle. The guards dragged a small emaciated young man into the center, barefoot, half frozen in rags, hands tied behind his back. Sentenced to death for attempting to escape, he was shot in the back of the head and went down like a marionette when the string is let go.

Following the execution, Ervin became ill. Terribly thirsty, he faded in and out of delirium. He could not stand, his toes were frost bitten and he developed bed sores. During roll call his companions held him up, then smuggled him back to the shed and covered his body in rags. The only person Ervin could think of was his mother, only she meant redemption.

By mid-March, Ervin began to recover and learned to stand by climbing up his own legs, like a child with muscular dystrophy. Starving and craving food, the prisoners' minds were filled with thoughts of it, a craving that brought them to the edge of decency and dignity. They counted their dead comrades and ruminated on why they remained alive. It was a question with no logic or principle to explain the luck of survival; existence was a statistical aberration.

The guards no longer let them out to work but continued to rampage. They shot a man in Ervin's hut for no reason and when a heroic rabbi attempted to fulfill his obligation to bury the dead they shot him too. The bodies lay alongside, unburied.

By the time of their delivery, the prisoners had buried 800 (about half) of their fellows and in Ervin's shed only eight were still living. As the Russians came close, the guards prepared to flee as darkness fell; they stopped outside the shed and demanded to know how many were alive. Hearing the answer "eight" they opened fire, repeating the question till the answer was "four". Satisfied, believing no witness would survive, they disappeared.

In the morning three men were wounded and one dead. Sitting quietly, the survivors tended the wounded. Suddenly the locked door was broken open by a young Russian soldier, soon followed outside by a tank with an officer on top. He spoke in broken German: "You are free, the camp is yours; your guards have run away. Go and eat from the storeroom, there is plenty of food. Take off your yellow ribbons."

Ervin was happy not to feel hungry or cold and relieved from constant fear of being brutalized, but overall being free was characterized by numbness, a lack of feeling. Ervin could not walk more than 100 yards but made up his mind to head for home as best he could. In three weeks, he travelled 200 miles by foot, truck and train, stopping briefly in a local hospital and an unexpected guest in the homes of two peasants, finally crossing the Danube on the only remaining bridge to reach Budapest, one of the first to return from a death camp.

Ervin went first to the Jewish Hospital and sat by the bedside of Uncle Hugo the day before he died from his injuries. Also giving comfort were his mother and grandmother. Added to the joy of re-union was the news that his brother had somehow escaped from his labor camp and was also safely home.

On liberation, their mother had left the ghetto and single-handed evicted the fascists who had occupied the family home, which remained in surprisingly good condition. Their father also survived two concentration camps; now fifty years old, he had returned reasonably healthy. Of all those closest to Ervin, only his sweetheart Anna failed to return. Three months later, her name was listed on those who died in Bergen-Belsen concentration camp.

Ervin had regained most of his weight and health by the summer but developed tuberculosis and spent time in a sanitarium; absent the availability of drugs to treat the condition, he stayed only until he enrolled in medical school among the 1000 applicants, many of them Jewish men and women previously denied acceptance.

By this time, Ervin and his brother had decided to shed their Jewish name Weisz, which attracted anti-Semite attention and was of little historical significance to them. Paging through the Budapest Telephone Directory, they picked an ecumenical run of the mill name with the longest list. Ervin Weisz became Ervin Varga, now embarked on what he hoped would become a discrimination free life as a future physician in Hungary.

Hungary Post World War II

Ervin's Memoir ends at age 20, when the social and political climate in Hungary left much to be desired. Russia pursued its aggressive role of Communist hegemony and neo-colonialism, invading the countries adjacent to its borders and establishing totalitarian regimes where the defeat of Nazi Germany had created a political vacuum embracing Greece, Hungary, Czechoslovakia, Latvia, Bulgaria and Poland, ultimately bringing down the Iron Curtain. For centuries anti-Semitism had been endemic in the Hungarian population, covert or overt, depending on the political climate. A majority of the population had actively or passively endorsed the Nazi goal of eliminating Judaism and after the Nazis left, it did not disappear overnight. The strategy of seeking secular anonymity with a name change would serve as only a slender shield for someone with Ervin's experiences and innate sensitivity.

Now medical school was a much awaited, long delayed reality but not an easy one, particularly the first year with 1000 students jostling for space and attention. But their numbers dwindled rapidly, more than two thirds dropped out and only 300 graduated, Ervin among them, as well as a future wife, found once the pain and loss of Anna had slowly melted away. In a population culled of young men by the Nazis, women outnumbered the male survivors.

To best understand the roots of Ervin Varga's medical and psychiatric education and its branches requires some background. Semmelweis University in Budapest was founded in 1789 and became independent of Budapest University after World War II, at the time Ervin began his studies. It enrolls around 10,000 students annually from 60 nations, offering undergraduate and graduate level courses in medicine, pharmacy, dentistry, health sciences and administration taught in English, Hungarian and German. It is home to the biggest medical library in the country and produces the greatest number of scientific publications (Wikipedia Encyclopedia, 2015).

The University of Pecs is the oldest University in Hungary with its own Medical School. As a medical student, Ervin attended both Universities, beginning at Semmelweis and transferring to Pecs after five semesters, as his interests evolved and then returning to Semmelweis for psychiatric residency.

A crucial influence on psychiatric education during that period was the Semmelweis Professor of Psychiatry, Gyula Nyiro. In 1933, he had worked with Von Meduna to introduce what became known as "shock therapy" for psychotic patients, induced first with chemical convulsants and later

by electricity. Nyiro, a brilliant clinician, diagnostician and teacher, published little but exerted a profound influence on a trio of students all of whom went on to make significant contributions in psychopharmacology. The first two were Ervin Varga and his contemporary in gymnasium and medical school, Joseph Knoll. The third was Tom Ban, younger by ten years when he enrolled at Semmelweis. For a fuller understanding of Nyiro's contributions, see Tom Ban's e-book on INHN (INHN in e-books; 10/10/2013). Tom believes that Nyiro provided the link between Wernicke's nosology and Pavlovian reflexology, bridging psychopathology with pathophysiology. When Tom escaped from Hungary in the mid 1950's, leaving most of his possessions behind, he tucked Nyiro's lecture notes into his briefcase.

Nyiro's influence on Ervin's career was direct and profound. As a medical student, his teaching reinforced Ervin's determination to follow in Uncle Hugo's footsteps as both a neurologist and psychiatrist. This motivated him to move to Pec's University to work under Professor Lissak, where he learned about high quality neurophysiology research. Here he also met his future wife Vera, a *magna cum laude* medical student. Ervin finished medical school at Pecs, completed a rotating internship there and obtained his MD Diploma in June 1951 from that University.

From 1951 to 1959, he returned to Semmelweis for residency training in both neurology and psychiatry in Nyiro's sphere of influence. He obtained boards in psychiatry in 1955 and neurology in 1962. During this time, his still untreated tuberculoma (due to the absence of drugs) was surgically removed along with an entire lobe of one lung, taking half a year to fully recover. While in residency, he embarked on a thesis supervised by Nyiro that led to a Ph.D. equivalent in 1962 as a Candidate in the Academy of Sciences. The core of his dissertation was the observation that normal speech made no sense until it was vocalized, after the brain had completed words and sentences. Ervin hypothesized that patients with schizophrenia lacked this ability; their utterances were immediate and often nonsensical. Over four years, Ervin developed neurophysiological methods to measure this phenomenon which Nyiro had named "delayed inhibition." Ervin published nine papers in both English and German, culminating with his Thesis, *Schizophrenic Perception. An Experimental Investigation* (Varga 1961).

During this time period, chlorpromazine became widely used to treat schizophrenia but Ervin did not study its effects on delayed inhibition, a missed opportunity he feels would be worth re-visiting today.

In the brief interval between finishing residency and starting his academic career, Ervin decided to attempt to implement an intrepid urge to visit the Maudsley Hospital in London, recognized as one of the leading centers in European excellence under Aubrey Lewis. This was a challenging task; under Communist rule, he needed a connection to the Hungarian authorities, a minimum fund for support and a letter of invitation to give a lecture. He obtained the economic support from his brother in California and the invitation from a former schoolmate working as biochemist at the Hammersmith Hospital in London. He rented a small apartment for a month's stay and his host arranged for him to meet Michael Shepherd, the number two academic at the Maudsley.

Shepherd was by no means the most popular person at the Maudsley but he and Ervin hit it off. "We immediately liked each other, I enjoyed his slightly manneristic, sarcastic style and he was glad to speak real psychiatry. He took me everywhere, tested my diagnostic skills, took me to his home, and gave me books to read." Michael also introduced him to senior colleagues well known for their research. Altogether, "My visit to the Maudsley changed my life …I liked everything." It also cemented a relationship that would have later consequences for Ervin's career and which energized him to engage in almost a decade of intense academic achievement.

Ervin returned to take up his post as Assistant Professor of Psychiatry and Neurology at Semmelweis and three years later was promoted to Associate Professor and Director of Psychopharmacology. While completing his thesis, Ervin had also worked as Chief of the Depression Unit, where he was disappointed with the effects of ECT and began developing an interest in the new drug treatments. His classmate, friend and now colleague, Joseph Knoll had decided to pursue bench research rather than clinical work and had joined the Department of Pharmacology, where he remained for the rest of his life. He became a Full Professor in 1963 and Head of the Department from 1962 until his academic retirement thirty years later in 1992, although still doing active research at the age of 91. His early research was with the MAO inhibitors and he had already supplied Ervin with Niamid for use in humans (Varga 1964). Aware of the "cheese effect" in humans treated with MAOI (Blackwell, 1963), Knoll was intrigued to

find that the MAO inhibitor he was now working on, Deprenyl (E-250), also inhibited the noradrenaline releasing effect of tyramine in rodents.

Ervin Varga's early role as the clinical component of this translational research is told in an interview of Knoll by Tom Ban at Budapest in 2002 for the *Oral History of Neuropsychopharmacology* (OHP) (Vol. 3; Series Ed. Ban TA; Vol. Ed. Sulzer F). This 32 page interview is probably the most lengthy of those in all ten volumes of OHP and is an enthralling micro biography of Joseph Knoll, as well as a powerful and enlightening testimony to the virtue of translational collaboration between bench and clinic.

"The first clinical trial with racemic Deprenyl in depression was done by my childhood friend, my schoolmate in gymnasium and classmate at the university. The preliminary results were presented at a conference in Budapest in 1965 (Varga 1966 c). The study was extended and was published (Varga and Tringer, 1967). The first clinical trial with the minus isomer, the drug now in use, was published by Tringer, Haits and Varga in 1971 (Knoll, 2002). In spite of their favorable findings, the possibility of introducing Deprenyl as an antidepressant remained unexploited for many years after."

That Ervin Varga was the first to show that Deprenyl did not interact with tyramine and was safe, but that this failed to save the MAOI from oblivion, contributes to my own expressed concern that these "drugs were too useful to be quickly abandoned" (Blackwell, 2014). This occurred despite the fact that we never fully defined the clinical characteristics alleged to benefit or took account of the fact that tranylcypromine (Parnate), probably the most widely used MAOI, also had mild amphetamine like euphoriant effects, a property that proved useful for the treatment of outpatient depression long before imipramine was discovered.

From an historical viewpoint, it is interesting to note that Knoll subsequently discovered that Deprenyl was the first catecholaminergic enhancer and that it prolongs the life span and sexual activity of rodents, an action that is under clinical investigation today in Japan.

The implementation of Ervin's plan to establish solid academic and research credentials, incubated at the Maudsley, ranged far beyond psychopharmacology influenced by his mentor's interests and teaching. In seven short years, he published 27 scientific contributions in German and English, of which he was first author on 25, covering nosology, natural history and social features of psychoses, neuroses and personality disorders (Varga 1965, 1966 a, b, c; Varga and

Haits 1966). This culminated in an authored book, *Changes in the Symptomatology of Psychotic Patients* (Varga, 1966 d). This prescient volume documented the decline of positive symptoms such as hallucinations but not the negative cognitive and behavioral features. This aspect of the response to antipsychotic drugs was a prelude to the ease with which patients could be released from asylums only to founder in the community.

Ervin notes two publications during this creative period he considers his most important contributions. The first, which had international implications, involved his return to the Maudsley for a second visit, sponsored by the World health Organization. Over a period of three months in London during 1966, he worked to support the work of Michael Shepherd and Jules Angst (from the Burgholzli Hospital in Zurich) in carrying out a retrospective evaluation of 910 depressed patients treated at the Maudsley between 1957 and 1963, in an attempt to replicate and validate the findings of the Medical Research Council's study of a similar population, published the previous year in the *British Medical Journal* (Report of the Clinical Committee, 1965). This creative and unique design resulted in supporting the conclusion that ECT and imipramine were superior to the MAO inhibitor phenelzine, failed to support the earlier finding of a gender difference in favor of females but was unable to clearly identify which clinical, demographic or social criteria characterized a failure to respond to all forms of therapy. Paradoxically, this finding may have made its own contribution to the demise of the MAO inhibitors, although its conclusion was based on the performance of only phenelzine. An earlier operational study of the use of MAOI at the Maudsley established that prior to 1965; tranylcypromine was the MAOI in widest use and suggested that it was more effective than other MAOIs (Blackwell and Taylor, 1967).

After the study was complete, Ervin was invited by Jules Angst to visit the Burgholzli on his way home; he was a guest in Jules house, attended the teaching conferences chaired by Bleuler and served as a consultant in helping to diagnose a complex case of a woman who spoke only Hungarian, before returning to Budapest a week later. His interactions with Angst cemented a relationship that stood him in good stead when he later escaped from Hungary.

After returning to Hungary, Ervin undertook a study of a smaller sample of 249 patients with severe depression treated at the Budapest Psychiatric Clinic with ECT, imipramine and phenelzine. The results confirmed the superiority of ECT over drug treatments noted in the London sample (Varga, Angst & Shepherd, 1967).

The second contribution identified by Ervin as important had its greatest impact within Hungary itself. Because of his established position as an expert in schizophrenia, he was asked by the Hungarian Academy of Science to review the history of the life and death of the famous Hungarian poet, Joseph Attila, regarded by many Communist citizens as "the poet of the proletariat." Ervin's findings were controversial (Varga, 1966), provoking debate and angry rebuttals that continue to this day. These focus on an interpretation of the poet's death, regarded by his many admirer's as martyrdom by suicide. The facts suggested otherwise. Attila had approached a stationary train at a crossing, unlatched the gate, crawled under the engine and fallen asleep. When the train started to move, he was crushed and died, an accident Ervin considered the result typical of schizophrenic thought and behavior. It is worth noting that Ervin's mentor Nyiro was admired for his willingness to stand up and maintain his independence under both Fascist and Communist regimes. Perhaps Ervin Varga was a kindred spirit?

Family Matters

The biographies of neuroscientists indicate that marriage does indeed matter, at times in a pre-emptive manner (See those of Jean Delay, Karl Rickels, Heinz Lehmann and John Smythies, in particular, on the INHN website in *Biographies).* There are reasons to suppose this may be even more so in understanding Ervin Varga's career choices and trajectory.

To begin with his marriage lasted almost 67 years and was a highly successful union. It took Ervin four years to resolve the grief and loneliness following news of the loss of his beloved Anna in 1945. But when he met Vera at Pec's University in medical school in 1949, they were married within three months, a union lasting until her death in July 2015. The couple bore two sons, Peter and John, born a year apart and ages 13 and 14 when they escaped from Hungary. Each is now a successful physician in Chicago, where Ervin lives in an apartment overlooking Lake Michigan, comforted by his dog, a Bassenji, and in frequent touch with his sons. Peter is an Associate Professor of Pediatrics at the University of Chicago and an expert in non-invasive cardiac imaging. John is the John and Nancy Hughes Distinguished Professor of Rheumatology at Northwestern University and a national expert in Scleroderma and its treatment.

So, all four members of the Varga family have been talented physicians. The tone and tenor of the parent's marriage is revealed in a eulogy John delivered at his mother's memorial service. As a 12-year-old he was so proud of his physician mother that he advertised her services to the

neighborhood kids, offering free check-ups and emergency services. "Anyu was an understanding lifelong partner to my Dad. The two of them were inseparable through 67 years of challenges including Communism, revolutions and emigration. *One of her enduring gifts to us, and to our children is her example of this special partnership"* (John's italics).

"Mom was the family bedrock as we rebuilt our lives in the new world. Peter and I never knew how hard she and Dad worked during these years, completing a demanding Residency at 40, while sending my brother and I to elite colleges … she never complained nor looked back."

John portrays her persona: "Most of all Mom had a big heart…She had a passion for words, literature and books. Mom was the most well-read person I knew, but she wore her erudition lightly. She could read and speak Hungarian, German, French and English but also knew some Russian, Spanish, Italian and even a smattering of Japanese. There will never be another one like her."

In addition to this extraordinary union to a unique partner, one must reflect on the valence and significance of marriage for Ervin. He grew up in a close knit and loving family disrupted by fascist anti-Semitism and in a decade, as a teenager and young adult, lost 40 of his family members to the Holocaust.

Every talented scientist devoted to his or her work must titrate that goal against a competing desire and love for family. For Ervin circumstances would dictate that the balance sometimes tilted more towards family.

Escape from Hungary

Towards the end of 1967, events came to a head in Budapest. Ervin's mentor, senior colleague and friend, Julius Nyiro, Head of the Department of Neurology and Psychiatry, died suddenly. Ervin Varga was expected by many friends and colleagues to be a natural successor, influenced by the solid academic credentials he had accumulated in eight short years as a faculty member. But Ervin's searing experiences inside Hungary and friendships with Shepherd at the Maudsley and Angst at the Burgholzli had exposed him to the very best in European psychiatry, on the far side of the border. Both Ervin and his wife were eager for a life free of totalitarian constraints with better prospects for their two boys. They had been planning and making preliminary moves for some time but Ervin was concerned that the husband of one of his patients might be a Communist

spy. Events finally determined the outcome. A school friend, whose son he had treated, worked for the police and called to warn him it was ‘now or never’. The Russians had invaded Czechoslovakia and the borders were about to close.

Leaving everything, except what they could carry, the family took flight for Italy and spent the next five months of 1968 in Rome, where Peter and John attended an international school. Jules Angst cared for their money in Zurich and his brother provided funds from California while Ervin cast about for a job opportunity in Britain or America.

Ervin and his wife were charged and convicted *in absentia* to two and a half years in prison. Years later, when a Democratic Government was elected, the sentence was annulled with apologies. A relative bought back some of their confiscated possessions at exorbitant and inflated prices, including several valuable pieces of art. The pictures were hanging on the walls of the family room when we visited in January 2016 to interview Ervin and meet his sons for lunch at a nearby Asian café in Chicago.

Through his contacts at the Maudsley, Ervin knew there were no job openings in the U.K. but he was soon contacted by Nathan Kline in New York who, presumably, had heard of Ervin’s availability from European contacts. He began an exhaustive and exhausting effort to recruit Ervin, calling from New York weekly and eventually sending an emissary to close the deal with increasing financial incentives that doubled what he might have expected in Britain. Eventually Ervin succumbed and the family moved to New York.

America: Stranger in a Strange Land

Ervin Varga is blunt; moving to America was the worst mistake of his life. By far, he would have preferred Britain whose people, culture and academic climate he preferred. In 1968, American academic psychiatry was dominated by psychoanalytic hegemony. Almost every academic department was chaired by an analyst; most of the residents were in analysis with a faculty member and as the US-UK cross-cultural study would show, nosology and taxonomy were derelict. Truth to tell, he was somewhat sheltered from this reality. The real work of psychopharmacology first took root in the state asylums, the V.A. and with a few private practitioners, like Frank Ayd (Ayd, 2011). Nathan Kline’s research was done at Rockland State

Hospital in New York (named after him following his premature death) and supplemented in Nate's fashionable and lucrative New York City private practice.

What were, however, inescapable was the culture at large and the shock it inflicted on Ervin's fragile temperament. From the rigid constraints of a totalitarian system he was in a land where he was unsure of the rules and had too many choices to make, creating feelings of insecurity that aggravated his strong sense of family responsibility. It felt like, "I was driving on the freeway without knowing the rules."

His initial assignment was to work with Nate Kline on a pet project – doing a demographic study of computerized psychiatric nosology in the seven Atlantic States. Computers were not a strong interest and, in addition, Ervin had to accommodate to Kline's controversial style. As editor of the 9th volume of the OHP, I dedicated it to Nathan Kline and described him in the Introduction (see Ch.8.) Nate was the polar opposite of Ervin's innate reserve and modesty concerning any accomplishment of his own. Nonetheless he saw and appreciated the good side of Nate's character and worked with him for two years, during which he published two papers, a follow up to an earlier paper on archaic schizophreniform symptoms in depression (Varga, 1971 a) and a psychopharmacology paper on Loxapine in destructive behavior (Varga, 1971 b).

After two years working with Nate, Ervin made a brief visit to Europe where he visited the Maudsley and renewed his acquaintance with Shepherd. There were clearly still no suitable work opportunities in Britain but he returned to America with written endorsements that might stand him in good stead in America. They provide an interesting view of the impression Ervin's career accomplishments created on two of the most critical thinkers in European psychiatry. Michael Shepherd wrote, "On the basis of my personal contacts and his professional reputation I know Dr. Varga to be a physician of outstanding ability and integrity. He is also a helpful and reliable colleague. On all these grounds I would strongly support Dr. Varga's petition for medical licensure in the State of New York."

A second letter by Sir Aubrey Lewis, Director of the Maudsley Hospital and Institute of Psychiatry is more broadly intended but equally positive coming from a person respected for his accurate but critical assessments (Goldberg and Blackwell, 2015). "Dr. Varga's medical attainments are those of a mature and well trained psychiatrist. He is engaged in research into problems of schizophrenic speech and thought disorder, psychopharmacology and social

psychiatry. His publications include a valuable monograph on the changes that occur in the clinical pattern of mental illness. His numerous other publications show that he is a research worker of proved ability.

In personality, clinical attainments and research record Dr. Varga seems to me to be fully equipped to hold a responsible post in a psychiatric research department or academic center."

Armed with such an endorsement from a highly respected source, Ervin might well have 3been influenced by the dominance of psychoanalytic influence over academic domains and sources of research funding as well as to existing opportunities at Rockland State with its established reputation, research support and large patient population. There were also research workers whose styles and temperaments were more compatible to Ervin.

So began a four year period (1972-1976) as an Attending Psychiatrist at Rockland Psychiatric Center when he collaborated with other like-minded scientists and clinicians in producing 14 publications on a wide variety of topics. Most prominent among his fellow workers were George Simpson and Tom Cooper, both migrants from the British Isles.

Ervin liked and admired both these men. Simpson's origins, temperament and career accomplishments as both a clinician and psychopharmacologist are related in Volume 4 of the OHP (Ed. Levine J, 2011) as a brief biography (Blackwell in *Dramatis Personae* lxxxvi-lxxxviii) and interview with Leo Hollister (Simpson, 2011 pp 373-384). Ervin's collaboration with George involved 6 publications. A report on the use of psychotropic drugs in a State Hospital (Laska, Varga & Simpson, 1973), a study of dosing schedules in schizophrenia (Lee, Branchey, Haher, Varga & Simpson, 1974), the equivalency of 3 brands of Thorazine (Simpson, Varga et al, 1974), prognosis and diagnosis of tardive dyskinesia (Simpson & Varga, 1974 a), a new antipsychotic clozapine (Simpson& Varga, 1974 b) and psychotic exacerbation produced by neuroleptics (Simpson & Varga, 1976).

Tom Cooper's background, career and expertise in biochemical pharmacology and the metabolism of drugs are related in Volume 7 of the OHP (Ed. Blackwell B, 2011) as a brief biography (Blackwell in *Dramatis Personae,* liii-liv) and interview with Tom Ban (Cooper 2011, pp 125-137). Ervin's collaboration with Tom involved 4 publications, 3 on lithium in the prevention of alcoholism (Kline, Wren, Cooper, Varga & Canal, 1973), (Kline, Wren, Cooper, Varga & Canal, 1974 a), and (Kline, Wren, Cooper, Varga & Canal, 1974 b). The other was on

bioequivalence of 3 brands of Thorazine (Simpson & Varga et al, 1974). The 4 papers with Ervin as first author in collaboration with others were on depression, osteoporosis and osteoarthritis (Varga & Kline, 1973), neuroleptic-induced Kluver-Bucy syndrome (Varga et al, 1975), a 2 year trial of Loxapine in chronic schizophrenia (Varga et al, 1976) and schizophrenia 50 years after the death of Kraepelin (Varga & Kroll, 1977).

First among Ervin's cultural concerns at this time were the economic issues of survival in an aggressively capitalist country. Accustomed to the socialist ideal of state funded education for all those able to benefit, he was confronted with the dilemma of finding and paying for College once his sons reached the appropriate age. As fate would have it, they applied for and were accepted to the two most expensive private institutions in New York, Peter at NYU and John at Columbia. Their parents had no knowledge concerning scholarships or tuition breaks and, only one year apart in age, they were heavily burdened with escalating debt.

This played a role in Ervin's decision to move from Rockland, when he was recruited by Arthur Sugerman, who had joined the Carrier Clinic in 1972 as Research Director. Arthur had worked collaboratively with Nate Kline and George Simpson on ECDEU projects from 1961 to 1972, so knew of and admired Ervin's work on the Kluver-Bucy syndrome at Rockland.

Arthur Sugerman's background, training and career are related in Volume 2 of the OHP (Ed. Fink. M), first in a brief biography (*Dramatis Personae*, xli) and then, in an interview with Tom Ban (Sugerman 2011).

Arthur began his education at the Jewish International School and then University in Ireland (Dublin) and medical school in England (London). Ervin and Arthur worked together for 9 years at the Carrier Clinic in what was a wonderful, friendly relationship. Ervin later joined him on the faculty of the Robert Wood Johnson Medical School as a Clinical Professor (1982-1992).

In his time at the Carrier Clinic, Ervin published 10 articles, 4 of them with Arthur, all on different topics; the prevention of ECT amnesia (Menken, Sugerman & Varga, 1979), the safety of hemoperfusion in schizophrenia (Kinney, Varga & Sugerman, 1979), codeine in involutional and senile depression (Varga & Sugerman, 1982 a) and the prevalence of spontaneous oral dyskinesia in the elderly (Varga & Sugerman, 1982 b).

Private Practice

By 1985 Arthur Sugerman stepped down as Medical Director at Carrier and was replaced by an administrator. This change triggered Ervin's decision to enter private practice, initially with a recent graduate from the Harvard residency program whose knowledge helped Ervin adapt to a new way of life. After a few months, he decided to become a completely independent solo practitioner working in two separate settings; an office in Princeton, where many of his patients were faculty members and another in Somerville, a nearby industrial area. Much to his own surprise, Ervin took to private practice like a duck to water. He liked working on his own and thoroughly enjoyed clinical work where his skills in diagnosis, psychopharmacology and psychodynamics ensured good results and personal satisfaction. He is proud of the fact he never had a patient commit suicide.

After 8 years, in 1993, he decided to cut back and switched to doing locum tenens work for a couple of months each year, much of it in New York and Manhattan but occasionally, as far afield as San Francisco. Apart from the fact that he could stay in the best hotels and dine in fashionable restaurants, he could synchronize his trips with visits to family and friends. This continued until 2015, when he finally retired (so he says) to live at leisure.

Synthesis

In relating Ervin Varga's family, culture and persona to his career challenges and accomplishments one must apply caution. The biographical details in his excellent, well documented memoir, *"Living and Dying in Hungary: Jewish Psychiatrist Looks Back"* (XLibris, 2012) are viewed with hindsight, recorded seven decades after he reached early adult life and perhaps colored by his career as a psychiatrist. But it remains a highly credible story, told with photographic precision in lucid prose.

The account suggests a genetic endowment from both paternal and maternal sides of a strong, upwardly mobile work ethic, coupled with an ethos of modest claims for personal accomplishments. The metaphor of *"bread"* is invoked on both sides; what work provides and what one does with it are vitally important. Ervin's father works diligently lifelong to *"bring home the bread"* while his maternal grandfather admonishes *"who does not slice bread properly does not deserve to eat it."* Advice to which Ervin responds*, "I still to this day slice bread properly";* a modest claim to which his abilities and how he uses them attest.

In addition to these dual generational role models, one takes note of others; a strong nurturing and protective mother, the only image Ervin can conjure as his life hangs in the balance towards the end of the *Holocaust*. His mother survives and it was she who earlier arranged for a tutor, Michael, to assist with Ervin's gymnasium studies and who became a powerful influence on his intellectual, literary and moral development.

More directly influencing his choice of medicine as a career was his Uncle Hugo Richter, a distinguished academic psychiatrist and neurologist, an early role model that led 7 year old Ervin to introduce himself to others as "Doctor". Ervin's admiration came with a caveat as, in late adolescence, he compares his own talents with Hugo's. *"I got everything; the ambition, the goal, the style, but was apparently not made of the same fabric."* The attribute Ervin believes he lacks is the confidence to face *"the relentless challenge to live up to his expectations."*

Finally, important to note, was the role of Gyula Nyiro, a distinguished mentor and role model whose guidance was a crucial element in shaping Ervin's early academic career and whose untimely death triggered his life changing decision to leave Hungary for America.

To these personal influences, one must wonder about the extent to which they are modulated by Ervin's experience in growing up in an increasingly hostile, dangerous and brutal anti-Semitic environment culminating in a *Holocaust* that caused the deaths of 40 of Ervin's relatives across both blood lines and several generations. Ervin declares that *'What decisively defined me was that I belonged to a persecuted minority."* At the end of the war, Ervin and his older brother decided to erase their patronymic identity of Weisz in favor of the most common "run of the mill" surname they could find in the Hungarian telephone directory, emerging as Varga. Although the Nazis were gone, the family still sought secular anonymity among native Hungarian citizens, who had often supported the invader's barbaric ideals, and many of whom were now Communists.

Ervin's families of origin and the value placed on them formed the template for his own idyllic and successful marriage with a nurturing spouse and two successful sons, all four of them physicians in different fields of endeavor. He never failed to place family interests and values at the forefront, preserving a balance between work and home.

Ervin's innate sensitivity to stress and control issues are suggested by the onset of panic attacks in childhood and a lifelong phobia, avoiding the flesh of fowls. To what extent might this

vulnerability have been influenced by exposure to brutal and life-threatening events in captivity during the final months of Nazi occupation?

The term "Post Traumatic Stress Disorder (PTSD)" entered the psychiatric lexicon of the Diagnostic and Statistical Manual (DSM) during the Vietnam War, but not with any clear or useful meaning. The existence of a catalogue of symptoms creates a stereotype that diminishes the nuances and individuality of human responses to extreme harm and threat. An important book, *Shook Over Hell* (Dean, 1997), brings an historical perspective to bear by comparing a sample of Civil War Veterans with other wars, including Vietnam and both World Wars. Among the author's conclusions is the following, "*The very real problems of Veterans, which are difficult to quantify, understand and discuss in the first place, are frequently, if not routinely, manipulated and exaggerated for a variety of purposes."* (Page 215). The data challenges the veracity that all veterans can be viewed as victims and advances the novel idea, citing examples, that some may achieve heightened coping responses. Ervin vehemently rejects the idea that such savage brutality can engender benefit of any kind although, after his own trial by fire, he sheds the victimization invited by his Jewish name and embarks on an arduous career path with a commitment to excel in his chosen profession. He is protected, however, to some degree, by the family ethos, avoiding immodest claims to success, shunning the limelight and minimizing exposure to undue stress.

The burdens and stress of a totalitarian regime, shared by his wife, certainly influenced Ervin's decision to escape into what he hoped might be a more enlightened environment of the kind he briefly experienced in Britain (the Maudsley) and Switzerland (the Burgholzli). Denied those possibilities, he opted for America, a choice that exposed him to culture shock – the stark difference between a totalitarian regime and an aggressive capitalist one. In his initial exposure to Nathan Kline he met a prototype of American exceptionalism; enormous talent and charm wed to brazen confidence and self-aggrandizement – the mirror image of his own family ethos of modest claims and muted accomplishments.

The absence of stress due to external control was replaced by the internal stress of adapting to a culture whose rules and mores were foreign to him. Initially, this tested his tender temperament but, as always, his adaptation was eventually exemplary, sufficient to meet his own expectations as a family breadwinner and talented collaborative scientist. The facts of his resume speak for themselves. For over two decades, living in an alien culture, Ervin worked on the frontiers of

psychopharmacology alongside some of its leading figures with results that touched many of the growing points in our field.

In his dealing with colleagues, nurturance of family and care of patients, Ervin Varga did indeed *"Slice bread properly."*

Author's Note: Ervin's second visit to the Maudsley in 1966 and his friendship with Michael Shepherd overlapped with my time as a registrar and work as a Research Fellow with Shepherd. We were never introduced although my own doctoral research on MAOI and tyramine was relevant to Ervin's experience with Knoll and to my comment on the findings of the MRC replication study concerning phenelzine. It was truly a delight to meet and get to know the person whose path I had unwittingly crossed and of whose work I had been ignorant.

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Kanellos Charalampous: Confronting the Zeitgeist

For more than two years it has been my privilege and pleasure to pen brief biographies for INHN of pre-eminent pioneers in neuropsychopharmacology. But an historical website also has an obligation to portray the endeavors, accomplishments and struggles of the journeymen in our field, like myself, whose more mundane lives may realistically mirror and shape the expectations of future aspiring neuroscientists. This is especially true at a time when the entire field of psychiatry is under duress, filled with questions and concerns about the future and viability of our profession.

We have documented how even the careers of distinguished neuroscientists such as Jean Delay (Ch.6) and Jose Delgado (Ch.10) have been shaped or disrupted when a changing Zeitgeist presents unanticipated social, political, scientific or economic barriers to their plans or progress. This essay will draw attention to how three characteristics of an individual's persona can help navigate the minefield of professional life; these are **prescience**, the ability to anticipate future trends, **fortitude**, courage in the face of adversity and **flexibility**, an ability to mobilize multiple talents in novel and creative ways.

Becoming Acquainted

Kanellos Charalampous, known to colleagues and friends as "Connie", is a Member-Emeritus of ACNP since 1965: he was interviewed by Tom Ban for the *Oral History of Neuropsychopharmacology* in 1999 (Charalampous, 1999). Recently, Connie became acquainted with the INHN website and our postings. Curious to learn more and perhaps contribute, Connie contacted me and I invited him to visit. Facing the vicissitudes of air travel at age 84, he flew from his home in Houston to Milwaukee. We may have met briefly in the past, perhaps many years ago, when we were both involved in drug testing on prison volunteers (Blackwell 1971) but we did not know each other well enough to be sure we would recognize one another. So I greeted him at Mitchell Field Airport wearing a pink cap and red shirt to facilitate recognition. In return, he had sent me a flattering photo attached to his C.V., which didn't alert me to his diminutive size (5 foot 3 inches at a stretch), a pronounced Greek accent, immaculate attire and dexterous handling of two suitcases, the larger of which I later learned contained the C-PAP machine that minimizes the late life sleep apnea that has hardly slowed him down.

We spent three days together indulging Connie's lifelong interest in art by visiting the Calatrava, Grohmann and Harley Davidson Museums, in between times, dissecting his interesting life and career experiences, which mirrored my own.

After he returned home Connie sent me over twenty essays he had written during his life and career. They display descriptive talent, humor and gentle satire, adding insight and anecdotal color to the material we had already shared. The outcome is an unusual hybrid document in which Connie's verbatim comments are inserted in italics to the larger text, resulting in an account partly autobiographical (KC) and partly conventional biography (BB).

What we discussed or viewed, what we have shared and concluded is what follows, embedded in the matrix of Connie's life.

Growing up in Greece

Kanellos D. Charalampous was born in Aigion, a city 80 miles west of Athens, in Greece in 1931 and he was 8 years old at the outbreak of the Second World War, when the Nazis occupied his homeland. This was followed, in 1944, by a Communist insurrection. His father, a family physician, served briefly in the Greek army fighting both these foes and having settled down in guerilla held territory, he was viewed with suspicion due to his right wing and religious

convictions. He was an excellent role model for Connie, whom he occasionally took with him on patient rounds; his mother was an attractive, flirtatious coquette, determined and controlling but seldom nurturing. Connie was the eldest of four children for all of whom she chose predestined careers. Connie was to be a doctor, his younger sister a dentist and the two youngest boys an engineer and a lawyer. Only the putative dentist rebelled, while all three boys achieved their allotted careers.

The stark background to this benign family portrait is revealed in Connie's essay, *"Diogenes".*

On October 28, 1940, Benito Mussolini's Italian army attempted to occupy Greece. The Greeks mounted a strong resistance, and the Italian armies were repulsed into Albania. This was the only victory of the Allies over the Axis in 1940-41. Nevertheless, Greece fell to the onslaught of the German Armies in April 1941. Two months later, in the summer of 1941, my family moved to a mountain village, Ampelokepoi, in northern Peloponnese. We left the city we had lived in since 1936.

The main reason for the move was my father's anxiety and other symptoms of stress. After his capture by German paratroopers at the Isthmus of Corinth, following the collapse of the front, my father was detained with a fellow soldier, both in uniform. Repeated attacks by the Stukas of the Luftwaffe roused sirens, the terror of which, coupled with many explosions of ships in the harbor, led to panic attacks. His blond friend became white-haired overnight. Following his release and return home, every time my father met German soldiers in the street, his symptoms worsened.

Another reason for the move was the need to raise some food. People in the cities were starving and over 300,000 died, in part because the Allies refused to allow the Red Cross to deliver provisions for fear the Germans would commandeer them. In the winters of 1941 and 1942, a cousin, a high school junior and her classmates, for weeks, would enter the homes of those who died of starvation to retrieve the bodies.

So, in the village, we planted wheat in the few fields that belonged to our family, and in a few more no one claimed. In the summer of 1943, our wheat was already harvested and we had time to secure an open space for threshing. The previous year, not having found an open space, we were obliged to thresh and store our wheat at the entrance to the village cemetery, where I had to sleep to guard the crop. Sleeping in a cemetery was not a pleasant experience for a lad of eleven.

Also malaria was endemic in Greece in the 1940's. Every summer, my mother with the four children would take shelter in the mountain village, above the mosquito line and stagnant waters of the littoral, taking our pink quinine tablets.

Village life had its own routine. After lunch people usually went home for a siesta; summers in Greece are hot. I would spend the noon hours in the village square; on one side was the church, on the other a coffee shop, the communal fountain on the third and a ravine on the fourth. A plain tree, genus Platanus, in the center of the square, provided ample shade with a little breeze and the cacophony of cicadas. The tree must have been there for centuries; two men with outstretched arms could barely encircle the trunk.

During the noon hour, the square was empty except for me but around 2:30 an average size man with receding blond hair joined me. He would sit across the table and read the daily papers, one at a time and then place them in a basket that contained about a dozen papers from Athens. Each was only four to six pages long, since newsprint was scarce and the news meager. The farmers showed up at the end of their workday to drink coffee, socialize, retrieve and read their newspapers before returning home for an early supper.

Every noon, before the farmers arrived, this man and I would read every newspaper in the basket. I learned he was a lawyer, a university graduate and an "intellectual". Disinclined to work and not expected to do so, he was supported by his family, while an attractive sister in-law fixed his meals and did his laundry. He was a serious man who rarely smiled and did not express much humor. But he had the illustrious name of Diogenes and was secretary of the Communist party in our area. Guerillas with fictitious names, supported by the Communist party, would come and go.

Diogenes and I did not talk politics. After reading the papers, when the heat subsided, I would go home, snack and then take my donkey to graze in the fields outside the village.

By that summer, I had completed the first two years of gymnasium and in the fall was due to attend classes in the city where we used to reside, living alone in our large empty house where an elderly aunt, almost blind, came in twice a week and cooked for me. On a cold winter morning, it took me twenty minutes to walk to school through the center of town, past the city square and on to the gymnasium a mile away. The all-male student body convened for a brief outdoor prayer, the announcements of the principal and inspection of the length of one's hair.

One morning, as I approached the square, from the corner of my eye I caught sight of a helmeted German soldier standing behind a machine gun on the balcony of the hotel facing the square. It was surrounded by acacia trees that shed their leaves in winter. Looking around I caught another sight. Five men were hanging, each from an acacia tree. I approached. The sight was ghastly. Two of the men were tall and almost touched the ground, with their heads in grotesque positions. Another had fallen in an awkward way; his eyes were open and his bluish tongue protruded.

The man in the middle, wearing a long khaki army coat, was hanging with his head facing forward and his eyes closed. He had not resisted the execution and I recognized him. It was Diogenes, my reading companion from the previous summer.

The Germans, during a sweep through the countryside, had picked him up. Apparently, they knew of his political affiliation. Although he had a rope attached to the sill of his second floor bedroom window in order to escape, he did not make the effort. When the Germans knocked at his door he opened it. He was brought to town and, the following morning, he and four others were hanged as a reprisal for the assassination of a German officer by the guerillas.

I watched the hanging men for a minute or two and continued my walk to school. My concentration in class was poor; that night and the following nights, my sleep was interrupted by nightmares.

In later essays (*The Pre-Med Experience and A Tumultuous Adolescence)* Connie tells of his late adolescent years and transition from Greece to America.

The gymnasium required a lot of study and was difficult. From 400 students that entered only 79 of us graduated. Ancient Greek and Byzantine history were my great pleasures. Every week we had to write a composition; I memorized whole paragraphs from different books and would insert them in the text. This made the results spectacular and often the professor would ask me to read my composition to the class. However, he never failed to complain about my terrible handwriting and the hard work I was putting him through to read and make corrections. Homework was always demanding and often I would get up at 4:30 am to study.

The teachers in the gymnasium, although Greek, taught in the French and German manner; didactic, remote, indifferent and punitive, contributing to an altogether toxic environment that incubated an unspoken determination to escape my native country for America at the earliest opportunity.

In the summer of 1943, as the Nazis were withdrawing, many people who had not joined the Communist Party were arrested. This included women and their children. They would be taken further up the mountain to be tortured and slaughtered. One summer evening after I had left Aigion to join the family, all the dogs in the village started barking. Alarmed, my mother went to find Triandaphyllos, a family friend, and asked him to find seven mules. During the night, we packed and at 8 o'clock mother went to the village square. The commandant of the guerillas was having his morning coffee. Calmly, she explained that usually in the late summer, we departed from the village and returned to Aigion for the kids to attend school. The commandant graciously gave a written note to my mother, who returned to the house, gathered us up, and we left. Forty minutes after our departure, the provincial leader of the Communist Party appeared in the village square and informed the commandant that the Charalampous family was on the list of reactionaries, suspected anticommunists, who would later be arrested and executed. A squad of guerillas was dispatched to bring us back. Fortunately, we had reached German occupied territory. We barely escaped.

After the departure of the Nazi forces, the Civil War continued. It came close to putting Greece behind the Iron Curtain. From 1947 to 1949, Aigion was attacked regularly by bands of communist guerillas every third night. Imagine the effects, not only from fear but lack of sleep. It was a period when every good friend I had perished. Also, the house I was born in and loved for its size and elegance was burnt to the ground. Another conflict related to the knowledge that my future depended on higher education, and the realization that my family lacked the resources to support me. The probability of following in my father's footsteps was always there but I had doubts about my ability to get into medical school and having the money.

I finished gymnasium with good grades and in the summer of 1949 I left for Athens to take entrance exams to the University. Walking down a corridor, I headed for the room where the candidates for law school were taking their exam but instead entered the room where the candidates for theology were. I passed that exam easily. When I announced to my parents I would

be attending theology school my father was pleased. But my mother asked, "What for?" Well, I said flippantly, "I'll become a bishop." In the Greek Orthodox Church priests can marry but bishops are celibate. Mother asked, "What do you propose to do for sex?" I had no answer.

In another essay (*Triantaphyllos; The Last Time I Saw Rebecca)* Connie tells the story of a family friend who helped out with family chores and assisted their escape from the Communists but whose ambition was also to become a priest.

Triantaphyllos was a tall man, with wavy brown hair, a charming smile and a pleasant voice. He was a carpenter. Often I saw him on the roof of the new church under construction. Triantaphyllos had only a grammar school education but he read a lot, particularly ecclesiastical books. He wanted to become the priest of our village. Despite the support of my parents and other families, he was not selected but he did not give up. When a position opened in a nearby village he applied. The local people had their own candidate and the bishop, although sympathetic was reluctant to make an early decision.

More than a year later, one cool night after finishing my homework, I went to bed around 9pm and fell fast asleep only to be awakened a few minutes later by Triantaphyllos, who said, "Connie, get up. We will go to my last movie show. The bishop just told me he is going to ordain me." Priests did not go to the movies in those days. We headed for the movie theater four blocks away and on the screen there were Lawrence Olivier and Joan Fontaine in Du Maurier's drama, Rebecca.

When I got up the next morning to go to school, Triantaphyllos was already gone. I never saw him again. A German soldier had been killed by the guerillas and true to their edict they had swept the countryside to arrest 30 civilians including Triantaphyllos. Those opposed to his selection as village priest had falsely betrayed him to the Germans as a communist.

The execution platoon of helmeted troops appeared early next morning with a heavy machine gun on the back of an army truck, and stopped outside a small warehouse. The prisoners were kept there and knew the moment had come. Triantaphyllos moved forward, faced the officer in charge and begged for a few minutes to prepare communion for himself and others who wished to partake. The request was granted. A little time later, the prisoners were taken outside, placed in a row against the wall and machine-gunned. The German officer was reported to have said, "Well that fellow surely was not a communist."

Connie continues his story (Pre-Med Experiences). *Because the theology courses at the University of Athens were inadequate, I started attending the Panteion University of Political Sciences as well. In Greece, it was not customary for a student to work while going to school but I thought to try. The National Bank of Greece offered exams so I applied. I made 100 on the test but the Director of Personnel told me I could not get a job because of my poor handwriting. I understood clearly that in Greece you could not get a job without connections.*

At this time, my Uncle Haralabos was visiting Athens on one of his regular business trips. He was a prominent businessman with important connections. On his visits to Athens, Uncle Haralabos would invite me out to lunch on a street where the restaurants specialized in succulent, charcoal- roasted lambs. During one such visit, he noticed that I looked unhappy. I related my experience at the bank and he said he knew the President of the Bank of Commerce and would recommend me for a job. They sent me for a pre-employment physical examination conducted by Professor Patronicolas, a tuberculosis specialist and brother in law of Aristotle Onassis. He took a chest x-ray and there was a Ghon tubercule, early pulmonary tuberculosis. At the time, I was practically starving, eating only watermelons and honey, a stupid and insufficient diet. The Professor told me he could let me work at the bank but in his best judgment he recommended a course of two medications, streptomycin and PAS with bed-rest for a few months. I followed his recommendation and was one of the first recipients of streptomycin in Greece. I continued attending classes at the two universities but never took the job at the bank.

My Uncle George also visited Greece from his home in Detroit for the first time since leaving at age 16. He was one of seven siblings and his father sent him to America with instructions to get an education, find work and, when successful, send money back to Greece. On Ellis Island, George changed his name to Harris and then worked for several years with Irish immigrants laying down railroad tracks, before going into the restaurant business in Detroit, close to the Ford Company executive offices, where many of the executives dined.

During George's visit, Uncle Haralabos spoke to him as businessman to businessman suggesting he help me find a university to enroll at in America.

A few weeks later, a letter came from Uncle George. On his way by train to retire in Arizona, at his physician's advice, he stopped in Fort Worth and remembered what he had been asked to

do. A lawyer he consulted told him that Texas Christian University, a fine school, was situated there and he registered me as a student. I obtained a visa after many months of delay, on Christmas 1950, packed my bags, bid farewell to my family and set out for America.

On the Cusp

I extracted the first paragraph of Connie's account of his *Pre-Medical Experience* and placed it here, as he is about to embark for America to fulfill his hopes and expectations. Understandably he is filled with anxiety from the past, projected onto his future, unaware of the assets his experience has accumulated. It reads as follows:

It is often said that many people would dearly love to regain some of their younger years, together with acquired maturity. I believe that very few would like such a time to include years from adolescence. My personal experience supports this notion. Not only adolescent turmoil, but the experience of the Communist Civil War that extended four more years beyond 1945 had created for me an unhappy and stressful period.

When one views the panorama of Connie's life after birth in Greece, one understands the desire to repress what he experienced in adolescence; the turmoil and torment of a nation torn by Axis and Communist barbarity; near starvation, dodging malaria and tuberculosis and negotiating the obstacles to obtain a university education.

But that hardscrabble crucible shaped a persona that created the traits, which would ensure success in his adopted country and chosen profession. This was, and always will be, the core of the immigrant experience, the sustaining lifeblood of a nation built by people who escape poverty and persecution for safe harbor and the opportunity to obtain work or an education.

Early Life in America

Connie already had ideas of medical school but with the mistaken expectation he could enter direct from high school. Fortunately, he was already enrolled in Texas Christian University (TCU) with a double major in Biology and Chemistry. Within a year, he determined medicine was his best choice and severed obligations to his uncle, became independent, but financially vulnerable. So he worked as a janitor to earn his tuition and then became a laboratory assistant and Instructor in marine biology at TCU. While doing so he obtained a fellowship to the Virginia Marine Institute,

where he studied oyster mortality supported by, and in defense of, the oil company accused of drilling that was alleged to destroy the crustaceans' habitat. A taste for his research subjects developed and we watched him consume Oysters Rockefeller with gusto at the Wisconsin Club.

In his junior year at TCU, Connie decided on medical school but when he graduated, in 1954 without citizenship, he was unable to enroll in a State Medical School. Although lacking funds from Greece, he was accepted by Baylor College of Medicine and, once again, needed work to support tuition. He did this exhibiting a vigorous work ethic as told in *In Pursuit of an Academic Career.*

Besides my work at the VA, I had another job at Hermann Hospital Xeroxing old hospital records. Also, I worked off and on in the Jones Medical Library classifying old books. At other times, I assisted the nursing staff at the Methodist Hospital making beds and other menial jobs. At Jefferson Davis Hospital, I prepped several hundred prospective mothers before delivery. While a junior at the medical school, during lunch at the VA, I was asked by a group of senior medical students to join them and do physical examinations on new admissions to the psychiatric wards. When I told them I didn't have enough experience, they assured me they intended to teach me. Thus I was doing physicals at the VA for room and board until graduation from medical school.

When I did physical exams on the psychiatric ward, I had to go through many locked doors. In addition, two black attendants walked in front and two behind; it looked like a small safari! A few years later, I was interviewing a patient on the same ward. Guided by some delusion or hallucination, he stood up, grabbed his chair and broke it into pieces, striking my desk. A nurse heard the commotion, locked me in the office with the patient and went for help. Minutes later, after she had collected six staff people, they unlocked the office door. By that time, the patient and I were standing there like nothing had happened. Obviously the arrival of psychotropic drugs made it routine for a doctor and patient to be left alone as with any other patient.

Connie does not bother to mention his capacity to remain calm in the face of danger, a trait acquired long before, with an obvious tranquilizing effect on an agitated patient.

Connie also obtained a number of paid stipends from the medical school, including assisting in a study of oxygen metabolism in polio patients on respirators. At the VA, he worked as a Lab Tech and phlebotomist before moving on to do statistical analysis for two psychiatrists on an early

study of chlorpromazine in patients with mental illness. He notes, *that was probably the only study worldwide that found chlorpromazine to be ineffective in schizophrenia. Another lesson; if you don't believe something you may affect the outcome of a study.* In another study during his junior and senior year, he assisted the chairman of anesthesiology in studies on the control of postoperative surgical pain. These research projects may have influenced his choice of specialty but Connie's main preoccupation was to mirror the faculty role models who inspired him with the idea that a complete physician should be a clinician, teacher and researcher. Among them were cardiac surgeon Michael DeBakey, for whom he scrubbed and Hebel Hoff, Professor of Physiology, who invented the physiograph to replace smoked drums – something we still used and I frequently smudged doing research in rats on tyramine and MAOI at the Maudsley Hospital in 1963. Also an influence was pioneer psychiatrist John Kinross-Wright, who was Director of one of the first six ECDEU Units funded by NIMH for psychopharmacology research.

By the time Connie began his rotating internship at Houston City Hospital, he fit in easily with his fellow interns outstripping them with skills he acquired as a lab tech and phlebotomist, inserting catheters with ease in the emergency room. For a short while, he contemplated surgery or internal medicine but was deterred by lifestyles he deemed too frantic. Considering psychiatry, he compared Europe with America and decided the latter was the new frontier in brain science. Despite fulfilling his mother's expectation he become a physician she disapproved of his choice of both specialty and country. It did not deter him.

Clearly viewed as a top candidate, Connie began residency (1959-1962) at Baylor, then affiliated with the Texas Psychiatric Institute (for research and training) the VA and Jewish Institute (for clinical and research experience) and the Jefferson Davis Hospital.

My class had six residents and my first rotation was the VA Hospital. Two were women, two were doctors who had been in medical practice and were invited to come to psychiatry with stipends from NIMH three times the amount the rest of us received (See Martin Kassel, below), *and a foreign colleague from Bulgaria who was assigned to the Jefferson Davis Hospital, where 33333333333333333333333333he received free room and board while I had to pay for mine at the VA. I visited the vice-chairman of the department, described this disparity and the following week I was transferred to the Jefferson Davis Hospital, where I began work as a resident, also with free room and board.*

At that hospital, I had rotations on the inpatient service, outpatient clinic, emergency room and consultation-liaison service. Starting at the inpatient service, I walked into the treatment room, where the chief resident was rendering trans-orbital lobotomies with what appeared to be an ice pick. I walked out and never saw the procedure performed again. On the inpatient service of 40 beds as many as 20 patients were receiving electroshock every morning.

The faculty director of the outpatient clinic left his position shortly after I arrived. Later I learned he could not accept research activities for patients with mental illness. His humanitarian concerns had to be respected but if there was a branch of medicine that needed research it was psychiatry. What stands out in my memory from the first year of residency is how little the faculty had to teach and how wise was the saying "the best teacher is the patient."

Unlike his contemporaries who concentrated their efforts on psychoanalysis, Connie chose to do a research elective under John Kinross-Wright who, while supportive, was aloof. Clearly, Connie had a mind of his own and was assertive in meeting his needs – an attitude that reminds one of those early immigrants whose flag and motto was "*don't tread on me";* an effective ideology for a fellow immigrant of short stature with a pronounced accent.

Fluphenazine Enanthate

By his third year of residency, Connie had established a reputation for hard work and accomplishment; he received the unusual compliment of being appointed Faculty Instructor, devoted to full time research. So, in 1961, he began pioneer work on fluphenazine (Prolixin) enanthate, first working in dogs and monkeys and then progressing to Phase 1 and early Phase II studies in prisoner volunteers at the Baylor facilities (Kinross-Wright & Charalampous, 1965). The manufacturer, Squibb, was tepid about the potential for this first long acting antipsychotic given by injection every two weeks. Deinstitutionalization had not begun in earnest and compliance did not emerge as a named problem until the mid-1970's. (See Ch.11). But Connie knew enough of the benefits from oral medication to foresee a need for a maintenance drug in patients discharged from closely supervised inpatient care to a community setting, a lengthy distance away with questionable continuity of care and the risk of non-compliance.

Connie began his postgraduate career in 1963 as an Assistant Professor at Baylor. His tasks were threefold. First, he became the Assistant Chief of Psychopharmacology under Kinross-

Wright and during the next three years, until 1966, they worked on over 100 experimental compounds in early Phase II studies. This was facilitated by his directing efforts to create a 380 bed psychiatric facility at the Wynne Unit of the Texas Department of Corrections. The body of drug research during this time produced 19 publications, on 15 of which he was first author.

Much of the drug research Connie accomplished was in prison volunteers in a correctional setting. He relates a colorful account of this in *My Life in Prison.*

In the 1950's, the Texas Department of Corrections (TDC) was a national disgrace. The barbarity of poorly paid guards was reflected in the brutal incarceration of 11,500 inmates. In the daytime they did agricultural work of a primitive kind, including picking cotton for hours under the hot Texas sun, sometimes lacerating their Achilles tendon to avoid working in the fields.

TDC acquired a new director, the remarkable pioneer O.B. Ellis, who transformed work to indoor acquisition of future work and educational skills. With a significant number of inmates with mental illness he contracted with Baylor Department of Psychiatry to develop a special program to meet their needs. As a second year resident, I was to spend one day a week developing the psychiatric unit, where we also hoped to begin drug research. Inside the prison for the first time, I felt self-conscious but the Superintendent and major in charge of security greeted me warmly, almost with a sense of relief.

The Wynne unit contained 400 individual cells on three floors guarded by uniformed officers and mental health trustees – prisoners who wore white uniforms, different from the striped ones of other inmates. Prison lore had it that unlike the general population many were sociopaths and the best were those who had committed murder. Polite and cordial, they introduced themselves and showed me the examination room, EEG and EKG labs then another room with locked cabinets for the pharmacy drugs. Preoccupied and under stress, absorbing all the security and other protocols, I drifted backwards towards the iron bars of the cells, when several of the trustees screamed at me to move away. I was standing in front of a cell containing "the beast", a large inmate, incarcerated for life and probably demented who, two weeks before, had killed two fellow inmates standing in front of his cell when he passed his huge arms through the bars, grabbed each inmate by the neck and crushed their skulls, killing both.

In a house nearby the closed unit, I met the full time psychiatrist in residence, an ex-general practitioner, who received a large NIMH stipend to obtain residency training in psychiatry. We had a pleasant visit, enjoying a beer until, at midnight, he explained he did rounds on the inmates at 2 am; during the day the temperature rose making the place unbearable. Obviously, I did not accompany him and going to the prison only once a week I did not meet him again until the trustees told me a few weeks later that he had stopped making rounds. I learned this talented man, also a great musician and vocalist, was a manic-depressive who injected himself with large doses of Thorazine to achieve a euthymic state in the days before lithium. A year later, this unfortunate colleague committed suicide.

One afternoon, as I was about to leave the Wynne Unit, the trustees ran to the freezers, got out 18 gallons of frozen urine, part of a research project, and loaded them into the trunk of my car. Driving back to Baylor it began to rain. I was thinking how beautiful it might be to sit on the porch of a farm house, looking across the meadow at the tall pine trees of the Sam Houston National Forrest, when suddenly the car drifted across a new concrete surface onto an asphalt pavement and lost traction; it slammed into a wood post on the highway divider, the trunk burst open and the jugs of urine spilled onto the highway. I opened my umbrella, walked up and down to collect them, fearful of an oncoming car. Fortunately none came, the car was drivable and I returned safely to Houston.

As my prison experience was coming to an end, the trustees asked me to facilitate the release of one of them, our EEG technician. I had a good impression of him, so I arranged with a rancher friend to employ him. A parole office visited me to approve. He was polite and deferential but his half Cherokee eyes looked at me with irony. The trustee got early release, left for Oklahoma, moved into his new apartment and went to work, but for one day only. He pled illness and left. Two weeks later the rest of the story appeared in the Daily Oklahoman. Our rehabilitated trustee, carrying a pistol without a trigger robbed seven Safeway stores before being arrested. The parole officer paid me a second visit, looking at me with unmistakable sympathy. I asked him how he had known. Cryptically he told me that anyone who left the red soil of eastern Oklahoma and saw the city lights was not about to return to a ranch. So much for this psychiatrist and his ability to predict future outcome.

If the gift of prescience, acquired in his unpredictable youth, had deserted Connie, he must have been comforted by knowing that his psychiatric brethren agreed they were unable to predict suicide or violence with any validity.

Secondly, Connie advocated successfully for the development of a psychopharmacology outpatient clinic in Houston, of which he became Director, linking Houston with the State Hospital in Austin, 164 miles away. He saw the benefit of the Kennedy sponsored Mental Health Act that funded Community Mental Health Clinics. Unlike many others who turned them into psychosocial agencies for the worried well, staffed by social workers, Connie cared for the de-institutionalized patients with serious mental illness, focusing on continuity of care, leaving their current medications intact and avoiding polypharmacy, while using fluphenazine enanthate as a tool when necessary.

Also aware of the needs of a neurotic population, he set up a second clinic to deal with anxious and depressed patients, staffed not by social workers but by nurses.

This creative and innovative planning was modeled on programs in the U.K. Connie had heard about for the rehabilitation of military personnel discharged with post-traumatic and other psychiatric disorders at the end of World War II.

The "Pink Spot"

Thirdly, Connie completed nuclear medicine training in the Endocrine Department and was among the first to undertake isotope studies on the metabolism of the parent compounds and metabolites of anti-psychotic and anti-depressant drugs. But, most importantly, Connie also became involved in studying the metabolism of mescaline, a compound with hallucinogenic effects. This would center on the presence, potential activity and alleged significance of the metabolite DMPEA, the so-called "pink spot" in the urine of some schizophrenic patients but not in normal subjects. This involved Connie in one of the major early controversies in psychopharmacology during the 1950's and 1960's.

The saga of the "pink spot" began in 1952 at the threshold of psychopharmacology with the discovery of chlorpromazine, when two British residents (registrars) speculated that a metabolite of mescaline might play a role in the etiology of schizophrenia (Osmond & Smythies, 1952). This

part of the story is told through the eyes of John Smythies (Ch.10). Humphrey Osmond would play the major role going forward, when lack of support in England led him to join Abraham Hoffer in Canada (Hoffer, 1998) for ongoing studies of what they termed the "adrenochrome hypothesis of schizophrenia", which also morphed into controversy over "megavitamin" therapy that involved Nobel Laureate Linus Pauling and "psychedelic therapy" advocated by Osmond. From 1954 to 1960, Hoffer and Osmond received a substantial six year grant from the Rockefeller Foundation to pursue these lines of research, which ended abruptly in 1960, when increasing street use of hallucinogenic drugs cast a shadow over psychedelic and megavitamin therapy. Nevertheless, research on the etiologic theory of schizophrenia continued, fueled by an article in *Nature* identifying DMPEA in the urine of schizophrenics (Friedhoff & Van Winkle, 1962). This is the point at which Connie became involved in several years of research funded by the US Public Health Service, studying C14-labeled DMPEA in prison volunteers (Charalampous, 1966). The results showed oral doses of DMPEA, twice those of mescaline that produced hallucinations, were completely inert even when the subjects were pre-treated with the MAOI pargyline in an attempt to enhance activity. These results were presented at the Fourth World Congress of Psychiatry at Madrid, in May1966, published in the Proceedings (Charalampous, 1966) and further elaborated on later (Charalampous, Walker, Kinross-Wright, 1966;Charalampous, Tansey, 1967; Charalampous, 1971).

It is incontrovertible that by the end of 1966 Connie's research clearly established that DMPEA was an inert, non-toxic substance with no conceivable etiologic role in schizophrenia. The research had been published in a leading scientific journal, presented at a World Congress and published in the Proceedings.

Three events would occur in the following year, 1967, which might seem to reflect world scientific opinion but which made no mention of Connie's research findings. The first key event was a symposium hosted by the Department of Psychological Medicine and its Chair, John Smythies, in Edinburgh, Scotland. The symposium was chaired by Seymour Kety and the proceedings were published later that year as a book, *Amines and Schizophrenia*, 1967, co-edited by Harold Himwich, Seymour Kety and John Smythies.

Secondly, a key paper presented at the symposium from the Nuffield Unit of Genetics at the University of Liverpool provided new evidence seemingly supporting the "pink spot" (Bourdillon

& Ridges, 1967). It included a study in 296 subjects where the investigators were blind to diagnosis and drug therapy. In 238 subjects assessment was possible; 20 out of 30 non-paranoid schizophrenic patients had the "pink spot" compared to only 7 out of 102 with paranoid schizophrenia and only 1 out of 68 non-schizophrenic patients. The authors concluded the "pink spot" was "a product of a metabolic abnormality connected with the disease process", not due to dietary causes or the duration of hospitalization.

The third occurrence was an anonymous editorial in the British Medical Journal (*Lessons of the Pink Spot),* published in February 1967 (Anonymous, 1967). In withering prose, it exposed the multiple clinical and biochemical flaws in contemporary data on the topic, discredited the results and concluded, "Perhaps it is time to stop investigating schizophrenics *en masse*" and concentrate on individual patients."

It remains to be said that neither the leading scientists who convened the Symposium, those who presented data at it or the author of the editorial cited mentioned Charalamapous' elegant and irrefutable demonstration that DMPEA was an inert substance and its presence in urine of schizophrenics, even if true, was meaningless. One may then ask how this could be possible. Did the protagonists fail to read the literature or attend the World Conference in the months preceding the Symposium? Was it too late to cancel the Symposium and save face? Or was it simpler to look the other way, dismiss the work of a relatively unknown junior scientist and, by doing so, preserve their reputations and research funding? We may never know but such behavior by senior scientists is not unknown (See Blackwell, 2014, b).

The "pink spot" saga had a 15-year life span. The Greeks have a word that often attaches itself to the birth of an idea but never to its demise, *Kudos,* (OED, praise or honor). Connie learned this lesson the hard way and perhaps it played a role in shaping his career, when his interests moved from bench research to clinical issues, where he demonstrated the same prescience, fortitude and flexibility in facing whatever the Zeitgeist had to offer.

As if professional life was not enough, Connie, with considerable prescience, set up the Dexion Foundation, a private means of sequestering funds for educational, cultural and philanthropic purposes. In addition, in 1965, he obtained a pilot's license, symptomatic of his intrepid temperament. The idea incubated and was implemented much earlier in 1959, at age 28, the year

he began residency, stimulated by an article in *Newsweek* about the Greek oligarchs (Onassis, Niarchos and Livanos). Niarchos had taken up flying and the story told of his emergency landing in the East River.

I was invited to my first lesson in September 1959, soloed after 18 hours and when I landed, the instructor was holding a bouquet of wild flowers collected from around the field, adding if I had not come down safely, he would have sent them to the funeral home. In July 1964, I had my first cross country trip, to Alice in Jim Wells County, Texas. A few miles out, I called the tower and was given instructions to land, but where? On Orange Grove Naval Air Landing Field, while Navy jets were flying in and out. A Navy pickup appeared with a large sign on the back FOLLOW ME. A junior officer smiled and said I was not the only one. After I signed close to 28 forms, the control tower told me to take off; a few minutes later I faced the real Alice airport and landed.

Over 40 years, Connie flew trips for business, pleasure and family affairs, twice with near fatal consequences. Once when he ran into a rainstorm and was forced to land on a farm road, where a low hanging cable smashed into the windshield and on another occasion when his pilot's seat pulled back suddenly and he could not reach the pedals for rudder control. Using the ailerons and horizontal control, he managed to land safely, left of the runway in tall wet grass from which a tractor pulled him out. In 1999, at age 68, he took his last flight.

I realized my knees could not support my legs for a jump in an emergency. Flying an airplane is not like riding a bicycle. On three different occasions, I lost my skill and had to learn flying 'de novo'. To maintain one's skills, a pilot should fly for a minimum of 12 hours a month, a large time commitment. A person should still be young or have retired at a young age. This was possible in Greece but we know what that has led to. Productivity and the pursuit of pleasure do not seem readily available to an American physician.

Confronting the Zeitgeist

In 1965, change occurred at Baylor. Shervert Frazer became Chair of the Department and Mental Health Commissioner of the State with a mission to make it a center of psychoanalytic excellence. Connie saw the writing on the wall for psychopharmacology and decided to accept the

position of Associate Professor and member of the Clinical Pharmacology Division in the Department of Medicine at the University of Oklahoma as well as Consultant in pharmacology to the V.A. Hospital. Connie was particularly attracted to the chance to work with Jolyon West, a creative, charismatic and flamboyant role model. However, Joly was an "editorial", not a hands-on researcher, who made a name for himself by killing an elephant in the Zoo with an overdose of LSD, while trying to induce a toxic psychosis. Soon after Connie arrived, Joly left for UCLA where he had friends among the Hollywood stars.

Located in a Department of Medicine with little commitment to psychopharmacology, Connie quickly realized he had made an "out of the frying pan into the fire" move. Looking for a new direction in research, he decided to pursue a timely interest in the use of hashish and marijuana.

Studies in Marijuana

Taking a self-imposed sabbatical, Connie travelled to London where, at the Library of the British Museum, he studied the six-volume report of the Royal Indian Hemp Commission, before flying to Geneva to consult with Dr. Norman Cameron, Director of the Drug abuse section of the World Health Organization. Following his direction, Connie travelled home to Greece to review Dr. M.G. Sringaris' treatise on hashish before discussing the author's findings and extensive experience. Next, he visited a psychiatric hospital in Istanbul, Turkey, where Turan Itil served as a translator, while he interviewed 13 chronic users of hashish. Finally, he travelled to Morocco to consult with other colleagues about their experience with users in that country.

On returning to the United States and after continuing to review all the available literature on the topic, he put the large body of information he had gathered to use in a series of lectures to the students and faculty at several universities, culminating in an invitation to develop a symposium on the topic to the annual meeting of the American Psychiatric Association in Boston, in the summer of 1968. Once again, he had run head on into the Zeitgeist, just at a time when THC had become viewed as the "gateway to heroin' and research on potentially addictive or hallucinogenic drugs was no longer funded or approved of.(See CH.10, Smythies) The symposium was disrupted by student activists from Boston and Harvard so had to be abandoned. Similar midlife turmoil affected the careers of Jean Delay and Heinz Lehmann, (See Chs 6&7). His experiences of the

drug culture during this rapidly changing era are described in a paper in the American Journal of Public Health (Charalampous, 1971, a).

Evolving Interests in Dallas

Looking for a calmer and more conducive environment, Connie joined the faculty at Southwestern Texas Medical School in Dallas, in 1968, as an Associate Professor, where he developed three areas of research and clinical interest, two of which were adaptations to a changing environment. His primary purpose was to help set up a Psychiatric Research Institute and he became the Chief of a Psychopharmacology laboratory as well as setting up an outpatient clinic for the treatment of anxiety and depressive disorders. This produced several papers on chlordiazepoxide (Charalampous, 1972 a), amoxapine (Charalampous, 1972 b) and chlorazepate (Charalampous, Tooley, Yates, 1973). During this period, he was also Clinical Director of an innovative 70 bed adolescent unit at Woodlawn Hospital, an affiliate of Parkland Hospital, which included a club for the patients in the basement. This may also have triggered an evolving interest in alcohol treatment that would later expand (Dun, Smith, Lemere & Charalampous, 1971). Finally, he consulted to the Maximum Security Unit for the criminally insane at Rusk State Hospital in East Texas, introducing upgraded medical care and rehabilitation treatments

(Clark, Huber & Charalampous, 1971).

Social and Community Psychiatry

Probably the most prescient of Connie's evolving interests in Dallas was in the rapidly developing field of community psychiatry, fed by the impact of de-institutionalization and the Kennedy administration's initiative providing funding for community mental health centers. (House Bill 88-164). Between 1968 and 1971, Connie attended three two-week seminars twice yearly taught by Gerald Caplan of Harvard Medical School and completed a fellowship in Community Psychiatry. This laid the groundwork for a life-long commitment to continuous, coordinated and collaborative outpatient care, including family involvement. The principals taught by Caplan built on seminars Connie had attended years earlier in Athens at the Institute of Ekestics, where the City architect and planner, Constantine Doxiades, taught a systems approach and

sensitized him to social issues, an input that would broaden his skills in psychopharmacology. He was also influenced by the models of care, developed in 1944 by Querido in Amsterdam and later by Sidney Merlis in America.

Back to Baylor

Connie's accomplishments in Dallas led to an invitation to return, in 1972, to Baylor in Houston, where his heart still was, and two years later, he was promoted to Full Professor in the Department of Psychiatry. Once again, he occupied several roles including initiating studies on cyclic nucleotides supported by NIMH. Also important was administering a large grant from the U.S. Department of Transportation to study vehicular deaths and ways to separate driving from drinking. This involved running an inpatient program for alcohol rehabilitation at Methodist Hospital, including multimodal and multidisciplinary treatments involving Alcoholics Anonymous and Family Education. These activities produced a significant body of research on addictions and their treatment both at the basic science and clinical level (Charalampous & Askew, 1974; Zung & Charalampous, 1975; Charalampous, 1977; Charalampous, 1976; Charalampous, 1997; Askew & Charalampous, 1977, a; Askew & Charalampous, 1977, b; Askew & Charalampous, 1977, c; Charalampous & Skinner, 1977; Charalampous & Askew, 1977, a; Charalampous & Askew, 1977, b; Skinner& Charalampous, 1978). Connie also produced 7 book chapters on aspects of alcohol treatment between 1976 and 1979 (Publications on record at INHN.org).

As was his custom, Connie ran an anxiety and depression outpatient clinic and was also Chief of Psychopharmacology Research at the V.A., clinical tasks that produced several publications on the treatment of anxiety and psychoses, (Charalampous & Keepers, 1978 b). He also contributed a book chapter on the pharmacotherapy of schizophrenia (Charalampous, 1978) and several educational cassettes and motion pictures on psychopharmacology topics funded by Sandoz Pharmaceutical Company.

Based on his now extensive knowledge of the field, Connie developed a curriculum for the training and certification of chemical dependency counselors that was adopted widely throughout the United States.

An Academic Exodus

In 1978, Connie made the final move of his fulltime academic career. He accepted the position as Chairman of Psychiatry at Texas Tech University School of Medicine in Lubbock. He describes this two-year experience as a "watershed moment", a period in which he was overwhelmed with administrative, clinical and teaching responsibilities with no time or money for research in programs distributed over five locations. Amarillo (child psychiatry), Des Plains (a mental health center), Big Springs (a VA and State hospital), El Paso (a County Hospital inpatient program) and Odessa (a Family Practice outpatient program).

During this period, Connie was also active on the Statutory Medical Advisory Committee, appointed by the Texas Mental Health and Retardation Commissioner; he served for 8 years (1974-1982) and was elected Chair by his fellow members. He was also asked to recruit a panel of nationally recognized experts to evaluate and report on the future of the Texas Research Institute of Mental Science (TRIMS). Included in the panel members were authorities like Don Klein and Robert Rose.

This experience must have alerted him to a developing climate that, beginning in the early 1980's, marked the threshold of a long winter of discontent for psychiatry, in general, and psychopharmacology, in particular. This inclement Zeitgeist included many co-occurring ingredients outlined in Chapter 19 and stimulated Connie's creative mind to develop the innovative approach discussed below.

An added incentive and strong personal concern Connie felt, at age 49, was time pressing with no adequate program for faculty retirement, including his own. After two years, he made a decision to quit academia and enter full time private practice in 1980.

A Model of Private Practice in the Community

Needless to say, Connie approached this aspect of his career with careful planning and considerable energy, developing a model of care in the community surrounding Houston based on principles he had already assimilated. It was designed to meet the radical changes he foresaw occurring in health care in the United States, offering cost-effective multimodal and multidisciplinary programs and services.

He opened five offices in Harris County, partly funded from the Dexion Program of Care – an extension of the family Foundation he incorporated as a 501 © 3 in 1963. These offices were staffed by social work counselors he trained and supervised in the principles of continuity and collaborative care. He obtained staff affiliations with 23 hospitals and inpatient programs and at one time or another, served as Director of inpatient programs at three of them.

Connie also obtained a faculty appointment as Adjunct Professor at the School of Public Health at the University of Texas Health Center in Houston (1980-1984) and later (1988 on), was appointed Clinical Professor of Psychiatry and Behavioral Sciences at the University of Texas Medical School in Houston. Working with the Texas Psychiatric Society, his Foundation donated funds to support the training of psychiatrists as administrators for this kind of program but these were subverted and the plan never came to fruition as lay administrators with business backgrounds focused on bottom lines took control.

All this helped secure Connie's future as an independent practitioner in a field of rapidly shifting sands, including managed health care, profit-driven health care corporations and deteriorating publically funded community mental health systems. It also attracted public approval. In 1984, he was selected to participate in *Leadership Houston,* a yearlong study of community organizations under the auspices of the Chamber of Commerce, to prepare citizens to serve on boards and executive committees of organizations that promoted quality of life. In 1996, Connie received the *Psychiatric Excellence Award* from the Texas Society of Psychiatric Physicians. Throughout this later time in his career, Connie continued to teach psychiatric and family medicine residents, substance abuse counselors and public health students. He also organized community wide scientific symposia on geropsychiatry and psychopharmacology.

During his long career, Connie was active in 35 professional Associations and Societies becoming a Fellow in the American Psychiatric Association (1961), the Academy of Psychosomatic Medicine (1966), the World Association for Social Psychiatry (1970), the American Association for Social Psychiatry (1983) and a Founding member of the Royal College of Psychiatrists in Britain (1965). He belongs to both the American (1983) and Texas (1986) Associations of Psychiatric Administrators. He has been a member of the ACNP since 1965 with Emeritus status.

Connie finally took down his shingle from full time practice in 1995 and for a four year period continued to do locums in South Texas until he grew disappointed with the authoritarian methods and lack of family involvement practiced by the physicians he was covering for.

Asked to look back over his life, he feels proudest of the way in which he could "see the way psychiatry was going", that he contributed "research that was credible" and always "protected his patients." The core of his contributions has been in psychopharmacology integrated with psychotherapy and sociotherapy. An essay on *Basic Research and Clinical Studies in Psychopharmacology* summarizes his thoughts as follows:

Recently with the supervision of psychiatry residents and locum tenens practice in both outpatient and inpatient settings, I came to appreciate the current treatment of psychopharmacology as well as psychotherapy and sociotherapy.

The use of psychotropics is chaotic. With the persistent input of pharmaceutical companies, treatment does not address diagnostic entities but clinical symptoms. As a result, an individual patient may receive four to six psychotropics, including atypical antipsychotics, anxiolytics, anti-manic and antidepressant medications. This may be in addition to medications prescribed for hypertension, type II diabetes and other co-morbid conditions.

I have observed the changes in patient care from locked wards to the emptying of the mental hospitals. This has all happened without the parallel activation of adequate mental health community programs envisaged during the Kennedy administration

In the age of managed care with continuously diminished resources, the ageing of the population and the ubiquitous use of drugs of dependence, one questions if the discovery of more and more psychotropic compounds may require greater discrimination in the application of clinical psychopharmacology. However, for me, psychopharmacology remains the most exciting part of my career.

Connie's biggest disappointment was a lack of strong mentoring in his early years and that he left Baylor prematurely, discouraged by a Chairman who was dismissive and discriminatory. His marriage following residency ended in divorce after 13 years to a wife who was not sympathetic or helpful to his career. Altogether, this is the portrait of a humble man of energy and diverse

interests with a prescient capacity to anticipate and confront whatever the Zeitgeist offered with fortitude and flexibility.

Perhaps the core of Connie's interests lies in an essay written in 2012, *Psychological Peregrinations.* In it he traces the historical and philosophical origins of his ideal based on the life and teachings of Socrates taught in the *phrondisteron,* the 'thinkery'.

Socrates, (470-399 B.C.) was a son of a sculptor and midwife. He was a philosopher who taught for free, did not develop a system, and wrote nothing. He had studied the natural philosophers but abandoned them for their lack of interest in human conduct. He studied the sophists but attacked them for their indifference to virtue. He believed that virtue comes from understanding, and that no man knowingly does wrong. Socrates, a patriot, fought and was wounded in battle. He believed that a citizen bound by conscience must obey the laws of the state. The Delphic oracle named him the wisest man of his time, and all his life he pursued the dictum, "know thyself". Socrates was reported to have said, "The unexamined life is not worth living."

Connie uses the Socratic template to compare it with the various forms and ingredients of psychotherapy and its place in the Hippocratic ideal for physicians, contrasting it with the shortcomings of contemporary psychiatric practice and managed care. He concludes:

Hopefully, with the study of both the ancients and contemporaries, we may acquire wisdom conducive to mental health, defined as creativity, productivity and the capacity for pleasure.

This is remarkably similar to the conclusion reached by Frank Berger, discoverer of the first minor tranquilizer in his postmortem book, *"A Man of Understanding",* on the relative roles of drugs and philosophy in mental health (See Ch.10).

Pastimes and Pleasures

Connie's two greatest pastimes and pleasures have origins in his Greek heritage, books and art. He was a "history buff" in high school and gave lectures to his classmates on such topics. Today, he likes to browse used bookstores seeking ancient tomes about Greek plays, philosophy

and historical figures. But his major avocation is collecting art, which he began in the early 1960's, inspired by his sister Doula's interest in the Byzantine era and the manner in which an innate sense of beauty in art made its contribution to the quality of life. His personal collection of over 700 artworks is garnered from world travels in such places as Haiti, Cuba, Vietnam, Mexico, Greece and China. Connie is currently seeking a congenial and caring environment to which he can donate and display a collection worth in excess of a million dollars.

Our time together in Milwaukee was divided between dissecting Connie's career and catering to his artistic interests by visiting three outstanding and unique museums. First and foremost was the internationally renowned Calatrava Museum, its cantilevered wings open towards Lake Michigan. On display this month was a travelling exhibit *"From Van Gogh to Pollock"* that traced the evolution of schools of art from the late 19th century to the present. Billed as "acts of creative rebellion" this might also be seen as the retrospective of an evolving artistic Zeitgeist.

Next was the Grohmann Museum at the Milwaukee School of Engineering (MSOE). Like Connie's, this is one man's collection of art dedicated to the "evolution of work in all its various forms", including trades, occupations and professions. Dr. Eckhart Grohmann is an engineer and successful entrepreneur; his collection of over 1000 pieces of art and sculpture dates from 1580 to the present, priceless and unique worldwide. Included is a section that portrays the beginnings of medicine at work as apothecaries, alchemists and barber-surgeons. A 16th century masterpiece in oils shows a surgeon operating on himself, a knife in one hand, a coil of intestine in the other, beneath a face distorted in agony. An additional recent display is of twenty 19th century paintings by a Milwaukee German artist, Carl Spitzweg. His most famous painting, *"The Bookworm"*, is hung in proximity to a modern portrait by Norman Rockwell with the same title.

Our final visit was to the Harley-Davidson Museum, which houses motorcycles from the inception of the company in 1903, displaying all the various designs through both World Wars to the present. A new adjacent display is devoted to the talents of Willie Davidson whose grandfather was one of the founders. Willie served as Chief Styling Officer and Head of Brand Development until his retirement in 2012 and is widely regarded as a popular "Brand Ambassador". As a young man, Willie attended art school and is a very talented watercolor painter; several of his works were on display, but not for sale. The synchrony between his vocation and avocation makes him comment, "I never worked a day in my life."

When our three days of talk and viewing were over, we drove Connie to Mitchell Field Airport, telling him on the way that it has the unusual attribute of housing a used bookstore, *Renaissance,* on the departure level, somewhere for a bookworm to browse while waiting for his flight home.

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Martin Kassell: One of a kind of psychiatrist

Martin Kassell was born on January 18th 1918 in Philadelphia, the first child of Russian Jewish immigrants. His father came from Odessa at age eight and his mother from Kiev at age 13. It was a hardscrabble time as the Great Depression began to evolve following the end of the Great War. Father was a journeyman printer and his mother, lacking much education, worked in a clothing factory.

Six years later his only sibling, a sister Sylvia, was born into an economically deprived household. Martin recalls the day "the family hit rock bottom"; after an unpaid utility bill their gas and electricity was suddenly cut off. The larder was bare so Martin roamed the local streets and purloined a few potatoes from a nearby store while his parents lit a coal fire over which they cooked a meager meal of potatoes and canned meat.

Economically deprived, Martin was genetically well endowed. His father lived to be 86 and his mother died at age 96, but only because she refused to wear a seat belt and was killed in a car crash. Martin's sister Sylvia is 94 and Martin celebrated his 100th natal day this January.

At age five Martin began his education at the South Philadelphia Public Schools. He did well academically always in the top decile of achievement through grade school, middle and high school, graduating at age 16. He did well in all subjects but especially enjoyed English classes where he learned to write concise, well worded essays. Latin was difficult and still a required subject for medical school; the teacher was remote and disparaging, so surprised at Martin's skill

translating a difficult text he refused to accept that the work was unaided and dealt him a failing D grade.

Poverty dictated Martin's work for a year as a stock boy in a clothing factory to earn tuition for college before entering Villanova University in 1935 – before the outbreak of the Second World War in Europe. Both his parents were supportive but also had high expectations. At the end of his first semester at Villanova he received a report card he shared with his parents over dinner. He had finished proudly as second in class, to which his mother responded, "Why not first?" It felt like a bucket of ice water and for the rest of that year deterred him from reading his assignments. None the less at the next report he remained second in class!

At that time the student body was barely a thousand strong and the only women were eight nuns. Martin's choice of Villanova was influenced by learning from an acquaintance that it had good access to local medical schools. This was a career choice he developed at around the age of eight when his paternal grandmother joined their household. She suffered from diabetes and was treated by a family doctor who visited the home to give her insulin injections daily. His bedside manner made Martin think "I want to be a doctor like that."

Philadelphia was blessed with four medical schools for which the graduates of all the city's colleges competed. Martin's grades from his professors at Villanova were all A's and his expectation of a top placement was high. Anxiously awaiting his final oral viva in Bacteriology, for which he was well prepared, the exam went badly; asked to provide definitions he knew were correct the professor disagreed and marked him down. Worse still, aggravated by Martin's refusal to defer to him, this professor falsified Martin's entire record and, as a result, Martin was denied entry to all four medical schools.

Fortunately, Martin's grandmother was a patient of the Chief of Staff at Hahnemann University Hospital who secured him a place; not Martin's first choice but close to home and named after a German homeopathic physician. Students graduated with doctoral degrees in both allopathic and homeopathic medicine, an unusual distinction.

Although clinical work was mainly doing "histories and physicals" he was impressed with two aspects of the curriculum. His mentor in the science and art of medicine was Garth Boericke, an internist who espoused the William Osler model of bedside teaching (McCarthy and Fins 2017).

Martin recalls he taught how to determine a patient's fitness for surgery by taking the pulse while telling the patient to hold their breath. Anyone who could do so for 25 seconds was safe for anesthesia and the knife. He also noted how Boericke came from behind his desk to sit

with patients, engaging them in a discourse that revealed the person beneath their problem.

The second feature of Hahnemann's curriculum that influenced his own future practice was the unique combination of allopathic and homeopathic procedures. This also influenced him to see patients in their entirety, beyond their symptoms alone.

While a student Martin helped finance his education by working in a cafeteria as a chef, earning a free lunch as well as a small wage. He was also an aide for the school's secretary for $30 a month – a job that gave him access to the files on admission. In 1939 admission was based on quotas influenced by religion, ethnicity and gender with a hierarchy from the top down; Christian non-Catholic, Catholic, Jewish, Black, but no women.

Martin also had a natural talent for surgery but was deterred by the scanty salary future surgeons earned while learning the trade. The psychiatry curriculum was limited to a couple of lectures without exposure to patients and failed to attract his interest.

After graduation in 1943 a year of rotating internship followed, during which time all of his classmates were drafted into the US Army. Martin was rejected when his EKG revealed a first-degree heart block. Feeling he needed to make reparation for his colleagues he delayed going into practice to take a two-year training program in internal medicine at the Lahey Clinic in Boston. The training was excellent; he learned to do and interpret both EKG's and X-rays of the upper and lower gastrointestinal tract. His mother's internist at the Hahnemann Hospital encouraged Martin to return to Philadelphia to join him working on the inpatient units. This was an unusual opportunity but after accepting the offer and leaving the Lahey Clinic it was rescinded by the Chief of Medicine, known for his anti-semitism.

Instead Martin decided to go into family medicine in which most general practitioners referred their complex cases and had office hours into the late evening; Martin equipped his practice with an X-ray machine and EKG as well as a lab technician and practiced general medicine using his

training at the Lahey Clinic to provide a high quality of care, hoping he could reduce the need to refer to specialists.

Martin's plans were almost disrupted when the Korean War broke out in the early 1950s and he was again drafted for military service. His physical exam was conducted in an armory that had two exits – one led to a bus waiting to shuttle recruits to boot camp, the other was passage back home. His EKG was read as "normal" by a military physician who clearly did not know how to interpret it. So, Martin offered his expertise and pointed out the heart block before dashing through the door marked home.

Martin's model for his own practice did not work out for two reasons. Patients themselves preferred referral to specialists. Increasing domestic demands at home eroded his time at work; he had married his wife Evelyn at age 22, two years younger than he was. Now they had two children, first a son, Neal, who was born with microphthalmia of the left eye that limited vision to shadows and carried the threat of developing cancer. This clouded the first five years of his life but Neal eventually has become one of the world's leading neurosurgeons. A second child, Stephanie, was born three years later; during her career as recruiter for physician office workers she remained single and is now her father's primary care taker.

In addition to child care Martin's time at work was cut short after his wife developed Multiple Sclerosis at age 32. Described as a very sweet, gentle, loving wife and mother she suffered from regular relapses that eventually invaded the central nervous system before her death of ovarian cancer at age 81.

Martin worked as a primary care physician for 22 years, which he found unrewarding both financially and intellectually. The hopes he had, based on mentoring in medical school and time at the Lahey clinic, went unfulfilled in a practice treating mild self-limiting conditions with little of interest to diagnose. In 1968 he began to consider residency in a discipline that might be more intellectually stimulating but also with limited night or weekend work that would allow more time devoted to his wife and children. Radiology, Dermatology and Ophthalmology came to mind but when the last became a possibility his wife had a relapse. His golf partner, Abe Friedman. was a Professor of Psychiatry at Jefferson Medical College (now the Sidney Kimmel Medical College in Philadelphia) and suggested Martin might try a new program set up by the NIMH to recruit primary

care physicians to train as psychiatrists. This was at a cross roads when biological psychiatry was seeking a foothold in the mainly psychoanalytic programs throughout America and psychopharmacology was in its heyday but still sparsely represented in academic teaching programs.

Martin was skeptical about all that "oral and anal crap" but the lifestyle sounded conducive for his family needs. He accepted the challenge and began to read Freud as a first-year resident; instantly falling in love with the insights of psychoanalysis and the opportunity to explore his patients in depth, a satisfying luxury missing in primary care.

Martin began his psychiatric training in 1968 and completed it in 1971. These were pivotal years in the evolution of the discipline in America only about two decades after the first anti-psychotic medication, chlorpromazine, was introduced into asylum care. On February 5, 1963, President John F. Kennedy addressed Congress to propose a new Federal program to fund Community Mental Health Centers (CMHC's): "Reliance on the cold comfort of custodial isolation will be supplanted by the open warmth of community concern and capability."

An early consequence of this well meant but flawed legislation was to speed up the discharge of persons with severe and persistent mental illness into communities poorly prepared to accommodate them, coupled with a marked reduction in inpatient beds.

American psychiatry was also ill equipped to cope with this new burden imposed on the profession. Almost all academic departments and training programs were chaired by psychoanalysts and some of the residents were in analysis with their mentors. Making matters worse, the national accreditation committee had absolved aspiring psychiatrists from the need to undertake a year of rotating internships; in addition, there were few psychopharmacologists to serve as mentors in biological psychiatry.

This zeitgeist created a unique opportunity for a mature skilled physician like Martin both during and after his training in psychiatry. One of his supervisors had spent two years with Freud in Vienna and played chess in Philadelphia with his neighbor, Einstein. Martin's psychological mindedness and understanding of patient dynamics prospered to the point where he considered a personal analysis and sought the advice of his Chairman. He was invited to consider the relative merit of spending $30,000 on analysis spread over several years compared to investing the same

amount in the stock market. Any ambivalence was dispelled by the news that consultation with his supervisors revealed they considered him a mature well-rounded individual with no need for analysis.

This outcome was best for Martin and the 2,000 persons awaiting his graduation who suffered with severe and persistent mental illness, lodged in the local asylum and about to seek a tenuous foothold in a Philadelphia community unprepared to accept them.

Martin was appointed an Assistant Professor in the Department and for the next five years spent his entire time developing an innovative spectrum of programs to serve these patients, including outpatient, emergency room, inpatient and outreach for vulnerable individuals.

> Instead of a 15-minute individual session with each patient, he dealt with the large volume of outpatients in a group setting; a number of oval tables arranged in a circle, amply stocked with coffee, orange juice, milk and day old "oral treats" that Martin purchased from a local bakery at modest cost. Every patient came with a family member or case manager in a climate designed to facilitate interaction and mutual interest. Meetings were held twice weekly in the morning and afternoon. A cadre of health professionals assisted: a nurse to help with prescriptions, a clerk to schedule follow-up appointments, a secretary to keep notes and social workers for home visits. An atmosphere developed akin to the Fountain House movement that began in New York where "peer pressure did the work for me." There was virtually no recidivism or "revolving door" to the asylum in this population. Even the most "rank" individuals were

capable of self-renovation – cleaning themselves up so they could earn promotion to become a "server" providing food to members of the group in session.

> The continuum of care Martin developed included a 20-bed inpatient program as part of a newly funded Community Health Center, staffed by psychiatric nurses and a resident under Martin's supervision. His own learning was enhanced by the tragic case of a middle aged Italian woman who requested additional Stelazine from her primary care provider. Admitted because she might be suicidal she presented herself the entire day as cheerful, dancing and smiling, interacting with others and participating in day long activities while still placed on 15-minute observations. She went to bed and at the next check was found

> dead with a silk stocking wrapped around her neck, attached to the door knob of her room. Martin developed an interest in such tragic occurrences and subsequently gave talks about suicide and the extent to which it was or was not a preventable condition.

He also developed a psychiatric intake program for the hospital's emergency room designed to create a supportive, non-threatening environment for patients and residents treating them; they were taught "Never to let the patient get between you and the door." Advice that one unfortunate resident overlooked when a paranoid patient appeared to settle down and asked to close the door. When granted permission he did so, and then turned on the resident and brutally attacked him with his fists, fracturing the resident's orbit, mandible and maxilla.

Finally, Martin also developed an outreach program for patients whose lack of skills impaired their community integration. He partnered with a highly creative African American woman, a mental health aide who was also a talented seamstress, skilled at making African costumes. Together they worked at a Mental Health Center in groups up to 16 people with a variety of problems, including communication and hygiene. He remembers a group of eight people who were virtually mute. So, he divided them into pairs and gave them five minutes to find out as much as they could about the other person and then report to Martin. It worked!

The spectrum of programs and innovative ideas Martin developed to deal with deinstitutionalization may well have contributed to the longtime reputation for excellence Philadelphia later acquired in community mental health care.

In 1976, after five years of work he loved and at which he excelled, Martin decided the family needed to move to a warmer climate – his wife's multiple sclerosis was deteriorating rapidly, demanding more of his time. Preparing for retirement he considered Mexico. On his way to a meeting in San Francisco he decided to stop and explore Phoenix. After a one-month trial they fell in love with the city and decided to stay.

His own sense of loss at what he had left behind in Philadelphia was profound and shared by those he had worked with. Several wrote letters asking, "Please come back." But within a month the innovative programs he had so successfully created were disbanded.

Nationally what happened in Philadelphia was the harbinger of worse to come. The fate of Kennedy's mental health initiative was told in a *Wall Street Journal* op-ed written on February 4, 2013, by E. Fuller Torrey, a psychiatrist at the Treatment Advocacy Center, headquartered in Washington DC. It tells of the bleak outcome of Kennedy's legislation. While this sealed the fate of asylums and speeded up deinstitutionalization it was seriously flawed and poorly implemented. Only half of the planned Mental Health Centers were built and most chose to deal with the "worried well" rather than severe and persistent mental disorders. None were fully funded and there was no long-term funding to follow up.

Belatedly, psychiatrists learned that while anti-psychotic drugs stifled the positive psychotic symptoms that led to institutionalization they lacked benefits for the negative cognitive and social deficits that led to failure in the community. This was a lesson Martin Kassell learned and successfully coped with in programs that disappeared overnight in Philadelphia in 1976.

So, Martin left Philadelphia for Phoenix, leaving behind an early innovative community mental health system. His formal career in this new environment lasted for 18 years, from 1976 until 1994, when he officially resigned his last post to begin an active retirement that has continued for more than two decades up until his present age of 100 - and still going.

Phoenix in 1976 was a pleasant environment to live in, raise a family and care for his wife, although it lacked the academic and urban sophistication of an ancient metropolis like Philadelphia. During this time Martin would work in several different clinical settings where his dual experience in medicine and psychiatry, coupled with an innovative energetic, clinical and management style, would serve patients, staff and trainees well in a variety of organizational settings.

Martin began as a visiting staff member and Lecturer at the University of Arizona and as Chief of Consultation-Liaison Psychiatry at the Maricopa County General Hospital. This included mentoring residents in medicine and psychiatry, a job ideally suited to his dual training and skills. Altogether he was "having a ball"; occasionally wearing a long white coat but always putting patients at ease, while tutoring residents at the bedside - sometimes as many as five at one time. Some of these residents are still in practice and stay in touch, one of whom came to his 100th

birthday party. The building was seven stories high and, using the stairs not the elevator, the team was kept fit and on its toes.

Unfortunately, Martin's nemesis was the university's head of psychiatry; a small man with a Napoleonic temperament. Over two years the Psychiatry Department built a new annex to house inpatients and Martin was assigned to become an attending psychiatrist on one of the units. It was a "take it or leave it" offer and when he demurred Martin was fired.

What followed was a six-month stint at the Phoenix VA hospital as staff person to a unit for alcohol and other drugs of abuse (AODA) patients relentlessly gaming the system, threatening suicide to gain admission, demanding and disrupting the milieu. Clearly, this was not a match for Martin's talent or temperament so he resigned and accepted a position at the Arizona state mental hospital with 1,500 beds, on the cusp of beginning deinstitutionalization, a problem he knew how to handle.

He had no formal teaching responsibility but the clinical task matched experience he used to re-organize a child and adolescent unit troubled by staff turnover, coupled with lack of discipline and clinical profiles. Martin went to work defining job descriptions and setting clear expectations until a therapeutic environment was restored

A period of institutional chaos ensued, the Director of Mental Health resigned, a business man took over who announced to staff that anyone who complained about an employee could be assured that person would be fired. A lazy internist almost lost a patient and when Martin disciplined him he complained to the Director who promptly fired Martin. The Superintendent then re-hired him as Chief Psychiatrist. This time he was assigned the chore of cleaning up and re-designing a chronic back ward, a task he relished. First by creating a cheerful milieu in which both staff and patients joined hands to paint the walls and hang pictures. To make a small day room seem larger Martin empowered a staff member to design a mural that depicted open windows looking out onto an attractive vista and had the patients paint it on the inside wall. Skeptics forecast it would soon be despoiled but patients were so proud of their accomplishment nobody dared lay a finger on it. Morale was excellent and the mood congenial. Then Martin soon realized the house keeping staff was good at talking to and bonding with patients, so he included them in staff meetings and evaluations. This paid dividends: one patient, incarcerated and ward bound for 20

years was able to leave the unit along with staff for the first time. While at the State Hospital he continued to supervise residents and, as always, received appreciative feedback.

In 1985 Arizona decided to set up a 76-bed Psychiatric Unit at the Durango Jail as a licensed Psychiatric Hospital, second only to the State Hospital, with two sections for men and women. With Martin as Chief Psychiatrist it obtained national, state and local accreditation and commendation. As usual he initiated innovative programs. The Correctional Officers became members of the treatment team and attended all its meetings, also participating in both group and individual treatment, a strategy that radically reduced the amount of acting out. He made the continuous patient record simpler and informative by having each discipline write notes in different colored inks: nursing used red ink, psychology purple and psychiatry blue. He replaced the traditional "subjective, objective, assessment, and plan" (SOAP) method of charting with PAR – **P**roblem, **A**ssessment, **R**esolution. In addition to supervising the different disciplines he also taught third-year University of Arizona medical students for a full day each month and received appreciative feedback from the Chair of the Department. Privacy was at a minimum; he held court and interviewed patients at his desk on the periphery of a huge day room; staff opinions of his demeanor were graded on four levels: barely audible, heard, elevated and reaming the patient out.

The end came abruptly and unexpectedly for political reasons in December 1994; until then Martin was on a 30-hour/week contract, allowing him sufficient time to care for his wife. An administration decided to replace all part-time staff with full-time personnel. Martin's farewell party is a fond memory; Martin was well known for giving the male inmates a hard time in therapy sessions but here they were, smiling and lined up to shake his hand and present him with a framed picture each of them had signed; embellished with a photograph of Freud. It hangs in his study at home, among his proudest possessions.

Martin also received a letter of commendation from the Directors of the Maricopa Health Services expressing their dismay and regret at his departure and eulogizing his accomplishments: "His quiet wit, his usually silent but not passive, participation in staff meetings, and his infrequent verbal opinions which, though gently delivered, always had the impact of a Sherman tank upon us all. He has been a good teacher to all of us, not free from a certain degree of obstinacy, yet open to criticism for he has a damned good sense of humor. We have never failed to know where Martin stands which, in these days of 'political correctness' has been refreshing."

The letter ends expressing the hope that he will be able return in the future to resume his teaching and training responsibilities. It was not to be. History repeated itself, within a month of his departure the innovative program he initiated was disbanded and became a traditional forensic unit.

Martin would not remain idle. He put the forensic skills he had acquired to good use as a consultant to the Maricopa County Superior Court, a position he filled until 2010. At age 92 he began to perform court ordered evaluations, advised the judges and gave testimony in court, enjoying word play while sparring with defense attorneys. When accused of prescribing the wrong drug to a client he was happy to point out that the plaintiff's attorney was quoting from a Physicians Desk Reference (PDR), used by lay persons while his own wise choice of the appropriate medication was from a volume by a widely accepted psychopharmacology authority, Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. Among his other triumphs was the exposure of a Vietnam War veteran, indicted for shooting and killing his wife then raping his step daughter, who was faking mental illness to avoid a lengthy prison term.

During this time Martin continued to see private patients and also initiated a monthly Koffee Klatch meeting, first at a coffee shop and later in his home, for psychiatric residents from the local academic program eager to tap into his experience and wisdom; fellow psychiatrists later joined, eager to "shoot the breeze." In a sad reflection of current orthodoxy, the residents eventually stopped coming and went in search of a mentor less psychologically minded to tutor them in psychopharmacology.

In the last six years Martin has received three well deserved awards for his career-long commitment to mentoring colleagues and residents. In 2012 the Arizona Psychiatric Society named him Best Teacher of the Year and in 2013 they awarded him their Lifetime Service Award. In 2014 the American Psychiatric Association recognized him as a Best Mentor of Residents and New Psychiatrists and also awarded him their Distinguished Lifetime Fellowship (DLF) Award.

On Reflection

The author's summary conversation with Martin Kassell

This biography was a delight and enlightening to pen. Martin and I spoke by phone weekly until its completion when we engaged in this final dialogue, a reflection on the whole.

My pleasure was kindled by realizing we were kindred spirits, not in age or precise parameters but with a synchronicity in style, interests, experiences and opinions. While my métier is the written word and I competed in the academic "publish or perish" sweepstakes, Martin's forte was the spoken (or unspoken) word; in his consummate skill as mentor and therapist across the full biopsychosocial spectrum.

In the material he provided me were two versions of a talk he had given on several occasions about the Psychology of Suicide: to the World Psychiatric Association Annual Meeting in Philadelphia, November 1981; to the Medical Society of America and Mexico Annual Meeting at Guadelajara, October, 2004; and, most recently, to the National Annual Meeting of the Creativity and Madness Society in Santa Fe, NM, August, 2006.

Over his career he had cared for about an estimated 200 attempted suicides, mostly during his work in Consultation Liaison at Maricopa County Hospital and the Forensic Unit at Durango Jail in Phoenix between 1976 and 1994. The essence of Martin's hypothesis is encapsulated in the following abstract from the larger of his two papers (Kassell 2006):

> *"Relatively few who are depressed or suffer commit suicide. This poses the question of what makes suiciders different… So, I began to ask the patient to go back to the time just before they began to think of the actual act of suicide. I would ask them what was happening in their life and what their thoughts and feelings were. I then decreased the time interval to when the act was just beginning, during the act, and even their last thoughts and feelings.*
>
> *"Using this approach, I was able to develop some patterns. The personality of most of the individuals was often either immature, narcissistic, passive or a combination. The IMPULSIVITY led me to believe that suicide is mostly NOT PREVENTABLE. Another was the presence of ANGER, the suicide act being the discharge of that emotion. It was often accompanied by the IDEATION such as I'LL SHOW YOU, OR I'LL GET EVEN WITH YOU, or YOU'LL BE SORRY (for what you made me do). These are manifestations of PASSIVE HOSTILITY … SPITEFULNESS. Another*

theme was ESCAPE. The background of these individuals suggested avoidance of conflict. Often the ideation was of going to sleep. An interesting addition to this occurred in some cases where there was an additional thought of REAWAKENING. This may have had its origin in childhood where being chastised, sent to the bedroom, going to sleep and, when awakening, all magically will be well."

This is a brief synopsis of a lengthy paper that provides several elegant and convincing case histories with additional speculation about the psychodynamic nuances in assessment and therapy. Martin related an illustrative vignette of a gay couple who had a contentious relationship prone to conflicts and fights, after which his patient repeatedly made a retaliatory suicide attempt with serious consequences. Finally, he jumped off a highway bridge fracturing both legs. In a therapy session on the day of discharge Martin said to him, "It seems peculiar to me that when I get upset with somebody I want to punch them out – but you seem to want to hurt yourself." At his next therapy session, the patient arrived with a large black eye: "I got into a fight, I hit him, I feel good."

What impressed and intrigued me was that while the initial suicide was impulsive and likely unpreventable Martin's elaboration of the psychopathology led to therapy that might well discourage future attempts. This aspect intrigued me because in my own study of suicide attempts on a neurology unit (see Ch.13), lacking any psychiatric training I never attempted therapy; the patient was discharged to the outpatient psychiatric clinic until I sometimes welcomed then back.

Impressed by Martin's work I consulted Google, typing in "Dynamics of Attempted Suicide." This produced a seminal paper titled, *Characteristics of impulsive suicide attempts and attempters* (Simon et al. 2001). Nearly two decades after Martin first proposed his theory the Abstract to this article reads as follows:

"Suicide attempts are often impulsive, yet little is known about the characteristics of attempted suicide. We examined impulsive suicide attempts within a population-based case-control study of nearly lethal suicide attempts among people 13-34 years of age. Attempts were considered impulsive if the respondent reported spending less than 5 minutes between the decision to attempt suicide and the actual attempt. Among the 153 case-subjects, 24% attempted impulsively. Impulsive attempts were more likely among those who had been in a physical fight and less likely among those who

> *were depressed. Relative to control subjects, male sex, fighting, and hopelessness distinguished impulsive cases bur depression did not. Our findings suggest that inadequate control of aggressive impulses might be a greater indicator of risk for impulsive suicide attempts than depression."*

This study has impeccable design, credible findings and has been cited in the medical literature more than 150 times since it was published. The first author is a psychologist and now Acting Branch Chief of the Surveillance Branch in the Division of Violence Prevention at the Atlanta Centers for Disease Control (CDC).

The fact that Martin described this syndrome almost 20 years before it was scientifically ratified reminds us that astute clinicians also identified the significant benefits of the first psychotropic drugs well before controlled studies confirmed their efficacy. We have no means of knowing the impact Martin's hypothesis may have had on the careers of those he mentored and lectured or their patients but the fact he was almost certainly first to describe the psychopathology of impulsive suicide attempts and suggest a strategy to prevent recurrence makes me wonder if this now widely recognized formulation might be fairly named "*Kassell's Syndrome,"* a fitting eponym with which to reward a centennial psychiatrist.

I also posed a series of probing questions for Martin to consider during our final discussion. Older than I and an experienced family physician Martin began his psychiatric career in 1971, three years after I arrived in America but at a time when we were both new faculty members in strongly psychoanalytic departments. This was also the "golden era" in psychopharmacology when biological psychiatry was beginning to gain a firm foothold in academia. I had also spent a brief time as a family doctor so we were both exposed to the novel concepts of psychoanalysis. Without blindly accepting the dogma Martin describes how becoming psychologically minded provided insights and intellectual satisfaction in patient care he had never experienced before, a benefit I also experienced. It was, "the best of times," with no regrets about his change of specialty and in similar circumstances he would do the same again, "helping people help themselves." Interactive dialog with patients and students was exceptionally gratifying.

Martin recalled and related several cases of successful therapy, sometimes assisted by hypnosis in which he also received training. A PTSD victim whose working life was disrupted by

sensitivity to loud noises was desensitized and returned to full time employment. A young woman who made repeated suicide attempts was treated with regressive hypnosis and recovered completely after he helped her recall the time her sadistic mother beat her with a bicycle chain when she was aged three.

Martin and I shared a primary care physician's experience with brief fifteen-minute interviews structured to enhance our relationship with the patient at the same time as systematically assessing treatment progress. Today's insurance mandate, the much maligned "15 minute med check," is a source of contemporary angst expressed both by patients and psychiatrists, many of whom have had no training in the art and science of brief sessions or their benign potential for cumulative benefit long term.

When asked if he would recommend psychiatry today to an interested medical student Martin was adamant. Psychiatry has become a business and not a profession; training has become almost exclusively biologically skewed and treatment has little to do with human nature and the whole person. This is abetted by the DSM, a "ridiculous system" that no longer diagnosed the human person but substituted symptom clusters called "disorders." A sentiment shared by many psychiatrists today.

Martin contrasted his life as a psychiatrist with his former unsatisfactory role as a family doctor whose popularity was linked to being a "nice guy" rather than a competent practitioner.

I asked Martin to what he attributed his longevity in addition to genetics. He replied that he had been overweight, ate unwisely and seldom exercised other than golf which he still plays thrice weekly, but no longer counts strokes. His other hobbies are playing poker with friends, ham radio, acrylic painting, attending concerts and ballet.

He does believe that longevity is helped by always maintaining a positive attitude, "dwelling on the bright side." This was enhanced when, late in his career he learned to listen. As an early psychiatrist in training he realized that as an internist he used to do all the talking, asked all the questions. Adapting to his new role he taught himself to listen by biting down on his lower lip until it bled. Once he learned to "listen with a third ear," he noticed what the patient was <u>not</u> talking about. Talking more to him about his demeanor with patients and those he taught sounded like the

equanimity that Osler saw as the essential ingredient of the “good physician,” putting himself, the patient or the other person at ease.

This style of practice, knowing his patients and pupils in depth, made distractions from work difficult but he learned to plan time to care for his wife and kids, without guilt.

Finally, I asked Martin if he had a philosophy or model from which he created the innovative treatment programs he instigated in the Arizona State Hospital and Jail. His answer was always to improve the situation as an innovator by utilizing the tools provided to create something more efficient and interesting. This included empowering and training housekeeping and correctional staff in how to deal with difficult patients. What made him proudest was the respect and gratitude he earned from those he helped, patients, employees and trainees of all kinds.

I also feel proud to have listened an

d learned from Martin Kassell, truly a “one if a kind” psychiatrist.

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Chapter 16

From Past to Present: Lessons Learned

A Mid-Century Madhouse: Enoch Calloway; Parts 3 & 4

Preamble

In Part 3 and 4 of his Memoir, Enoch Calloway extrapolates from past to present as an examination of the flow of events up to the time of its publication in 2007. It provides an intriguing account of lessons leaerned in the pioneer period that still apply today in the modern era.

Doubt about the tenets of psychoanalysis had its beginnings at the Asylum in 1950 and was spawned by exposure to so many patients who had failed psychoanalysis or would be unlikely to benefit –often verbalized first by resident's wives, living alongside in the asylum. Doubts grew at a snail's pace in America even after the arrival of effective drugs from 1949 on. First lithium, then major and minor tranquilizers, antidepressants and mood stabilizers all had a dramatic influence elsewhere in the world while America remained in thrall with psychoanalysis.

. Noch notes that empiricism and the need for scientific proof of efficacy also had its beginnings among the talented residents and staff at Worcester Asylum, but only began to flourish elsewhere when drugs started to appear; the placebo response was acknowledged and controlled double-blind studies became mandatory. Nate Kline played a pivotal role in Noch's enlightenment at Worcester (before moving to Rockland State Hospital) when the earliest enthusiasm for drug treatments and research was outside academia and developed in the VA hospitals and State Asylums, initially funded by the Federal Government via the Early Clinical Drug Evaluation Units (ECDEU).

By the mid to late 1970s the Zeitgeist had begun the change, DSM III was on the horizon and the money made by Big Pharma was beginning to trickle down to the benefit of academic departments and professional organizations, like the ACNP. Chairmen became eager to recruit psychopharmacologists to attract a share of the largesse.

Even so, many academic departments were wise enough not to throw out the baby with the bathwater. Some Freudian tenets were worth retaining and psychological mindedness remained an essential element of training an empathic psychiatrist. Noch notes that "even compassion can be taught."

The eventual burning down of the Worcester Asylum provided a metaphorical impetus for Noch to conclude his retrospective update of events in 2007 with the rhetorical question: "How far has the United States really come to solving the problems of mental illness?" Noch expresses pessimism over the "destructive impact" of the anti-psychiatry movement and the Scientology cult. He is also disappointed about the partial failure of de-institutionalization due to the inability of the antipsychotic drugs to improve social and cognitive functions essential for survival in the community. One senses his nostalgia for something better than prisons, forensic units and the homeless on city streets. He complains that despite the benefits of psychotropic drugs there remain many whose needs are not met in a "profit driven" health care environment– the antithesis of caring that includes denial of effective psychotherapy which can reduce the cost of co-morbid medical care; the so-called insurance "off-set."

Asylum: A Mid-Century Madhouse and It's Lessons about Our Mentally Ill Today:

Parts 3 & 4

Part Three: *Leaders of the Vision* (Chapters 40-48) is still linked to experiences at the Asylum but with larger contemporary implications. In *Fabulous Phonies* (Chapter 40) Noch exposes questionable aspects of psychoanalysis through the careers of two prominent analysts: Gregory Zilborg, who never visited the asylum, was an analyst, scholar, author and brilliant speaker but "his self-promotion was outrageous" (Zilborg was analyzing George Gershwin for difficulty playing the piano with his left hand; a problem the analyst attributed to masturbatory conflicts "until his right parietal brain tumor became obvious"); and John Rosen, who did visit Worcester and made a clinical presentation that bewitched the residents, illustrating his method of Direct Analysis by offering a manic patient a sexual interpretation that reduced him to tears, allegedly because it revealed "underlying homosexual conflicts." Noch contrasts this with his subsequent experience watching patients switch from mania to depression spontaneously without analytic interpretations and also documents how Rosen's claims were subsequently discredited.

In Chapter 41, *The Psychoanalytic Innovator,* Noch examines the fate of psychoanalytic theory current during his time at Worcester due to the passage of time. Helen Deutsch published her famous book, *The Psychology of Women,* in 1945 but, "today feminists would burn her in effigy." Helen's husband, Felix, developed the concept of *"Sector Analysis"* and demonstrated the

technique at Worcester on a patient presented at a resident's conference. It consisted of focusing on a specific conflict, often repressed hostility that could be resolved via interpretation without the risk of "symptom substitution." Noch points out that other forms of psychotherapy have since yielded impressive results without involving hostility, but that the practice of focusing as opposed to "free association" now seems "so obvious as to be banal."

In Chapter 42, *How Fortune Came to Favor the Foundation and the Hospital,* Noch examines the asylum's Camelot Years and the outcomes that have contemporary relevance. He gives credit for this period from 1921 to mid-century (as mentioned earlier) to two hospital administrators who had "the talent, vision and altruism to build, to facilitate and to leave the hands-on-fun to others while he or she juggles the resources."

The Schizophrenia Project (1921-1944) made three seminal contributions. First it documented the ignorance and oversimplification on which contemporary knowledge was founded; primarily from single clinicians based on limited data. Second, it expanded the data base to include a large asylum population with "scrupulous observations and careful measurements." Third, it made a careful and long term clinical study of insulin shock therapy that compared treated patients with matched untreated controls. This laid the basis for subsequent demise of this labor-intensive treatment once chlorpromazine was discovered in 1952.

The second coup was the relationship between the asylum with the Physiology Department at Clark University and recruitment of Hudson Hoagland from Harvard. This was of particular value to Noch whose interest in endocrinology began in medical school and flourished under Hoagland's mentorship -- his "scientific role model." Further, it led to work on the newly developed technique of electroencephalography (the EEG) and finally to Hoagland's collaboration with Howard Pincus. What began as hope that female endocrinology would shed light on mental illness morphed into the Worcester Foundation for Experimental Biology which migrated from Worcester to nearby Shrewsbury in 1945 where Pincus was introduced to Margaret Sanger, leading to the discovery of the contraceptive pill. The chemistry lab remained at Worcester where its lead scientist became another mentor to Noch who was also designated a "Foundation Fellow." Minks were the experimental model for fertility and in *On Mink Mating and Money-Making,* (Chapter 44), Noch describes how an ingenious animal psychologist designed a fur hand puppet that allowed for the collection of sperm from the male minks used to artificially inseminate females, thus

increasing the frequency of litters and generating money from pelts to fund the research. Unfortunately, the law of supply and demand lowered their worth and so the "Foundation did not make the expected fortune."

Noch pays generous tribute to role models that shaped his career in *Marvelous Mentors* (Chapter 46) and in the preceding chapter devotes special attention to Nathan Kline who served as Director of Research at Worcester in the waning days of Noch's apprenticeship. Nate involved Noch in research on autonomic responsiveness in depression during which he served as an experimental control in a double blind experiment and was injected with a saline solution to which he had a "brisk cardiovascular response" due to what turned out, to Noch's chagrin, to be placebo! Nate Kline went on to win two Lasker Awards for his pioneer work on the earliest antipsychotic and antidepressant medications while founding his own research center at Rockland State Hospital (later named after him) where he espoused many of the same strategies and principles Noch describes at the asylum. (See Ch.8)

Part Three concludes with a final chapter, *Footnotes on Psychotherapy* (Chapter 48), an expansive review of advances in the field of psychiatry and what Noch learned at the asylum. He summarizes his view of what science demands of psychiatry by quoting a commentary by Edmonds and Endow of Sir Karl Popper's 1945 book, *The Open Society and its Enemies:* "Attack authoritarianism, dogma and historical inevitability; stress tolerance, transparency and debate; embrace trial and error; distrust certainty and espouse humility."

Part Four of the book is titled *It's Only the Castle Burning* (Chapters 49-54). It serves as a contemporary epilogue to all that goes before. *Welcome to the Third Millennium* (Chapter 49) is a balanced view of the current status of psychiatry in 2007, its prestige (or lack thereof) as a discipline, the shifting balance between biological psychiatry and psychoanalysis, the evolving field of genetics, the role of the ACNP and ending with, for Noch, the inevitable question, "How far has the United States really come towards solving the problems on mental illness?"

Visits with Those Left Behind (Chapter 50) is a late life view of what remains of asylum care and for whom? It relates how de-institutionalization and the failure of community care led to homelessness and criminalization of the mentally ill who are now housed in prisons and State hospital forensic units.

This is prelude to *Are promises Made to be Broken?* (Chapter 51), a reprise of the volatile history of the asylum culminating in Noch's concluding thought that he, "Enjoyed Worcester at the crest of the last wave. But when that broke the Worcester State Hospital had no tomorrow."

The final three chapters analyze the influences that brought about that demise beginning with *The Seeds of Deinstitionalization* (Chapter 52). It identifies the events that invoked the end of asylum care; the libertarian Zeitgeist of the 1960s; the shortcomings of the new drugs that enabled the optimistic move into community; and the inadequacy of what was available there. Noch briefly traces the evolution of anti-psychotic drugs noting that while they effectively stifled the positive symptoms of schizophrenia they did little to repair the negative social and cognitive deficits that made a normal life in community possible or tolerable. Nor did the often serious side effects encourage compliance with treatment. The chapter ends by remarking that the programs and population-based solutions of so called community care often fail to match the needs of individuals with severe and persistent mental illness.

The penultimate chapter, *The Unholy Allian*ce (Chapter 53), deals with the destructive impact of the "anti-psychiatry" movement which Noch experienced first-hand; when teaching medical students about schizophrenia he was, "attacked as a dupe of the oppressive establishment and was informed that mental illness was nothing but a myth used by the State to enforce conformity." Noch identifies the Scientology cult and their "captive psychiatrist" Peter Breggin in a 1970s' movement that terminated the distinguished career of neuroscientist Jose Delgado. Not mentioned by Noch is the part played by a Trotskyist movement in France that terminated Jean Delay's career, the distinguished scientist whose team had introduced chlorpromazine to psychiatry. (See Chs. 6&10) Also indicted are the bizarre and convoluted legal impediments to emergency treatment and commitment procedures that are often counterproductive. Noch succinctly summarizes the dilemmas involved in finding solutions to a problem that requires laws and treatment programs which reconcile conflicting goals and that "(a) guard society against violence, (b) protect the incompetent from self-harm, and (c) protect civil liberty."

The final chapter is *Postscript: So What? With Notes on the Culture of Caring* (Chapter 54). It begins by stating the paradox that while "millions of people are enjoying the advances psychiatry has made in the last half century …many of those who need help the most are no better off or even in worse condition than the patients I knew at Worcester."

Noch acknowledges another paradox: the more scientists study the brain the stranger and more complex it seems to become. This reality is embedded in a health care environment that is profit driven -- "the antithesis of the culture of caring." Despite ample evidence that certain types of psychotherapy are effective and can reduce the cost of co-morbid medical care such interventions are often denied.

Finally, Noch makes a plea for the preservation of time to teach residents "the skills of listening and interviewing. Even compassion can be taught." He advocates for the integration of social and medical interventions. But above all, he repeats concerns that infuse this entire book - the need to test any theory against reality (empiricism) and while doing so to demonstrate compassion: "How society treats its most vulnerable members tells who we really are."

In this slender and pithy volume Enoch Callaway tells a clear-sighted, wise and compassionate story with humor and humility. Viewed through the prism of a distinguished career, from resident to Emeritus Professor, Noch relates how far psychiatry has come, yet still needs to go. Despite its discoveries and advances our discipline cannot claim with reliability and specificity how to repair a broken brain or calm a troubled mind. This is a story for every student in any of the mental health and neuroscience disciplines; it tells how an enquiring and bright mind can absorb the principles of analyzing data and acting compassionately that lay the basis for a successful career, whatever it may bring.

Chapter 17

Changing medical practice and education; MaritimeMetaphors

Preamble

Maritime Metaphors is the response to a posting by David Healy on INHN titled "Shipwreck of the Singular" (Healy 2016).

David is a distinguished British psychopharmacologist, author of 20 books including Pharmageddon (Healy 2012), a well-reviewed and scrupulously researched book which relates the damage done to individual patients by the corrupting influence of the pharmaceutical industry on modern medical practice, particularly in America. His 2016 essay is a recapitulation of how the dialectic between biological, psychological and social factors in illness and disease has evolved over the centuries and is currently distorted by a variety of cultural trends that over emphasize the technical aspects of healing and degrade the skill of physicians at listening to, seeing and touching individual patients at the social and psychological level, leaving them "shipwrecked."

David's thesis focusses mainly on scientific and cultural forces operating at the macro level with scant attention to the evolving and fluctuating role of medical education and economic factors that shape practice models, patient beliefs and the behavior or skills of doctors in their day-to-day dealings with patients.

This essay in response extends David's shipwreck metaphor to include a detailed examination of how changes in medical education and patterns of practice have evolved to affect the dyadic physician- patient relationship that has influenced the lives and prescribing practices of all physicians including psychopharmacologists and psychiatrists as well as the expectations of their patients.

That said, our conclusions coincide; we agree that at both the cultural and personal level medical care has deviated too far in a technical and impersonal direction to the patient's detriment.

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Maritime Metaphors

"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all."

William Osler (From the essay, *"Books and Man")*

This maritime metaphor was one of many pithy sayings by William Osler, who practiced medicine in Canada, America and Britain in the late 19th and early 20th century. During that time, the medical profession evolved from an apprenticeship model in the community to an academic discipline in universities.

That Osler would pen a maritime metaphor is no surprise. His father, Featherstone Osler, was a Lieutenant on Nelson's Flagship, the *HMS Victory*. Invited to serve as science officer with Charles Darwin on the *Beagle*, he declined; his own father was dying. In later life, Featherstone became a minister of the Church of England in Ontario, Canada, where William was born. He originally planned to follow in his father's footsteps but instead enrolled in the University of Toronto Faculty of Medicine in 1868, moving to McGill University in Montreal and graduating in 1872.

Osler, often regarded as the "Father of Modern Medicine," was an innovator with strong ideals from the start. He created the first formal journal club in 1884, was one of seven founding members of the Association of American Physicians in 1885, dedicated to the "advancement of scientific and practical medicine" and was Chair of Clinical Medicine at the University of Pennsylvania. When he left to become the first Physician in Chief at Johns Hopkins University in 1889, his famous valedictory address, *Aequanimatas*, preached the virtue of a calm demeanor for physicians. At Johns Hopkins, he set about accomplishing what he hoped would become his epitaph: "He brought medical students into the wards for bedside teaching."

Osler's ideas and initiatives were 20 years in advance of the Flexner Report, published in 1910, an overview of medical education in America, conducted for the Carnegie Foundation. Abraham Flexner was neither a physician nor scientist but a respected educator who visited all 155 medical schools in America to produce a blistering report on the parlous state of the discipline. His overall experience of the schools was, "Each day students were subjected to interminable

lectures and recitation. If fortunate to gain entrance to a hospital they observed more than they participated." The worst he described were the 14 medical schools in Chicago, "indescribably foul… the plague spot of the nation." At Johns Hopkins, Flexner encountered Osler's heritage, "the model for medical education," which he recommended as the template for twentieth century medicine in America. But by then, Osler was long gone, accepting the Regius Chair of Medicine at Oxford, England, in 1905 until his death in 1919, at age 70, stricken in the influenza epidemic and saddened by the death of his only son at the Battle of Passchendaele in 1917.

It is ironic that within a very short time the rigorous scientific and educational requirements set by Flexner, based on Osler's model, would perversely create tension between mastering the life-saving technology of medicine and preserving intimate contact with the patient's needs and circumstances.

Eight short years after Osler's death, Francis Peabody, a distinguished internist spoke to the Harvard medical students in 1927, "Young graduates have been taught a great deal about the mechanism of disease but very little about the practice of medicine – or, to put it bluntly, they are too scientific and do not know how to care for patients."

If anyone was listening, not much changed. Over a half century later in 1958, George Engel, another distinguished internist, proposed a new biopsychosocial model and echoed Peabody's concerns: "Medical education has grown increasingly proficient in conveying to physicians sophisticated scientific knowledge and technical skills about the body and its aberrations. Yet, at the same time, it has failed to give corresponding attention to the scientific understanding of human nature and the social and psychological aspects of illness and patient care."

In 1957, the year previous to Engel's article, I left Cambridge University and began my clinical training at Guy's Hospital in London. Osler's model of bedside teaching was in full force. Medical students rotated through the various wards as part of medical or surgical teams and under the supervision of a hierarchy of junior or senior registrars and consultants, employed by the National Health Service as full-time educators and clinicians, apart from a few sessions as private practitioners, often in Harley Street. Students interviewed and examined their patients, presenting and defending their findings at the bedside, then quizzed by the consultant and responsible for

recording the team's conclusions in the patient's chart. The ratio of science to empathy varied with the rotation and the consultant.

Beginning my psychiatric residency at the Maudsly I was fortunate to be promoted to the Professorial Unit after discovering the MAOI-tyramine interaction required to wear a white coat and coming under the eagle eye of Professor Aubrey Lewis. Aubrey's approach to patients was influenced by time spent with Adolf Meyer in America at the Phipps Clinic at Johns Hopkins, where Meyer was Director from 1910-1941. This involved developing a case formulation on each patient that incorporated all the biological, psychological and social factors and symptoms, including the putative etiology and prognosis, as well as a diagnosis informed by Kraepelinian and analytic insights. Information obtained from relatives was considered mandatory and it was a requirement that all new patients attending the outpatient clinic brought a family member with them. Worth noting is that Adolf Meyer became the first Professor of Psychiatry at Johns Hopkins five years after Osler left for Oxford. Although from different disciplines, their comprehensive approach to patient care shared common principles and objectives. Like Adolf Meyer, Aubrey Lewis was cautious, moderate and skeptical of psychoanalytic concepts but he did not scorn them.

Overall, my five years as a psychiatric resident and research fellow gave me a broad exposure to the basic and clinical aspects of psychopharmacolgy and my subsequent year in family practice provided insights into the anxious and depressive components of mild and early affective disorders as well as the helpful, cumulative and interactive benefits of brief theraspy and modest use of psychotropic medication.

David Healy expresses concern that "The use of rating scales and operational criteria" leads to "informational reductionism," which "dehumanizes the human encounter." He quotes Michael Shepherd as later conceding that largescale Epidemiological Catchment Area studies, using such scales, "Sorcerer's Apprentice like created markets for pharmaceuticals." This is very much a *"post hoc, propter hoc"* proposition, not due, I believe, to the use of rating scales - which alerted primary care physicians and their individual patients to the existence and vocabulary of mental illness in primary care - but to the incessant and importunate siren songs of the pharmaceutical industry. The prescribing pen remains in the doctor's hand and the extent of its use depends on the guidelines our educational and professional organizations provide, as long as they remain inured to commercial influences that carry a corrupting *quid pro quo* component.

It took a year to absorb the lessons and limitations of family medicine and by then, I realized I would return to psychiatry. There were too many intriguing questions that needed time and study to answer at the interface of medicine and psychiatry in people's individual unique responses to disease and illness. A way ahead soon declared itself.

I was offered a job as Director of Psychotropic Drug Research in Cincinnati, interviewed and offered a job at four times my current income. I didn't need a license to work in industry and would have one day a week to teach medical students and residents at the University. I accepted.

My subsequent two years in industry, followed by four years as a faculty member in Psychiatry and Pharamacology in a psychoanalytic department as Director of the Psychosomatic Unit (see CH.13) deepened an appreciation of the nuances, benefits and drawbacks of a balanced role for medication, dynamic psychotherapy and cognitive-behavioral interventions in psychosomatic disorders.

.Intrinsic and External Factors

David Healy's analysis of causes for *the shipwreck of the singular* hinges on a balance of intrinsic and extrinsic factors that shape public and professional opinions going back to the early 19th century and before. The extrinsic factors enumerated by David include "malign influences or physical miasmas from without." These gave rise to epidemiology as a means to eradicate epidemics, creating footholds for public health and social medicine in academia. Though distinct from Biomedicine, this duo united to form a triumvirate that enabled a powerful pharmaceutical industry to invent "magic bullets," reinforcing intrinsic responsibility.

Next, David notes "the emergence of a biopsychosocial approach to medicine that appears to be the height of reasonableness, but which also strengthened the influence of "public health mavens" and the "social side of medicine."

Both factors are clearly necessary. Viewed through a metaphorical telescope, the cultural influences including epidemiology, RCT's and industry yield interesting generalizations that are sometimes flawed. Seen through the microscope, biopsychosocial and illness behavior formulations enlighten a person's singular predicament with nuance, subtlety and ambiguity. David focuses more on the former than the latter. So here are two single case studies that illustrate

the complexity of therapeutic interactions that deal with a kaleidoscope of both internal and external factors at the individual patient level.

The first is a case study published in ***JAMA*** with the title, "Primary Care Psychiatry" and subsequently featured on the cover of the journal's Japanese edition (Blackwell 1983):

> "My next outpatient, referred by Medicine, was late. I leafed through our Primary Care Clinic's chart. The referral slip said, "Impotence, psychotic?" The workup was thorough; no diabetes, no neurological signs and a normal review of systems. But after that the resident's notes betrayed frustration, 'Impossible to interview; maintains a monologue with vague delusional statements and demands for meds.' When Joe showed up in the psychiatry clinic, I was surprised. Half of our referrals from primary care don't come; perhaps they feel accused of inventing or imagining their ailments. As I left my office to greet him, Joe was delivering a sermon in the waiting area on some aspect of his religious convictions. A four-square physique and a name full of c's, y's and z's suggested a home on the South side. That is a culture with strong values and clear-cut beliefs. Few psychiatrists work there, and their offices, like adult bookstores, have front and back entrances. If my stereotype was accurate, plain talk would be in order; psychological jargon would not. Looking me in the eye, Joe launched into his monologue. He had suffered from epilepsy all his life and borne the stigma with fortitude until he retired from the brewery five years ago. Deprived of the dignity of work, Joe had bolstered his manhood with an affair that quickly ended in remorse and return to the religiosity that consorted with his seizures. After a period of conscious-stricken prayer, God and two fellow helpers appeared at the foot of his bed to tell him his suffering would cease if he agreed to lead a better life. When Joe believed his part of the bargain was fulfilled, the seizures stopped and he no longer needed anticonvulsants. Two years later, the unearthly trio reappeared; promising continued good health in return for good behavior. Joe complied.
>
> "But now he was 70 and his wife was dying in a nursing home. He had just moved from their home into an apartment with a woman friend who wanted more than

companionship. Joe was pushing hard to prove himself and find some comfort, but his body wasn't cooperating. He felt inadequate and a trifle guilty.

"Joe had taken some practical steps to solve his new problem. He visited a urologist who examined him, found nothing wrong, and declined Joe's request that he prescribe testosterone (or anything else). Later, after taking all the vitamins and potency pills he could buy in a health foods store, but to no avail, Joe had turned to the Primary Care Clinic. And now, Psychiatry.

"At this point, I interrupted him with a question (time was passing) – what did he want from me? Joe didn't answer because he was very deaf. Again, I interrupted, this time shouting my question. He answered 'Testosterone.' Either by needle (he pointed to his rear end), or under the tongue (he opened his mouth). Unable to communicate with Joe verbally, I wrote out my recommendations, numbering them as follows:

1. The urologist said you don't need testosterone. I agree.
2. Your problem will go away when

(a) You stop trying so hard.

(b) You are less worried.

3. Try prayer. It worked before.

"Joe took the pad but looked puzzled: 'I don't have any glasses.'

"The end of our consultation had arrived and the next patient was waiting. Throwing caution and confidentiality to the winds, I shouted my advice into his ear. Joe listened carefully, became thoughtful and then nodded.

"Reading the nonverbal signs that our interview was over, Joe held out his hand and thanked me kindly, saying he would be back for further advice when he needed it. Later, as I struggled to code our encounter for billing purposes, I had the comforting thought that if psychiatry does become extinct (as some predict), I might enjoy being a primary care practitioner again."

Seen today, Joe would be prescribed Viagra or Cialis by his primary care doctor and probably never referred to a psychiatrist.

The second singular case was a private patient seen in my office, not the clinic. It is published in my memoir (Blackwell, 2012) with the title, "For Sale" in *The Bread and Butter of Psychiatry*:

> "I was rummaging through some papers on my desk, waiting for Sophie, when she marched briskly through the open door and plumped herself down on the sofa. She had on a silver fox fur cape topped by a scarlet beret that matched her lipstick. Before I could close the door or sit down myself, she announced emphatically, 'I'm a whore.'
>
> I paused a second or so before inviting her, in a deliberately neutral tone, to "say some more."
>
> She did. '"It's disgusting, don't you think, for a 75-year-old woman to be going with two 80-year-old men at the same time?"
>
> "'Two?' I asked innocently, knowing about Max from earlier sessions. Sophie had taken up with Max soon after her last husband had died. He balanced her checkbook, chauffeured her to the grocery store, and snored next to her in the movies. Early in therapy, when she began an antidepressant, she had complained her orgasms were inhibited. After the dose was lowered, she said no more. Twice, I tried to stop the drug, but each time, the grayness descended, and all her pleasure dwindled.
>
> Taking my knowledge of Max for granted, Sophie told me about the second man in her life. It was an old flame, rekindled. "His name's Sid. He asked me to marry him in 1929, but I told him no because I wanted to work. Sid said I could work, and he'd quit but then the Depression came. We both had to find jobs. Now he lives in Cincinnati, and his wife's in a nursing home with Alzheimer's or something. She doesn't even know his name." Sophie paused to reflect on this and then added, "I'm glad all three of my husbands died suddenly."

Ignoring this digression, I asked Sophie to say more about Sid. In the past month, Sid had become more ardent, driving his Lincoln Mercury 50 miles to Dayton several times a week and often arriving unannounced. Like a timid teenager from 60 years earlier, Sophie strove to keep her two suitors apart. This caution eased a nagging concern that my chemical tinkering might have tipped Sophie from sadness into an erotic mania of insatiable urges and unchecked impulses. She told me that Sid was Chairman of the Board for a large paper corporation. Like all of her husbands, and like Sophie herself, Sid was successful and self-made. Once Sophie was over her initial depression she was a match for anyone. Sophie played demonic bridge, entertained lavishly and insisted she got credit for the senior citizens' courses she enrolled in at the university. When an instructor at the YMCA questioned her wisdom in joining an aerobics class, she produced a certificate from her internist to prove she was in shape.

As her therapist I was unsure of what Sophie needed from Sid now. She surely wasn't having doubts about the wisdom of sex after seventy. For Sophie, sex simply wasn't sinful. It was a practical matter. Earlier in therapy she had told me of how she had been driving to a party with her first fiancé when she realized they hardly knew each other. Sophie ordered him to turn the car around and take her to bed. That must have been the man she married instead of Sid.

Nor did Sophie seem to need help with strategy. I recalled the courting of her third husband, a distinguished professor in the English Department at the university. They had met soon after he became a widower. Instantly smitten, the professor declared his interest but coupled it with the intention of remaining in mourning for a year. She understood his need for the delay but saw no reason to deny themselves sex. They were married two months later.

Often in therapy there were doubts about what my patients wanted. Only a few had wild psychoses or aberrant chemistry that taxed my training. More often, like Sophie, they came for advice, absolution, or an opportunity to iron out an ambivalence or two. I met all these needs like a bartender sworn to secrecy, a minister without a collar, or a friend whose only obligation was to listen and nod.

When I was down on myself, I complained to my wife that all I ever did was to sell solace that had as little to do with doctoring as work in a massage parlor had to do with a degree in physical therapy.

My mind drifted back to Sophie sitting on the sofa, and my own thoughts merged with her predicament. An image crystalized in my mind. After all these years living with three husbands she must feel like an empty house, up for sale. I shared the metaphor with Sophie, wondering what she would make of it. Sophie stayed silent for a long time. A sheen of sorrow spread across her eyes. When I saw the tears glisten I asked how she felt.

"Used up. But it's true I'm available. So, what do I have to offer?'

"Offer?' I echoed, wondering if Sophie saw in herself only what she thought the world would see. A widow turned 70 proffering sex?

The thought was mirrored in my own mind. A doctor turned therapist prescribing drugs? I knew that danger well; it was both the product and producer of bad thoughts, spiraling down to depression. When Sophie spoke, it affirmed my hunch that she was dwelling on the dark side. 'My daughter will think it's disgusting. At my age.'

"Intuitively I sidestepped her statement. Instead I used the time left to attack its roots; I gently reminded Sophie of the things she did so well and the companionship she had to offer. At the end of the hour I asked, according to ritual, if she needed another prescription. Sophie said "no, not this time" When she stood to leave she seemed calmer than when she came.

Later, we will return, (**Unique to America)** to place the give and take of these singular encounters and the role of a psychiatrist in the context of contemporary clinical and insurance practices.

Moving On

By 1974, I felt equipped to seek broader horizons. The Federal Govermnet had funded 30 new medical schools in communities remote from academic ivory towers and dedicated to training humanistic primary care physicians willing to work in underserved areas.

My background in psychiatry, pharmacology and family medicine seemed suited for this task, so I applied for and was appointed as the Founding Chair of Psychiatry at Wright State University in Dayton with professorships in psychiatry, medicine and pharmacology.

The charter class assembled in 1975, diverse in backgrounds, along with a faculty committed to the intended goal. This included a Medicine in Society Program, staffed by an ethicist and sociologist. An innovative curriculum included a first-year course taught with the English Department on classical literature that reflected physician and patient roles in coping with illness (Wilson and Blackwell 1980) and a "Student-Cadaver Encounter" designed and taught by faculty from Anatomy, Pathology, Psychiatry and Medicine in Society (Blackwell et al. 1979).

An inevitable tension between mastering the technical aspects of medicine and preserving or encouraging the empathic (singular) aspects of patient care is reflected in modern media's contrasting stereotypes of Marcus Welby and Patch Adams versus Dr. House and Doc Martin. Robin Williams's brilliant portrayal of Patch Adams displays the competing mind sets of a rigid academic Dean, committed to a Marine Corps boot camp ideal of medical training, contrasted with Patch Adams' empathic, humorous and impulsive attempts at humanism.

The perhaps necessary endpoint for two types of physician became apparent to me when my son fell and fractured his ankle close to the epiphysis at the critical age of nine. We consulted two surgeons. The first was brusque, matter of fact and ignored Simon; the second was friendly, chatty and explained the X-Rays to him. Asked which doctor he preferred he replied, "I'd like the first to operate on me and the second to look after me afterwards."

There is a need but not enough comfortable room for both approaches, especially as technology expands and demands larger amounts of time within the frozen limit of a four-year curriculum. In more than a century since the Flexner report, the time devoted to Behavioral Medicine has expanded from 26 to 362 hours between admission and graduation (most in the first two years) (Blackwell and Torem 1982). Our national survey recorded programs with 43 different names with as many as seven different departments collaborating.

There is an innate dehumanizing aspect inherent to medical education I discovered, when I combed the literature in preparation for our task and later published (Blackwell 1977). Particularly impressive were the comments of a female journalist, Joan Priestly, who entered another medical school the same year ours began. Here is how she describes the experience:

> "As students we become adjusted, inured and, finally, oblivious to our situation. Our experiences as medical students are subtly conditioning us to become cerebral and unfeeling to the point of brutal insensitivity. The acronyms – SLE, EMG, PNM, PNS – which cover anything from anatomical features to devastating diseases… a new vocabulary of over 13,000 words has to be mastered. The obscure language certainly exerts a strong influence. Our lecturers discussed babies with ghastly deformities in terms of 'this interesting case.' We have had experiences shared by only a fraction of the population … how many people can say; I got up at 8: 00 a.m. today – to saw a human head in two; to hold a human heart in my hand; to do a glucose tolerance test; to pick apart a dead man's genitals.
>
> "This school is not just a series of lectures and homework; it is a rite of passage we endure together. We have immersed ourselves in an environment that is not only new, but alien, and we are somehow persevering to survive the constant drain of nonstop studying and weariness and trauma and lack of sleep and lack of sex and loneliness and tears and spaciness and unexpressed frustration and anxiety ridden tensions. I succumb now and then to the ego-inflating lure of feeling 'special' and have become more arrogant and aggressive, less patient and tolerant, when dealing with 'lay people'."

One final piece to understanding the enigma of stifled humanism in medical education entered my personal awareness when I was asked to address the incoming charter class on the topic of "Being a Physician" (Blackwell 1984). Anxiety about giving the talk played on my unconscious and shortly before I was to deliver my address, I had a dream. I was treating a woman newly admitted to hospital with a bleeding disorder. I decided to set up an infusion but was uncertain which drug to use. The ward copy of the *Physician's Desk Reference* was missing and I was forced to leave the unit and continue a fruitless search elsewhere. When I returned to the patient's bedside, still in doubt, the intern had set up an infusion. As I approached the bed, the patient began to bleed

around the infusion needle. The flow of blood grew rapidly from a trickle to a deluge. I grabbed at the sheets and bedclothes in a futile attempt to staunch the bleeding and at the same time was aware of the beseeching eyes of the intern, the recriminatory eyes of the nurse and the terrified eyes of the patient. Then I awoke.

The dream encapsulated the unique stresses of the physician's role; the necessity to make decisions in ambiguous situations, to take control in emergencies, to be responsible for finding a cure. I used the material in my talk, presenting it as a case that had actually occurred. Afterwards my vice chair, who was a psychoanalyst, asked who the patient was? This stimulated my associations to two cases I had been involved with immediately after graduation at Guy's Hospital as the house surgeon to Britain's pre-eminent breast surgeon.

First was a woman who noticed a lump in her breast while bathing and had been admitted for emergency biopsy. At surgery, an inner quadrant, hard, pinkish gray tumor was found on frozen section to be consistent with anaplastic carcinoma. A mastectomy was performed and as the patient was leaving the operating room, the pathology laboratory called to say the peripheral blood smear showed acute leukemia and thrombocytopenia. We began an anxious watch for hemorrhage from her wound and menstrual period which started several days later. She required several pints of blood as her hemoglobin level fell relentlessly. Fourteen days after surgery and a month to the day after noticing the lump in her breast, she died. Autopsy disclosed undiagnosed leukemic deposits throughout the internal organs. I published this case in the *British Journal of Surgery* (Blackwell 1963a) hoping to assuage my guilt at having failed to diagnose her leukemia before surgery.

The second case was even more painful and personal. Years previously, my mother had a hysterectomy and now developed adhesions and intestinal obstruction. My attending agreed to admit her for surgery and I signed off the case. The operation was difficult and afterwards my mother developed delirium. I had not revealed that she was an alcoholic. The following day, I was sitting at her bedside when the senior registrar asked me to take a tube of her blood to the lab for clotting factors; she had continued to bleed after surgery. Feeling hopeful and responsible, I got to the lab as it was closing and the technician refused to take the sample. My mother slipped into coma and a few days later died, without recovering consciousness.

By the time the charter class graduated in 1980, the problems of accomplishing the goal of training a new breed of humanistic primary care physicians and its likely failure were already apparent. In 2010, when I was invited to give an address to the graduating residents in psychiatry 30 years later, the founding principles were long forgotten and Wright State was a medical school like any other. But I was delighted to see that the Department of Psychiatry was thriving under the Chairmanship of a former resident I taught in Cincinnati. I chose a satirical title for my talk, "A 15 minute ed-check," a play on words to reflect the widely expressed contemporary concern that psychiatrists were little more than pill-pushers, poorly trained in psychological understanding and psychodynamic principles. Instead, the Wright State program was known and respected for having shunned this false mind-body dualism by developing innovative ways to train psychiatrists with sophisticated biopsychosocial knowledge and talent (Blackwell 2012a).

Earlier, in 1985, with hindsight, I had written an editorial for *General Hospital Psychiatry* titled, "Medical Education and Modest Educations" (Blackwell 1985). It discussed the sources of failure, citing as an example the failure of our experiment with *The Student Cadaver Encounter* (Blackwell et al. 1979):

> "Others have documented, tongue in cheek, the difficulties of designing a 'benign behavioral health course.' The fate of one such experiment can probably serve as a stereotype for similar efforts. The concerns that are voiced about medical practice and the biomedical model originate from the time when Christian orthodoxy permitted dissection of the body provided that strict segregation was kept between the physician's province of the body and the church's domain of the mind and spirit. This dichotomy fostered an attitude in which life is stripped of its social and psychologic complexity and reduced to a technology reliant on physical phenomena. In medical school, this dualistic approach is fostered by the psychologic defenses students mobilize to cope with exposure to the cadaver. We designed an experience to heighten the student's awareness of this situation and its relevance to future practice. Faculty from the departments of anatomy, pathology, psychiatry and the humanities met the students on the first day of class to discuss their feelings and formally share in the introduction to their cadaver. That evening the student wrote a fictional biography of the cadaver and the next day shared this

and the experience of their first dissection alongside the faculty. A content analysis of the essays found them to be somewhat mundane and mainly influenced by autobiographical details.

"The experience in humanizing the student-cadaver encounter was originally popular with the charter class but failed to survive for reasons intrinsic to the problems of changing traditional medical education. In order to create a summer break for students the task of dissecting the entire body was condensed from two semesters to one. Some of the founding faculty who designed the class left, and were replaced by more skeptical faculty. The class size expanded, made up of fewer idealists and more traditional students; after three years tension between students and faculty was such that the experiment was dropped. The paradox is that the very scientific advances that create a need for humanism simultaneously crowd it out of the curriculum; philosophy confronted logistics and lost. Our failure was symbolized when a student who participated in the experiment cut the penis off his cadaver and flashed it on campus.

"On further reflection my conclusion was that there is a limited degree to which education can abbreviate experience and a greater extent to which time tempers science with the art of medicine. Physicians often discover equanimity when they relax after years in practice and find their encounters are enhanced if they are able to share their own and their patient's beliefs and uncertainties. In return for more modest expectations about what medical education can accomplish, the profession may feel less frustrated, the public less disappointed and individual practitioners less prone to impairment."

In 1980, I accepted an interesting but different challenge. A well established and traditional medical school at the University of Wisconsin was seeking to expand its urban training experiences for residents and medical students by opening a campus in Milwaukee with its large inner-city population of underserved citizens in poor health, many living in poverty without health insurance, particularly those with severe mental illness.

The Jewish hospital, Mount Sinai, was eager to preserve its inner city location but under financial pressure to move to the affluent suburbs. This became a "marriage of convenience"; the hospital hoped an academic affiliation would enhance prestige, attract patients and fill beds while the revenue derived would fund the salaries of faculty to train students and residents in urban medicine.

The challenge of again creating an entirely new department but in a completely different environment was appealing, especially when the Dean, during a recruitment interview, assured me the finances were "as safe as Fort Knox," a prediction that would prove wildly inaccurate due to an unforeseen but impending healthcare holocaust.

I was Chair of the Department at the Milwaukee Clinical Campus of the University of Wisconsin at Madison from 1980 until 1994 with joint appointments in Medicine and Psychiatry. During this time, we recruited a talented faculty, obtained accreditation of a new residency program at the first attempt and were able to fill our slots with a mix of American and foreign graduates. Collaboration with colleagues in medicine was excellent, cemented by joint research and teaching projects, including my management of the consultation-liaison service. Working with residents from both medicine and psychiatry allowed me to teach the biopsychosocial model we had developed in Cincinnati and incorporated at Wright State. I was able to adapt the illness behavior model to the benevolent care of patients in primary care, who had unexplained bodily concerns (Blackwell and De Morgan 1996) as well as promoting an approach to developing a therapeutic alliance to deal with the ubiquitous problem of compliance (see Ch.11)

Among the research projects was a continuation of interest in development of the physician role, moving from medical student to resident. Norman Cousins had published his provocative editorial in a leading medical journal, describing residency training as "the weakest link in the entire chain of medical education." Aware of the rate of resident suicides, Cousins questioned whether residency was "a legitimate preparation for practice or a hazardous form of hazing."

Together with a senior faculty psychologist and the Chief Medical Resident (a woman), we developed a 60-item questionnaire to measure attitudes, stressors and coping strategies during residency training. It was mailed to more than 1,000 residents in all the primary care and specialty

programs in Wisconsin during 1992, endorsed by the Chief Resident in each program. The results were published in *General Hospital Psychiatry* (Blackwell, Gutmann and Jewel 1984).

The results are summarized as follows: "Successful role adoption (making difficult decisions, displaying leadership, dealing with uncertainty, being responsible for patient care), is the primary task of residency, balanced by an increasing stress in maintaining personal social support systems in family and peer groups. Work factors that create tension between these two aspects create the most stress. The degree to which role adoption is accomplished, the stress imposed and coping strategies employed, differ significantly with gender, specialty and program type."

A Health Care Holocaust

In Milwaukee, before and after an abbreviated sabbatical, changes in healthcare were occurring in ways that would impinge on, and eventually destroy, an environment conducive to practicing and teaching a model of medicine that dealt with an individual's manifestations of health and disease.

These events are succinctly described in a "*Piece of My Mind,"* published in *JAMA* (Blackwell 1994), titled "No Margin, No Mission":

> "For psychiatric educators, like me, who direct a consultation-liaison service, the integration of mind and body has always presented a clinical and pedagogic challenge that is being accentuated by the economic environment and recent influx of managed care. When I first came to work in our urban teaching hospital 13 years ago in 1980, the inner city was served by five hospitals; four have since merged and then gone bankrupt, and ours is the only one remaining. As each of the others closed it passed on its population of uninsured, underfunded Medicare and Medicaid patients. The State of Wisconsin took two actions that unwittingly made matters worse for our impoverished institution. It deregulated hospital construction, inviting an influx of for-profit psychiatric hospitals, siphoning patients with indemnity insurance to the suburbs. This simultaneously reduced the number of people receiving integrated care in my hospital and increased its economic plight by limiting cost shifting. Second, the state obtained a federal waiver from the

Medicaid freedom of choice stipulation and placed the city's entire welfare population of mothers and children into health maintenance organizations (HMO's) although they had more complex and costly conditions.

"Many of these patients customarily received care in our hospital, and I and my colleagues lobbied to provide it. But by the mid-1980's hospital administrators had learned the lessons of survival and the language of the business schools with such slogans as 'No margin, no Mission'and 'Every bucket must carry its own water.' Hospitals and HMO's began to barter with each other, ratcheting down fees and divesting themselves of expensive Medicaid subpopulations to low cost providers. Recently our hospital sold its entire HMO population to a national organization, which divested the mental health capitation to its "behavioral health" subsidiary. They in turn kept the commercial patients but sub-capitated the Medicaid population to yet another agency unaffiliated with our institution. The sickest and poorest of our patients and those in most need of integrated care could no longer obtain my services in the same hospital where my colleagues cared for their medical needs. Clearly this was not what Congress had intended when it mandated that Medicaid patients should obtain both their medical and psychiatric care in general hospitals.

"Recently I was asked to offer a consultation on a man with acute post-surgical delirium whose HMO had sub-capitated its mental health services to another hospital. First, I was asked questions I could only answer if my consultation had already been performed, and then the patient was offered an outpatient appointment. Finally, when I explained the patient was pulling out his intravenous lines and needed immediate attention my inquisitor asked: 'What is delirium?' Such 'little battles' sometimes yield grudging approval; others end in delay or denial, necessitating a lengthy appeal that is often not responded to.

"As managed care looms, some of its implications need closer scrutiny. Few people, me included, doubt the need to control mental health costs. Vague end points, diagnostic ambiguity, and elastic interventions create considerable 'moral hazard' which can readily jeopardize a capitated system. Some element of management is

inevitable. In HMO's primary care providers have traditionally served as gatekeepers to specialty care (as they do in the British NHS). However, presumably because they are considered ill equipped to do so in psychiatry, it's now become traditional for HMO's to separate the capitation for medical services from that of mental health and substance abuse. Access to care is limited or approved by telephone managers and medically untrained case managers. The system is often referred to as a 'carve-out.' This appropriate surgical metaphor is softened by adding the prefix 'behavioral health carve-out.'

"But there is a tradition to the use of the word *'behavioral'* in medicine that is associated with the application of psychological principles to medical practice. The new usage of the term '*behavioral'* has become a synonym for all psychiatric services. Paradoxically, 'behavioral health carve-out' describes the segregation of psychiatric and medical services, the polar opposite of the original meaning of the term.

"This is not only antithetical to the 'biopsychosocial' treatment model that educators like me espouse, but it has paradoxical insurance implications. A frequent argument to support provision of mental health services is they produce a reciprocal reduction in the costs of general medical care (the so-called offset). I cannot see how this is facilitated by dividing the patient's care into separate domains. In my experience, once the capitation is split 'health maintenance' occurs in name only. Neither side willingly accepts fiscal responsibility for primary or secondary preventative programs such as smoking cessation, weight control, and pain management.

"Of broader concern is the question of access of the general population to mental health services. A majority of contemporary mental health care is provided by the primary care sector. Can this population be diverted to the specialty mental health sector? If so, people with psychosomatic complaints are likely to be seen by the least expensive mental health provider and doubly deprived of physician contact.

> "In community hospitals like mine psychiatric educators must prepare to have their philosophical assumptions and populations they serve compromised and eroded. Clinical revenue to support faculty positions may dwindle and physician role models who teach mind-body medicine to students and residents will be endangered. As educators we are learning a hard lesson: no margin no mission."

By the time this essay was published, the writing was on the wall; the remaining Milwaukee hospitals had coalesced into three major allegedly "not for profit" entities but with an eagle eye on their bottom lines. Primary care and specialties like psychiatry based on personal care and without remunerative technical procedures were doomed. The largest, most aggressive of these organizations took over Mt. Sinai which became known as Aurora-Sinai. The Dean fled back to Madison, I stepped down as Chair and within two years, Aurora pulled the plug on the psychiatric inpatient service, effectively ending the residency, disbanding the academic program and cutting off the supply of new psychiatrists in an area of serious shortage.

Internal Medicine and Family Medicine lasted a little longer, until Aurora issued an edict that faculty members were no longer to treat Medicaid patients. Those who refused were asked to resign or fired. Those who submitted became "Aurora doctors" but no longer faculty. There was no one to teach and no patients to teach on. The former Chair of family medicine joined Aurora, later became its CEO and is now earning over $4 million annually.

After I retired in 1998, at age 64, I abandoned medicine and enrolled as a lay student in the local Catholic Seminary. I gave up medicine (but not sex) to begin a Master's degree in Applied Pastoral Studies, exploring my long neglected spiritual side and attending excellent small classes, alongside young seminarians and middle-aged women seeking second careers as administrators in parishes to help the priest shortage. Eventually, I realized I was "spiritually handicapped" and returned to work part-time as the only psychiatrist at Catholic Charities, caring for indigent and Medicaid patients, who could not find a private psychiatrist willing to take their insurance. Following this, I worked for four years, again as the sole psychiatrist, in the Wisconsin Correctional System taking care of that half of the population in a Women's' Minimum Security Prison who had a mental illness often embedded in a matrix of economic and social problems that received scant attention in the community, inviting recidivism.

In 2007, I attended the annual meeting of the ACNP where Tom Ban invited me to join him in editing the 10 volume Oral History Project (OHP) in time for the ACNP's 50th Anniversary in 2011. I ended up editing two volumes and writing over 50 brief biographies of pioneer neuroscientists (*dramatis personae)*.This provided insights into the career patterns and modus operandi of these pioneers. Coupled with more than 45 years as a member of the organization it also created a perspective on how far it had drifted from its founding principles, casting light on the differences between the Golden and Modern Era.

Sea Change or Tsunami?

Hypothesis One*: History is more or less bunk. It's tradition. We don't want tradition. We want to live in the present and the only history that's worth a tinker's damn is the history we make today.* (Henry Ford)

Hypothesis Two: *What's past is prologue* (William Shakespeare – *(The Tempest)*

This rather volatile and unpublished essay, was written only for distribution by e-mail to all the members of the ACNP.. It produced modest approval from a handful of ageing members, mostly clinical psychopharmacologists, and stony silence from basic neuroscientists and leadership. It is published in my Memoir, *Bits and Pieces of a Psychiatrist's Life* (Blackwell 2012).

> "I read the President's September First and earlier blogs and also received the *ACNP Bulletin* (Volume 17) describing a 'Sea Change' in the format of the annual meeting. This derives from the President's mandate to the program chair to minimize the past, pay no respect to stature, rank or seniority and provide every opportunity to the young and inexperienced. This is consistent with the President's declared libertarian beliefs that are defined in the *Oxford English Dictionary* as 'an extreme laissez-fairer philosophy advocating only minimal intervention in the lives of citizens.' His blogs make it clear the President attributes the ACNP's current ailments to a complacent oligarchy of old-timers, who have stifled youth and innovation. Consequently, the ingredients of the 'Sea Change' are mini-panels devoid of discussion and a 'data blitz' of apprentice investigators presenting 'rigorously timed five-minute presentations.' This might be a laudable experiment in normal circumstances, but current problems confronting ACNP merit a response more appropriate to a tsunami than a sea change. To extend the maritime metaphor

- this sounds like a 'ship of fools' crewed by midshipmen, heading for an iceberg. Will the officers remain on the bridge and go down with the ship?

"Satire aside, there are serious concerns about what this belief system and its simplistic solutions have drowned out. As a Life Fellow since 1970, I was active in the ACNP's earlier years but drifted away to pursue other interests before returning two years ago to assist in work on the OHP. This complemented my earlier work on *Discoveries in Biological Psychiatry.*

"In both these data bases, most of the pioneers were experienced clinicians with long exposure to large populations with untreated severe and persistent mental illness, mostly in nonacademic settings, including the VA, state hospitals, and private practice. They became motivated by dramatic changes they saw in people never previously exposed to effective treatment, and they quickly developed valid, reliable rating instruments and research protocols. They also recognized, from the start, the need for close collaboration and communication with basic scientists in an extended environment conducive to translational dialogue. This is why and how the ACNP was born in 1961.

"For the first decade (1962-1972), this was a fruitful enterprise driven by intellectual curiosity and a profound desire to help people with severe mental illness return from asylums to life in the community. They succeeded but this atmosphere, its motivations and rewards, were quickly and progressively eroded and no longer exist. Over the next four decades (1972-2012), the complexity of mental function and the difficulty of translational dialogue became increasingly clear.

"Receptors, enzymes, and transmitters, often with manifold functions were modulated by multiple messengers. Genes, like Shakespeare's sorrows, came 'not as single spies but in battalions,' expressing themselves in uncertain ways and frustrating fifty years of wasted effort on the DSM fantasy that phenotypes, derived by political consensus, might be linked to drug function and specificity.

"In short, neuroscience prospered while psychopharmacology dwindled. The only truly innovative drug discovered in forty fallow years of research was Viagra.

> Decades after chlorpromazine, serendipity still colludes with science in unexpected ways and places!
>
> "While worthwhile improvements in clinical care were minimal, there was insidious, perhaps understandable, erosion of scientific motivation away from curiosity and concern in favor of fame and fortune. This coincided with a shift from clinical to academic settings as psychoanalytic hegemony yielded slowly to psychopharmacology and neuroscience. Fame became congruent with prolific resumes, publication citations, academic promotion, prizes and awards. Fortune was fed by industry largesse and emulation of profit making procedures; universities filed patents, investigators founded for-profit corporations and faculty signed contracts to endorse new drugs with dubious benefits and dangerous side effects. The highly touted 'second generation' drugs were dressed in the Emperor's clothes, designed by creative marketing forces and endorsed by willing academics. The origin, details and outcomes are fully explored in Chapter 19.

"ACNP did little to oppose these changes; instead it swam with the tide. Its membership ballooned to include a majority of basic and jointly trained members, accompanied by a dramatic decline in sophisticated clinical researchers. Increased attention was given to programs devoted or linked to posters on esoteric neuroscience topics by multiple authors (sometimes twenty or more) with little or no clinical relevance and not subjected to independent review. Ethical guidelines were promulgated but little was done to enforce them or sanction those who violated them. Members dutifully recited their corporate affiliations but nobody cared that naming a conflict of interest did not eliminate it.

> "It is doubtful if the founding members of ACNP would recognize or endorse its current form. But if, or how change can occur is highly questionable when foxes are loose in the hen house. But if ever there was a time for fundamental and decisive leadership, it is now. Laissez-faire principles and bottom up tinkering are hardly the answer.

> "Not only does libertarian philosophy shun authority and experience, but it subscribes to Ford's epigram; 'history is bunk.' What followed was the Edsel, the biggest design failure in the history of the automotive industry. The ACNP has entered an Edsel era. It will not be bailed out this time by government or industry. Big Pharma has killed the golden egg by degrading clinical research and making manifestly false claims for its products. Slender profits from generics may further trim its sails, although some smaller firms are establishing monopolies and raising prices to outrageous levels. Tea Party deficit hawks and Congressional investigative committees may yet stifle some of the symbiotic greed that binds academia to industry.
>
> "As a result, slim economic times might shrink the ACNP, shed some of its fortune seekers and citation hunters and revive the lost commitment to better, safer, more affordable treatments, evaluated by skilled clinicians, free from commercial incentives and motivated by love of science and concern for their patients."

That is the way it once was. One final maritime metaphor describes how it is today. The ACNP is like a ship cut from its moorings, adrift on the ocean. It has failed in its two primary purposes; sophisticated, productive, ethical research translated into safe, effective, affordable treatments derived from creative, relevant basic science. Instead, a core of distinguished and talented clinicians is dwindling and dying, unenlightened by their translational aspirations. Should the ship be salvaged or allowed to sink?

One possibility would be to recommission the vessel as the "American College of Neuroscience" (ACNS) and vigorously advocate for the revival of a Federal Drug Evaluation Program (FDEP). Its task would be threefold. The first would be to conduct small intensive studies designed to link individual drug response to the genotype and its phenotype using symptom specific rating scales and avoiding DSM categories of disorders. The second would be to use this seedbed for the selection of novel compounds to compare to generic prototypes in studies of sufficient size, statistical power and duration to ensure safety, efficacy, generalizability and economic utility. These studies would be funded but not managed by pharmaceutical companies in return for patent rights on genuinely innovative and cost-effective compounds. Direct advertising to consumers would be banned. The third task would follow naturally from the first

two; the creation of a new cadre of highly trained and well paid investigators with lengthy tenure coupled to incentives for productivity and creativity. These scientists would be encouraged to obtain academic appointments but forbidden to engage in any industry involvement during or following their federal contracts.

The renamed ACNS would meet regularly with the FDEP investigators to discuss potential translational topics, carefully chosen by independent peers free of commercial conflicts of influence. Annual meetings would be modelled on the early ACNP principles with limited attendance and leisurely agendas, conducive to extended and collegial dialogue. Participation and funding by industry would be encouraged but without involvement in the selection of topics or compounds.

The currents and tides swirling around the ACNP are symbolic of a tsunami, not a sea change. Proportionate prophylactic action is called for. Last week I receive an e-mail from the ACNP announcing that the Exedutive Committee wqs considering altering the title of the organization and its bye-laws to become :The American College of Neurosciences and Psychiatry. I sent them a copy of the above essay written a decade previously but have not heard back!

Unique to America

The two single case vignettes given earlier **(Intrinsic and Extrinsic Factors)** set the stage for understanding changes in health care unique to America. Because we do not have a government run "single payer" system, other than Medicaid and Medicare, access to treatment and what that involves is controlled and governed primarily by for profit insurance companies and to a lesser extent by alleged "not for profit" health care corporations with an eagle eye on their bottom lines and bloated administrative salaries, **(No Margin, No Mission).**

Until the early 21st century, people with severe and persistent mental illness (SMI) were denied health care insurance in the private sector. There was no parity between medical and mental health coverage and, even if applied for, it was routinely rejected as a "pre-existing condition", since almost all SMI conditions begin in adolescence or early adult life. Even after parity was mandated by Congress, the Federal Government was slow to issue guidelines and reluctant to enforce them; tardiness that insurance companies used to define their own restrictive policies.

As told earlier, people like Joe with complex medical and psychiatric problems were later denied the services of psychiatrists skilled in this arena by means of insurance "carve-outs". Others, like Sophie, where the intricate interplay of medication and psychotherapy is crucial to sound singular management, had these two components severed. It was cheaper to purchase therapy from lower cost providers (psychologists, social workers and assorted mental health counsellors) and limit psychiatrists to medication management (15-minute med-checks). No requirement or payment was made for interdisciplinary dialog.

Mammon and Modern Medicine

Mammon is an archaic word of uncertain, possibly Aramaic, origin. In the Bible, it refers to a deity, personifying greed or avarice but no such God has been revealed. I like to imagine Mammon was the twin brother of Midas, cornering the market on creating money and hoarding it. The M&M twins? In contemporary usage, devotion to Mammon conveys the antithesis of charity and benevolence, so it is often invoked to imply the lack of responsibility by an individual to maintain a balance between acquisition of wealth and generosity towards others in need.

In medicine, technology has purchased affluence and stifled empathy. Like alcohol, opiates and nicotine, money is addictive; its brand name is greed and, measured in millions, it is as infectious as influenza.

A Personal Anecdote

At age 84, I now live at the distal end of the stethoscope, a problem to be solved, seldom a person to be understood, often an aggrieved patient, greeted by Mammon in a doctor's office. :

> "In the mid 1990's I acquired a kidney stone, too large to pass, which required the services of our itinerant community lithotripter. Awaiting my turn in the hospital, a urologist inserted a stent in my ureter, creating passage for the coming fragments of stone.
>
> "Soon after discharge, still recovering from a savage attack of pseudo-gout and wrapped in a protective diaper, I visited the urologist's outpatient clinic. The crowded office was festooned with notices warning of the dire consequences for

> unpaid bills. An hour later, a nurse shunted me into an empty cubicle where I stripped naked and robed myself in one of those scanty and revealing hospital gowns. After a significant time lapse, I was ushered into the urologist's suite; he was absent, but I climbed onto the cold metal operating table with my legs placed in stirrups, ready for the scope to be inserted into my penis to withdraw the stent.
>
> "At this moment, the nurse, previously silent, thrust a sheet of paper into my hands, instructing me to read and sign it. But I had left my glasses along with my clothes. So, I invited her to do the reading for me. In a voice filled with purpose but devoid of feeling, she said, "If Medicare refuses to authorize the procedure the urologist is about to perform, I acknowledge full responsibility for the cost." Realizing I could not live with a stent in my ureter for life, I did my best to append a signature without my glasses and, like any other patient, kept my mouth shut. You don't want to piss off your surgeon as he is about to perform a delicate procedure."

At the medical school where my son graduated, outside the library, stands a more than life size statue of Hippocrates. Reciting his oath is a rite of passage at graduation. In its classical form, translated from Greek, the opening statement says: "To hold him who has taught me this art as equal to my parents and to live my life in partnership with him, and *if he is in need of money to give him a share of mine,* and to regard his offspring as equal to my brothers in male lineage and to teach them this art, if they desire to learn it, *without fee or covenant"* (italics added).

After the Flexner revolution, as science and technology invaded the curriculum, Mammon was doing well in the run-up to the Great Depression. Some schools chose to drop the Hippocratic Oath and any mention of fiscal generosity to the needy, including fellow practitioners and students, "professional courtesy".

Other schools substituted the Oath of Maimonides, which includes the statement: "May the love of my art activate me at all times, may neither *avarice nor miserliness* (italics added), nor thirst for glory, or for a great reputation engage my mind."

Finally, a so-called "modern version", was crafted in 1964 by Lou Lasagna, father of modern clinical pharmacology, when he was Dean at Tuft's University. This Oath leaves out all mention of generosity to peers or students but does state: "I will remember that I do not treat a

fever chart or a cancerous growth but a sick human being whose illness may affect the person's family and *economic stability"* (Italics added).

When I edited Volume 7 of the OHP, I dedicated it to Lou Lasagna, who was President of ACNP in 1980.

The way we treat our colleagues and students today has more to do with Mammon than any of the oaths we ask our students to swear by. "Professional courtesy" disappeared during the early 1980s and in the 1990s, medical schools began escalating tuition and stopped providing health care to students. In 1992, the average debt of a new doctor was around $25,000. By 2010, when my son was a student at the local medical school, tuition was $40,000 a year and the accumulated debt averaged $160,000, while a quarter of students owed more than $200,000. Despite having a large flourishing practice organization staffed by faculty, students were not provided health care. Those over age 26, like my son, were ineligible to be on their parent's insurance, but were offered an additional $10,000 a year loan to buy insurance. Adam declined, applied for and was granted Medicaid and offered food stamps.

Burdened by debt, graduating students choose careers in lucrative, procedure oriented specialties, turning their backs on the 'talking' professions, including family medicine, pediatrics, psychiatry and geriatrics. So, the doctors most likely to detect and deal with disease in its social matrix at its earliest and most treatable time are shrinking in numbers while specialists know more about less but become wealthy faster. With an ageing population, subject to falls, I suspect most orthopedic surgeons are millionaires by mid-life.

The doctors who remain in primary care often become salaried employees of large healthcare corporations, seduced by high salaries and freedom from practice management. But they are constrained by "productivity" criteria that reward quantity not quality, encouraging them to limit complex, chronic or time-consuming patients, such as those on Medicaid and Medicare.

King Canute and the Waves

12th Century legend (Henry of Huntingdon)

This ancient legend is most often misquoted as illustrating the King's arrogance by claiming he could stop the tide coming in by commanding it to stop. In fact, he gathered his flattering courtiers around to demonstrate the opposite. It was actually an act of humility:

> "Continuing to rise as usual, the tide dashed over his feet and legs without respect to his royal person. Then the king leapt backwards, saying, let all men know how empty and worthless is the power of kings, for there is none worthy of the name, but He whom heaven, earth, and sea obey by eternal laws." He then hung his gold crown on a crucifix, and never wore it again "to the honor of God the almighty King."

So, an event often misquoted as demonstrating hubris is actually an act of humility.

The relevance of this metaphor in its broadest (not religious) interpretation is that powerful, naturally occurring phenomena, can challenge and frustrate the most determined and diligent protagonist. As illustrated in this volume the biographies of many leading psychopharmacologists, display how often a changing economic, political, social or scientific Zeitgeist has intruded in their careers or obstructed their plans. David Healy catalogues many such fluctuations in the evolution of ideologies influencing his hypotheses about social change in the balance of public attention to intrinsic and extrinsic factors influencing healthcare, going back centuries. My own career trajectory has been influenced also by political and economic forces and changing patterns of healthcare delivery beyond my control, some peculiar to America but confined to the 20th and 21st Centuries. The editorial on "Medical Education and Modest Expectations" (Blackwell 1985) concludes: "There is no Holy Grail; like Canute I have learned that the tides of medical education cannot be turned."

Perhaps the major difference between my approach and David Healey's is his focus on changes in society at large while mine has been confined more to changes within medical practice and medical education which I believe are the major determinants of how doctors and individuals view illness and disease, perhaps also the most important influence in shaping public opinion.. That said we are united in our common concern about the **"**Shipwreck of the Singular." If we are to reverse this trend, the solution will lie, in America at least, in two areas. First, by strengthening the role of primary care practitioners as gatekeepers to specialty care, while assuring ready access

to behavioral consultation and support for their patients. Secondly, removing the insurance barriers in America to integrative biopsychosocial care and restoring the psychiatrist's ability to provide it. This offers the best hope for singular and integrated care with preventative possibilities, as well as a reduction in healthcare costs overall.

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Chapter 18

The Biological Basis of Psychitric Diagnosis & Treatment

Diagnostic Illusions

The Flawed DSM System

Biological Formulations in a Multiaxial System

Preamble

In the 19th century, pioneers like Thudichum believed, without clinical evidence, that disorders of the brain were linked to the chemical composition of the brain (Chapter 1). Early in the 20th century, response of specific symptoms to particular drugs (chloral hydrate, paraldehyde, bromides, barbiturates and amphetamine) reinforced that belief. In mid-century, Joel Elkes (Chapter 3) provided the missing link between physiology and chemical changes in the central nervous system shortly before the first drugs were shown to be effective for particular psychiatric disorders (Chapters 4, 5 and 6).

This opened the door to attempts to link specific drugs to diagnostic systems described in the essay below, *Diagnostic Illusions*

Diagnostic Illusions

OED: *illusion;* a deceptive appearance or impression; a false belief or idea

Until the mid-20th century psychiatric disorders were seldom, if ever, based on the response to treatment – there were none – beyond stifling selected symptoms (barbiturates, bromides, chloral, amphetamine, paraldehyde etc.)

Instead, classification of disorders was based on clinical features such as presumed etiology (familial, environmental or "endogenous"), nosology, natural history, prognosis, (the mark of a good clinician) and outcome. Notable systems were defined by Kraeplin, Schneider, Wernike-Kleist and Leonard (WKL) among others less well accepted.

The discovery of effective remedies in mid- 20th century sparked interest in a putative connection between particular drugs and specific disorders. A flock of diagnostic systems

evolved in rapid succession. The International Classification of Disorders, ICD (UK), the Diagnostic and Statistical Manual, DSM (USA), Prototypes (France), Neuropathology, (Germany), CODE (Ban), Selective Neurotransmitters (NIH), Genetic Diathesis (Universal) and RDoc (NIMH). The hard earned clinical knowledge accumulated in the 19th century was soon abandoned and, to all intents disappeared from educational programs and clinical practice.

The Flawed DSM System

In the Pioneer Era (1949-1980) hopes of biological specificity in treatment began to fade until DSM III ushered in a new multiaxial system designed to incorporate the biological, social and psychological components of each disorder. Introduced in 1980 by the American Psychiatric Association in America, it replaced the pre-existing clinical formulations with symptoms derived from a consensus of clinical experts (often after contentious debate) and largely uninfluenced by earlier knowledge from the pre-drug era concerning etiology, nosology, natural history, prognosis and outcome. Faults in the system appeared quickly and were not corrected. That the system was used primarily to justify insurance payments for drugs emphasized Axis One (Biological features) and the fact each diagnostic category included a Not Otherwise Specified (NOS) category encouraged slipshod diagnosis, a tendency that might have been checked by appropriate quality assurance criteria in clinical settings. These flaws also exposed the DSM system to corruption by industry and its hired KOL's encouraging spurious specific drug-diagnostic correlations and over prescribing (Chapters 19, 20 and 21).

"Biological Formulations" below is a chapter from the book *Psychiatric Case Formulations* (Sperry et al. 1992) part of an effort by the authors to address the problems of the DSM system by stringent use of the multi-axial format as well as incorporating information from earlier classification systems. The authors collaborated in sharing their areas of expertise: Sperry (Cognitive-Behavioral), Gudeman (Psychoanalytic), Blackwell (Biological) and Faulkner (Community psychiatry). Published a quarter century ago, the text remains remarkably relevant, testimony to the slow pace of innovation in the modern era. (1980-present).

A biological formulation incorporates four elements: evidence for a structural or biochemical etiology; the relationship between psychiatric and physical features; the availability

of biological markers, laboratory tests and imaging techniques; and treatment choice, efficacy and side effects.

Also described are features of history taken from the patient and significant others; examination of the mental and physical state; results of appropriate laboratory or test procedures; and, finally, treatment choices and prognosis. All this information is presented as both a Case Formulation and a DSM 5 axis diagnosis.

Biological Formulations

Formulation is a succinct statement of the patient's problem. It captures the essence of each person's predicament and offers an opportunity to transcend the descriptive parsimony of DSM-III-R (American Psychiatric Association 1987) by portraying a complete biopsychosocial perspective without adding axes to an overloaded schema.

Formulation may also be performed within the framework of a particular ideology or body of knowledge, be it biological, behavioral, or psychodynamic. This may seem antithetical to convergent biopsychosocial thinking but is a necessary task that illustrates a pedagogical paradox. Teaching is facilitated by considering the parts to a whole, even though such reductionism seems inconsistent with an integrated approach intended to stress systemic, nonlinear interactions.

Throughout the history of medicine, biological schemata have been part of almost every framework to understand and treat mental illness, although their significance has waxed and waned with philosophical and scientific change (Hunter and Macalpine 1964). The turn of this century marked a clear point of divergence between the proponents of descriptive and biological psychiatry and psychological theories of behavior. The former were epitomized by Thudichum, Kraepelin, and Greisinger, each of whom believed that psychiatric disorders were predominantly brain diseases. The psychological theories were represented by scientists of equal stature, including Freud, Adler, and Jung. Freud, however, also relied consistently on medical models and metaphors. His Preference for psychological understanding was related as much to the limitations of contemporary technology as it was to ideological principles (Jones 1953, p. 395):

> "We have no inclination at all to keep the domain of the psychological floating, as it were, in the air, without any organic foundation. But I have no knowledge, neither theoretically or therapeutically, beyond that conviction so I have to conduct myself as if I had only the psychological before me."

Psychiatric Case Formulations

Interestingly enough, the biological-descriptive approach held sway in Europe, while thepsychological-dynamic theories became increasingly influential in the United States. For a brief period, Adolf Meyer's psychobiological approach offered a tentative synthesis, reflected in the nomenclature of DSM-I (American Psychiatric Association 1952). By midcentury and DSM-II (American Psychiatric Association 1968), the pendulum had swung back in a more purely psychodynamic direction (Spitzer et al. 1980). Even while this was occurring, observations and discoveries were being made in neuropsychiatry that laid the groundwork for a paradigm shift in a more biological direction. These included the protean psychiatric manifestations of neurosyphilis, which were benefited first by fever therapy and finally by penicillin (Sirota et al. 1989). The psychiatric sequelae of viral encephalitis following the worldwide influenza pandemic also provided striking testimony for a brain-behavior link (Lishman 1978). Impairment of intellectual development and behavioral abnormalities in phenylketonuria demonstrated that such changes could be due to biochemical and not just structural lesions (Szymanski and Crocker 1989). These etiologic clues were coupled with therapeutic strategies, which, while poorly understood, produced benefits that could be explained predominantly in biological rather than psychological terms. Included were the effects of electroconvulsive therapy, insulin coma, lobotomy, the amphetamines, and the barbiturates (Kalinowsky 1984).

By mid-century, the basis for a more biological understanding certainly existed, but the dominant paradigm in the United States remained psychological. Biological etiology was still poorly understood, and the treatments were either drastic, selective, or relatively ineffective. As Thomas Kuhn (1970) pointed out, such an ideological plateau is customary when evidence is not yet conclusive enough to overwhelm resistance to a new paradigm, which comes from practitioners of the prevailing "normal science." In the last half of this century, four concurrent trends have pushed the pendulum strongly in a more biological direction. First came the serendipitous discovery of almost all the major categories of psychotropic drugs within a single decade (1950-1960) (Ayd and Blackwell 1984). Second, the shortcomings of American nosology revealed by the United States and United Kingdom cross-cultural diagnostic project provided an impetus toward the more rigorous descriptive and non-etiologic DSM-III (American Psychiaric Association 1980) method of classification (Cooper et al. 1972). Third, rapid technological advances in several areas facilitated brain-behavior understanding. These included recombinant DNA methods with gene mapping (Gershon et al. 1987), receptor assays producing more specific drugs (Snyder, 1985), biological and endocrine markers leading toward improved diagnosis (Whalley et al. 1989), and scanning techniques that display both structural (magnetic resonance imaging [MRI]) and functional (positron-emission tomography) aspects of brain function (Andreasen 1989). Fourth, and most recently, has been the social and economic impetus for short term, more definitive and cost-

effective forms of treatment that has favored biological over psychodynamic interventions (Parker and Knoll 1990). Societal adaptation to these trends is epitomized by legislative mandates that certain psychiatric conditions (such as bipolar disorder) be considered medical diseases and afforded the same insurance benefits as other physical illness.

Whether or not the current state of knowledge amounts to a full paradigm shift remains debatable, at least in the United States. Contemporary texts devoted to neuroendocrinology (Donovan 1988) and psychopharmacology (Meltzer 1987) are certainly encyclopedic, but, as noted recently by a reviewer in the American Journal of Psychiatry (Waziri 1990), books with a descriptive or biological bent are still outnumbered by those with a psychodynamic or psychotherapeutic bias. Despite the increasing pace of biological discoveries, there remains vehement opposition and criticism of the "disease model" in psychiatric practice (Johnstone 1989).

Whatever the contemporary Zeitgeist and however dominant the biological paradigm may appear, the practical question is the degree to which a core of scientific knowledge is available and useful to psychiatrists in everyday understanding and treatment of patients. Is there a body of biological information that illuminates formulation? As Lazare (1989) noted, a biological formulation can be made based on the extent to which the information gathered meets four underlying hypotheses or assumptions:

1. The patient's problem can be understood, in part, as resulting from a known organic/medical disease.
2. The patient's problem can be understood, in part, as being related to a concomitant physical condition.
3. The patient's problem can be understood, in part, as a functional psychiatric disorder characterized by genetic transmission or biological makers that may predict treatment response.
4. The patient's condition is known to be treatable, in part, by psychopharmacologic agents or other biological treatment.

It will be noted that three of these assumptions are basically explanatory, and two include treatment implications. Although the discussion that follows provides some evidence to support these hypotheses, it would be presumptive to claim proof. The brain is a sensitive and finely tuned but well-protected organ, and most of our etiologic theories remain just that. In the single diagnosis where DSM-III claims an organic etiology (primary degenerative dementia), our clinical criteria are still often inconclusive with regard to underlying pathology. In one study, a third of patients diagnosed with Alzheimer's disease failed to show the appropriate postmortem neuropathologic findings to support the diagnosis (Risse et al. 1990).

Efforts to demonstrate a structural or biochemical basis for the major psychiatric disorders have been arduous and exciting but remain frustratingly inconclusive (hypothesis 1). In schizophrenia, for example, recent attempts to demonstrate brain abnormalities have focused more on neuroanatomy and neurophysiology than on biochemistry (Mesulam. 1990). Neuroimaging techniques have sometimes shown an increase in the size of the frontal and temporal horns of the cerebral ventricles and a decrease in the size of the hippocampus. The ingenious application of these strategies to study the brains of monozygotic twins discordant for schizophrenia has shown that some of these structural changes are probably acquired and not genetic (Suddath et al. 1990). In addition, the overlap between "normal" controls and schizophrenic patients is substantial, and the findings are not specific to schizophrenia but can also occur in Alzheimer's disease and manic-depressive disorder. Similar uncertainties exist in interpreting the findings based on regional metabolic brain activity. Studies have reported both hypometabolism of the frontal lobe and hypermetabolism of the left temporal lobe. The findings bear an exciting correlation to the clinical manifestations of schizophrenia, with the negative symptoms of the illness resembling the results of frontal lobe damage and the positive features likened to manifestations of temporal lobe epilepsy. Again, however, it is unclear whether such changes truly reflect the underlying etiology of the disorder or if they are secondary manifestations of ongoing behavior or treatment. A recent editorial on this topic (Mesulam 1990) drew the following conclusion:

> It is currently impossible to distinguish primary pathophysiologic processes from secondary epiphenomena or idiosyncratic observations from those that are universal. Chances are that schizophrenia is a disease of the brain but it is unlikely that such a complex, multifaceted, and fluctuating condition could be caused by fixed damage to a single brain site or neurotransmitter pathway. (p. 843)

Despite this absence of conclusive evidence of a general nature, the author of the editorial makes a telling point with regard to the biological formulation of individual cases in our current state of knowledge and its relationship to the use of contemporary diagnostic schemata:

> The evidence strongly suggests that at least some patients with schizophrenia have detectable structural and physiological abnormalities of the brain. Item E of the criteria for schizophrenia listed in DSM-III-R, the inability to establish an organic factor, may need to be eliminated. Perhaps this will start a trend towards the total elimination of the term "organic" which is often a source of obfuscation and an obstacle to lucid differential diagnosis. (p. 844)

The relationship of psychiatric manifestations to concomitant physical conditions (hypothesis 2) is well accepted and has been repeatedly demonstrated. One review lists more than 50 physical disorders in different categories that may present with psychiatric symptoms (Kirch 1989). These include neurological, endocrine, metabolic, toxic, nutritional, infectious, autoimmune, and neoplastic disorders. Almost half of our patients have undetected medical problems, and in about half of those there is a direct contributory link to the patient's psychiatric symptomatology or mental status (Hall 1980). The extensive literature on this topic is consistent and compelling enough to justify the conclusion reached by Jefferson and Marshall (1981) that

> "there are few if any, psychiatric symptoms that cannot be caused or aggravated by physical illness. The non-specificity of altered mood, behavior or perception requires a clinician to continually contend with the possibility that there maybe an underlying non-psychiatric disease process accounting entirely for or contributing to an apparent "functional" disorder." (p. 1)

In addition to direct biological evidence of causation, clinicians and researchers have been eager to discover diagnostic tests or markers of disease that would assist in classification or treatment choice (hypothesis 3). Such attempts have a long but frustrating history influenced as much by fashion and the theories of the time as by sound scientific evidence. Historical examples include mapping bumps on the head (phrenology), culturing the bacteria in patients' stools (intestinal autointoxication) and, more recently, measurement of urinary metabolites (the biochemical classification of depression) (Kirch 1989). Among the most consistent attempts to identify a biological basis for clinical conditions has been evidence of genetic transmission. Pedigree analysis and twin and adoption studies have provided sound evidence for the biological contribution to many psychiatric disorders. The application of this information to the formulation of an individual case, however, has relatively weak predictive power. The development of gene mapping technology (Gershon et al. 1987) may alter this by providing the means of identifying the individual's personal genotype, as is already the case for Down's syndrome. In Huntington's chorea, linkage analysis of the potential patient and of affected and unaffected relatives allows almost certain prediction of the likelihood for developing the condition (Brandt et al. 1989). Unfortunately, this is a disease with no treatment, and genetic screening is fraught with psychosocial problems. Findings in major psychiatric disorders have been tantalizing but remain inconclusive. Individual kindreds have shown linkage for chromosome 11 in bipolar disorder and chromosome *5* in schizophrenia, but others have not. The impediments to accurate conclusions from linkage studies are considerable, and real progress is unlikely until the genes themselves

are isolated (Merikangas et al. 1989). Even then it is almost certain that in psychiatric disorders more than one gene will be implicated and more than one neurochemical or physiologic process is involved.

The list of putative biological markers and laboratory tests used in psychiatric practice is extensive and includes imaging, electrophysiology, endocrinology, biochemistry, toxicology, hematology, serology, and microbiology. Only a minority of those tests studied for research purposes have proven practical and useful in clinical practice, although others have certainly supported the significance of biological contributions to causation. Examples include polysomnograph studies of rapid eye movement sleep (Roffwarg and Erman 1985); the use of blood platelets to study drug binding and receptor sites (Kafka and Paul 1986); and the various endocrine techniques used to study the hypothalamic-pituitary axis, including dexamethasone suppression and the thyrotropin-releasing hormone test, (Loosen and Prange 1982).

It is frustrating, however, to note the disappointing outcome of some earlier attempts at investigations intended to enhance biological formulation. For a brief while, there was excitement about the ability to categorize depression into biochemical subtypes that would influence choice of medication, but it is now clear that most patients respond equally well to drugs that alter norepinephrine or serotonin or that may share some as yet unknown common mechanism of action, (Kirch 1989). Equally disappointing has been the failure of the dexamethasone suppression test to achieve widespread utility. Its sensitivity and predictive value fell to unacceptable levels when the test was used in less selected populations than those in which it was developed (Carroll 1985). It remains possible that such tests may be refined or may have a selected use in a particular context—the prediction of suicide risk is one such possibility. Another is the finding that a positive dexamethasone suppression test is correlated with a poor response to a placebo, indicating the need for pharmacologic treatment. However, response is not coupled with benefit to any particular type of antidepressant (Peselow et al. 1989)

It is in the domain of treatment (hypothesis 4) that we have attained more conclusive data. The scientific rigor of the double-blind, controlled trial at least allows some certainty in statements about the specificity of treatment outcome compared with placebo response or spontaneous remission. For both methodological and ethical reasons, such control measures are seldom applicable to outcome studies of psychosocial interventions, and although alternative strategies exist, the results are often less conclusive or compelling (Strayhorn 1987).

What such studies have shown is that biological treatments make a consistent contribution to improved outcome in most of the major psychiatric disorders (Ayd 1984). The treatment of schizophrenia has been transformed by neuroleptics, contributing to widespread closure of psychiatric facilities. A majority of patients with bipolar disorder benefit significantly and for sustained periods with the use of electroconvulsive theory, lithium, and a variety of

antidepressants. New categories of compounds with more specific pharmacological effects are beginning to appear. The anxiety disorders show more varied and less global benefits, although there is increasing evidence that patients with obsessive-compulsive disorder improve specifically with somatic therapy. In conditions with a clear-cut organic etiology, such as Alzheimer's disease or Huntington's chorea, patients presently remain unhelped, but our rapidly advancing knowledge of their pathophysiology will eventually yield specific biological remedies.

The quality if evidence garnered from clinical trials may be constrained by flaws or limitations in the methodology (Newcombe 1988), and however compelling the results, they sometimes fail to influence practice because of stigma and social prejudice. For example, although research evidence shows clearly that electroconvulsive therapy is effective, opposition to its use persists, perhaps contributed to because its mechanism remains unclear, although hypotheses abound (Fink 1990). A similar controversy surrounds the use of cingulotomy for refractory obsessive-compulsive disorder (Bouckoms 1990). In the field of antidepressant drug therapy, Paykel (1989) reviewed the relevance of the research literature to clinical practice and concluded that the former certainly illuminates the latter with regard to general effectiveness but only "to some extent" in relation to specific treatment choices for an individual patient.

As in the rest of medicine, knowledge about the patient is derived from two primary sources: the history and the examination or investigation of the patient. These provide us with the symptoms, signs, and markers of disease. These two sources of information will be examined to illustrate the part they play in revealing biological factors that influence each of the components of a formulation: explanation (or etiology), description (or diagnosis), and treatment choice and prognosis

.**Explanation and Description**

Information may come from both the patient and other informants, including relatives or care providers. The latter may be most valuable in patients whose memory, judgement or insight is eroded by biological impairment of brain function. The topics of particular relevance to biological formulation are family history and the possible precipitants, natural history, and symptoms of the condition.

In obtaining a family history, much may be forgotten and repressed or its significance missed or denied. Elicitation of a family tree across at least three generations (grandparents to children), specific questions about particular conditions, and use of cultural metaphors (e.g., "nervous breakdown") may help (Baker et al. 1987). Comorbidity should be considered (e.g., alcoholism in affective disorder) and atypical features (which often breed true) noted. Polygenic inheritance, incomplete penetrance, and cultural plasticity ensure that family histories of mental illness are seldom clear-cut or dramatic except in special circumstances with rare dominant pedigrees, such as Huntington's chorea or sequestered subcultures like the Amish.

History taking may reveal a number of etiologic factors that indicate a biological component. Existing medical diseases and their treatments contain manifold causes for a change in mental status, especially in anxiety and affective disorders or delirium and more rarely in psychotic phenomena. Communication with the patient's primary care practitioner may prove invaluable. Cause and effect are often attenuated; a drug or disease may enhance the vulnerability to a psychiatric condition rather than being a single or simple cause for it. A58-year-old, black. middle-aged bus driver whose hypertension had been controlled with reserpine for 10 years became severely depressed for the first time after his wife's death. His depression did not respond to grief therapy or antidepressants until after his antihypertensive medication was changed. Presumably reserpine, with its tendency to deplete catecholamines, had created a biochemical vulnerability. Until this was corrected, other usually effective treatments did not produce a response.

Information on use of street drugs or dietary substances (e.g., caffeine in coffee or cola drinks) that may mimic, provoke, or exacerbate a psychiatric condition, particularly an anxiety disorder, should be requested.

Multiple organic factors may contribute to a final psychiatric outcome. For example, an 82-year-old woman living alone developed an early dementia and as a result forgot to nourish herself properly, then became dehydrated, and finally developed pneumonia, followed by delirium.

In relatively rare instances, an occult and previously undetected organic condition will manifest itself as a psychiatric disorder. Examples are legion and include thyroid disease, pancreatic carcinoma, and thiamine deficiency. At times the psychiatric presentation will be so textbook or classic that underlying organic etiology is discovered only during routine physical examination. Sometimes, however, there is a telltale amplification of particular features. The patient with myxedema underlying a depression may have extreme slowing of cognition or lethargy. The man with depression and pancreatic carcinoma may have weight loss disproportionate to change in appetite; the palpitations of a woman with thyrotoxicosis may be unrelated to psychological triggers.

An often-neglected aspect to identification of biological features of a disorder is that illnesses with a significant biochemical component tend to follow a predictable course. They behave like other medical conditions with a more or less clear-cut onset and natural history. There is an obvious point at which the person’s behavior differs from his or her customary self in ways that may at first be more noticeable to others. This distinction between what is new (Axis I) and what is enduring (Axis II) is important, but not always easy to make since personality features may also modify or amplify the manifestations of the primary disorder. A successful young attorney who had always been the soul of discretion began to make sexually provocative remarks at the office and spent his entire savings on a trip to Hawaii accompanied by his secretary. Knowledge that he had a sexually repressed childhood and an unsatisfactory marriage should not postpone treatment with lithium before he bankrupts himself, ruins his career, or further damages his marriage.

The fact that failure to distinguish between a new major disorder and its effects in amplifying preexistent personality traits can have a potentially disastrous impact is illustrated by the *Osheroff v. Chestnut Lodge* controversy (Klerman 1990). A physician was treated for 7 months as an inpatient with intensive individual psychotherapy. His condition deteriorated markedly but he recovered within a few weeks after transfer to another hospital and treatment with psychotropic medication. The expert testimony that followed during legal proceedings focused on the issue of whether or not certain behaviors reflected a narcissistic character disorder or were attributable to untreated major depression. There seems little doubt that medication was inappropriately withheld, and the case has been widely construed as illustrating a paradigm clash between psychodynamic and biological models. However, it can also be seen as an issue of opinion versus evidence, with a rigid adherence to only a single approach when both medication and psychotherapy would have been indicated either concurrently or sequentially (Stone1990).

Symptoms play a vital role in indicating a biological etiology. Alterations in orientation and memory are the cardinal features of an organic condition affecting the brain. A 45-year-old woman was brought to the emergency room by her husband while on vacation with the history that she had been drinking excessively for several months. On the morning of admission, he had found her in the hotel room confused and complaining of a severe headache. The emergency room physician diagnosed alcohol withdrawal, but the psychiatrist determined that recent alcohol consumption had been modest, the onset of headache was sudden, and the confusion was disproportionate to other signs of alcohol withdrawal. A computed tomography (CT) scan revealed evidence of a recent intracranial bleed. In the absence of trauma, a diagnosis of cerebral aneurysm was made and confirmed at subsequent craniotomy.

Other Axis I conditions not categorized as organic disorders may also have core symptoms that are empirically associated with a response to drugs and linked to a hypothesized biochemical defect. In major depression, these are the features of a presumed hypothalamic-pituitary dysregulation manifested by “melancholic” symptoms, including anhedonia, sleep disturbance, loss of libido, anorexia, and weight loss. Among the anxiety disorders are the protean symptoms of autonomic arousal that have been treated for centuries as somatic in origin. In schizophrenia, the core feature is a breakdown of integration between thinking, feeling, and behavior (“intrapsychic ataxia”), which manifests itself in Schneider’s first-rank symptoms that are frequently responsive to those drugs that block dopamine receptors.

Interpretation of somatic complaints is particularly vital to accurate biological formulation. Their presence may serve to obscure, amplify, or mimic a psychiatric disorder. In consultation to medically sick individuals, the complaints due to organic disease may be indistinguishable from the somatic manifestations of depression or anxiety. Only such cognitive features as negativistic ruminations, hopelessness, suicidal ideation, or unrealistic fears may indicate the accompanying psychiatric disorder. A previously independent, active 40-year-old business executive developed an unexplained cardiomyopathy that required intensive medical management. During a prolonged stay in intensive care, he experienced multiple complications, including deep vein thrombosis, pulmonary embolism, and renal insufficiency. Assessment of a possible depression was complicated by extreme daytime lassitude, nighttime insomnia due to pulmonary embolism

and fears that there was no end in sight to his suffering. His cognitive state was judged appropriate to his predicament and improved dramatically when an individual team member was assigned to explain interventions, plan daily assignments, and plot a rehabilitative course to create “light at the end of the tunnel.” This case also illustrates the difficulty of differentiating a major depression (obscured by symptoms of organic disease) from an adjustment disorder with depressed mood in a medical setting, where symptoms of demoralization may be secondary to a protracted stay and multiple surgical or medical interventions (Snyder et al. 1990).

The meaning of symptoms can be modified not only by the patient’s bodily condition but also by the mind-set of the observer. We can all be blinded by our role as psychotherapists and by the seductive influence of psychodynamics. At times we need to be reminded that as psychiatrists we are first physicians and as physicians it is our duty “to physich.” This imperative to seek out, identify, and treat the biological components of illness is part of our social mandate. Even those of us who believe firmly in this obligation may be reminded of it by our own oversights. A few years ago I was treating a young woman referred to me by an expert psychopharmacologist who had completed a thorough medical workup. Her atypical depression and somatic complaints yielded temporarily to medication, but since she also had severe developmental psychopathology that disrupted her work and marriage, we met weekly for psychotherapy. Engrossed in the dynamics, complacent with my colleague’s work up, and seduced by the early response to medication, both I and my patient minimized and misinterpreted her deteriorating physical condition. When her symptoms worsened abruptly, she attended an emergency room and was referred to a neurologist, who called to tell me that my patient had multiple sclerosis. The patient was not angry at my oversight, and our psychotherapy continued, but its focus shifted from interpreting or ignoring symptoms to adapting and coping with them.

A difficult aspect of biological formulation is the accurate assessment of bodily symptoms in the somatoform disorders, particularly in patients with accompanying medical conditions. This may call for considerable clinical acumen since the fundamental task is to determine the degree to which disability is disproportionate to known organic disease (Blackwell and Gutmann 1987). Neurologists and internists make this diagnosis on the basis of discrepancies or inconsistencies between signs or symptoms and the known pathophysiology of the condition, but psychiatrists have the added responsibility of eliciting what primary or secondary gain exists to amplify suffering beyond what disease can account for. What irreconcilable conflicts or irresistible rewards have driven or seduced the patient into the sick role? A 52-year-old, devout, Catholic Puerto Rican mother of two teenagers developed a relatively rapid onset paraplegia for which the neurologists could find no organic cause. Careful history taking revealed the symptoms began 24 hours after her 15-year-old daughter announced she was pregnant and 1 week after her son was arrested for dealing drugs. Her husband, from whom she was separated, had returned home to help deal with the family crises and had assumed all household responsibilities as a result of her sickness. The presence of such dynamics, however, should not blind us to the fact that fully a quarter or patients diagnosed as conversion disorder subsequently develop a physical condition (Watson and Buranen 1979).

Whatever our hopes for the biological revolution in psychiatry, we remain far more heavily dependent than the rest of medicine on history taking. However, examination and investigation are becoming increasingly important and contributory to formulation.

Examination includes both the patient's physical condition and mental status. Psychiatry still suffers from the psychodynamic excesses of the 1940s and 1950s when our specialty abolished the internship and espoused a "hands off" approach to evaluation. As part of the tragic error of "demedicalization," as recently as 1975 only 7% of psychiatrists believed that physical examination was indicated or useful (McIntyre and Romano 1975). However, of those who did their own physical examination, 94% found them useful in establishing the diagnosis. Even today the task of examining the patient physically on admission to the hospital is still too often delegated to unlicensed physicians or moonlighting medical students who may have little understanding of how occult physical illness can cause or aggravate the patient's mental condition. This absurd dualism will continue as long as our training programs perpetuate it. Recently I evaluated an elderly man about to be discharged to a nursing home with a treatment refractory retarded depression. The internist who admitted him had missed the significance to his slow pulse, sluggish reflexes, and dry skin. The psychiatrist who treated him unsuccessfully with antidepressants had overlooked the abnormal thyroid function test. After correction of his thyroid status and treatment with electroconvulsive therapy, the patient's condition improved significantly, and he was again able to care for himself.

Equally important are the nuances of the mental state that may indicate a biological component. These are mainly those impairments of cognitive function in orientation, memory, and judgement that can be elucidated by the Mini-Mental State Exam (Folstein et al. 1975). Because fluctuations in mental state are a cardinal feature of organic impairment, it is often useful to examine the patient more than once (especially in the evening, when "sun-downing" occurs) and to obtain information from the patient's relatives or care providers.

It is especially important for the psychiatrist to be aware of the cognitive and emotional changes that may be related to structural lesions in the brain (Solomon and Masdeu 1989). On occasion, particularly early in the disease process, these may provide important clues to localization or etiology. Lesions of the frontal lobe (Ron 1989) are especially prone to present in an insidious manner that may mimic psychiatric disorder, resulting in delayed surgical intervention, sometimes with tragic consequences.

In addition to history taking and examination, laboratory tests and investigations may also contribute to biological formulation in two ways. First they help reveal or exclude concurrent medical conditions that may be causing or contributing to changes in mental status. Second, they may provide diagnostic confirmation of the psychiatric diagnosis itself. Precisely what tests are ordered should certainly be influenced by such factors as the patient's age, symptomatology, medical history, and proximity of previous physician visits. It is customary to include urinalysis, a complete blood count (including folate and vitamin B_{12} levels), and tests of hepatic, renal, and thyroid function. Electrolytes, blood glucose, a toxic screen (for drugs or alcohol), and syphilis serology are also important. Coupled with a chest X ray and physical examination, such a panel

is usually adequate to rule out the majority or potential underlying organic conditions or to reveal the more common toxic, metabolic, or nutritional causes for a delirium. An Interesting challenge to indiscriminate broad-scale laboratory tests (White and Barraclough 1989) found that only thyroid function tests (in women), urinalysis (in women), white cell counts, and syphilis serology were justified by frequency of abnormal results. Obviously the quality of primary medical care in the population screened is significant, and it would be unwise to extrapolate such results from one culture (in the case Britain) to all other cultures, particularly when medico-legal considerations may be operative (as is true in the United States). An electroencephalogram may also be helpful in the diagnosis of protracted delirium or in revealing epileptiform processes that sometimes contribute to psychoses. CT or MRI provide clinicians with increasing specificity in the diagnosis of dementia, and neuropsychological testing may be valuable in the localization or cortical lesions.

In today's cost-conscious climate, clinicians should be aware of the criteria for imaging techniques (Weinberger 1984). There is increasing evidence that MRI may reveal more detailed and specific pathology than CT in some conditions (Jordan and Zimmerman 1990). Of special interest to psychiatrists is the finding of subcortical white matter lesions in various forms of psychosis (Colon et al. 1990; Miller et al. 1989). Recently my colleagues and I investigated three elderly patients with late-onset paranoid delusions who had relatively intact cognition. Each had an abnormal MRI that showed subcortical encephalopathy. Although this may be a chance finding between a common clinical symptom and a new sensitive test, it illustrates the exciting possibilities that new techniques may offer in understanding etiology and enhancing diagnosis.

More specific neuroendocrine tests such as dexamethasone suppression or thyrotropin-releasing hormone stimulation are probably best reserved for those treatment-refractory cases (Zohar and Belmaker 1987) where it may be helpful to establish an organic basis for the condition before initiating more aggressive treatment strategies, such as electroconvulsive therapy or combination chemotherapies.

Finally, it should be remembered that an increasing number of patients with AIDS may present initially with a psychiatric syndrome (King 1990). The central nervous system manifestations of this condition are as protean as those due to syphilis in an earlier era. Human immunodeficiency virus testing with appropriate confidentiality may therefore be indicated, particularly in individuals who are members of at-risk populations.

Treatment and Prognosis

Biological features may also influence choices of treatment and prognosis. Drugs are not equally effective across the spectrum of Axis I disorders; biological agents are most likely to exert benefit in those conditions with most evidence for a biochemical etiology (Blackwell 1975). Disorders that can be provoked by chemical means may benefit from them. Reserpine can cause

depression, amphetamine can cause a reactive psychosis indistinguishable from schizophrenia, and lactate infusion will induce panic attacks. Benefit derived from drugs in these disorders is due to their *specific* biochemical action (as opposed to change because of placebo response or spontaneous remission). These two latter sources of improvement are ubiquitous but variable with regard to diagnosis. A finding from controlled studies is that patients with obsessive-compulsive disorder show virtually no placebo response, so that although benefit from the active agent is seldom dramatic and often incomplete, it is always specific (Thoren et al. 1980). The elderly, on the other hand, who may be isolated and lonely, often display a large nonspecific response to low dosages of safe drugs that are little more than rational placebos. Patients with medical conditions tend to respond poorly to antidepressants, are often sensitive to side effects, and show little specific or nonspecific improvement. The use and outcome of medications in personality disorders are colored by the condition. Dependent patients may be difficult to wean; aggressive people may become disinhibited; and borderline patients will react to drugs as they do to people, with alternating idealization (a wonder drug) or disparagement (terrible side effects).

Beyond these broad generalizations, psychiatry finds itself at a disadvantage relative to the rest of medicine. There is no solid evidence for treatment specificity when selecting among drugs in a particular category to treat a defined Axis I disorder (Paykel 1989). For example, all antidepressants irrespective of their mechanism of action are equally effective and attain a comparable 70%-80% good outcome when given to a large, heterogeneous group of depressed individuals. The search for a specific responder to monoamine oxidase inhibitors has lasted for 30 years with results similar to the search for the Loch Ness monster—reliable observers report infrequent sightings but each describes something different (Blackwell 1986). More confusing still is the fact that drugs called antidepressants can benefit diverse conditions, such as chronic pain, enuresis, and panic disorders, often independent of a consistent improvement in affect (Blackwell 1987).

Faced with this lack of treatment specificity relative to the clinical syndrome, the choice between drugs is often influenced by other features of a disorder. The most reliable is a history or response to a particular drug in a previous episode; not only may this predict the degree or response but also its rapidity and completeness. Less often available and supported by a slender research literature is the notion that the response of blood relatives may predict benefit in a proband. Recently I treated a young woman with an atypical bipolar disorder who responded well to lithium after 10 years of chaotic life on the streets. When her mother witnessed the improvement, she insisted that her husband, who had been treated for years with phenothiazines at another institution, also receive lithium. He too obtained considerable benefit, and both father and daughter, who share similar clinical conditions, are now well stabilized.

A second avenue of influence on choice between biological interventions is the need to match the side effect profile of the drug to the susceptibility of the patient. An elderly man with a large prostate may develop urinary retention on a sedative tricyclic compound; an older woman placed on phenothiazines may begin to display parkinsonism. The elderly in general are vulnerable because of their altered metabolism, concurrent medical conditions, and other medications with which psychotropic drugs may interact (Raskind and Eisdorfer 1978). At times, electroconvulsion therapy may be the safest option for such patients.

Choice among medications is also dictated by the experience of the practitioner and the logic that underlies sequential exposure to different drugs. “First-choice” medications have the seductive property of reinforcing the prescribing prejudice of the practitioner, since spontaneous remission and placebo responses are added to the specific pharmacologic benefit (Blackwell and Taylor 1967). Subsequent exposure of treatment-refractory patients to second-choice agents or augmentation protocols often follows a law of diminishing returns. An ideal “first-choice” drug is one that does not hamper subsequent treatment if it fails; fluoxetine (with its lengthy half-life) and monamine oxidase inhibitors (with their prolonged enzyme inhibition) have obvious drawbacks. A major contribution of biological treatments to psychiatry has been the methodology of controlled trails, which can protect us from the referral biases and self-fulling prophesies of our own practice (Paykel 1989). Biological formulation is informed by the research literature as well as by individual experience.

Except on those occasions when they facilitate diagnosis, special investigations and laboratory tests provide little guidance for treatment choice in psychiatry. An exception is the use of plasma level monitoring for those drugs whose bioavailability and metabolism make such information useful in determining compliance, the adequacy of treatment, or its relationship to adverse effects (Kirch 1989). Lithium treatment and prophylaxis is undoubtedly the best example, but the use of blood levels may also be valuable in high-risk populations or treatment-refractory patients in whom the need to titrate medication carefully can dictate choice of a drug (such as nortriptyline) where there is a reasonably reliable relationship between plasma levels and outcome. Monitoring for blood dyscrasia is also routine in the use of carbamazepine and clozapine.

While prognosis is a part of formulation, it is a most uncertain art. In some of the brief reactive or schizophreniform psychoses, good outcome is linked to rapid onset, clear psychosocial precipitation, and affective features. In general, however, the heterogeneity of even our major classifications (Bleuler’s “group of schizophrenias”) and the multiplicity of biopsychosocial factors almost guarantee an unpredictable natural history in any individual, although it is true that controlled trials provide statistical blueprints within which to speculate about outcome. The likely length of any biological treatment is logically related to the natural history of the untreated and underlying biochemical condition (Blackwell 1975). But we have had

biological treatments since the mid-1930s and effective drugs since the mid-1950s, so it is difficult to find untreated populations that will provide yardsticks. Age at onset, severity of symptoms, comorbidity, previous episodes, and psychosocial stressors may all enter the predicative equation, but often we have only a stereotype of good prognosis that applies to all interventions, biological or otherwise. Those likely to do well have a good premorbid personality; occupational, marital, and social stability; and a clear onset related to a defined precipitant. Nowadays one hardly needs to add that such individuals are more likely to have good insurance. A counterpoint to the uncertain prognosis in psychiatric patients is that medical residents who rotate through our inpatient services express surprise at the good response of psychiatric patients to medications compared with the chronic treatment-refractory patients they commonly encounter on medical floors.

The Case of Mr. A

The formulation of the case of Mr. A will be presented in two stages: first, a lengthy exposition that illustrates components with their underlying logic, and second, a pithy succinct synopsis that provides the essence of a model formulation.

Case Summary

Mr. A is a 42-year-old businessman who presents with complaints of loss of interest in his job, hobbies, and family over a period of 6 weeks. He acknowledges periods of profound sadness, reduced appetite with significant weight loss, insomnia, fatigue, and recurrent thoughts of death, but denies suicidal indeation. He denies any precipitants, but does admit that his expected job promotion has not materialized.

Mr. A describes himself as unusually serious, conservative, and relatively unable to express affection. He also acknowledges trying to be perfect, needing to be in control of every social situation, and having an excessive commitment to work.

Mr. A indicated that his marriage has been worsening for several years and describes his wife as flighty, overemotional, and helpless under stress. For the past several years, she has been angry and distant and has declined to be involved sexually with him. Since the onset of his symptomatology, however, she has been solicitous and obviously concerned. The A's have two children, a 12-year-old girl and a 10-year-old boy, who appear to be doing well at school and at home.

Mr. A describes his family origin as very poor. His father deserted his mother when the patient was 12 years old; as the oldest child, he had to take considerable responsibility for younger siblings, as well as to work part-time while attending school. Mr. A's maternal

grandfather committed suicide, and two maternal uncles were alcoholic. A paternal uncle died in prison after a long period of antisocial behavior.

Physical, laboratory, and neurologic studies are negative. The DMS-III-R multiaxial diagnosis is as follows:

Axis I Major depression, single episode (296.22)

Axis II Obsessive-compulsive personality disorder (301.40)

Axis III No relevant current physical disorder

Axis IV Severity of Psychosocial Stressors: 3, with moderate stress due to marital discord and work problems

Axis V Current Global Assessment of Functioning (GAF) score: 52; highest GAF score past year: 6

Formulation

Mr. A's family history suggests a genetic predisposition to affective disorder, both directly on the maternal side with his grandfather's suicide and indirectly by comorbidity with alcoholism and sociopathy in uncles on both side of the lineage. Other potential etiologic factors that need to be excluded by further history taking would include the absence of physical illness or the use of any medications and abuse of recreational drugs (particularly cocaine) or alcohol. In addition to facts obtained by history taking, these possibilities should be pursued with information from the patient's primary care practitioner and another family member who knows Mr. A's habits well. The negative results of the routine panel of laboratory tests (presumably including thyroid function) would also help rule out any biological factors contributing to etiology.

Description

Two aspects of the illness itself support biological formulation. The onset is relatively abrupt and marks a clear-cut change from a customary level of function. Second, there are features suggestive of melancholia that are often attributed to hypothalamic dysfunction. These include insomnia, weight and appetite loss, and anhedonia. Not mentioned but to be inquired about would be any changes in his sexual interest or activity (inside or outside the marriage).

Treatment and Prognosis

Outpatient treatment would be indicated by continued ability to work, absence of suicidal ideation, and support and involvement by his wife in medication management

Since there are no previous episodes of illness, no family members treated for depression, and no concurrent physical illnesses or medications to influence treatment, the choice of an antidepressant would be dictated by need for some sedative properties to deal with Mr. A's

insomnia. A tricyclic compound such as nortriptyline, imipramine, or amitriptyline would be selected, any of which could be subsequently monitored by plasma levels if response is problematic or if serious side effects occur. Before initiating treatment, discussion with Mr. A would determine his attitudes, beliefs, and concerns about the appropriateness of medication. Given his obsessional personality characteristics, some concern about the possibility of drug dependence might be anticipated. On the other hand, it is also likely that he would not be particularly psychologically minded and that an explanation based on a possible chemical imbalance would be appealing to him. Assuming Mr. A's concurrence with treatment, the benefits, side effects, and time course of response to medication would be explained. Immediate improvement in sleep would then be predicted, to be followed by more insidious uplift in mood. A relatively low starting dosage would be given 2 hours before bedtime and titrated upward in small increments to obtain 6-8 hours of restful sleep with tolerable side effects. This dose would be maintained unless the predicted improvement in melancholic symptoms did not occur after 2-3 weeks, in which case the dose would be further escalated.

The prognosis given Mr. A would be good for this episode and somewhat more guarded for future affective illness. Of 10 individuals, 7 or 8 respond well to antidepressants, and Mr. A's history reveals several good prognostic features, including melancholia, a good premorbid personality, and a high level of social and occupational function although there are problems in the marriage and being passed over for promotion at work. With affective illness, 50% manifest as a single lifetime episode, but future relapses would be more likely if etiologic factors remain unresolved. Both the duration of drug treatment and likelihood of future relapses might therefore be related to the extent to which concurrent psychotherapy (psychodynamic or behavioral) and social change (e.g., divorce or job change) occur.

The average length of an untreated first episode of depression was about 6-8 months before there were effective treatments. Mr. A would be told that medication should be continued for at least this time period and that cessation of drug therapy would also depend on the extent to which life stress was reduced and his coping capacity had improved these in turn depending on any marital or personal therapy. When these criteria were attained, medication would be slowly weaned over 2-3 weeks to avoid withdrawal and treatment would be terminated after a further month or so of drug-free well-being.

The formulation of the case of Mr. A merits a final word of caution and comment that incorporates explanatory, descriptive, and treatment implications. Mr. A may invite the same kind of single-minded error illustrated in the *Osheroff* case (Klerman 1990; Stone 1990). Personality quirks are common, and nobody's life is free of blemish or painful incident. In this instance, the outstanding feature of the case is not the presence of such everyday occurrences, but the onset for the first time in mid-life of a new, severe, and incapacitating condition with no clear-cut cause. In the past, such illnesses were often considered "endogenous" and were typified by their rapid and complete resolution with biological treatment alone. It is distressingly simple to construct a web of psychodynamic speculation and, in doing so, to be seduced into withholding drugs while the patient is encouraged to "work through" his or her imagined predicament. Worse still, drugs may be pejoratively view as "trivializing the illness experience" or "stifling affect," with recovery dismissed as a "flight into health". Mr. A deserves better, and although he may benefit

in the long term from psychological insights, he should never be denied psychotropic medication. The clinical criteria for different types of psychotherapy (cognitive, psychodynamic, or interpersonal) in depression have been well described (Karasu 1990), but it should be remembered that drugs alone would be the treatment choice in some cultures, that even if combined with psychotherapy they make the major contribution to variance in outcome for Mr. A's type of illness, and, finally, the rules of parsimony suggest that the simplest, most effective treatment be offered first followed or accompanied by marital and individual therapy once the major depression has responded to treatment.

The Biological Formulation

This 42-year-old married, white father of two children has experienced a 6-week onset of his first episode of major depression characterized by melancholic features but without suicidal ideation. The family history is positive for affective disorder and comorbid conditions, but there are no other biological predisposing factors. Although without clearcut precipitation their is evidence of problems in the marriage and at work. Outpatient therapy with a tricyclic antidepressant is predicted to produce an excellent response based on good prognostic features, including premorbid personality and relative social stability. Prognosis for future episodes is more guarded and may be influenced by response to psychological interventions and social change.

Summary and Conclusion

In this chapter, we have considered biological formulation from several perspectives. First, we examined the degree to which technological advances as well as social and philosophical change have contributed toward a paradigm shift that attributes increasing significance to the biological understanding of psychiatric disorders. Next, we reviewed the extent to which existing knowledge supports the four basic hypotheses on which a biological contribution may be assumed. Finally, the way in which such knowledge is put to use in making a formulation has been discussed, both in general terms and then in specific relationship to the case of Mr. A. While primary and predominant the biological approach acknowledges the social and psychological matrix in which it is embedded

Chapter 19

The End of the Beginning: The Beginning of the End?

Corporate Corruption in the Psychopharmaceutical Industry

Preamble

The essay about corporate corruption that follows tells an alarming and well-documented tale of corporate corruption and greed in the pharmaceutical industry beginning in the mid-1970s when it shifted its motives and resources from the discovery of innovative drugs to aggressive marketing of derivative "me too" compounds. The details are derived from nine well reviewed and researched book published between 2004 and 2016.

Momentum was provided by legislative changes enabling transfer of knowledge from academia to industry, lax FDA oversight, ingenious advertising, collusion by leading psychiatrists and the evolution of DSM diagnostic criteria that endorsed and encouraged biological approaches, medicalizing the profession and stifling psychosocial approaches and their proponents.

Co-incidentally, the Federal Government discontinued involvement in early testing of psychotropic compounds and reduced funding for academic research by more than a third. Industry income from prescribing increased at an alarming rate. It manipulated and extended patent rights; employed 675 lobbyists in Congress; funded political campaigns, professional and lay advocacy organizations; corrupted medical education at all levels; flooded doctors' offices with free samples; recruited and bribed key opinion leaders (KOL's) to exert their influence as journal reviewers, members of expert panels and authors of best practice guidelines.

For-profit research organizations (CROs) replaced independent academic and Federally-funded drug testing which resulted in concealment of negative findings, corrupt data analyses, ghost writing, surrogate authorship and paid endorsements. Professional and academic institutions did little to define, monitor, control or eliminate obvious and declared conflicts of interest.

The impact on professional ethos and medical ethics has been devastating, contributed to by legal strategies and settlements that stifle disclosure or opposition invoking a form of moral paralysis to be commented on later.

Corporate Corruption in the Psychopharmaceutical Industry

As a well-published but retired psychopharmacologist and amateur historian, I feel overwhelmed by the conflict between a strongly felt need and the futility of addressing this topic. Everything I write has been said or published before, but to no avail. The capacity of the industry to deploy its strategies and use its spoils to stifle the truth has been overwhelmingly successful. Just as the NRA bribes politicians to obstruct legislation that would save lives and the NFL corrupts science to expose its players to brain injury, so Big Pharma uses its vast fortune to seduce and silence all opposition at the cost of injury and death to the patients who consume its products.

Industry has taken over and corrupted clinical trials, bribed academics to be complicit, infiltrated medical education and its curricula, seduced professional and consumer organizations, lobbied politicians to relax regulations, partially funded the FDA, influencing its decisions, meanwhile vastly inflating the populations at alleged risk for mental disorders and the willingness of physicians to medicate them, a process aided and abetted by the DSM diagnostic system coupled with misleading advertising direct to the public and dubious marketing strategies for gullible doctors.

All this has happened despite an overwhelming amount of information in books documenting the damage but little, and now less, in scientific journals whose editors publish flawed and corrupt data they are slow to retract but also reject submissions that seek to expose the truth for fear of losing advertising revenue.

In the 12 years between 2004 and 2016, the nine volumes listed below provided a compelling indictment of the industry at large, much of it about psychopharmaceutical "blockbuster" drugs generating billions of dollars annually. The authors of these books are leading scientists, researchers, physicians, two former journal editors and investigative reporters. Every book is copiously referenced from primary sources and all have been well and enthusiastically reviewed.

1. *Overdosed America.* John Abramson, M.D. Harper Press. 2004

2. *The Truth about Drug Companies: How they deceive us and what to do about it.* Marcia Angel, M.D. Random House. 2005

3.Selling Sickness. Ray Moynihan and Alan Cassells. Nation Books. 2005.

4.On The Take. Jerome P. Kassirer, M.D. Oxford University Press, 2005

5.Law and Ethics in Biomedical Research: Regulation, conflict of Interest, Liability. Trudo, Lemmens and Duff Waring. University of Toronto Press. 2006.

6.Our Daily Meds. Melody Peterson. Picador. 2008.

7.The Anatomy of an Epidemic: Magic bullets, Psychiatric drugs and the astonishing rise of mental illness in America. Robert Whitaker. Crown Publishing. 2010.

8.Pharmageddon. David Healy, M.D. University of California Press, 2012.

9.A.D.H.D. Nation. Alan Schwartz. Scribner, 2016.

The Problem at Large

All nine books listed document a belief there is a major problem; an escalating population of medicated citizens to which psychotropic drugs contribute a major portion. But they differ somewhat as to the exact nature of this phenomenon. Metaphorically there is an elephant in the room whose identity is variably defined by blind commentators groping different parts of the animal. Others, equally blind, deny it exists.

The best attempt to quantify this entire problem, described in the title as an "epidemic," is by Robert Whitaker, also characterized in his best seller as "a modern plague." Using data from SSI and SSDI recipients he graphs a four-fold increase between 1987 and 2007 involving both children and adults. Whitaker acknowledges that decreasing stigma and increasing diagnosis may contribute to the problem but alleges the major cause is "a period when prescribing of psychiatric medications has exploded." He attributes this to misleading academic and commercial claims about the alleged biochemical specificity of these drugs on brain metabolism. Instead of healing a broken brain they inflict unspecified harm that creates chronicity.

In a review of the book Fuller Torrey (Torrey 2016), acknowledges there is evidence of worse outcomes in schizophrenia during the 1980s and 1990s due to a narrower definition of schizophrenia introduced by DSM III in 1980. But he refutes as unsubstantiated the claim that

there is any evidence of brain damage while he also acknowledges Whitaker "got many things right" and that polypharmacy and overprescribing are in play.

Taking a different tack, David Healey labels the vast increase in the use of all drugs "Pharmageddon," a term coined by Charles Medawar (Medawar 2007). The OED definition and etymology of "Armageddon" implies that Pharmageddon predicts a battle to the death between the hubris and hegemony of Big Pharma contra a constrained and proper use of its products in an idealized and nurturing physician-patient relationship. Healey castigates the disproportionate production of palliative drugs designed, not to cure, but to enhance or prolong life including cardiovascular, acid reflux, hypoglycemic, cholesterol lowering, asthma relieving and psychotropic drugs prescribed for newly invented DSM disorders such as social anxiety disorders, panic disorder and mood stabilization.

The bulk of these products are "blockbuster" drugs (more than $1 billion annually), patent protected, available only on prescription, never compared to cheaper generic prototypes and sometimes recommended in "best practice" guidelines. Consumption of these drugs increased from 6% to 45% between 1991 and 2006. Out of a global cost of $900 billion, half was in the USA. The best sellers were antidepressants and mood stabilizers ($50 billion), ahead of cholesterol lowering drugs ($34 billion). Blockbuster drugs are growing 10-20% worldwide, often with markups of several thousand percent.

Viewed through the eyes of an academic family doctor, Abramson (2004) describes the problem thus in his book: "When the history of this era of American medicine is fully written there is no doubt that many of the scientific and technological advances will stand as great achievements. But I hope that the erosion of the healing alliance between doctors and patients will be looked back upon as a cultural aberration, a consequence of the unrealistic belief that good health is primarily a product of medical science rather than the natural consequence of a healthy lifestyle and environment."

Melody Peterson, an investigative reporter for *The New York Times,* expressed this viewpoint in her book as follows: "Once the most successful pharmaceutical companies were those with the brightest scientists searching for cures. Now the most profitable and powerful drug makers are those with the most creative and aggressive marketers. The drug companies have become

marketing machines, selling antidepressants like Paxil, pain pills like Celebrex and heart medications like Lipitor with the same methods that Coca Cola uses to sell Sprite and Proctor and Gamble uses to sell Tide. *Selling* prescription drugs - rather than discovering them - has become the pharmaceutical industry's obsession."

A review of the book by a leading health writer, Roy Moynihan, and an academic pharmaceutical policy researcher, Alan Cassells, reads as follows: "By exposing how the pharmaceutical companies actively set out to make us feel sick, so they can sell drugs we don't need, this brilliant book blows the lid off the carefully cultivated image of medical authority and benign concern. The drug companies turn out to be the worst sort of corporate pirates – read this book and rage" (Clive Hamilton, the Australia Institute).

In their multi-authored book on Law and Ethics, Trudo Lemmens and Duff Waring note the following in their Introduction: "While medical research has been integrated into a competitive commercial environment, it is still too often approached as if it were purely driven by humanistic ideals." They devote four chapters to "conflict of interest" and cite the case of a well credentialed psychopharmacologist recruited to be a senior faculty member of a major university Department of Psychiatry whose appointment was rescinded because his criticism of industry involvement in clinical trials might deter the flow of pharmaceutical support to the University.

In *On The Take* Jerome Kassirer, former Editor in Chief of the *New England Journal of Medicine* (1991-1999), examines how the medical profession has been complicit with industry in endangering health. He covers the entire spectrum of corruption from medical student to the pinnacle of academia and the administrators of the NIH, exploring the methods and motivations of "Money Warped Behavior." In addition to individuals, he covers professional organizations, industry and researchers. Perhaps, most importantly, Kassirer offers an insightful analysis of the dynamics of conflict of interest in the chapter, "Influenced by Gifts? Not!"

Of all nine books, the most recent, *A.D.H.D.Nation*, by *New York Times* reporter Alan Schwartz, is the most exhaustive and elegant, a finalist for the Pulitzer Prize by an author with unblemished reporting and well-deserved praise for more than 100 articles exposing the NFL cover-up of concussion sequelae, leading to safety reforms.

While this book deals with just a single psychiatric disorder the depth and breadth of information and analysis that describes a fabricated "epidemic" is expressed in lucent prose, scrupulously reported and fairly presented. In addition to more than 100 interviews with patients, clinicians and researchers, there are footnotes to every chapter, an extensive bibliography and comprehensive index. The bibliography includes 73 books, followed by 123 medical, website and periodical citations, then 188 scientific articles in leading medical journals and finally 46 "other sources" including legal testimony, government documents (FDA and SAMHSA), patents, TV programs and Congressional testimony.

Setting the Stage

Real innovation in the psychopharmacology industry existed between 1954 and the mid-1970s after which the era of me-too compounds was ushered in by a changing zeitgeist that set the stage for corporate corruption. None of it was the fault or brainchild of the industry, but it was an opportunity seized upon.

Asked why I came to America in 1968, I proudly proclaimed: "It's the land of opportunity." Merrell Corporation, for whom I worked, saw a burgeoning field for psychotropic medications that lay ahead and hoped to put the thalidomide tragedy behind them. It was a time on the cusp between the politically enlightened and upwardly mobile Eisenhower-Truman era and a modern era of greed, Congressional gridlock and income disparity that laid the foundation for Big Pharma to take advantage of four components in this changing zeitgeist.

Evolving FDA Regulations and Government Intervention

By the time the first psychotropic drugs became available in the mid-1950s the AMA and the pharmaceutical companies had already developed an alliance for promoting new medications that stemmed from the 1953 Durham-Humphrey Amendment requiring that all drugs be prescribed by physicians. Monitoring of safety was lax and requiring proof of efficacy was lobbied against by the AMA and did not become law until the Harris-Kefauver Amendments in 1962, following thalidomide (Whitaker 2010).

The criteria for FDA's novel responsibility to approve new drugs were determined by a method that primarily judges efficacy. In 1962 the new discipline of clinical pharmacology was

entranced with the randomized controlled clinical trial (RCT), a double blind comparison of the candidate against placebo for as many patients and as long as it takes to reach statistical significance. This usually means a small carefully selected, sometimes unrepresentative, sample for as little as six weeks, barely enough time to judge only common side effects. Just two such trials are required. As early as 1956 this was described in the proceedings of an early psychopharmacology conference (Cole 1956) as "scientific myopia" (Zubin 1956), but that standard remains in place today.

The election of Ronald Reagan as President in 1980 fostered a pro-business, pro Big Pharma Congress that promptly passed the Bayh-Dole Act to promote "technology transfer" and speed translation of the fruits of tax-supported research from academia and NIH into commercial products. This well intended legislation bred dubious consequences. Non-profit medical schools and teaching hospitals became partners with industry. Faculty founded biotech companies, owned equity in them and patented their discoveries for a share in future profits. Industry licensed and sold these new drugs from academia with two outcomes: "a growing pro-industry bias in medical research" and an increasing tendency for medical schools to "put more resources into commercial opportunities" feeding faculty members' expectation that if they were smart they should also be wealthy (Angel 2005). Conflicts of interest grew like weeds.

Beginning in 1987 with the Hatch-Waxman Act and continuing into the 1990s, Congress extended the monopoly rights for patented drugs. Then, in a chapter titled *"Handing FDA to Industry,"* Marcia Angel describes how Congress passed the Prescriber Drug User Fee Act in 1992. Designed to expedite the approval of new drugs it required the FDA to charge industry a fee for each approval. Starting at $ 310,000 it was later raised to $ 576,000 generating an annual total of $360 million a year, about half the agency's budget. "That made the FDA dependent on the agency it regulates" (Angel 2005).

With the exception of New Zealand, America is the only nation that allows industry advertising directly to the public. Initially, companies mostly abstained due to FDA's stringent rule that full information of all side effects be included. In 1997 FDA relaxed that rule to require mention of major side effects only (Angel 2005).

When Medicare added a drug benefit in 2006 it was forbidden to bargain over prices with manufacturers and patients were constrained by a 1987 law that forbade importing cheaper drugs (often made by the same manufacturer) from Canada.

The Changing Face of Psychiatry

Of all the medical disciplines, psychiatry may be the one most shaped by the pharmacology revolution unfolding in the mid-20th century. Until then, psychoanalysis with DSM 2 ruled in America while Britain and Europe had evolved a skeptical brand of empiricism and rigorous descriptive psychiatry focused on etiology, nosology and the natural history of mental disorders.

The advent of the first generation of psychotropic drugs for each of the major disorders was complete by the mid 1970s and gave birth to modern "Biological Psychiatry." At the time this was an over simplified designation; the biographies of the pioneers on the INHN website, the *dramatis personae* in the 10 volumes of the Oral History of Psychopharmacology (OHP) and the first-person accounts of their often-serendipitous discoveries (Ayd and Blackwell1970) attest to a broad interest in the social and psychological dimensions of people they treated.

Instead, what would shape future practice and its troubling symbiosis with the pharmaceutical industry was the evolution of the DSM 3 beginning in 1975. This derived from a number of prior influences. The weakness of DSM 1 and 2 revealed by the US-UK cross cultural study (Cooper et al. 1969) and by the development of alternative diagnostic schemes. The Feighner Criteria, developed while he was a resident at Washington University in Saint Louis, and the Research Diagnostic Criteria (RDC) developed later by Endicott and Spitzer at the New York Psychiatric Unit. This was preceded by a thought provoking study, "*On Being Sane in Insane Places" (*Rosenhan 1973), that stirred national interest and concern about the validity of psychiatric nomenclature. Shepherded by Robert Spitzer and colleagues, these forces coalesced to produce DSM 3.

Rapidly and widely adopted in America and around the globe, the project secured its survival by earning the American Psychiatric Association (APA) $5 million annually, accumulating to in excess of $100 million. Based on the clinical wisdom of selected experts, determined by vote, it has been widely criticized as lacking objective criteria, reliability and validity.

Spitzer predicted that DSM 3 "would serve as a defense of the medical model as applied to psychiatric problems" (Wilson 1993). The President of the APA opined that the manual would, "clarify to anyone in doubt with regard to psychiatry as a medical specialty" (Kirk and Hutchins 1992). A number of prominent physicians pitched in with supportive articles in leading journals (Sabshin 1977; Ludwig 1977; Blaney 1975). Sabshin would later claim, "Psychiatry now had its bible … an amazing document, a brilliant *tour de force"* (Sabshin 1990).

Reacting to this chorus of approval, an equally vehement opposition has evolved to DSM 3 and beyond. Marcia Angel writes of *"The Myth of Reliability of DSM"* (Angel 1994). Alan Frances, in a *New York Times* editorial, *"Diagnosing DSM 5,*" describes it as "Designed to medicalize normality and result in unneeded and harmful drug prescriptions" (Frances 2012). The Director of NIMH, in his blog, pronounced DSM's academic death knell with a decision that the agency would no longer fund research based on the DSM system (Insel 2013).

This counterpoint has the dimensions of a Greek tragedy. Originally well-intended to bring consensus to diagnostic chaos, the multi-axial system invited the integration of biological, psychological and social dimensions. What was lacking was any control over how the system was used or abused by the APA, drug companies, complicit academics, prescribing physicians and insurance companies.

A suggestion that the DSM system, if constructively used, might be employed to develop case formulations that included the biopsychosocial ideologies and also a European type emphasis on the etiology, natural history and prognosis went nowhere (Sperry et al. 2012).

Whitaker (2010) summarizes all this by noting that psychiatry had "donned the white coat" and in doing so had vanquished its rivals including Freudian and social psychiatrists, as well as ignoring studies that showed social interventions superior to drugs in the treatment of some psychotic disorders. Also excluded were psychiatry's rivals denied the benefits of this biological revolution: "...the mental health professionals seeking patients and prestige" (Sabshin 1980).

Resources Diverted or Discontinued

In 1960 the Psychopharmacology Center at NIMH, under Jonathon Cole, began to set up and fund a national network of research centers known as the Early Clinical Drug Evaluation Units

(ECDEU). These were to provide scientifically sophisticated, independent and ethical evaluation of compounds developed by industry. By 1962, 15 units were established in America and Canada in VA Centers, State Hospitals and Academic Medical Centers capable of studying drugs of every kind in child, adolescent and adult populations.

The program developed protocols, research designs, 28 rating scales and 15 independent measuring instruments and collaborated with the George Washington University Biometrics lab for data analysis. Units communicated regularly, worked to standard protocols and met annually.

By 1967, the program was fully developed and by 1970 had produced an Assessment Manual and Workbook. By the mid-1970s innovative compounds were decreasing and industry had the resources to fund its own studies. As projects ended units were closed and NIMH began to devote more money to basic research and away from clinical trials.

Beginning in 1980, during the Reagan administration, the NIH also began reducing grant support in general and by 1990 two thirds of grant applications went unfunded.

These twin initiatives had a profound effect on Academic Medical Centers. Starved of Federal funds they turned to industry for support and by 1990 they were testing 80% of industry compounds.

The Tipping Point

In 1980 three primal forces would coalesce setting the stage for corporate corruption on an unprecedented scale. Ronald Reagan was elected President for eight years of Republican hegemony, Congress and the lobbyists would hold sway and craft industry friendly legislation. That same year DSM 3 was published providing psychiatry and industry the tools to medicalize the profession and the public's ailments. Contemporaneously, innovation in psychopharmacology slowed to a crawl; the approval of new compounds by the FDA dwindled (Angell 2005). Patents were expiring and although some blockbusters still held sway, the second-generation drugs were dressed in the Emperor's clothes, thinly disguised "Me-too" compounds. Responding to this unholy trinity, science took second place behind skillful selling sufficient to satisfy stockholders, devise new ways to expand markets and corrupt clinical trials, endorsed by complicit, money hungry academics.

The payoff for industry was huge; between 1980 and 2003 the amount spent on prescription drugs rose from $12 to $197 million (Petersen 2008).

Strategies of industry corruption

Inflating Cost and Extending Patents

In order to justify its profits and prices, to magnify them and fight off price controls that industry alleges would "harm millions" (Holmer 2001), it employs two basic strategies. First it inflates the cost of doing research to introduce new compounds; this is described as "blackmail" (Angel 2005). Much of the evidence is proprietary, hidden in a "black box." Using a variety of sources including the Public Citizens Advisory Group, Angel estimates the cost per drug to be $100 million compared to the industry claim of $802 million derived from the Tuft's Center for the study of Drug Costs, a group of economists largely supported by the pharmaceutical companies (DiMasi, Hansen and Gradowski 2003). Angell dissects and disputes their estimate.

Industry lawyers are adept at manipulating and extending patents and exclusivity rights granted by the FDA using five strategies. These include altering drugs to extend exclusivity or patents, filing multiple patents, testing in children and colluding with generic companies to delay their approval. How these were applied to Prozac and Paxil is described in detail (Angell 2005).

PhRMA: Congress and the FDA

The Pharmaceutical and Research Manufacturers of America, (PhRMA), has "a death grip on Congress" (Pear 2003). Its lobby is the largest in Washington, employing 675 lobbyists including (in 2002) 26 former members of Congress and 342 congressional or government officials. From 1998 to 2004, 43% of Congress members took lobbying jobs after retirement. Perhaps the wealthiest recipient of Big Pharma largesse was Billy Tauzin (R-LA) who made almost $20 million lobbying for the pharmaceutical industry between 2006 and 2010 (Burke 2016).

In 2003, PhRMA increased its spending by 23% to $150 million annually at the Federal and State level. This included $18 million to fight price controls and protect patent rights, $12 million to lobby physicians, patients, academic and minority organizations and $5 million to lobby the FDA (Angell 2005). In addition, industry spent $85 million on political campaigns in 2000,

80% to Republicans. Included was the CEO of Bristol, Myers, Squibb who contributed and solicited $2 million, receiving an Ambassadorship to Sweden as a reward.

When the US Supreme Court passed “Citizen’s United” legislation it also loosened the regulations regarding a capacity for the public to identify donors or the purposes for which that money was used. This created an upsurge in the number of not for profit organizations receiving and using what became known as “black money” PhRMA has taken advantage of this situation to conceal the distribution of the considerable profits it uses to influence legislative actions of Congress and to support the political candidacy of preferred legislators sympathetic to industry goals,

In 2018. a reporter for the Kaiser Health News wrote an article for the New York Times providing an example of how PhRMA takes advantage of this situation (Hancock, 2018).

The American Action Network (ANA) is one of these “dark money” organizations to which PhRMA donated $6.1million in 2017. ANA was heavily involved in support of Republican efforts to repeal Obamacare, legislation that included eliminating the $ 28 billion fee the pharamaceutical industry is mandated to pay the government every decade.

Like Congress, the FDA is subject to industry influence and corruption in addition to the fees it receives for expedited approvals (Angell 2005; Petersen 2008). Its 18 advisory committees, made up of academics, largely determine the fate of industry drugs. An examination of FDA records in 2000 (Couchon 2000), found that 92% of meetings had at least one member with a financial conflict and at 55% of meetings half or more advisors had one. The head of a Government Reform Committee concluded certain committees were “dominated by individuals with working relationships with drug companies” (Gribbins 2001). Evidence suggests the FDA became complicit after the Prescription Drugs User Fee Act (1992). FDA officials themselves identified 27 drugs approved between 1995 and 1998 that should not have been. As a probable consequence, the number of drugs withdrawn from the market after approval increased from 1.6% between 1993 and1996 to 3.3% between 1997 and 2000. Seven of the drugs withdrawn after 1993 because of serious side effects were suspected of causing more than 1,000 deaths and none were lifesaving compounds.

Coopting Academics, Education, Professional and Consumer Organizations.

Without industry money, professional dues, meeting attendance and continuing medical education costs would be far higher. Marcia Angell cites the APA's Committee on Commercial Support: **"**The pharmaceutical companies are an amoral bunch. They're not a benevolent organization." So, they subsidize, but there must be a *quid pro quo.* By calling marketing "education" and doctors "consultants" they evade kickback legislation.

Continuing Medical Education (CME)

CME is mandatory for professional licensure of physicians and has become an open door for industry influence on prescribing practices. It manifests via conferences and lectures, commercial support for which doubled between 1996 and 2000, amounting to three-fifths of the total in 2001 (Abramson 2004). This led the editor of the NEJM to lament the "Decline in quality from the sober professionalism of a few decades ago to the trade show hucksterism of today" (Relman 2003). Drug companies work hard to draw doctors into an atmosphere of "Food, flattery and friendship," one that strains ethical boundaries (Katz, Caplan and Merz 2003). Abramson recalls offers of "weekends in the best hotels plus $500" and occasionally giving into them (Abramson 2004). Despite denials that it works, the data prove otherwise. Nearly half of the task force establishing guidelines for industry sponsored CME are their paid consultants.

An extreme example of industry corruption of physician education is Purdue Pharma, maker of OxyContin, giving $3 million to Massachusetts General Hospital to rename its pain center the MGH Purdue Pharma Pain Center, which would conduct CME seminars using Pharma curriculum to encourage doctors and pharmacists to prescribe its products. Abramson comments, "Doctors who allow their reputations and academic position to be leveraged by drug companies for commercial purposes, provide a crucial link in the chain of corporate influence."

Other levels of medical education

The tentacles of industry reach into all levels of medical education. The exposure of medical students and residents to pharmaceutical promotion and its effects are well documented. (Lancet 2000; Steinman, Shilpak and McPhee 2001).

Providing free samples by drug reps to office-based physicians tripled in 10 years, totaling $7 billion annually; 80% are willing to listen, although 42% of the material "Made claims in violation of FDA regulations" (Chen and Landfeld 1994).

The technique to influence the use of SSRI's during the 1980s and 1990s focused on doctor office visits and free samples, tripling their use for a sale total of $20 billion (Moynihan and Cassels 2005). This success was augmented by public advertising and physician education based on the twin concepts of "chemical imbalance" coupled with "unmet needs" in the population including children and adolescents, a claim ultimately disproved and stifled by an FDA "black box" warning.

Increasing Use, Creating an Epidemic

Moynihan and Cassels devote entire chapters to how industry promoted and expanded the uses of drugs to doctors for ADHD, premenstrual dysphoric disorder and social anxiety disorder

Two of the nine books use the word "epidemic" in their titles. That by Whitaker (2010) is questionable and somewhat hyperbolic, but Schwartz (2016) is compelling and judicious in laying out the elements for ADHD. The story is told through the biographies of three people, Keith Conners, the scientist whose lifetime was devoted to research on the topic, and two young patients, Kristin and Jamison, who became victims of stimulant overuse.

Conners, a psychology graduate from Harvard and supported by government funding, discovered, described the syndrome and developed rating scales to measure it and then demonstrated the efficacy of amphetamine and Ritalin in stifling symptoms of what was first called Minimal Brain Disorder and then ADHD. Schwartz makes clear that this is a real disorder that "effects about 5% of children, primarily boys." Due to influences he describes, the number in America has tripled to 15% overall, 20% in boys, but in areas of the South (Mississippi, South Carolina and Arkansas) it is 30% and in some Louisiana counties half of all boys in grades three through five are involved. Some of this is due to the fact there is no certain diagnostic test or cure.

Kristin is a young girl whose anxious parents and teachers are complicit with a psychiatrist willing to prescribe stimulants although she denies having symptoms on the Conner's scale. The boy, Jamison, notices a friend with ADHD who does well in class, cadges one of his Ritalin pills,

loves the euphoriant and energizing effects, then artfully cons his mother into taking him to a psychiatrist where he fakes the Conners test and "reluctantly" accepts a prescription.

Thus, a pliable and easily manipulated stage is set for the "hijacking" in which "Conners was the epitome of what the industry euphemizes as a key opinion leader or KOL." He is soon joined by fellow academics, Joe Biederman, Russell Barkley and a cadre of "pharma- subsidized ADHD researchers who churned out papers, delivered countless lectures and refuted mounting evidence that millions of children were being miss-diagnosed and improperly medicated." The amounts of money that lubricated their livelihood amounted to five or six figure sums annually. "Psychiatry journals teamed up with more than a thousand studies on ADHD by Biederman, Barkley and other pharma-sponsored scientists.

The FDA relied on these tainted sources when green lighting the medications as safe and effective. Their findings served as the backbone for lectures that drug company KOLs delivered worldwide. "The whirlwind created a self-affirming circle of science, one that quashed all dissent."

In the medical journals, there were "resplendent full-color advertisements derived from those studies positive findings … but the underlying facts went through so many spin cycles they emerged barely recognizable." By now the ADHD drugs had become a "billion dollar market, one that was expected to double every three to five years … Adderall and Concerta became the ADHD industry's Coke and Pepsi, fighting for every scrap of market share."

FDA oversight was lax; it mandated advertising acknowledge the most common side effects, but "allows these to be communicated in type so small and language so oblique it would be laughable if not so manipulative." Claims were extended far beyond any evidence. These addictive drugs would "reduce conflict with parents; deter substance abuse and sexually transmitted diseases."

Hyperbole and dissimulation were in the face of mounting evidence that some teenagers were crushing and snorting their pills for transient highs, including Jamison, now a freshman in College, engaged in "a mood modulating kaleidoscope haze of alcohol, Adderall and Valium" that ended in a car-crash, jail and drug rehab where Jamison met Kristin whose trajectory into substance abuse equaled his, first snorting Ritalin and then cocaine.

Meanwhile, Keith Conners career long honeymoon with industry came to an abrupt halt when Eli Lilly introduced a non-addictive drug for ADHD which he studied and lectured about, being paid thousands of dollars for each talk. His research showed, and lectures reported, that Strattera was safe, but also less effective. Troubled by that caveat, a Lilly executive remonstrated: "If you stray from what we ask you to talk about we won't be able to use your services anymore." Knowing he spoke the truth, Conners never lectured for the company again.

Late in life, comfortable and retired, Conners read Alan Schwartz's articles about, "Improperly diagnosed kids feeling inferior, damaged and sometimes addicted." Curious and conscious stricken, he accepted an invitation to meet Kristin and Jamison who were now grown up, recovered and working in a small town called Bethlehem. Remorseful and reconciled Keith Conners acknowledged: "I struck a match and didn't know how much tinder there was around." He now had misgivings about his role in a "national disaster of dangerous proportions."

Direct to Consumer Advertising

Pharmaceutical companies spend 25% of their revenue on advertising, a substantial portion direct to the public. TV advertising increased dramatically in 1997 due to the relaxation of FDA guidelines by Acting Commissioner Michael J Friedman. In 1999, at the appointment of Commissioner Henney, he resigned to become a senior vice President at Searle just as they marketed Celebrex. In America in 2005 the overall amount spent on advertising was $250 billion. In 2009, the cost of prescription drugs exceeded the gross domestic product of Argentina and Peru. In 2004, America spent more on prescription drugs than gasoline, fast food, higher education or cars. Between 1980 and 2003 the amount increased 17-fold (Peterson 2008). In 2005, seven of the top 10 biggest advertisers on CBS evening news were pharmaceutical companies; 25% of American adults said an advertisement prompted them to ask their physician about a drug.

No better example of industry influence on the blurred boundaries between marketing and education exists than the *"Patient Panel"* funded by Big Pharma, but sponsored by GE, that provides a free TV program to hospitals around the country (800 in 2003) carrying half hour segments tied to specific ailments interspersed with paid commercials which the marketing director tells the sponsor will "directly associate their products with a patient's condition in a hospital setting." Both the Joint Commission for Accreditation and the Health and Human

Services Director have expressed mild concern about blurred boundaries, but have taken no action (Angell 2005).

Industry also gives educational grants and sponsors talks to consumer advocacy groups. The National Alliance for the mentally ill (NAMI) is the best endowed. In the first quarter of 2009, Eli Lilly gave $556,000 to NAMI and its local chapters. Lilly also gave $465,000 to the National Mental Health Association.

There are also examples of industry collaborating with educational organizations to promote specific disorders. After Prozac was launched, NIMH produced a campaign to inform the public that depression regularly went "undiagnosed and untreated" while Upjohn partnered with the APA to tell the public that panic disorder was common after Xanax was marketed, examples of what has come to known as "disease mongering."

Corrupting Academia

Whitaker (2010) comments: "The pharmaceutical companies would not have been able to build a $40 billion market for psychotropic drugs without academic medical centers." The industry calls faculty members "key opinion leaders" (KOL) and their activities were exposed by Iowa Senator Charles Grassley's investigative committee. Whitaker cites many names, but I will mention only three described by reputation not name.

A leading KOL was paid almost a million dollars to promote Paxil and Wellbutrin by Glaxo Smith Kline (SKF). He is a member of the American College of Psychopharmacology (ACNP), a council member for five years and then President. He is the author of a leading textbook of psychopharmacology and of a book for lay readers, "Peace of Mind Prescriptions." Recently, he authored a scientific article complaining that industry was coercing scientists like him to endorse their products and disparage competitors. Having made himself a millionaire by doing just this one can only conclude he and his sponsors are morally handicapped and ethically blind.

A second KOL is a child psychiatrist who took $160,000 for promoting the use of Paxil in children, as well as co-authoring an article that falsely reported data on a study she performed. Her deposition in litigation against her and the drug company is a recitation of "I don't know or I don't recall," the legal defense against perjury. While this was occurring, she became a member of the

ACNP without ethical challenge and was elected President of the American Academy of Child and Adolescent Psychiatrists.

Finally, a former Director of the NIMH and a member of GSK's speaker's bureau was paid $1.2 million from 2000 to 2008 to promote mood stabilizers for bipolar disorder. He is also author of an authoritative textbook on that disorder and host of NPR's "*The Infinite Mind."* In an interview with the *New York Times,* he explained he was "Only doing what every other expert in the field does" (Harris 2008).

KOLs are "stars" in influencing peers at the national and international level. At a step below are "consultants" giving lectures at medical schools or talks at lavish dinners for psychiatrists in the community. Minnesota and Vermont have "sunshine" laws that reveal the flow of money from industry to influential psychiatrists. In Minnesota in 2006, the total was $2.1 million; recipients included seven Past Presidents of the State Psychiatric Society and 17 faculty members of the University of Minnesota. Altogether, 187 of the State's 571 psychiatrists shared $7.4 million, higher than any other discipline. The top paid psychiatrist, who received $570,000, was a member of the State Medicaid formulary committee. Vermont tells the same story: psychiatrists received more industry money than any other specialty. Drug companies do set limits below the KOL and influence mongering level; GSK to $2,500 and Eli Lilly to $3,000 per psychiatrist (Whitaker 2010)

Another method of influencing prescribing practices is through clinical guidelines, intended to guide physicians "best practices" based on reliable research and often sponsored by government agencies or professional organizations like the APA. In 2002, JAMA published a study showing that four out of five experts on panels formulating guidelines had financial relationships with industry, averaging 10 companies a person; 59% had a relationship with the company whose product was prescribed for the condition covered by the guideline (Choudry, Stelfox and Detsky 2002).

Perhaps the most amazing and compelling example of corruption is that of an entire medical school being in thrall to the pharmaceutical companies and their largesse. It involves the University of Iowa, the subject of investigative reporting for *The New York Times* by Melody Petersen, winner of the Gerald Loeb Award in 1997 (Petersen 2008). A Director of the University Hospital who sat on the Pfizer Advisory Board established an "Office of Corporate Partnerships"

which helped physicians and scientists obtain grants, each for $65,000, to become a "Pfizer Fellow" in their specialty, including biological psychiatry. The Director of the Research Park explained: "If you were involved in business you were a bad academic, now it's almost considered a badge of honor." Industry paid academics to give speeches about their products, sit on advisory boards and work as consultants. They were only required to report payments over $10,000 from each single company and records were kept secret. The Dean of the School of Medicine gave a speech to faculty that referred to industry grants as "technology transfers," called for new rewards for faculty who obtained them and declared that in addition to caring for citizen health the school had a responsibility to create wealth.

In 2004, the university had 136 scientists managing clinical trials. Although there were ethical guidelines for work with industry, most cases were "managed," explained away or granted a "waiver." One faculty member in the Department of Public Health who disclosed working for 12 different pharmaceutical companies stated she had "Resolved all these conflicts of interest" without explaining how.

This chapter, with the intriguing title of *"Midwestern Medical Show,"* does not have an end to the story, but a later chapter reveals all is not well in the State of Iowa. Medicaid prescription costs have surged 25% from 2001 to 2003 and medical costs have increased faster than inflation. The State has been forced to divert funds away from independent living for elders and reduce funding for its three universities, increasing tuition and student debt. Presumably, faculty members at the medical school are doing better than their fellow citizens.

Corrupting Clinical Trials

One fruit of the poisoned tree of academia has been the profound corruption of the whole business of clinical trials, their design, performance, analysis and publication. Abramson documents the profound shift in how clinical trials are conducted from the time in the late 1970s when "Scientists thumbed their noses at industrial money." In 1991, four out of five studies were still conducted in academic settings, but with increasing support and controls by industry (Bodenheimer 2000). By 2002, 80% were managed by Contract Research Organization (CRO's) taking control over all aspects of the methodology (Beckelman, Li and Gros 2003).

As direct control slipped out of their hands, academics became increasingly involved in activities financed by industry that created profound conflicts of interest including ghostwriting, surrogate authorship and paid endorsements of results in ways that biased them. A review of the results of FDA-initiated inspections of research sites tabulated the objectionable practices and violations observed and whether or not they were mentioned in the peer review literature (Seife 2014).

Fifty-seven published trials identified one or more problems: falsification of data 39%, inadequate side effect reporting 25%, protocol violations 74%, innadequate record keeping 61%, safety of patients or informed consent compromised 53% and violations not otherwise categorized 35%.

Out of 78 publications that resulted from trials which found violations only 4% mentioned them and there were no corrections, retractions, expressions of concern or comments acknowledging the issues identified. The author's conclusion is: "When the FDA finds significant departures from good clinical practice, those findings are seldom reflected in the peer reviewed literature, even when there is evidence of data fabrication or other forms of research misconduct." The FDA turned a blind eye.

An analysis of the legal consequences of ghostwriting finds several areas of serious concern (Bosch, Esfandiari and Lemmon 2012). The authors note that pharmaceutical companies, universities, medical journals and communication companies have failed to adequately stem the problem. This potentially incurs liability for the authors of journal articles that contain misleading information and that paying ghostwriters may influence clinical judgement, increase product sales and put patients at risk by misrepresenting risk benefit. Both sponsors and authors may be responsible under Federal anti-kickback laws. Ghostwriting is fraud and First Amendment rights do not protect.

Another article on the topic of ghostwriting (Busch and Ross 2012) notes that "This practice is currently perceived as a slight, easily comprehensible moral failing rather than unethical… even those exposed have, for the most part, suffered minimal shame or academic consequences."

Abramson identifies a variety of other practices engaged in by industry to inflate the value of their drugs including a young population unlikely to suffer side effects, stopping a study prematurely when the results appear unpromising and failing to publish negative outcomes.

A particularly devious way of increasing a drug's indications and sales is industry promotion and manipulation concerning "off label" usage. FDA forbids companies from promoting these, but has no mandate to prevent physicians prescribing as they see fit. Industry exploits this distinction by encouraging doctors to experiment, collecting outcomes and using them to become hired consultants and persuade others. Petersen (2008) describes this practice by Parke Davis in marketing Neurontin and the steps taken to ensure secrecy in her chapter "*Neurontin for Everything."*

An International Committee of journal editors (Schulman, Seik and Timble 2001) expressed concern and recommended that researchers retain control of their data, analysis, write up and publication of their research. However, the journals themselves are confronted with problems when their reviewers are paid consultants to industry or when industry threatens to withdraw advertising if editors refuse to publish or agree to redact flawed studies (Abramson, 2004). Many of the drug advertisements themselves are flawed; 44% have misleading information about prescribing and 92% violate FDA rules.

Conflict of Interest

As long ago as 2004, Kassirer notes in *"On The Take"* that industry spent $21 billion on advertising, 88% of which went to physicians in the many ways documented in this essay, sufficient to purchase a $10,000 family health insurance for two million uninsured Americans.

He undertakes an elegant and nuanced analysis of "conflict of interest" which he defines as placing personal gain over patient welfare, in direct contravention of the Hippocratic ideal. While physicians often acknowledge this conflict they almost universally claim their objectivity in accepting industry largesse and deny any bias in doing so despite cited evidence to the contrary due to a combination of self-deception, an innate tendency to reciprocate and the social role of culture: "Everyone is doing it." To the extent medical schools and professional organizations are aware of conflicts of interest among members, they are disinterested, ignore, condone or conceal its extent and impose minor constraints.

Kassirer also indicts the "remarkable conversion of the health care system into a commercial enterprise since the 1980s … physicians' perceptions about competition between personal profit and patient welfare became blurred." In academia, the Bayh-Dole Act resulted in more than 100 medical schools and universities investing in new companies; in 1998 the number of patents they produced increased 20-fold and 150 institutions had "technology transfer offices."

The Commercial Zeitgeist

In the last two chapters of *On The Take,* Kassirer explores the culture that gave rise to conflict of interest and the greed it feeds upon. Early on he quotes Supreme Court Judge Louis Brandeis's (1916-1941) definition of a profession: "it is an occupation which is pursued largely for others and not merely for oneself … it is an occupation in which the amount of financial return is not the accepted measure of success."

From this beginning, Kassirer notes that "physicians do not exist in isolation; rather they are subject to the changes in the culture and to the norms of society." Then he itemizes ubiquitous conflicts of interest in various professions including the Environmental Protection Agency, the collapse of Enron, the banking industry and among 230 federal judges who accepted trips to resort areas to attend conferences funded by special interest groups on issues under litigation.

Kassirer also identifies the changing circumstances that "drove much of the charitable ethos out of medicine." Beginning with fee-for-service in Medicare coupled with rising costs which bred questions about the wisdom of physicians and doubts over professional integrity. This was further fueled by denials of treatment from HMOs and managed care for which physicians were often blamed, accompanied by a decline in public trust.

Added to this were significant changes in patterns of care. Individual hospitals went bankrupt or coalesced in large, competitive, health care corporations, allegedly "not for profit," but focused on their bottom lines and governed by highly paid administrators. The archetypal and much beloved individual practitioner began to disappear. Lucrative subspecialists, like orthopedics and cardiology built their own hospitals while many primary care practitioners became employees of healthcare corporations exchanging the rigors of practice management and billing procedures for a secure salary. In doing so they endured 'productivity' expectations as well as sacrificing autonomy and collegiality, coupled with political clout.

What Can Be Done?

This is the title of Kassirer's last chapter. Published 11 years ago things look even less hopeful than his suggestions were then. Perhaps Louis Brandeis's most prescient quote (not cited by Kassirer) is: "We can have democracy in this country, or we can have great wealth concentrated in the hands of a few, but we can't have both."

The legislative enactments that laid the foundation for conflicts of interest among academic physicians and the administrators of the FDA were created mainly by Republicans. Today, their billionaire candidate, now President of the United States has accepted only flimsy protections from his own conflicts of interest while withholding the documentation that reveals its scope.

Nevertheless, the following five specific suggestions might be made available to Democratic legislators in the hope of attention at a more clement time.

1. Revise the Bayh-Dole Act to better define "technology transfer," restoring the integrity of academic programs and restricting the ability of industry to co-opt or control research while preserving its capacity to finance development.

2. Revise the Hatch-Waxman Act to restrict monopoly rights on patented drugs and limit the capacity to extend patents for trivial modifications.

3. Revoke the Prescriber Drug Use Fee Act and divert funds paid to FDA by industry to NIMH ($360 million annually).

4. Use the money diverted to NIMH to restore one or more federally funded National Drug Evaluation Unit (modelled on the NCDEU). Industry would be allowed to fund studies, but not to control design, data collection, statistical evaluation or publication.

5. Congress would require FDA to revise and modernize the IND process including the mandatory inclusion of effective generic prototype compounds for comparison in Phase 2 and post marketing studies.

Considering what might be done by the medical profession itself, it is appropriate to question whether the will to act exists. Both academics and journeymen practitioners have achieved sufficient benefits from the *status quo* to feel reluctant to relinquish or define their

conflicts of interest. However, without such a gesture of concern Congress might well consider this a reason not to act.

Perhaps the best that can be done is to draw the attention of academic administrators, CEOs of health care corporations and the leadership of professional organizations to the following five suggestions.

1. Instead of or in addition to swearing the Hippocratic Oath at graduation new doctors should be required to sign a pledge rejecting all financial gifts or inducements from industry – the scope and nature of which should be itemized.

2. On the completion of residency training graduates should sign a comparable pledge to avoid all consultations to industry other than those about scientific matters and to refrain from endorsements or marketing drugs or devices in which they have a financial interest.

3. Every doctor's office should prominently display an annually updated disclosure of any conflicts of interest relating to patient care or research. This should include, the source, amount of financial aid and services rendered.

4. Journal editors and their reviewers should be devoid of any conflict of interest as should be leaders of academic institutions and officers of professional organizations. This requirement should be included in the by-laws of an organization and allow sufficient time for nominees to divest themselves of any conflict.

5. All conflicts of interest among lecturers or authors must be fully disclosed in terms of financial payment and services provided in a manner and format accessible to independent ethical scrutiny.

Synopsis

This chapter reveals the brazen scope and toxic brew of brass-knuckled and subversive tactics deployed by the psychopharmacological industry to infiltrate and corrupt every nook and cranny of our discipline. In doing so, it has stifled and silenced our traditional avenues of debate and disclosure. So, we owe a great debt of gratitude to the investigative reporters and bold

professionals in our disipline for exposing what our scientific journals, professional associations and academic institutions have sometimes chosen to deny or conceal.

The fundamental problem stems from a broken political system corrupted by personal greed, fed by corporate money. Congress is so in thrall to that addiction that it no longer protects the public it represents by failing to radically reform the regulatory system intended to ensure the safety and efficacy of the drugs we prescribe.

Bill Burke, Trek's politically independent CEO in *"12 Simple Solutions to Save America."* (Burke 2016) provides Solution 9: "*Fix the Health Care System"* It states: "The health care industry should be embarrassed. They are responsible for providing the nation with the highest health care costs in the world, along with the worst results and then they spend $5 billion to keep the same crooked game in place."

Source Material

The bulk of this article is derived from the nine volumes referenced in the text. Each of these books has extended supportive end notes and/or bibliographies that include scientific articles and books, investigative reports in leading newspapers and magazines, government agency publications, interviews, personal communications, internet websites, FDA and industry documents and litigation records. Altogether there are an estimated more than 2,000 citations.

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A changing Zeitgeist

I am grateful to INHN colleagues interested in our field for their supportive comments. Taken together they project a broad but bleak consensus about the current situation coupled with a profoundly pessimistic outlook for change.

These cogent commentaries portray a spectrum of contributory factors including archaic FDA guidelines, politically contrived information transfer, shrinking Federal support for quality research, commercialization of the discipline and a flawed diagnostic system.

Superimposed on influences particular to our profession is toxic change in the political and social Zeitgeist. Income disparity and "growth of the super-rich" exert a malignant effect by corruption of the political process via corporate lobbying. This may indeed be the primary process, with the contemporary political scenario its logical endpoint.

Five years ago, I published my memoir, *"Bits and Pieces of a Psychiatrist's Life"* (Blackwell, 2012). Included in it were two prescient essays, printed below.

Greed: The Deadliest Sin

Greed is expansive; it feeds on itself at the expense of principle. There is never enough. It betrays family, friends, colleagues and fellow citizens. Greed is corrosive; those that succumb to its lure no longer work for pleasure, no longer teach for joy or perform research with integrity or for the thrill of discovery. Greed is infectious; it spreads from person to person and place to place,

bred in environments that lack intellectual, emotional and spiritual rewards. Greed takes over whenever science becomes mundane, repetitive, boring or duplicative. Greed perpetuates itself, producing nothing innovative, creative or unique; it cultivates its own sterile, infertile seedbed. Greed is cunning; it hides behind platitudes, excuses, rationalizations and deceit. Greed is ubiquitous in industry, finance, politics, medicine, education and entitlement programs; its tentacles spread throughout society. Greed is tenacious; it can destroy cultures, institutions, nations, organizations and individuals. Civilization rests on the triumph of generosity over greed, of equity over avarice. Not between conservatives or liberals, deism or atheism, constitutions or commandments. Today the outcome is in doubt.

Is Greed an Addiction?

Humans are the only animals, outside the laboratory, that abuse their own appetites and can become addicted to their sources of gratification. Drugs (including alcohol and nicotine) sex, money and foods are included, defined as compulsive activities an individual is unable to stop abusing despite negative consequences.

In recent years America has seen an upsurge in food addiction, resulting in an epidemic of morbid obesity and its medical complications. The addiction already associated with money is gambling. Sixty percent of the population gambles in any given year using casinos, lotteries, the Internet, card rooms and bingo halls.

It seems logical to consider the possibility that addiction to money is not confined to casinos and may have spread to corporate headquarters and the boardroom. Greed is defined as *"intense and selfish desire for wealth, power or food"* (OED). Greed feeds on its own appetite. For food this is often takeout or fast food chains, "all you can eat buffets" and obscene portion sizes; for money addiction may be reinforced by stock options, bonuses and salary not linked to productivity.

In 2008 the highest paid CEO in America made more than $700 million. The next person in line took home $556 million despite a 21% drop in the corporation's stock price. The bottom CEO of the top ten earned a meager $72 million – $60 million as stock options in a year when the price of corporate stock dropped 70%, suggesting a questionable relationship between performance and reward. These amounts are so beyond the common person's experience or imagination they must inevitably call into question what possible appetite or motive drives them.

With this kind of income, few, if any, of the normal checks and balances exist to keep the addiction to wealth at bay such as shame, bankruptcy, declining health, public stigma or family concerns. On the contrary families feed from the same trough, corporate health benefits are princely and lobbyists bribe politicians to avoid or minimize regulations that might constrain profit margins.

In Greek mythology, King Midas of Phrygia came to rue the God-given ability that turned everything he touched into gold because it included the food he needed to eat and his own daughter. Starving to death and grieving for his child Midas implored the gods to cancel his golden touch, and they generously obliged.

In today's non-mythic world money addicts have no reason to seek relief but can gloat in private or public over their growing hoards. The only people held responsible for this largesse are those who feed the beast by buying what is offered. The doctrine of *caveat emptor* (Latin for let the buyer beware) was established in U.S. law with a Supreme Court decision written in 1817 by Chief Justice Marshall. It states that a buyer is responsible for assessing the quality of a product or service before purchasing it. Over the years this ruling has been modified by consumer protection laws and regulations against fraud. But anyone who has bought a used car or stocks from Bernie Madoff knows this is still a bumpy road to travel.

Greed may not be bloody or lethal and it is not a capital crime, but it deserves credit as the deadliest sin because it is so pervasive and insidious. It can operate whenever goods or services are sold for profit, and it frequently corrupts those government agencies charged to define standards to protect the public from fraud. Witness the SEC's (Securities and Exchange Commission) failure to investigate Madoff.

> Greed is also enabled by politicians who claim that competition always drives down costs. This may be true for everyday products like clothes, computers and cars, but is seldom true for those who want to enhance or extend quality of life seeking health care, education, safety or a home of their own. When a buyer wants the best in these areas which most do, and the seller knows that, the table is set for excessive lending and profit, usury, price fixing or fraud. This story ends in underwater mortgages, crushing college loans

beyond early redemption and untreated illness leading to foreclosure, bankruptcy and death.

If, as a society, we decline to set standards or limits on how much wealth is enough we will inevitably enable a growing addiction to greed. Today's numbers indicate it is thriving, is unrestrained and is increasing. It is upsetting the balance and distribution of wealth in our civilization and could destroy it. The normal addict, like Midas, places his own life at risk. The greed addicts like Madoff, Wall Street CEO's and the barons of Big Pharma gamble for higher stakes, blind to the welfare of others.

These words were written seven years ago; welcome to the world of the morbidly wealthy!

Chapter 20

The ADHD Controversy

Keith Conners in his own words

Preamble

One of the books in the previous chapter is ADHD Nation (Schwartz 2016). It provides perhaps the best example of the way in which the pharmaceutical industry operates to inflate the use of their products in a manner harmful to the community. This case deals with the use of addictive stimulant drugs in children diagnosed with what was originally known as Minimal Brain Disorder (MBD), but became Attention Deficit Hyperactivity Disorder (ADHD) in the DSM diagnostic system.

The ADHD Controversy

Big Pharma's *modus operandi* to inflate use is to recruit leading academics and researchers, so called Key Opinion Leaders (KOL's), who are highly compensated – five to six figures

annually, for research, lectures and advocacy of the drugs. In this instance, it led the FDA to greenlight the compounds as "safe and effective" and created "a self-affirming circle of science that squashed all dissent." The end result was a billion-dollar annual market expected to double every three-five years. This Chapter offers a unique insight into this process via an interview with Keith Conners, an involved, major lifelong KOL.

Alan Schwartz began his work as a reporter for the New York Times and his book, *ADHD Nation*, became a successful best seller, in part because of the skillful, well-reasoned manner in which the story was told. Schwartz acknowledged the reality of the condition and the reasonable estimate of its prevalence in 5% of children. He demonstrated this had tripled overall, but also affected up to half of all children in selected sub-populations. He identified the cause as misdiagnosis and over-prescribing, magnified by claims that the drugs "reduced conflict with parents, deterred substance abuse and sexually transmitted diseases."

The book was cleverly designed to highlight the manner in which two children were lured into inappropriate use of stimulants to which they became addicted, disrupting their education and persisting into adult life.

Alan also focusses on the roles of two prominent psychiatrists, Paul Wender and Keith Conners. The latter developed a lifelong interest in MBD while a Ph.D. psychology student at Harvard; developed valid rating scales used worldwide to diagnose the condition; and became a KOL for Eli Lilly and their drugs during his career. Eventually, when the risk of addiction was acknowledged, Lilly developed a new compound that was non-addictive but also less effective, a caveat Keith Conners mentioned in his lectures. Lilly objected and threatened to end their lucrative contract. Keith refused to compromise, resigned and retired.

When Keith eventually read Alan's articles in the Times they communicated and he was invited to meet the two now adult and abstinent characters. Realizing he had participated in a "national disaster of dangerous proportions" he encouraged Alan to write his book.

Below is a verbatim account of Keith Conners' thoughts and feelings in his own words during a phone conversation five months prior to his death.

Reference: Schwarz A. ADHD Nation. Children, Doctors, Big Pharma, and the Making of an American Epidemic. Little, Brown, 2017.

Keith Conners

(1933-2017)

In his own words

On January 26, 2017, five months before his death, I spoke with Keith Connors for more than 30 minutes to obtain his general views on Alan Shwartz's book *ADHD Nation*, as well as his specific opinions concerning the overall field of ADHD, the role played by Paul Wender and manner in which this is portrayed by Swartz.

At the time of my phone interview Keith was an inpatient on a cardiac care unit where he had been hospitalized for almost two weeks. He was quite lucid and thoughtful and gave permission to cite his opinions as a personal communication. I indicated that if this were to occur I would share any material prior to posting on INHN.org. We did this and he approved of what follows.

I was surprised to learn that Keith Conners had become a close confidant of Alan Shwartz, had not only provided much of the material in the book, but had been instrumental in persuading Shwartz to write it. He expressed admiration for the author's statistical skills and decision to leave journalism to become a high school math teacher.

At the same time Keith gave a fair-minded appraisal of the book noting that Schwartz had adopted a tone and theme that earned a Pulitzer Prize nomination. It is structured like a novel, (almost a detective story), in which Keith is a sympathetic lead character and Paul Wender is portrayed as a foil and "firebrand."

With regard to the whole ADHD controversy Keith saw it as an "eye of the beholder" phenomenon in which folks could view the same data differently and even the same person might "flip images." Keith saw himself as starting as a "true believer," originally a Big Pharma KOL, who eventually realized he had made a terrible mistake in what had become a tragedy for the profession. Paul Wender's role had been more nuanced but less volatile. Like Keith, he began as

a true believer and remained one, far too much an independent thinker to become a KOL, whose research was funded more by NIMH than industry.

Keith believed Paul felt that the pharmaceutical industry had made skilled use of complicit academic psychiatrists in inflating the prevalence of ADHD and use of stimulants in children, including memberships in associations promoting increased drug usage.

In Paul's involvement with the 1980 revision of DSM III he was ahead of his time in noting the different ADHD symptom profiles between genders with the virtual absence of hyperactivity in girls. Another major contribution was Paul's advocacy for extending the ADHD diagnosis to adults. Keith regarded Paul as a brilliant and innovative clinician with a sharp wit and provocative style whose valid clinical observations were categorized by Shwartz as designed to inflate usage of stimulants. At the same time Keith agreed with Shwartz that the DSM criteria might contribute to inflating the prevalence of ADHD by advocating a "stripped down" version of the Conner's Scale using duplicative symptom criteria.

Keith also felt that industry had developed its own poorly validated and corrupt rating scales used by KOLs and pharma reps to train primary care providers in the presumptive diagnosis of ADHD and use of stimulants.

Paul Wender's other major but still controversial contribution was his advocacy for extending ADHD diagnosis to adults. The epidemiologic evidence for an inflated prevalence of ADHD diagnosis and use of stimulants in children (particularly boys) is convincing in some sub-populations but its presence, symptomatology and response to treatment in adults is still not well defined. However, research in New Zealand has recently confirmed that in up to a third of children with ADHD symptoms persist as adults, with a reduction in over activity but persistence of internal restlessness. A type of adult onset ADHD clearly occurs and can persist into the 80s but response to stimulants is more variable. Keith notes this adult ADHD population may be double in size to childhood forms creating a large, lucrative and appealing target for industry abetted by KOLs and new rating scales.

ADHD Nation was published in 2016 and Paul Wender died of a heart attack in July. Keith did not know if he knew or not of the book's existence and the unjust role Schwartz assigned him.

Keith died at age 84 on July 5th, 2017 (my own 83rd birthday). Shortly before his death he collaborated with Allen Frances and Bernie Carroll who helped him write his own Obituary for the British Medical Journal, a final warning about the over diagnosis of ADHD and inappropriate over prescribing of stimulant drugs engineered by the pharmaceutical companies, abetted by compliant academic psychiatrists bribed to be Key Opinion Leaders (KOLs).

Chapter 21

The Baby and the Bathwater

Preamble

Chapter 21 comprises three recent contributions to the INHN network, the original Baby and the Bath Water essay, the response from Edward (Ned) Shorter, a distinguished psychiatric historian, and my reply.

This series raises an important question; how to find an epistemological standard for discriminating the baby from the bathwater in today's murky scientific environment?

Shorter states that "experienced clinicians often have a gut feeling for what works." This is a valuable reminder that is true of the earliest effective discoveries in psychopharmacology (Chapters 3, 5, 6 and 7). After decades of observing futile asylum attempts to alleviate the major psychotic disorders clinicians, nurses, relatives and patients themselves were appropriately pessimistic but primed to acknowledge real change. The benefits of the first drugs like lithium, chlorpromazine and imipramine were so dramatic they did not need to impose an epistemological standard to confirm what was clearly in plain sight.

But in todays contaminated and toxic environment who are the "experienced clinicians" we can trust? Conflict of interest is a buzz word, highly rewarded, seldom defined and never prosecuted. It is important to recall that in the pre-FDA days, before thalidomide, most of placeboes, panaceas and snake oils were enthusiastically endorsed by self-nominated experts with their accompanying biases.

A final puzzle that remains to be solved is how can we establish a valid epistemological standard for drug trials? Placebo controlled trials may be rendered obsolete when so many chemophilic subjects with a pre-exiting ailment may have responded to numerous highly promoted drugs with seductive "mechanisms of action" making placebos and hypothetical new drugs impossible to distinguish. Even by an expert bribed to do so.

The Baby and The Bath Water

Recent writing assignments have brought to mind the idiomatic expression; "*Don't throw out the baby with the bath water."* The phrase originates from a German book by Thomas Murner,

Appeal to Fools, written in 1512, more than half a millennium ago. It is illustrated by a woodcut of a woman tossing out a baby along with waste bathwater. The use of the idiom acquired philosophical connotations in the writings of Martin Luther, Goethe and Thomas Mann, among others, presumably to denigrate those who they believed advocated foolish ideas.

Its modern usage is allied to another philosophical term, Epistemology – **OED**: The theory of knowledge, especially with regard to methods, validity and scope. From *episteme,* Greek for knowledge.

Applied to the contemporary domain of science in general and psychiatry in particular, the idiom expresses what is appropriately retained as essential and truthful or rejected as false and inessential. In medicine it can be used to segregate placebos, panaceas and snake oil from safe and effective remedies. Psychiatry probably has the most difficulty in determining what to keep and what to discard due to a paucity of valid and reliable outcome measures. Recent examples come to mind: Freud's seductive use of deductive reasoning, embraced by John Cade (Blackwell, 2017), but artfully debunked by Michael Shepherd in his short book, *Sherlock Holmes and the case of Dr. Freud,* (Shepherd 1985). Also, the declining veracity of double-blind placebo-controlled trials, initially regarded as the gold standard in biological psychiatry, now manipulated and debased by the pharmaceutical industry under the FDA's blind eye (Blackwell 2017b). Psychoanalysis and me-too drugs become candidates to be flushed with all the other forms of therapy considered lacking in value.

A willingness to throw out remedies is facilitated by false promises, such as the Nobel award for pre-frontal lobotomy and the intractable worldwide delusion that insulin coma cured schizophrenia. Such examples encourage skeptics and scientologists to metaphorically pull the plug on all biological treatments. At mid-century Peter Breggin, biological nihilists and conspiracy theorists colluded to succeed in persuading Congress to cut off all funding for brain stimulation research, effectively ending the career of Jose Delgado (Ch, 10).

Such incidents have encouraged other attempts to throw out all biological treatments including ECT, lithium and even the modest effective use of a spectrum of specific drug treatments most discovered by serendipity between 1949 and 1975, but effective enough to meet contemporary epistemological standards. Primary and most forceful have been the nine books written in the 12

years between 2004 and 2016 (Blackwell 2016) which present a compelling story of over diagnosis and drug usage described by two authors as "an epidemic" (Whitaker 2010; Schwartz 2016). Incriminated have been ill considered legislation, a corrupt pharmaceutical industry, complicit psychiatrists, many of them academic superstars and, finally, a lax FDA, economically in thrall to the industry it regulates (Blackwell 2017).

Some of this information is inaccurate or hyperbolic, but much is true and compelling so the overall effect is to blur the epistemological boundary between truth and falsehood, muddying the bath water and concealing a biological baby that is beloved and retained by some or reviled and cast out by others.

Applying a metaphor that has survived more than 500 years becomes a game of blind man's bluff. Now that commerce and money trump epistemology where is the baby and who are the fools?

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Edward Shorter's Comment

Barry Blackwell's thoughtful and learned comment immediately invites the response: First, what is baby and what is bathwater? And second, how do we tell them apart?

So first**,** most of the field probably agrees on the following judgments: psychoanalysis (throw); neurotransmitters (keep); insulin coma therapy (throw); mood stabilizers (keep). These are not really scientific judgments but cultural opinions based on optics. We cling to neurotransmitters (despite 50 years of failure in drug discovery), because neurotransmitters have made a good marketing trope for the pharmaceutical industry. We throw out psychoanalysis because we find biological treatments more effective, even though the many illnesses caused by stress and misery do not respond to biology; we discard insulin coma therapy because it looks awful (and that nasogastric tube at the end, please!); and we like mood stabilizers because we buy into a theory that a special kind of illness causes mood "instability" and that this illness requires special treatments. All of these judgments are questionable, at least. So, throw vs keep, let's proceed with caution here.

Secondly, how do we tell baby from bathwater? How do we *decide* what to throw and what to keep?

Barry Blackwell rightfully casts doubt upon the usefulness of randomly controlled trials: In theory, they should be a gold standard of evidence; in practice, the influence of the pharmaceutical industry has hopelessly corrupted the integrity of many trial reports -- and therewith the integrity of much of the literature -- and it would be rash indeed to base one's judgment of whether SSRIs represent important drugs for depression on the basis of the trial literature. Here, as Barry Blackwell and others have shown, the literature has been heavily influenced by senior clinicians who have really cashed out in alliance with Pharma (and are now disparagingly referred to as KOLs)

So, how do we sort out baby and bathwater? Here clinical science comes to our aid. Experienced clinicians often have a gut feeling for what works and what doesn't, despite what "the literature" says. Take, for example, the issue: Do the SSRI-style antidepressants evoke suicidality in a subset of depressive patients? The epidemiological literature has been unable to confirm a connection. Yet many clinicians have seen in their practices patients becoming suicidal or homicidal after initiating a course of SSRI treatment. Here there is no question: the temporal relationship is powerful and immediate; it happens to their patients under their own eyes!

If we aggregate these impressions, what we have is clinical science. It is a science not bolstered by epidemiology, because the relationships are submerged in the great mass of numbers. It is a science not bolstered by genetics, because, when you get right down to it, what diseases are reliably caused by genetics? Family tree, for sure, and in our schizophrenic and melancholic patients there are illnesses all over the family tree. But genetics? So far, little has panned out. "Schizophrenia" does not breed true. Yet we know, in our heart of hearts, that these pathological affinities exist in family trees, and it is not a stretch to call this certainty clinical science. The field needs to give this more thought.

One final comment: Barry Blackwell trashes insulin coma therapy as bathwater, a dangerous antique that, thank God, we are rid of. I think a second opinion is possible on ICT. It definitely helped many patients, and not all these patients would have been relieved by neuroleptics. There was something there, something about the effect of insulin on the brain that you have to see to know that it exists, but after you see it, you know it.

Barry Blackwell's Reply to Edward Shorter

Ned Shorter's comment gives added scope to the issue raised in my essay. One could go further to note that throughout our everyday life we are constantly retaining or discarding all manner of ideas, situations or acquisitions, often on slender or intuitive grounds. However, we tend to cling to what we need, value or pleases us.

But in scientific matters we rely on epistemology to rid us of those domestic reflexive responses in evaluating our own or colleague's opinions or conclusions. (**OED:** *epistemology*; "The theory of knowledge, especially with regard to the methods, validity or scope").

As a trainee at the Maudsley in the early 1960s under Aubrey Lewis and Michael Shepherd, a core concept of the curriculum was a rigorous and skeptical analysis of all therapeutic claims, a reaction to centuries of speculative dogma and deductive reasoning bolstered and backed up by charismatic clinicians and their reputation among peers (Blackwell and Goldberg 2015).

It was Aubrey Lewis's goal for the Institute he founded to transform European psychiatry into a scientific discipline on an equal footing with the rest of medicine while America was still mired in psychoanalytic mania (Goldberg, Blackwell and Taylor 2015). This scrupulous ideology

sanctified controlled double-blind trial designs which promptly rid the world of insulin coma, but snared me in trouble over Schou's discovery of lithium prophylaxis, the outcome of astute conclusions based on careful scrutiny of individual patients including his own brother who suffered from treatment resistant recurrent unipolar depression. Unfortunately, the design he chose to support his hypothesis was seriously flawed, encouraging us to make a critical rejection of the conclusions. With hindsight, we were wrong for the right reasons, but in the language of the metaphor "we threw the baby out with the bathwater." Something we were justly castigated for.

So, this essay, with that title, was triggered by confronting a similar dilemma while writing two book reviews that together constitute a detailed biography of John Cade and his rediscovery of lithium for acute manic excitement in 1949 (Schioldann 2009; de Moore and Westmore 2016). This was the first substance, a metallic ion, to be effective for a specific psychiatric disorder; work which, years later, became the primary stimulus to Schou in his discovery of lithium prophylaxis for recurrent bipolar disorder.

I will not recapitulate the conclusions arrived at in my two reviews but read them for yourself and note they are heavily influenced by the fact that Cade and his discovery have attained a reputation of mythic proportions in Australia and around the world that is impervious to epistemological dispute in the absence of striking new contemporary or collateral evidence, which is lacking. Both baby and bathwater remain intact, but the latter is somewhat muddied, blurring an observer's conclusions.

Finally, I shall make a gentle riposte to Ned's defense of insulin coma. Undoubtedly the treatment did something for some patients that encouraged a personal conviction of value among some clinicians (Cade was among them). Many more would maintain that, like chlorpromazine, it produced sufficient transitory benefit to justify discharge from an institution, but relapse and readmission were frequent outcomes.

The epistemology of insulin shock therapy leaves much to be desired. To begin with, patients were selected of good prognosis, recent onset and likelihood of remission. In fact, the remission rate did double but it did not reduce the relapse rate. The side effects were severe obesity, prolonged or irreversible coma, brain damage and death (1-5%).

The first and conclusive double-blind study was performed at the Maudsley in 1957 and published in the Lancet where it attracted international attention, provoking an immediate decline in the treatment (Ackner, Harris and Oldham 1957). Opinions were also influenced worldwide before and after the Maudsley study (Bourne 1953; Bourne 1958). Bourne's succinct opinion was that "It made them (physicians) feel like real doctors instead of just institutional attendants."

The world took note (Russia was slow), but the overall impact was clear, the baby was gone from the bathwater and nothing of significance remained.

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EPILOGUE
The "Pioneer" and Modern" Eras.

The comparison between two time periods was not an original intention but evolved as the story emerged. It is between the Pioneer Era (1949-1980) and the Modern Era (1981-Present). The distinction was not arbitrary nor was it intended to laud one period or disparage the other. It is clearly the product of radically different Zietgeists.

In America, and to a lesser degree other nations, the cultural climate altered radically beginning in the 1970's. Changes were political, social, and economic creating income disparity, changes in social policy and legislation affecting all sectors but especially health care, the pharmaceutical companies, the FDA, the behavior and life style of physicians in general and psychiatrists in particular (Ch.19).

The Foundation of the Odyssey

The intellectual foundation to this Odyssey was laid by two German immigrants to Britain in the wake of the first German war with Norway in the 19th century and prelude to the second British war with Germany in the 20th Century. It began with a conviction promulgated by Thudichum (Ch. 1) that mental disorders must originate from alterations in brain chemistry. The links from chemical to physiological change and ultimately to functional brain activity amenable to the action of drugs were provided by Elkes, (Ch.3).

The Status Quo Ante

Our story begins with a picture of asylum care before effective treatment, shown visually to the public in a movie, *The Snake Pit* (1948) and to the readers on this volume in early chapters with elegant portrayals penned by early pioneers in psychopharmacology of asylum care prior to the mid 1950's. Enoch Calloway provides a description of life as a resident from 1948 to 1950 in what was then a leading edge American asylum, (Ch. 2). John Cade describes an Australian mental hospital in the days leading up to the Second World War. (Ch.5). Heinz Lehman provides

his tale of a German immigrant's work in a Canadian institution at that same time and Deniker gives an account of the backwards in a French asylum prior to chlorpromazine. (Ch.6).

That therapeutic impotence at this time was not due to lack of effort is attested to by two Nobel Awards for putative treatments which both failed to fulfill their early promise. Wagner Jaureg in 1927 for malaria fever treatment in *dementia paralytica* and Egan Moniz for lobotomy in schizophrenia in 1949, on the threshold of the modern era. By that time Electroconvulsive Therapy (ECT) for melancholia and Insulin Coma Therapy (ICT) for schizophrenia held promise of recovery but prior to routine muscle relaxants and anaesthia their image stifled public approval and fostered stigma. There were symptomatic palliatives available in asylums but not cures, and often with side effects, dependency or addiction. There were bromides, barbiturates, chloral, and paraldehyde to calm excitation and amphetamine to stimulate lethargy or depression

The Pioneer Era: 1949-1980

The first glimmer of a new era came in 1949 from Australia with John Cade's re-discovery of lithium as a remedy for psychotic manic excitation (Ch.5). Its international impact was impeded due to a contemporary ban on lithium by the FDA in America following deaths from toxicity when used as a salt substitute in cardiac conditions. It was also hampered by several deaths in Australia, by Cade's ban on its use in his own hospital and by his reluctance to endorse or encourage the use of effective plasma monitoring of lithium levels, discovered by colleagues in Melbourne shortly after his own discovery and publication.

The long hoped for breakthrough in the drug treatment of severe and persistent mental disorders came in a flurry of discoveries, many of them facilitated by the juncture between prepared minds and serendipity. First, in early 1952, came chlorpromazine, the brainchild of Jean Delay and his team at the Institute of Psychiatry in Paris, a leading European academic and interdisciplinary environment, (Ch. 6).

The team's lead clinical investigator, Pierre Deniker reported chlorpromazine's effect at stifling the positive symptoms of schizophrenia (hallucinations and delusions), restoring the capacity for sane decision making but with little or no effect on the negative (deficiency) symptoms. These changes were so dramatic and convincing to both staff and relatives that they

were reported in the literature on less than 40 patients with no felt need to employ controls. The first confirmatory study of any magnitude published in the English language was not made until 1954 in Canada by Heinz Lehman and a young resident (Ch. 7), and, in the same year, the first double blind placebo controlled study was by Joel Elkes and his wife in England. (Ch.3).

International dissemination of information about chlorpromazine and its effects was facilitated by Jean Delay, Co- convener of the First World Congress of Psychiatry with Henry Ey, head doctor at the Bonneval Asylum. (Ch.6). Soon after it was further enhanced by the founding of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) in 1957, a forum with annual meetings for all nations to share progress in the field.

The main, perhaps only, failure to appreciate and laud the virtue of chlorpromazine came from the academic sector in America, mired in its infatuation with psychoanalysis. Here drugs were at best seen as stifling the patient's affect, considered essential to gaining insight, and worse, as the therapist's sadistic response to the failure of therapy. Residents and young faculty interested in pursuing a career in psychopharmacolgy were offered similar interpretations of their motives.

Between 1949 and 1975 new drugs were discovered for all the major psychiatric disorders. After lithium arrived; so-called anti-psychotics or major tranquilizers- although they were first characterized as benefiting undifferentiated psychotic excitement. Next the anti-anxiety drugs, first meprobamate then the benzodiazepines, a category for which there was no perceived need by the medical profession but which took off like a rocket, creating their own large market. (Ch. 13). Then in sequence, a series of anti-depressants; first the MAO inhibitors, (Ch.8) followed by tricyclic compounds, selective Serotonin Re-uptake inhibitors (SSRI) and finally, a slew of mood stabilizers to compete with lithium in bipolar disorders.

Perhaps the biggest disappointment of the Pioneer Era was failure to be able to link a specific biochemical mechanism of action to a particular disorder. Shildkraut (1965) proposed a linkage between cathecholamine metabolism in the brain and some, but not all, drugs that benefit depression, a theory that gained traction when Axelrod and collegues (1970) were awarded the Nobel Prize for research on norepinephrine pathways. But subsequent clinical studies indicated that other drugs and neurotransmitters were also implicated in depression. After the sequencing

of the human genome, research in the 21st Century switched from neurochemical to pharmacogenetic research which to date has also been inconclusive.

Despite this major disappointment the pioneers and the research they generated cast valuable light on other aspects of treatment including side effects, drug interactions, dosage schedules and methods of measuring blood levels for some drugs.

A Rewarding Zeitgeist

Psychiatrists working in this"honeymoon"pioneer period experienced a variety of powerful affirmative influences. Foremost was the gratification of working with effective treatments in patients formerly considered by staff and family members as permanently sick or insane. Research was especially productive and rewarding. There was need for rating scales, outcome measures, protocols and statistical procedures. Using these tools almost every intervention produced findings that were significant and worthy of publication. Nor was it difficult to find untreated patients willing to enroll in studies of the new drugs, even those that might be placebo controlled.

An added benefit was an ability to observe the course of previously untreatable disorders without insurance driven constraints on duration of treatment or the need to name everything (Ch.12). There were no Institutional Review Boards (IRB's) or similar constraints. Academics learned how to write grant applications and get them funded, quickly compiling a bibliography that ensured promotion and tenure. The working style of the pioneers, often living in close proximity to the patients, was characterized by hard work, long hours and interdisciplinary collaboration. A free-wheeling research environment described by Calloway (Ch.2) was in existence even before the arrival of the new effective drugs.

Although mostly characterized as a "biological" revolution the pioneers' ideology was more practically biopsychosocial; both Jean Delay's Institute in Paris and Aubrey Lewis's Institute in London, based on Adolph Meyer's approach, employed this model long before George Engel advocated for it in America. (Ch, 6 & Ch.11). It was also what drove Joel Elkes's decision to name his new Department at Johns Hopkins *The Department of Psychiatry and Behavioral Medicine,* contemporaneous with launching a combined M.D/Ph.D. training program. (Ch.3). Also, when the pioneers founded the American College of Psychopharmacology in 1961 a guiding principal was to encourage the integration of preclinical basic neuroscience with clinical

psychopharmacology. Concerned about the quality and objectivity of early trials conducted by industry the Federal government funded and the NIMH set up a national system of drug testing centers in the early 1960's named the Early Clinical Drug Evaluation Units, (ECDEU), mostly in State Mental Hospitals and the Veterans Administration. A lead and intensely productive unit was begun at Verdun in Canada under the joint administration of Heinz Lehman and Tom Ban. (Ch.7). Mostly funded by industry, studies were conducted using shared protocols, study design and data analysis.

Contributions by women pioneers were prominent in several areas. (Ch. 9). Included were Pediatrics (Barbara Fish, Nina Schooler, Judith Rappaport, Paula Clayton and Rachel Kline), Neuroanatomy of suicide (Victoria Arango), Psychometrics (Jean Endicott), Eating disorders (Katherine Halmi). Schizophrenia (Nina Schooler), and epidemiology and interpersonal psychotherapy (Myrna Weissman)

Early Public Protests

In the late 1960's and early 1970's segments of the public began to express vehement opposition to experiments and drugs affecting the brain. They included scientologists, communists and conspiracy theorists. In France a Trotskyist revolution accused Delay of being an agent of government control over people suffering severe mental illness and students ravaged his Institute. Delay quit psychiatry for literature, his first love, and occupied his seat at the *Academie Francaise* until his death. (Ch.6) In Canada Heinz Lehman was made of sterner stuff and rebuffed a similar challenge by communists in Ontario at a public debate,(Ch.7) In America Jose Delgado's pioneering research in electrical stimulation of the brain was cut short by a scientologist (also a psychiatrist) and conspiracy theorists who lobbied Congress to ban funding of the research,(Ch.10). Also in America John Smythies, with a lifelong interest in the transmethylation hypothesis of schizophrenia and the effect of hallucinogens, which began as a resident, was stifled after public and government sentiment was aroused by drug abuse in the hippie culture of the 1960's. (Ch.10)

Optimism, Skepticism and Controversies

By the mid 1970's most of the benefits and drawbacks of the available psychotropic drugs had revealed themselves. Optimism and ambiguity (Ch.10), caution and skepticism (Ch.11) were all

apparent. Among the disappointments, as noted above was the increasing awareness that the hoped for gold standard of treatment, categories of drugs for specific disorders, was dwindling. The sequencing of the human genome at the end of the 20th century saw a switch from biochemical to pharmacogenetic speculation which also became clinically unproductive. During this time period major scientific controversies developed in Britain and America concerning the validity of claims for lithium and prophylaxis in affective disorders (Ch. 12) as well as the appropriateness of drugs used to treat anxiety.(Ch.13 and Ch.14) in which the discoverer of meprobamate played a nuanced role,(Ch.10).

Somewhat belatedly the topic of Compliance came to the forefront during the mid-70's confirming that no drug was useful unless it was taken, an outcome fostered by a therapeutic alliance (Ch.11).

Characteristics of the Clinicians

The personas and accomplishments of all the pioneers are best conveyed in more than 200 interviews conducted by accomplished peers in the *Oral History of Psychopharmacology* (OHP) Series; Editor Tom Ban (2011) and over 50 mini-biographies (*Dramatis Personae)* authored by myself. This volume contains 14 detailed biographies of men from various sources and 9 mini-biographies of women taken from the OHP volumes.

Only 3 of the male pioneers are American born (Calloway, Kline and Kassell). and the remaining 11 are from 7 different nations, several of them victims of Fascist, Nazi, Communist or Anti-Semitic persecution. Three pioneers were without formal psychiatric training, (Elkes, Lehman and Berger).

As illustrated by their biographies and bibliographies almost all pioneers were highly productive and generative in psychiatry and psychopharmacology. Several held leadership positions in academic and professional organizations and some were renowned educators and mentors. Two had careers disrupted by controversy (Delay and Delgado). Women's' accomplishments equalled those of men.

The Modern Era (1981-Present)

By 1980 a large number of changes coalesced and began to influence psychopharmacology and the lives of its practitioners. (Ch.19) These included political, legislative, economic,

professional, societal and organizational issues which will be discussed in a chronological framework.

Powerfully complicit was a national climate of corporate greed, addiction to money and income disparity that transformed medicine from a caring profession into a business.

The seeds for radical change in the arena of psychopharmacology were sewn in the mid 1970's when the Federal Government shut down the highly productive early clinical drug testing units (ECDEU), unmindful that the reason for their existence had been to remedy industry greed and incompetence. Those seeds germinated in the 1980's when during 8 years of the Reagan Administration (1981-1989), Republican politics melded with the machinations of an army of industry lobbyists to instigate legislation that turned incompetence into malfeasance. (Ch.19)

This included allowing "information transfer" from academia to industry and requiring FDA to increase payments by industry to the FDA for approval of new drugs amounting to half of the FDA's budget, creating an obvious conflict of interest and erosion of objectivity.

This was also a time when innovative drug discovery had stalled and the industry switched its resources from creative research to seductive marketing yielding enormous economic rewards that allowed them to establish hegemony over corrupt clinical trials, all levels of medical education, patient advocacy groups (like NAMI), professional organizations (like APA and ACNP), and a cadre of academic psychiatrists, (KOL's), who colluded in corrupting the design, analysis and publication of flawed data.. Their conflicts of interest contaminated FDA Advisory Councils, Best Practice Committees and Journal Review Boards These conflicts might be glibly acknowledged but they were never defined or sanctioned by academic or professional organizations fracturing the relationship and roles of academic psychiatry and industry (Ban, 2006). Matters were made worse by a major reduction in Federal funding for research from psychopharmacology to genetics making some academics vulnerable to bribes from industry (See Ch.19).

The 1980's also ushered in dramatic changes in patterns of health care delivery and insurance practices. First came government mandates limiting duration of inpatient stays according to Diagnostic Related Groups (DRG's), followed by Managed Care requiring prior approvals for "medical necessity" of inpatient and outpatient care. Inner city hospitals (including those with academic affiliations) were overwhelmed with the economic burden of reduced bed

occupancy and increased numbers of Medicaid or uninsured citizens as well as patients with mental illness denied insurance parity. Absent appropriate care in the community they sometimes became homeless. When Congress belatedly mandated insurance parity for mental illness the Federal Government was slow to define its parameters and the insurance companies invented their own. A pattern of hospital mergers or closures in urban areas spread nationwide. In Milwaukee 7 inner city hospitals disappeared between 1980 and the end of the century, including an academic psychiatric residency training program in a city short of psychiatrists with a County Behavioral Health Division overwhelmed by recidivism due to inadequate community care.

Insurance companies seized the opportunity to only authorize psychotherapy by non-medical providers, confining psychiatrists to "15 minute med checks". Psychiatrists in private practice reacted by declining to treat Medicaid patients as did many of the Health Care Organizations that survived the health holocaust despite their alleged "not for profit status", an abdication the Government chose not to challenge. The concupiscence and cunning of these organizations and government apathy led to the paradoxical outcome that America became the only nation on the planet where health care was for profit. (Ch.19) fueled by the myth that health care, like all consumer products could be controlled by market competition.

Decades of seductive television advertising of psychotropic drugs and complicit KOL endorsements tilted public opinion and medical practice in a biological direction reinforced by insurance company's reluctance to reimburse more expensive psychological and social interventions, despite convincing evidence that treatment costs for co-morbid conditions declined (the medical offset). (Ch.17).

By the dawn of the new millennium morale among psychopharmacologists had reached its nadir, the line between truth and disinformation was blurred and the future seemed bleak. (Ch.21).

Two recent innovative proposals

In 2008, as DSM V was about to be unfurled, leadership at the NIMH decided to intervene by announcing a new initiative to reframe research efforts and challenge the hegemony of the DSM system. Echoing widespread concern about the fact that drug development appeared to be at a full stop and concern that diagnosis based on consensus symptom clusters was a contributory

factor (Ch.18), the NIMH proposed to cease funding research using DSM as an outcome measure and replace it with *The NIMH Research Domain Criteria* (**RDoC).** These criteria were eventually published two years later, (Insel et al, 2010). The basic intent was to link biological and behavioral components including genetic neuroscience, imaging, behavioral and clinical studies. The authors defined the domains and emphasized this was a research and not a clinical replacement.

Two years later, three clinicians published a critical analysis of the impact of the RDoc criteria, "*The good, Bad and the Ugly*." (Weinberger, Glick and Klein, 2010). An accompanying JAMA editorial concluded the system "lacked the very scientific foundation that it proclaims."

Four years after the RDoC were proposed the National Research Council announced a project titled, *Precision Medicine*; (National Research Council, 2012) somewhat akin to the NIMH proposal it identified "a critical need for deconstructing current diagnostic groups with biomarkers and to improve response to treatment."

In an attempt to link these two innovative proposals Insel published an online commentary (Insel, 2014) posing the question, "What would precision medicine look like for psychiatry?" His pessimistic response reads "So far we don't have rigorously tested reproducible, clinically actionable biomarkers for any psychiatric disorder... genetic findings are statistical associations of risk, not diagnostic of disease; neuroimaging findings report mean group changes, not individual differences; and metabolic findings are not specific (See Ch.18). We can improve the resolution of each of these modalities, but we may never have a biomarker for any symptom-based diagnosis because these diagnostic categories were never designed for biological validity."

The response to these two innovative proposals is perhaps understandable in a profoundly pessimistic Zeitgeist but it might be noted that although psychopharmacology has wilted in the Modern Era neuroscience research funded by government and Foundations continues to flourish and ultimately may spawn a new productive era when better understanding of brain function facilitates the discovery of new treatments based not on serendipity but on science. The ACNP, leading organization during the pioneer era, recently announced it was considering altering its title and bylaws to become The American College of Neuroscience and Psychiatry

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Resurrecting the Past

The contrast between the rapid pace of innovation in the Pioneer Era and the stagnation of new drug development in the Modern Era has raised concerns that useful drugs from the first era may have been prematurely discarded and should be reconsidered today. To date two candidates have been identified, the MAOI inhibitors for depression and the benzodiazepines for panic disorder. In both these categories concern about side effects and doubts about efficacy and specificity were discussed in Chapter 11 (Adumbration) and Chapter 13 (The Anxiety Enigma). The contemporary view concerning the MAOI is raised by the Australian psychiatrist Ken Gillman in an appeal to both colleagues and patients on the Google website in 2018 based on an earlier journal review (Gillman, 2011). His rationale is based on the accurate premise that the avoidable interaction with tyramine containing foods has been exaggerated and conjecture that, "it seems that the financial power of the pharmaceutical companies which dominate post-graduate education and have aggressively promoted the supposed advantages of new and more expensive drugs, has made a deleterious effect and has seriously unbalanced the optimal use of many medications. (Gillman, 2018).

The case for the benzodiazepines is made by an International Task Force of 17 psychopharmacologists, chaired by Antonio Nardi from Brazil based on a recent publication (Nardi et al,2018) promoting "An Evidence Based Educational Approach". The major concerns leading to controversy and conservative use are identified as drug dependency, withdrawal symptoms and problems managing them. In addition caution is triggered by the estimated 80 million retail prescriptions written annually for these drugs in America. The concluding sentence

states the authors' purpose. "We hope that in our search for new treatments we do not underestimate an established and proven treatment for Panic Disorder. It is essential to keep benzodiazepines in the armamentarium, and keep them as first-line pharmacotherapy, along with the SSRI's."

This is essentially the same side of a contentious argument examined in more detail in Chapter 13 (The Anxiety Enigma), but it does acknowledge the need for "long-term cognitive behavior treatment to prevent recurrence" although this is costly and sometimes denied by insurance companies". The article ends with **Author Disclosure Information** which states, "*The authors declare no conflicts of interest."* This may be true in the present but skeptics will call into question that it may not have been so at the time when some of the authors who performed their research were KOL's for industry and its largess, sometimes including stock options in today's drugs.

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A Benefit of the Modern Era; Homes for the Homeless

Homelessness is endemic in America, subject to fluctuations during inclement times. My advent to urban Milwaukee in 1980 coincided with a surge triggered by the election of Ronald Reagan and his commitment to "trim the welfare rolls", cause for an inundation of homeless folks with mental illness on the streets, often lacking Medicaid financial support or health insurance.

As Chair of an academic department I was encouraged to engage in charitable enterprises which began as *pro bono* work in a homeless clinic and then graduated to becoming a member and eventually the Chairperson of the not for profit Milwaukee Health Care for the Homeless Organization. In due course this led to a Governor's appointment as a member and eventually Chair of the Wisconsin State Mental Health Council that disbursed the Annual Federal Mental Health Block Grants, a portion of which trickled down to homeless clinics and organizations.

The evolution of the homelessness problem during the early1980's is told in *Under the Safety Net* (Brickner et al., 1990)... In 1982 the United States Conference of Mayors issued a report on the escalating scope of the homelessness problem in 55 inner cities and documented the inadequacy and chaos of attempts to deal with the problem. This clarion call was responded to by the *Robert Wood Johnson and Pew Foundations* who combined to offer $25M in grants, soliciting bids from the 51 largest cities in America. 25 responded and 19 were funded, including Milwaukee who's Mayor, Henry Maier, was named Chair of a National Organizing Committee.

Over the next four years the cities were required to collect data on interventions and outcomes, providing the contents of *Under the Safety Net.* I was invited to be lead author to write the chapter on *Psychiatric and Mental Health Services* in collaboration with multidisciplinary colleagues from three other cities, Albuquerque, Baltimore and San Francisco (Blackwell B, Breakey W, Hammersley D, Hammond R, McMurray-Avila M, Seeger C., 1990).

Stirred into action by the Foundations' initiative Congress passed the Stewart B McKinney Homeless Assistance Act in 1987. This in turn created an awareness of a need for co-ordination between government agencies in coping with the problems of homelessness and severe mental illness. Included were HUD, HCFA, SSA, the VA, NIMH, The Department of Labor and the White House. Given my experience and eligibility for a sabbatical I was invited and accepted the role of Staff Director to the Interagency Task Force in October 1990.

I moved to the NIMH in Washington DC, leaving my wife and son behind. It was not a happy or inspiring experience. My arrival coincided with a struggle for who should chair the Task Force. The head of HUD, a member of the President's inner circle, trumped the head of NIMH, a psychiatrist who promptly resigned and was replaced by a psychologist, the first ever. My position at NIMH initially had no office, no telephone, no secretary and no parking place (I found my own outside a Chinese laundry). The work was tedious and marked by inter-agency squabbles, stifling political correctness and lack of innovative solutions. (Blackwell, 2012). My

work was primarily preparing agendas and writing minutes so when my boss complained that "I wrote like an Englishman" I knew it was time to prematurely return home to Milwaukee to cope with a deteriorating economic and political climate that threatened and eventually led to the dismantling and closure of both the Department of Psychiatry and its residency training program.

During my involvement with the problems of homelessness and mental illness at the local, state and federal level the clinical approach had inevitably included a combination of medical management of psychosis coupled with social supports such as daily respite programs, overnight shelters, mobile outreach teams, food clothing and showers. By and large the recipients reluctantly accepted the social supports, shunned the meds and remained homeless. There was little innovation or creativity in finding a solution at either the local or national level.

History helps to explain why. When the Federal Government shunned responsibility for serious mental illness it devolved first to the States with large asylums in remote rural locations. When drugs led to their closure the problem shifted to the County and urban level where communities struggled with inadequate funding and where despite innovative case management protocols the problem persisted. By and large the mega "not for profit" corporations were expert at shunning responsibility for severe and persistent mental illness with inadequate Medicaid funding and troubling behaviors that might threaten their pristine inpatient milieus.

But the County is the administrative level that seems to have solved the problem of homelessness, not Federal or State government and not via academic wisdom but by the simple expedient of attention to what has always been in plain sight. The problem is lack of a home; the solution is to provide one. The economic aspect of doing so is resolved by capturing the "medical offset"; the savings acquired from reduced crisis services, decreased emergency room visits, closure of shelters and respite programs, with less police, medical and legal costs.

A comprehensive overview of the evolution and cost effectiveness of Housing First Programs is found in Wikipedia with relevantly scant information in traditional academic journals.

The first such effective program is attributed to Los Angeles in 1988 as a response to a sharp increase in homelessness involving families with children where homes were provided by *Beyond Shelter*, organized by Tanya Tull. Four years later, in 1992, Dr.Sam Tsemberis, a faculty member at New York University founded the "*Pathways to Housing Program*".

Approval and endorsement at the Federal Level occurred in 2007 first by HUD, followed by the Federal Interagency Council on Homelessness citing it as a "best practices" procedure in 2008.

In 2007 HUD reported a 30% decline in national homelessness on the streets, attributed to Home First programs. Cost savings due to these programs were quickly noted supported by evidence of reduced use and closure of shelters, respite services, decline in emergency room visits as well as reduced medical and legal costs (Larimer et al, 2009).

Most major cities in the United States now have such programs and other nations have adopted Housing First policies, including Australia, Canada, U.K, Finland, France and Japan.

In Milwaukee during fall of 2015, an organization "*Housing First*" was established in coordination with the County Behavioral Health Division. A survey revealed 1521 chronically homeless persons. Over the next two years $3.4M was spent providing housing; supported by intensive case management. A quarter of the chronic population is now in permanent housing, a process that generated $3.4M in cost savings.

Although not reported on in the literature it goes without saying that the effective use and compliance with psychotropic medications must be vastly improved when people with major mental illness are in housing with case management and not living on the streets.

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The Odyssey

The differences between the Pioneer and the Modern Era are stark. However the singular failure of the former, an inability to define treatment specificity remains the unsolved dilemma of the latter despite innovative attempts. That said, the accomplishments and satisfactions of the Pioneer Era have been largely denied to those in the Modern Era.

Fluctuations in good and bad times during an odyssey were sometimes historically attributed to punishment by the Gods, with hubris leading to nemesis; the ancient acknowledgment of the modern aphorism that "pride comes before a fall".

That the early pioneers felt pride in their accomplishments is testified to by the comments of a select group in Volume 9 of the OHP, consisting of 20 interviews conducted between 1997 and 2008 that included 8 founding members of the ACNP from 1961 and 4 Presidents. Contributors were asked to share their opinions of progress and problems in the field up until publication. (Blackwell, 2011).

Jerry Levine, editor of Volume 4 in the OHP series (Psychopharmacology) summed up his own sentiment shared by many of the pioneers. "There are a lot of definitions of utopia and mine is that someone will pay you for the work you love to do; that's how I feel about psychopharmacology." (Levine, 1911).

There is no comparable concise commentary by those who work in the Modern Era but events documented in this volume clearly suggest widespread dissatisfaction. In the talk I gave in 1970 on *The Process of Discovery* at the Symposium on *Discoveries in Biological Psychiatry* (Blackwell, 1970) I cited the work of pioneer Lawrence Kubie (Kubie, 1954). Commenting on problems in a psychiatric career he warned that "scientific success is often determined by social forces outside individual creative capacity and will to work hard." He went on to speculate about the possibility of "a new psychosocial ailment which may not be wholly unrelated to the gangster tradition of dead end kids." This brings to mind the behavior of some academics, who confronted by a bleak research environment with slender rewards, opted to become highly paid KOL's for the pharmaceutical industry. In drawing attention to Kubie's concern Robert Merton offered a more benevolent proposition. "For most of us artisans of research getting things in print becomes a symbolic equivalent of a new discovery." (Merton, 1957). But not if one's funding and entire clinical, program have been eliminated and the research process itself has been contaminated and suborned by industry.

A Contemporary view of the Modern Era

Chapter 19 documents ten volumes supporting my own opinions about the medicalization of psychiatry and the widening gap between mind and body, therapy or medication that has replaced an integrated biopsychosocial model in our practice. The sole psychiatrist supporting

my thesis is David Healey, also a voice from the pioneer period. Recently I came across Daniel Carlet's intriguing best seller, "Unhinged" reviewed, commented and posted on INHN (Blackwell, 2019). This provides compelling support from a practicing psychiatrist who began residency training in 1992 at Massachusetts General Hospital (MGH) whose experiences cast light on the rapid pace of changes in psychiatric training and practice. In just over a decade psychoanalysis had dwindled dramatically and been replaced by rabid adherence to biological determinism. This is displayed by dissatisfaction with the15 minute med check *modus operandi* Daniel describes in treating patients he refers to other mental health professionals when they need therapy. In an epiphany he exposes and explores his practice style's origins in flawed role models and seduction by industry into the lucrative role as a KOL (see this volume Ch,20). He indicts both the DSM system and disease mongering by industry abetted by sleazy marketing techniques and profiteering. Next he critiques the profession's adoption of flawed money generating devices and procedures.

Finally, Daniel proposes a menu of four potential solutions from an educational perspective. The first involves trimming the 4 preclinical years in medical school, abolishing the year of rotating internships and replacing them with material more relevant to psychiatry. However he is skeptical of medical school altogether because, 'It indoctrinates an excessively biomedical view of multidisciplinary problems." This only accommodates students, like Daniel, who decide on psychiatry before medical school. Two ideas involve adding prescribing rights to psychologists or expanding psychiatric nurse practitioner training with a year of psychopharmacology and the third option was an actual experimental Doctorate in Mental Health, a hybrid of medical and psychology graduate schools that graduated a first class in California but was denied licensure by both the California Medical and Psychiatric Societies, Daniel realizes all of these novel ideas would have to contend with "guild issues".

So profound are Daniel's experiences and opinions that they radically reformed not only his own practice but led to his publication *The Carlat Report* in which he continues to document and expose dubious practices by industry.

A Final Word

Truth to tell, a fair and clear understanding of the difference between then and now exists not by one era disparaging the other, the answer lies in a changed Zeitgeist and inability to remediate it.

OED: Zeitgeist – *"The defining spirit or mood of a particular period in history"*

Ger: Zeit- Time **Geist-** Spirit

Since 1980 we have been living in a rapidly evolving culture of social, political and economic change characterized by income disparity, corporate greed and addiction to money, facilitated and condoned by legislative gridlock in which rigid ideology and lack of compromise block consensus for change. This has enabled a corrupt pharmaceutical industry, a weak FDA, and a "not for profit" health care system that is the opposite of what it claims to be, in tandem with heartless insurance companies. All this is coupled with corrupt academic or professional organizations and journals that condone or ignore "conflicts of interest" and have suborned scientific integrity. The sum total impact of this environment is a stultifying paralysis of will, lacking desire or ability to attempt remediation..

I am joyful about the past I was fortunate to share but mournful for the future. There is more to look back on than to look forward to with no clear solution in sight. The Zeitgeist in America is what it is; impervious to singular or short term change. For that to occur would require discoveries in neuroscience which create the foundation for a new generation of psychotropic drug research, a legislature immune from lobbyists, willing to empower the FDA to constrain industry, backed by a medical profession able to ensure an ethically cleansed academic environment and a Federal Government willing to reinvest in psychopharmacology and its role in ethical investigation of new drugs

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