

International Network for the History of Neuropsychopharmacology
Educational E-Books

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PREFACE

The International Network for the History of Neuropsychopharmacology (INHN) was founded in mid-2012 for developing education pertaining to the history of the field. The objectives of INHN were initiated with 12 designated projects. The Network launched its website on May 23, 2013 and began posting material intended for discussion by members of the field and by the end of the year 9 of the 12 projects of the Network were in operation.

On December 25, 2014, the material posted in 7 of the 9 operating projects in 2013 was assembled in a volume, *INHN 2013*, and presented as an electronic book (e-book). It included all postings in: Historical Dictionary of Neuropsychopharmacology (Project 1 - Dictionary), Historical Drug Inventory (Project 2 - Drugs), Profiles of Distinguished Neuropsychopharmacologists (Project 4 - Profiles), Controversies in the History of Neuropsychopharmacology (Project 5 - Controversies), Textbook on the History of Neuropsychopharmacology (Project 6 - Textbook), Information on Books in Neuropsychopharmacology: Classics and Current (Project 8 - Books), and Biographies, Autobiographies and Selected Writings of Neuropsychopharmacologists (Project 9 - Biographies). There were a total of 57 postings by 20 INHN members in the 7 operating projects: 9 by Ban; 6 by Blackwell; 5 by Katz; 4 each by Bech, Gershon and Martin; 3 each by Devenyi and Knoll; 2 each by Brown, Klein, Konofal, Serfaty, Shorter, Sulser, Winokur, and 1 each by Hojajj, Miklya, Moussaoui, Petrie and Torres-Ruiz. In addition, there were a total of 29 postings by 8 contributors to the two projects, Electronic Archives in Neuropsychopharmacology (Project 11 – Archives) and Educational e-books (Project 12 – e-books), from which the postings were not included in the compendium: 20 by Ban, 2 by each Gershon, Katz and Wegener; and 1 each by Berger, Castillo and Gyermek. The three projects that could not be implemented in 2013 were: Photo History of Neuropsychopharmacology (Project 3 - Photos), Discoveries That Have Not Been Followed Up and Experiments That Could Not Be Replicated (Project 7 - Discoveries), and Historical Perspective in Neuropsychopharmacology: Information from and Comments on Current Publications (Project 10 – Perspective).

The number of operating projects decreased from 9 to 8 in 2014 and the present volume, *INHN 2014*, includes all postings from 6 of these 8 projects: Dictionary, Photos, Profiles, Controversies, Books and Biographies. In 2014, one of the three projects, Photos, which could not be implemented in 2013, became operational, whereas 2 of the projects to which contributions were made in 2013, Drugs and Textbook became inactive. Similar to 2013, postings from two projects, Archives and e-books are not included in *INHN 2014*. Yet to provide some information on these projects, the Personal Collections opened in Archives and the E-Books presented on website in 2013 and 2014 are listed.

INHN 2014 is divided into seven sections. Six of these sections comprise the postings from the six projects enumerated in the previous paragraph; the seventh section provides content listings of the remaining 2 projects combined.

Section One, Historical Dictionary of Neuropsychopharmacology, was launched in December 12, 2013 with an Introduction by Carlos R. Hojaj, the project coordinator, but no entry in the Dictionary was made in 2013. All the 30 entries we have listed were entered in 2014. The entries in this section are presented in alphabetical order of the terms that are defined, which were submitted by the following authors: Jules Angst (2 entries), Thomas A. Ban (4 entries), Samuel Gershon (1 entry), Carlos R. Hojaj (7 entries), Martin M. Katz (5 entries), Joseph Knoll (10 entries) and Antonio E. Nardi (1 entry).

Section Two, Photo History of Neuropsychopharmacology, was launched on April 10, 2014 with an Introduction by Edith Serfaty. It comprises individual photos (13 photos) and photo collections (a total of 48 photos derived from 13 conferences or scientific meetings). Individual photos appear in alphabetical order of the person listed first in the legend of the given photo and photo collections in chronological order according to the date of the scientific meetings. Photos in each collection are from meetings of each scientific organization and appear in their own section in which photos are presented in alphabetical order according to the first person on the photo from the left. The photos posted were contributed by Julien Mendlewicz (15 photos), Irwin J. Kopin (14 photos), Simone Radouco-Thomas (9 photos), Thomas A. Ban (8 photos, of which he received 6 from the late Oakley S. Ray), Eugene S. Paykel (7 photos), Joseph Knoll (3 photos), Leonard Cook (2 photos) and 1 photo each from Aitor Castillo, Carlos R. Hojaj and Moussa Youdim.

Section Three, Profiles of Distinguished Neuropsychopharmacologists, launched on June 13, 2013 with an Introduction by Edith Serfaty, has 17 entries (vignettes) presented in alphabetical order of the distinguished neuropsychopharmacologists: Julius Axelrod by Irwin J. Kopin; Hassan Azima by Antonio E. Nardi; Hans Berger by Antonio E. Nardi; Hermann Blaschko by Joseph Knoll; Philip B. Bradley by Marina Dyskant Mochovitch; Alfred M. Freedman by Sergio Machado; J. Christian Gillin by Bruno Nazar; Turan M. Itil by Antonio E. Nardi; Hitoshi Itoh by Hajime Kazamatsuri; Paul Kielholz by Antonio E. Nardi; Heinz E. Lehmann by Antonio E. Nardi; Laszlo J. Meduna by Antonio E. Nardi; Dionisio Nieto Gómez by Antonio Torres-Ruiz; Juri Saarma by Jaanus Harro; Sydney Spector by Fridolin Sulser; and Joseph Wortis by André B. Veras.

Section Four, Controversies in the History of Neuropsychopharmacology, launched on May 13, 2013 with an Introduction by Barry Blackwell, includes 7 essays: Barry Blackwell: Adumbration: A history lesson; Barry Blackwell: The anxiety enigma; Barry Blackwell: The lithium controversy: An historical autopsy; Samuel Gershon: The trazodone controversy and its potential fatal consequences; Martin M. Katz: Component-specific vs. diagnosis-specific clinical trial in depression; Martin M. Katz: Multivantaged vs. conventional assessment method; and Martin M. Katz: Onset of

clinical action of antidepressants. It also includes 10 interactions (comments, replies, responses), all but one of which are related to an essay (Thomas A. Ban: Conflict of interest in neuropsychopharmacology: Marketing vs. education) that was posted in 2013. The interactions were contributed by: Barry Blackwell (4), Thomas A. Ban (2), Donald F. Klein (2), Jose de Leon (1) and Larry Stein (1).

Section Five, Books in Neuropsychopharmacology: Classics and Current was launched by Samuel Gershon on July 11, 2013. It was relaunched with a second introduction on September 18, 2014 by Carlos Morra. This section includes, in addition to Morra's Introduction, 24 postings based on book reviews, including reviews of 21 books by their authors and three classical books reviewed by Carlos Morra, and 22 postings based on interactions concerning the books reviewed in 2014 and interactions concerning two books reviewed in 2013 (Per Bech: Psychometrics and Martin M. Katz: Depression and Drugs). The books reviewed in 2014 are presented in alphabetical order of authors/editors and in case of more than one book by the same author/editor, in order of year of publication. The books reviewed are: Jules Angst: Classification and Prediction of Outcome of Depression (1974); Thomas A. Ban: Conditioning and Psychiatry (1964); Thomas A. Ban: Schizophrenia: A Psychopharmacological Approach (1972); Thomas A. Ban: Recent Advances in the Biology of Schizophrenia (1973); Thomas A. Ban and Heinz E. Lehmann: Experimental Approaches to Psychiatric Diagnosis (1971); Thomas A. Ban and Bruno Silvestrini: Proceedings of the First International Symposium on Trazodone (1974); Samuel Gershon and Baron Shopsin, editors: Lithium Its Role in Psychiatric Research and Treatment (1973); Lothar B. Kalinowsky and Paul Hoch: Shock Treatments and Other Somatic Procedures in Psychiatry (1946); Martin B. Keller: Clinical Guide to Depression and Bipolar Disorder (2013); Donald F. Klein, Rachel Gittelman, Frederic Quitkin and Arthur Rifkin: Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children (1983); Donald F. Klein with Alfreda Howard: Psychiatric Case Studies: Treatment, Drugs and Outcome (1972); Joseph Knoll: The Theory of Active Reflexes: An Analysis of Some Fundamental Mechanism of Higher Nervous Activity (1969); Joseph Knoll: The Brain and Its Self. A Neurochemical Concept of the Innate and Acquired Drives (2005); Heinz E. Lehmann: Non-Tricyclic and Non-Monoamine Oxidase Inhibitors (1982); Heinz E. Lehmann and Thomas A. Ban: The Butyrophenones in Psychiatry (1964); Heinz E. Lehmann and Thomas A. Ban: Toxicity and Adverse Reaction Studies with Neuroleptics and Antidepressants (1965); Heinz E. Lehmann and Thomas A. Ban: Pharmacotherapy of Anxiety and Tension (1970); H.E. Lehmann, M. Berthiaume and T.A. Ban: Trimipramine: a New Antidepressant (1964); Peter R. Martin, Bennett A. Weinberg and Bonnie K. Bealer: Healing Addiction: an Integrated Pharmacopsychosocial Approach to Treatment (2007); Bertalan Pethö and Thomas A. Ban: DCR Budapest-Nashville in the Diagnosis and Classification of Functional Psychoses (1988); David R. Rosenberg, John Holttum and Samuel Gershon: Pharmacotherapy of Child and Adolescent Psychiatric Disorders (1994); David R. Rosenberg, Pablo R. Davanzo and Samuel Gershon, editors: Pharmacotherapy of Child and Adolescent Psychiatric Disorders, 2nd Edition (2002); David R. Rosenberg and Samuel Gershon, editors: Pharmacotherapy of Child and Adolescent Psychiatric Disorders, 3rd edition (2012); and Charles Shagass: The Role of Drugs in Community

Psychiatry (1971). The following contributors provided the total of 22 interactions posted in 2014 (concerning books first reviewed in 2013 or 2014): Donald F. Klein (9), Martin M. Katz (8), Per Bech (2), Joseph Knoll (2) and Larry Stein (1).

Section Six, Biographies, Autobiographies and Selected Writings of Neuropsychopharmacologists, the final section, begins with Barry Blackwell's Introduction from November 13, 2014, when he relaunched this project (it was first launched by Blackwell on November 13, 2013). This section has seven entries, including a biography of Hassan Azima by Hector Warnes; a review by Barry Blackwell of Frank M. Berger: *A Man of Understanding: A Noted Scientist's Guide to Happiness and Success* (2013); a review by Barry Blackwell of Enoch Callaway: *ASYLUM: A Mid-Century Madhouse and its Lessons about Our Mentally Ill Today* (2007); a review by Barry Blackwell of Driss Moussaoui: *A Biography of Jean Delay* (2002); a biography of Turan M. Itil by Martin M. Katz; a biography of Paul Kielholz by Raymond Bategay; and a review by Barry Blackwell of Karl Rickels: *A Serendipitous Life: From German POW to American Psychiatrist* (2011).

Section Seven differs from the first six in that it comprises two lists from which, in one, all individuals with a Collection posted in INHN Archives by the end of 2014 are identified and in the other, all educational e-books posted on the INHN website in 2013 and 2014 are presented in alphabetical order of their authors/editors.

INHN 2014 concludes with a brief Postscript that provides information on the changes related to the operation of the Network from 2013 to 2014.

We hope that further editing of the vignettes, essays, and reviews has improved comprehensibility of the posted material in this e-book. We trust that organizing the material within each section in a conventional manner, i.e., alphabetical in the first order and chronological in the second, has rendered the vignettes, essays, reviews and photos more readily accessible for historical research and understanding of the field of neuropsychopharmacology. Undoubtedly, the presentation of the vignettes, essays, reviews and photos as parts of a book made proper referencing of individual contributions possible.

Peter R. Martin
November 23, 2015

**HISTORICAL DICTIONARY IN
NEUROPSYCHOPHARMACOLOGY**

**Historical Dictionary in Neuropsychopharmacology
(Dictionary)
Project One
Coordinated by Carlos R. Hojaij**

The Historical Dictionary in Neuropsychopharmacology comprises a comprehensive vocabulary of terms/words used in the different areas of research in neuropsychopharmacology and in education and clinical practice with psychotropic drugs. The project was launched in December 12, 2013 with an Introduction by Carlos R. Hojaij, the project coordinator. No entries in the Dictionary were posted in 2013 and thirty entries were added in 2014.

Active reflex by Joseph Knoll

The term active reflex was coined by Joseph Knoll, in 1956, in the fifth part of his paper on “Experimental studies on the higher nervous activity of animals”, published in *Acta Physiologica Hungarica*. One year later, in 1957, in the sixth part of the same paper, he defined it as a conditioned motor chain reflex, analogues to conditioned chain reflexes developed by Frolov and Fursikov in Ivan Petrovich Pavlov’s laboratories, in which the conditional stimulus of a well established conditioned reflex served as an unconditional stimulus of the consecutive conditioned reflex in the chain (Ban 1964; Pavlov 1927). The properties of the “active reflex” were defined and presented in a monograph by Knoll (1969). A behavioral pharmacological test with the capability to differentiate “tranquilizers” by their selectiveness of blocking the “active reflex” from known central nervous system depressants, like the barbiturates, was first published in 1958-1959 (Knoll and Knoll 1958, 1959).

Ban TA. Conditioning in Psychiatry. Chicago: Aldine; 1964, p.23.

Knoll J. Experimental studies on the higher nervous activity of animals. V. The functional mechanism of the active conditioned reflex. *Acta Physiol Hung* 1956; 10: 89-100.

Knoll J. Experimental studies on the higher nervous activity of animals. VI. Further studies on active reflexes. *Acta Physiol Hung* 1957; 12: 65-92.

Knoll J. The Theory of Active reflexes. An Analysis of Some Fundamental Mechanisms of Higher Nervous Activity. Budapest/NewYork: Publishing House of the Hungarian Academy of Sciences/ Hafner Publishing Company, 1969.

Knoll J, Knoll B. Methode zur Untersuchung der spezifisch depressiven Wirkung von “Tranquilizern” auf das Zentralnervensystem I. *Arzneimittel-Forschung* 1958; 8: 330-3.

Knoll J, Knoll B. Methode zur Untersuchung der spezifisch depressiven Wirkung von “Tranquilizern” auf das Zentralnervensystem II. *Arzneimittel-Forschung* 1959; 9: 633-6.

Pavlov IP. Conditioned reflexes. (Translated from the Russian original into English by GV Anrep). Oxford: Oxford University Press, 1927.

March 20, 2014

Amine oxidase by Joseph Knoll

In 1937, Blaschko, Richter and Schlossman demonstrated that tyramine oxidase, the enzyme discovered by Hare in 1928, noradrenaline oxidase and aliphatic amine oxidase was the same enzyme. They referred to the enzyme as “amine oxidase”. In the same year, 1937, as Blaschko and his associates demonstrated the presence of “amine oxidase” in the liver, Pugh and Quastel demonstrated the presence of the same enzyme in the brain. One year later, in 1938, after Zeller’s separation of diamine oxidase from “amine oxidase”, the term was replaced by the term “monoamine oxidase” to indicate that its function is restricted to the oxidative deamination of monoamines.

Blaschko H, Richter D, Schlossman H. The inactivation of adrenaline. *J Physiol* 1937; 90: 1-17.

Blaschko H, Richter D, Schlossmann H. The oxidation of adrenaline and other amines. *Biochemical Journal* 1937; 31: 2187-96.

Hare MLC. Tyramine oxidase I. A new enzyme system in the liver. *Biochemical Journal* 1928; 22:968-79.

Pugh C, Quastel JH. Oxidation of aliphatic amines in brain and other tissues. *Biochemical Journal* 1937; 31: 286-91.

Zeller EA. Über den enzymatischen Abbau von Histamin und Diaminen. *Helvetica Chimica Acta* 1938; 21:881-90.

June 26, 2014

Anna Monika Prize by Samuel Gershon

The Anna Monika Prize is a monetary award that is awarded bi-annually to clinical scientists who have made major contributions to the understanding of the neurobiology of depression and who advanced the pharmacological options for the treatment of affective disorders. The awards are given by the Anna Monika Foundation, a private foundation, founded by Peter Rehme, an international merchant with the assistance of Professor Florin Laubenthal of Essen by approval of the Minister of Interior of North Rhine-Westphal, in Dusseldorf, Germany, on June 9, 1965. Rehme named the Foundation after his Mother, Anna and his daughter, Monika Rief.

July 24, 2014

Ataraxic drugs by Carlos R. Hojaij

The term “ataractic” is derived from the Greek adjective “ataractos” that translates into English “without confusion, cool and collected” and from the Greek noun “ataraxia” that translates into “peace of mind” or “freedom from confusion”. In 1955, in a paper published in the *Journal of the American Medical Association*, Howard Fabing and Alister Cameron, a professor of classics, proposed that chlorpromazine and similar drugs which produce “ataraxia”, i.e., absence of emotional upset and a condition of imperturbability, be called “ataraxics” (Fabing 1955; Berger 1976).

Berger A. History. In: Usdin E, Forrest IS, editors. *Psychotherapeutic Drugs*. Volume One. New York/Basel: Marcel Dekker; 1976, pp. 111-57.

Fabing HD. Designation of tranquilizing agents in neuropharmacology. *JAMA* 1955; 158: 1461.

March 27, 2014

Catecholaminergic activity enhancer effect by Joseph Knoll

“Catecholaminergic activity enhancer effect” refers to an increase of catecholamine synthesis induced by a substance. The term was introduced by Joseph Knoll in 1998 in reference to findings that in rats treated for 21 days with deprenyl (0.01 mg/kg/day), a synthetic β -phenylethylamine derivative, the release of dopamine from the corpus striatum, substantia nigra and tuberculum olfactorium, and norepinephrine from the locus coeruleus was statistically significantly ($p < 0.001$) increased 24 hours after the injection of the last dose (Knoll and Miklya 1994). He also used this term in reference to deprenyl-induced enhancement of electrical-stimulation-induced release of tritiated catecholamines from isolated rat brainstem (Knoll et al. 1996).

Knoll J. (-)-Deprenyl (selegiline) a catecholaminergic activity enhancer (CAE) substance acting in the brain. *Pharmacology and Toxicology* 1998; 82: 57-66

Knoll J, Miklya I. Multiple, small dose administration of (-)-deprenyl enhances catecholaminergic activity and diminishes serotonergic activity in the brain and these effects are unrelated to MAO-B inhibition. *Archives Internationales Pharmacodynamie de Therapie* 1994; 328: 1187-209

April 17, 2014

Component specific clinical trial by Martin M. Katz

The term, “component-specific clinical trial” (CSCT), first appeared in a paper by Martin Katz, Charles Bowden and Alan Frazer, published in 2010. It was more completely defined three years later in 2013 by Katz, as a trial in which the method for measuring outcome is profiling the specific drug effects on the principal behavioral, mood and cognitive components of a disorder instead of focusing exclusively on changes in the overall severity of that disorder. The CSCT was employed in a series of clinical trials in the study of drug effects in depression in the early years of the 21st century, the findings of which were reviewed in Katz’s monograph, *Depression and Drugs: The Neurobehavioral Structure of a Psychological Storm*, published in 2013.

Katz MM. *Depression and Drugs: The Neurobehavioral Structure of Psychological Storm*/ Berlin: Springer; 2013, pp. 61-71.

Katz MM, Bowden CL, Frazer A. Rethinking depression and the actions of antidepressants: Uncovering the links between the neural and behavioral elements. *J Affective Disorders* 2010; 120: 16-23.

April 3, 2014

Dahlem Conferences by Jules Angst

The Dahlem Conferences, named after the area of Berlin in which they were held, were inaugurated in 1974 under the joint sponsorship of the German Science Foundation (Deutsche Forschungsgemeinschaft) and the Association for the Promotion of Science and the Humanities in Germany (Stifterverband für die Deutsche Wissenschaft). Ever since, they have provided an innovative format for expert scientific exchange on a wide range of topics, in the form of one-week workshops (over 100 to date), consisting of short presentations and intensive discussions. In the 1980s, three Dahlem conferences were devoted to psychiatric topics: "The Origins of Depression: Current Concepts and Approaches", organised by J. Angst in 1982; "Biological Perspectives of Schizophrenia", by H. Helmchen and F.A.Henn in 1986; and "Etiology of Dementia of Alzheimer's Type", by A. S. Henderson and J. H. Henderson in 1987.

Angst J, editor, The Origins of Depression: Current Concepts and Approaches. Berlin: Springer; 1983.

Helmchen H, Henn F, editors. Biological Perspectives in Schizophrenia. Chichester: Wiley;1987.

Henderson AS, Henderson JH, editors. Etiology of Dementia of Alzheimer's Type. Chichester: Wiley; 1989.

October 2, 2014

Delay's classification by Carlos R. Hojaij

In 1957, in the “Psychopharmacology Symposium” at the Second World Congress of Psychiatry, organized by the World Psychiatric Association (WPA) in Zurich (Switzerland), Jean Delay (1959a) proposed to classify “psychiatric medications” into three groups: “psycholeptics”, “psychoanaleptics” and “psychodysleptics”. In the same presentation, he defined “psycholeptics”, as substances that produced relaxation and depressed mental activity; “psychoanaleptics”, as substances that simulated mental activity; and “psychodysleptics”, as substances that disturbed mental activity. He further divided “psycholeptics” into “depressors of vigilance” (hypnotics) and depressors of affect (tranquilizers) and “psychoanaleptics” into “stimulants of vigilance” (psyhostimulants) and stimulants of affect” (antidepressants). Delay (1959b) repeated the same proposition, in 1958, at the 1st Congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) in Rome (Italy).

Delay J. Intervention à propos de la terminologie et la classification des médicaments psychiatriques. In: Kline NS, editor. Neuropsychopharmacology Frontiers. New York: Little Brown; 1959a, pp. 426-9.

Delay J. Discussion: Fourth Symposium. In: Bradley PB, Deniker P, Radouco-Thomas C. Neuropsychopharmacology. Proceedings of the First International Congress of Neuro-Pharmacology. Amsterdam: Elsevier; 1959b, pp. 167-72.

August 7, 2014

Depressors of affect by Carlos R. Hojaij

“Depressors of affect” were defined as substances which regulate the oscillation of “emotional tone” between an “apathetic”, or underresponsive and “pathetic”, and an over-responsive pole, and by their action replace a “pathetic” with an “apathetic” affective tone. They are one of the two groups of “psycholeptics” in Delay’s (1959a,b) classification of “psychiatric drugs”, presented in Delay and Deniker’s monograph published in 1961. “Depressors of affect” include the “minor tranquilizers”, also referred to as “anxiolytics”, and the “neuroleptics”, also referred to as “major tranquilizers” and “antipsychotics” (Ban 1969).

Ban TA. Psychopharmacology. Baltimore: William & Wilkins; 1969, p. 368.

Delay J. Intervention à propos de la terminologie et la classification des médicaments psychiatriques. In: Kline NS, editor. Neuropsychopharmacology Frontiers. New York: Little Brown; 1959a, pp. 426-9.

Delay J. Discussion: Fourth Symposium. In: Bradley PB, Deniker P, Radouco-Thomas C. Neuropsychopharmacology. Proceedings of the First International Congress of Neuro-Pharmacology. Amsterdam: Elsevier; 1959b, pp. 167-72.

Delay J, Deniker P. Méthodes Chimiothérapeutiques en Psychiatrie. Paris; Masson et Cie; 1961.

January 30, 2014

Depressors of vigilance by Carlos R. Hojaij

“Depressors of vigilance” were defined as substances which depress the level of consciousness, lower noetic (intellectual) activity, produce a “hypnoid” state, and induce clinical and electroencephalographic sleep. They are one of the two groups of “psycholeptics” in Delay’s (1959a,b) classification of “psychiatric drugs”, presented in Delay and Deniker’s monograph published in 1961. “Depressors of vigilance” include the “hypnotics” (Ban 1969).

Ban TA. Psychopharmacology. Baltimore: William & Wilkins; 1969, p. 368.

Delay J. Intervention à propos de la terminologie et la classification des médicaments psychiatriques. In: Kline NS, editor. Neuropsychopharmacology Frontiers. New York: Little Brown; 1959a, pp. 426-9.

Delay J. Discussion: Fourth Symposium. In: Bradley PB, Deniker P, Radouco-Thomas C. Neuropsychopharmacology. Proceedings of the First International Congress of Neuro-Pharmacology. Amsterdam: Elsevier; 1959b, pp. 167-72.

Delay J, Deniker P. Méthodes Chimiothérapeutiques en Psychiatrie. Paris; Masson et Cie; 1961.

January 23, 2014

Electroencephalogram by Antonio E. Nardi

The electroencephalogram (EEG) is the record of brain electrical activity obtained by means of an electroencephalograph (Stedman 1990). The term was introduced in 1929 by Hans Berger in the title of his paper (Über das Elektrenzenkephalogram des Menschen) published in the *Archiv für Psychiatrie und Nervenkrankheiten*. It was the first of a series of papers in which Berger reported on his research that dealt with the recording of electric currents (action potentials) of the brain in man. Recognition that electrical activity is a natural property of the living brain dates back to detection of electric currents from the peripheral nerves of frogs by a galvanometer reported by Emil du Bois Raymond, in 1848. His discovery that the living brain generates electricity was substantiated independently, in the mid-1870s by Richard Caton (1875) and Vasilij Jakovlevich Danilevsky (1875), who recorded electrical currents and the fluctuations of these currents from the cerebral hemispheres of rabbits, monkeys and dogs (Ban 2011). Yet, it was Berger, who first succeeded with the recording of spontaneous electrical activity of the brain of man in 1924, using electrodes attached to the intact skull. By the early 1930s, he introduced electroencephalography, a technique for recording electrical activity of the brain and showed that the spontaneous waking EEG was “sensitive to” hypoxia, hypocapnia, barbiturates, bromides, caffeine, cocaine, chloroform, morphine, scopolamine and insulin coma (Berger 1929, 1938; Gloor 1969; Fink 1978).

Ban TA. Preface, in *An Oral History of Neuropsychopharmacology - The First Fifty Years: Peer Interviews* (Thomas A. Ban, editor), Volume 2- “Neurophysiology” (Max Fink, volume editor). Brentwood: American College of Neuropsychopharmacology; 2011, p. X-XXII.

Berger H. Über das Elektrenzenkephalogram des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten* 1929; 87: 527-70.

Berger H. Über das Elektrenzenkephalogram des Menschen. Vierzehnte Mitteilung. *Archiv für Psychiatrie und Nervenkrankheiten* 1938; 106: 577-84.

Caton R. The electrical currents of the brain. *Br Med* 1875; 2: 278-9.

Danilevskii V Y. *Research on the Physiology of the Brain*. Moscpw: Thesis; 1875.

Fink M. Psychoactive drugs and the waking EEG. 1966-1976. In: Lipton MA, DiMascio A, Killam KF, editors. *Psychopharmacology. A Generation of Progress*. New York: Raven Press; 1978, p. 691-8.

Gloor P. The work of Hans Berger and the discovery of the electroencephalogram. *Electroencephalogr Clin Neurophysiol* 1969; 28 (Suppl): S1-S36.

Stedman's Medical Dictionary, 25th edition. Baltimore: Williams & Wilkins; 1959, p. 496.

July 10, 2014

Endogenous enhancer regulation by Joseph Knoll

The term “endogenous enhancer regulation (EER)” refers to the existence of enhancer-sensitive neurons in the brain, which have the potential to increase in a split second their activity in response to a specific endogenous enhancer substance, such as β -phenylethylamine and return equally rapidly to their original activity level in the absence of the enhancer substance. The term was coined by Joseph Knoll in his monograph, *The Brain and Its Self. A Neurochemical Concept of the Innate and Acquired Drives*, published in 2005. The concept of EER is based on the finding that electrical stimulation-induced increase in norepinephrine and dopamine levels in the brainstem was significantly greater in animals after PEA administration (Knoll et al 1996).

Knoll J. *The Brain and Its Self. A Neurochemical Concept of the Innate and Acquired Drives*. Springer, Berlin/Heidelberg/New York, 2005, pp. 25-94

Knoll J., Miklya I., Knoll B., Markó R., Rácz D. Phenylethylamine and tyramine are mixed acting sympathomimetic amines in the brain. *Life Sciences* 1996; 58: 2101-2114

October 23, 2014

Endogenous enhancer substance by Joseph Knoll

The term “endogenous enhancer substance” refers to brain constituents which increase the activity of special neurons which are sensitive to them, as for example, β -phenylethylamine (PEA) increases the activity of catecholamine producing neurons. The term was coined by Joseph Knoll in his monograph *The Brain and Its Self*, published in 2005. The recognition that PEA is an “enhancer substance” and the introduction of the concept of “endogenous enhancer substance” was based on the finding that on a perfused rabbit central ear artery a low concentration of PEA did not affect smooth muscle resting tone but increased (enhanced) in a dose-dependent manner the muscle contractions in response to electrical stimulation (Knoll et al. 1996).

Knoll J. *The Brain and Its Self. A Neurochemical Concept of the Innate and Acquired Drives*. Springer, Berlin/Heidelberg/New York, 2005. pp. 25-94

Knoll J., Miklya I., Knoll B., Markó R., Rácz D. Phenylethylamine and tyramine are mixed acting sympathomimetic amines in the brain. *Life Sciences* 1996; 58:2101-2114

November 13, 2014

Enhancer substance by Joseph Knoll

The term “enhancer substance” refers to chemicals which increase the activity of special neurons which are sensitive to them, as for example, selegiline increases the activity of catecholamine producing neurons. The term was coined by Joseph Knoll in his monograph *The Brain and Its Self*, published in 2005. It was based on Knoll and Miklya’s findings reported in 1994 that subcutaneous administration of selegiline in the daily dose range from 0.01 to 0.1 mg/kg to rats for 21 days significantly increased catecholamine levels in the striatum, substantia nigra, tuberculum olfactorium (dopamine) and locus coeruleus (norepinephrine).

Knoll J. *The Brain and Its Self. A Neurochemical Concept of the Innate and Acquired Drives.* Springer, Berlin/Heidelberg/New York, 2005. pp. 25-94

Knoll J., Miklya I. Multiple small dose administration of (-)-deprenyl enhances catecholaminergic activity and diminishes serotonergic activity in the brain and these effects are unrelated to MAO-B inhibition. *Archives Internationales Pharmacodynamie de Therapie.* 1994; 328: 1-15

October 16, 2014

Glass-cylinder seeking drive by Joseph Knoll

The term “glass-cylinder seeking drive (GCSD)” was coined by Joseph Knoll in 1969, in his monograph entitled *The Theory of Active Reflexes*. The glass-cylinder is a 30 cm high, 16 cm (bottom) to 12 cm (top) wide cylinder-shaped open box, with a metal plate on the bottom and a side opening, through which a rat of up to 350 to 400 g body weight can enter (Knoll 1956; Knoll and Knoll 1958). The GCSD is based on a conditioned motor (avoidance) reflex in which rats are conditioned to jump to the upper rim of a glass cylinder in response to an auditory (sound of a bell) conditional stimulus (CS) to “escape” burning heat (60 degree Celsius); the unconditional stimulus (US) is delivered via the metal plate at the bottom of the cylinder. Rats that acquired the GCSD, jump to the upper rim of the cylinder as soon as placed into the cylinder, even without the sound of a bell (CS) by developing a second order visual conditional (chain) reflex to the glass cylinder itself. The GCSD is so strong that even if there is a receptive female and/or food at the bottom of the cylinder, rats ushered into the cylinder jump to the ceiling of the cylinder. In some rats, the GCSD qualifies for an “in-extinguishable active reflex” that is retained for a lifetime (Knoll 2014). Knoll (1969, 2005) perceives GCSD as a specific acquired drive, an unnatural urge that overrides innate drives, such as hunger or sexual drives. GCSD was initially employed in a series of behavioral pharmacological studies conducted with centrally acting drugs by Knoll (1968) in the late 1950s and 1960s. After the demonstration by Berta Knoll in 1961 that GCSD cannot be acquired in the mouse, the study of GCSD became central to Knoll’s research in the evolution of homo sapiens. The findings of this research and the conceptualization of these findings were presented by Knoll (2005) in his monograph, *The Brain and Its Self* (Knoll 2014).

Knoll J. Experimental studies on the higher nervous activity of animals. V. The functional mechanism of the active conditioned reflex. *Acta Physiologica Hungarica* 1956; 10:89-100.

Knoll J. *The Theory of Active Reflexes. An Analysis of Some Fundamental Mechanisms of Higher Nervous Activity*. Budapest/New York: Publishing House of the Hungarian Academy of Sciences. Hafner Publishing Company; 1969, pp. 54-63.

Knoll B. Certain aspects of the formation of temporary connections in comparative experiments on mice and rats. *Acta Physiologica Hungarica* 1961; 20:265-275

Knoll B (1968) *Comparative physiological and pharmacological analysis of the higher nervous function of mice and rats (in Hungarian)*. Thesis. Budapest: Hungarian Academy of Sciences; 1968

Knoll J (2005) *The Brain and Its Self. A Neurochemical Concept of the Innate and Acquired Drives*. Springer/Berlin, Heidelberg, New York; 2005. (inhn. Books, January 23, 2014).

Knoll J. Active reflex. inhn.org. Dictionary, March 27, 2014.

Knoll J, Knoll B. Methode zur Untersuchung der spezifisch depressiven Wirkung von

“Tranquilizern” auf das Zentralnervensystem I. Arzneimittel-Forschung 1958; 8: 330-333.

April 10, 2014

International Group for the Study of Affective Disorders (IGSAD) by Jules Angst

The International Group for the Study of Affective Disorders (IGSAD) was founded in 1970 by Jules Angst, Jan-Otto Ottosson, Carlo Perris and George Winokur. The inaugural meeting of IGSAD was organized by Pierre Pichot in Paris, in 1970. The meetings of IGSAD provided a valuable forum for leading mood researchers to meet with some regularity in order to exchange and discuss their findings. The first meetings dealt with the classification and long-term course of mood disorders and with the prophylactic efficacy of lithium. The last meeting of the IGSAD took place in 1990.

September 18, 2014

Monoamine oxidase by Joseph Knoll

Monoamine oxidase is the enzyme that metabolizes monoamines by oxidative deamination in the body. The generic name, “monoamine oxidase”, was given to the enzyme by Albert Zeller, in 1938, in order to differentiate within “amine oxidase” -- shown to be present in 1937 in the liver by Blaschko, Richter and Schlosberg, and in the brain by Pugh and Quastel-- the enzyme that metabolizes monoamines from the enzyme that metabolizes diamines in the body. The enzyme is also referred to as “mitochondrial monoamine oxidase” because it is located intracellularly on the outer membrane of mitochondria.

Blaschko H, Richter D, Schlossmann H. The oxidation of adrenaline and other amines. *Biochemical Journal* 1937; 31: 2187-96.

Pugh C, Quastel JH. Oxidation of aliphatic amines in brain and other tissues. *Biochemical Journal* 1937; 31: 286-91.

Zeller E.A. Über den enzymatischen Abbau von Histamin und Diaminen. 2. Mitteilung. *Helvetica Chimica Acta* 1938; 21:880-90.

May 22, 2014

Monoamine oxidase A by Joseph Knoll

Type-A monoamine oxidase (MAO-A) is the form of monoamine oxidase (MAO) that is sensitive to clorgyline. Clorgyline, 3-(2, 4-dichlorophenoxy)-N-methyl-N-2-nylpropan-1-amine, is an irreversible MAO inhibitor substance, structurally related to pargyline. This term was coined and introduced, in 1968, by Johnston, to distinguish between clorgyline-sensitive and insensitive forms of monoamine oxidase (MAO) enzymes that he referred to as Type-A monoamine oxidase and Type-B monoamine oxidase, respectively. MAO-A was found to be present in the neurons, astroglia, gastrointestinal tract, liver and placenta (Neff and Gorodis 1972). By the early 1970s, it was recognized that MAO-A is primarily responsible for the oxidative deamination of the monoamines serotonin, melatonin, noradrenaline (norepinephrine) and adrenaline (epinephrine), and not only of serotonin, as originally proposed (Costa and Sandler 1972).

Costa E, Sandler M (editors). Monoamine Oxidases – New Vistas. Advances in Biochemical Psychopharmacology. Volume 5. New York: Raven Press; 1972.

Johnston JP. Some observations upon a new inhibitor of monoamine oxidase in human brain. *Biochemical Pharmacology* 1968; 17: 1285-1297.

Neff NH, Gorodis C. Neuronal monoamine oxidase: specific types and their rates of formation. *Advances Biochemical Psychopharmacology* 1972; 5: 2017-23.

August 14, 2014

Monoamine oxidase B by Joseph Knoll

Type-B monoamine oxidase (MAO-B) is the form of monoamine oxidase (MAO) that is insensitive to clorgyline. Clorgyline, 3-(2, 4-dichlorophenoxy)-N-methyl-N-2-ynylpropan-1-amine, is an irreversible MAO-inhibitor substance, structurally related to pargyline. The term was coined and introduced, in 1968, by Johnston, to distinguish between clorgyline-sensitive and insensitive forms of monoamine oxidase (MAO) enzymes, referred to as Type-A monoamine oxidase and Type-B monoamine oxidase, respectively. MAO-B was found to be present in the neurons, astroglia and platelets (Neff and Gorodis 1972) and was primarily responsible for the oxidative deamination of beta-phenylethylamine and benzylamine (Costa and Sandler 1972). In 1971, it was shown that MAO activity progressively increased in the aging brain (Robinson et al. 1971) and, by 1980, it was also recognized that this was due entirely to the increase in MAO-B concentrations in brain tissue (Fowler et al. 1980). The first selective MAO-B inhibitor, (-)-deprenyl/selegiline, an (R) -N- methyl-N-(1-phenylpropan-2-yl) prop-2-yn-1-amine, was identified, in 1972, by Knoll and Magyar.

Costa E, Sandler M (editors). Monoamine Oxidases – New Vistas. Advances in Biochemical Psychopharmacology. Volume 5. New York: Raven Press; 1972.

Fowler CJ, Wiberg A, Oreland L, Marcusson J, Winblad B. The effect of age on the activity and molecular properties of human brain monoamine oxidase. *Journal Neural Transmission* 1980; 49:1-20.

Johnston JP. Some observations upon a new inhibitor of monoamine oxidase in human brain. *Biochemical Pharmacology* 1968; 17:1285-97.

Knoll J, Magyar K. Some puzzling pharmacological effects of monoamine oxidase inhibitors. *Adv Biochem Psychopharmacol* 1972; 5: 393-408.

Robinson DS, Davis JM, Nies A, Ravaris C.L, Sylwester D. Relation of sex and aging to monoamine oxidase activity in human brain, plasma and platelets. *Archives General Psychiatry* 1971; 24:536-9.

August 28, 2014

Multivantaged assessment method by Martin M. Katz

The term “multivantaged assessment method” (MVAM) was introduced, in 1984 by Martin M. Katz and co-investigators in their report of the U.S. National Institute of Mental Health (NIMH) Collaborative Study of the Psychobiology of Depression. It is based on a dimensional conceptualization of mental disorders and the assumption that mental disorders are structured by interaction between their measurable emotional and behavioral components. Because of the many ways these components can be manifested, in a multivantaged assessment, methods of assessment from several “vantage” points are combined. The prototype multivantaged assessment includes quantified observational methods, such as ratings scales by experts, subjects’ judgment on current state and measurement of cognitive and psychomotor performances. The multivantaged assessment method was employed in a series of studies in depression in the Departments of Psychiatry and Pharmacology in the University of Texas Health Science Center at San Antonio by Katz and his associates, and the term reappeared in 2004, twenty years after its introduction, in a report of these studies on the “onset and sequence of clinical actions” of antidepressants, published in the *International Journal of Neuropsychopharmacology*. Information on the development and definition of the concept of MVAM was presented by Katz in 2013, in his monograph, *Depression and Drugs: The Neurobehavioral Structure of a Psychological Storm*.

Katz MM. Depression and Drugs: The Neurobehavioral Structure of a Psychological Storm. New York; Springer: 2013, pp. 21-34.

Katz MM, Houston JP, Brannan S, Bowden CL, Berman N, Swann A, Frazer A. A multivantaged behavioral method for measuring onset and sequence of the clinical actions of antidepressants. *International J of Neuropsychopharmacology* 2004; 7: 471-9.

Katz MM, Koslow SH, Berman N, Secunda S, Maas JW, Casper R, Kocsis J, Stokes P. A multivantaged approach to the measurement of behavioral and affect states for clinical and psychobiological research. *Psychological Reports Monograph* 1984; 55: 619-73.

May 1, 2014

National Advisory Committee on Psychopharmacology by Martin M. Katz

The National Advisory Committee on Psychopharmacology was established in 1956 by the National Institutes of Health (NIH) to guide a new program of the National Institute of Mental Health (NIMH) that would stimulate research in the new science of psychopharmacology. The new program was implemented with the establishment of the Psychopharmacology Service Center (PSC) from the 2 million dollars allocated in 1956 by the US Congress to the NIH in response to the discovery of new drugs for the treatment of mental disorders. The Committee consisted of expert psychiatrists, pharmacologists, psychologists and statisticians. Its members included Louis Goodman (Pharmacology), Seymour Kety (Biological Science), Nathan Kline (Psychiatry), Morton Kramer (Biostatistics) and Joseph Zubin (Psychology). The appointed Chairman of the Committee was Ralph Gerard; the Executive Secretary, Martin Katz (Katz 2011). The role of the Committee was to both guide the activities of the PSC and its leader, Jonathon Cole and staff, in implementing the program initiatives and to review applications for research grants from outside investigators in the field (Cole 2011). In the early 1960s, most of the Committee's research grant review function was transferred from the NIMH to the NIH. Its prime function, following the PSC becoming the Psychopharmacology Research Branch in 1965, was to advise on ongoing and planned clinical research goals of the psychopharmacology program.

Cole JO interviewed by Ban TA in *An Oral History of Neuropsychopharmacology - The First Fifty Years: Peer Interviews* (Thomas A. Ban, editor), Volume 10- "History of the ACNP" (Martin M. Katz, volume editor). Nashville: American College of Neuropsychopharmacology; 2011. p. 45-53.

Katz MM interviewed by Ban TA in *An Oral History of Neuropsychopharmacology - The First Fifty Years: Peer Interviews* (Thomas A. Ban, editor), Volume 10- "History of the ACNP" (Martin M. Katz, volume editor). Nashville: American College of Neuropsychopharmacology; 2011. p. 77-81.

November 6, 2014

National Institute of Mental Health Collaborative Study by Martin M. Katz

The National Institute of Mental Health Collaborative Study refers to the study the Psychopharmacology Service Center (PSC) of the National Institute of Mental Health (NIMH) was charged with to carry out under the guidance of the National Advisory Committee on Psychopharmacology (Katz 2011). It was a nationwide controlled study of phenothiazine treatment in acute schizophrenia that was led by principal investigators Jonathon O. Cole, Gerald L. Klerman and Salomon Goldberg and carried out in disparate public, private and university hospitals (National Institute of Mental Health, Psychopharmacology Service Center Collaborative Study Group 1964; National Institute of Mental Health, Psychopharmacology Research Branch Collaborative Study Group 1967).

Katz MM interviewed by Ban TA in *An Oral History of Neuropsychopharmacology - The First Fifty Years: Peer Interviews* (Thomas A. Ban, editor), Volume 12- "History of the ACNP" (Martin M. Katz, volume editor). Nashville: American College of Neuropsychopharmacology; 2011. p. 77-81.

National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group. Phenothiazine treatment of acute schizophrenia: Effectiveness. *Arch G Psychiat* 1964; 10: 246- 261.

National Institute of Mental Health Psychopharmacology Research Branch Collaborative Study Group. Differences in clinical effects in three phenothiazines in acute schizophrenia, *Dis Nerv Syst* 1967; 28: 369 - 383.

October 16, 2014

Neuroleptics by Thomas A. Ban

The term “neuroleptic” first appeared in 1955 in the title of Jean Delay and Pierre Deniker’s paper, “Hibernothérapies et cures neuroleptiques en psychiatrie”, published in the *Bulletin of the National Academy of Medicine (Paris)* for the designation of a new class of drugs. By introducing the term, Delay and Deniker linked the specific therapeutic activity of this new class of drugs to particular neurological effects. The term reappeared in the title of the International Colloquium on Chlorpromazine and Neuroleptic Drugs in Psychiatric Treatment, held in Paris from October 20 to 22 in the same year. At the First International Symposium on Psychotropic Drugs held in May 1957 in Milan, “neuroleptics” were defined by Delay and Deniker as drugs which (i) induce a “psycholeptic state without hypnotic effect (i.e., indifference, affective and emotional neutrality) and decrease initiative and motor activity without gross alteration of vigilance and cognitive functions; (ii) control (treat) excitation, aggressiveness and agitation in manic and psychotic patients; (iii) improve (decrease) acute and chronic psychotic symptoms (hallucinations, delusions), ameliorate deficit symptoms of schizophrenia and control the symptoms induced by psychodysleptics; (iv) induce neurovegetative and neurological side effects; and (v) exert their action at the sub-cortical level (brainstem reticular formation, diencephalon) (Crocq and Macher 2006). The definition includes their description of the effects of chlorpromazine, published in 1952, in a paper coauthored by Harl (Delay, Deniker and Harl 1952). The criteria were simplified in 1961 in their monograph, *Méthodes Chimiothérapeutiques en Psychiatrie*, in which to qualify for a neuroleptic, therapeutic effects in psychoses associated with neurological signs sufficed (Delay and Deniker 1961). It was this simple definition of neuroleptics that was adopted in 1967 in Number 371 of the *Technical Report Series of the World Health Organization (WHO)*.

Crocq M-A, Macher J-P. The history of psychotropic drugs in France. In: TA, Healy D, Shorter E, editors. *Reflections on Twentieth-Century Psychopharmacology*. Budapest: Animula; 2006, pp. 124-32.

Delay J, Deniker P. Hibernothérapies et cures neuroleptiques en psychiatrie. *Bull Acad Nat Med (Paris)* 1955; 139: 145-7.

Delay J, Deniker P. Caractéristiques psychophysiologiques des médicaments neuroleptiques. In: Garattini S, Ghetti V, editors. *Psychotropic Drugs*. Amsterdam: Elsevier; 1957, pp. 485-501.

Delay J, Deniker P. *Méthodes Chimiothérapeutiques en Psychiatrie*. Paris; Masson et Cie; 1961, p.14.

Delay J, Deniker P, Harl JM. Traitement des états d’excitation et d’agitation par une méthode médicamenteuse dérivée de la hibernothérapie. *Ann Medicopsychol (Paris)* 1952; 110: 267-73.

International Colloquium on Chlorpromazine and Neuroleptic Drugs in Psychiatric Treatment, Paris; 20-22 October 1955 *Encephale* 1956; 45: 301-1266.

World Health Organization. Research in Psychopharmacology. Technical Report Series 371. Geneva: WHO; 1967.

January 16, 2014

Pharmacopsychology by Thomas A. Ban

The term “pharmacopsychology” was introduced in Emil Kraepelin’s Thesis for his “habilitation”, the German equivalent for a PhD, published in 1892 with the title *Über die Beeinflussung einfacher psychischer Vorgänge durch einige Arzneimittel (On the Modulation of Simple Psychological Processes by Some Medicines)*. It defined an area of pharmacological research that studied the effects of nervina (centrally acting drugs) on mental processes, such as attention, memory, language, etc., with the employment of psychometric performance tests in normal subjects (Muller, Fletcher and Holger 2006). Kraepelin (1881, 1882a, b, 1883), began with his investigations that led to the concept of pharmacopsychology in Wilhelm Wundt’s (1910) laboratories of experimental psychology in the Department of Philosophy at the University of Leipzig in Germany, in 1881; he continued his research in Dorpat (now Tartu, Estonia), and completed it in Heidelberg, in 1892 (Steinberg 2001; Steinberg and Angermeyer 2001). Included among the substances he studied were common recreational “drugs”, such as alcohol, coffee, and tea, and medicinal products, such as amyl nitrite, chloral hydrate, chloroform, morphine and paraldehyde. It was in the course of this research that Kraepelin (1882b) had shown that increasing the amount of alcohol in the blood by having more drinks led to a measurable lengthening of reaction time and proposed the use of dose-response comparisons in determining the clinical effects of a drug (Bech 2012). In the 8th edition of his textbook, published from 1909 to 1913, Kraepelin extended the scope of pharmacopsychology to the study of the psychotherapeutic effect of some drugs, such as chloral hydrate, morphine and phenemal in psychiatric disorders. In 1920, the term psychopharmacology, a synonym for pharmacopsychology, was introduced by David Macht and in the years that followed virtually replaced the use of Kraepelin’s (1892) term.

Bech P. *Clinical Psychometrics*. Chichester: Wiley-Blackwell; 2012, pp. 6-9.

Kraepelin E. Über die Dauer einfacher psychischer Vorgänge. *Biol Zentralbl* 1881; 1: 654-72.

Kraepelin E. Über die Einwirkung einiger medicamentöser Stoffe auf die Dauer einfacher psychischer Vorgänge. *Zwei Abteilungn Philosophische Studien* 1882a; 1: 417-62.

Kraepelin E. Über psychische Zeitmessungen . *Schmidts Jahrbucher der in – und ausländischen gesammten. . Medicin* 1882b; 196: 205- 13.

Kraepelin E. Über die Einwirkung einiger medicamentöser Stoffe auf die Dauer einfacher psychischer Vorgänge. *Zwei Abteilungn Philosophische Studien* 1883; 1: 573 - 605.

Kraepelin E. Über die Beeinflussung einfacher psychischer Vorgänge durch einige Arzneimittel. Jena: Fischer Verlage; 1892.

Kraepelin E. Psychiatrie in Lehrbuch für Studierende und Ärzte 8 Aufl. Leipzig: Barth; 1909 – 13.

Müller U, Fletscher PC, Steinberg H. The origin of pharmacopsychology: Emil Kraepelin's experiments in Leipzig, Dorpat and Heidelberg (1882-1892). *Psychopharmacology* 2006; 184: 131-8.

Steinberg H. Kraepelin in Leipzig. Eine Begegnung von Psychiatrie und Psychologie. Bonn: PsychiatrieVerlag; 2001.

Steinberg H, Angermeyer MC. Emil Kraepelin's years at Dorpat as professor of psychiatry in nineteenth-century Russia. *His Psychiatry* 2001; 12: 297 - 327.

Wundt W. Die Institut für experimentelle Psychologie zu Leipzig. *Psychologische Studien* 1910; 5: 279-93.

February 13, 2014

Psychoanaleptics by Carlos R. Hojaij

“Psychoanaleptics” are substances which stimulate mental activity. They are one of the three groups of drugs in the classification of “psychiatric drugs” proposed by Jean Delay (1959 a, b), first in 1957, at the Second World Congress of Psychiatry, and subsequently in 1958, at the First Congress of the Collegium Internationale Neuropsychopharmacologicum. The term was adopted in Delay and Deniker’s (1961) monograph, *Méthodes Chimiothérapiques en Psychiatrie*, in which “psychoanaleptics” were divided into “stimulants of vigilance” and “stimulants of affect” (Ban 1969).

Ban TA. Psychopharmacology. Baltimore: William & Wilkins; 1969, p. 368.

Delay J. Intervention à propos de la terminologie et la classification des médicaments psychiatriques. In: Kline NS, editor. Neuropsychopharmacology Frontiers. New York: Little Brown; 1959a, pp. 426-9.

Delay J. Discussion: Fourth Symposium. In: Bradley PB, Deniker P, Radouco-Thomas C. Neuropsychopharmacology. Proceedings of the First International Congress of Neuro-Pharmacology. Amsterdam: Elsevier; 1959b, pp. 167-72

Delay J, Deniker P. Méthodes Chimiothérapiques en Psychiatrie. Paris; Masson et Cie; 1961, pp. 14-7.

February 6, 2014

Psychodysleptics by Carlos R. Hojaij

“Psychodysleptics” are substances which disturb mental activity. They are one of the three groups of drugs in the classification of “psychiatric drugs” proposed by Jean Delay (1959 a, b), first in 1957, at the Second World Congress of Psychiatry, and subsequently, in 1958, at the First Congress of the Collegium Internationale Neuropsychopharmacologicum. The term was adopted in Delay and Deniker’s (1961) monograph, *Méthodes Chimiothérapiques en Psychiatrie*, in which, “psychoanaleptics” were defined as substances which disturb mental activity by their action that can be antagonized by various “psycholeptics” (Ban 1969). The term was also adopted by the World Health Organization (WHO) Study Group in Research in Psychopharmacology in 1967, and in the *WHO Technical Report Series Number 371*, “psychodysleptics” were redefined as substances which produce abnormal mental phenomena, particularly in the “cognitive” and “perceptual spheres”.

Ban TA. Psychopharmacology. Baltimore: William & Wilkins; 1969, p. 368.

Delay J. Intervention à propos de la terminologie et la classification des médicaments psychiatriques. In: Kline NS, editor. Neuropsychopharmacology Frontiers. New York: Little Brown; 1959a, pp. 426-9.

Delay J. Discussion: Fourth Symposium. In: Bradley PB, Deniker P, Radouco-Thomas C. Neuropsychopharmacology. Proceedings of the First International Congress of Neuro-Pharmacology. Amsterdam: Elsevier; 1959b, pp. 167-72

Delay J, Deniker P. *Méthodes Chimiothérapiques en Psychiatrie*. Paris; Masson et Cie; 1961.

World Health Organization Study Group on Psychopharmacology. Technical Report Series No. 371. Geneva: World Health Organization; 1967.

March 6, 2014

Psycholeptic by Carlos R. Hojaij

The term “psycholeptic” was coined by Pierre Janet (1906), who used it for “mental troubles which develop stormily reaching climax sufficiently quickly to constitute a veritable crisis”. Jean Delay (1959a, b) adopted the term for one of the three groups of substances he proposed to classify “psychiatric (psychotropic) drugs” first in 1957, at the Second World Congress of Psychiatry (WPA), and then, in 1958, at the First Congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP). In their monograph, *Méthodes Chimiothérapiques en Psychiatrie*, published in 1961, Delay and Deniker defined “psycholeptics” as substances which produce relaxation and depress mental activity and divided “psycholeptics” into “depressors of vigilance” and “depressors of affect” (Ban 1969).

Ban TA. Psychopharmacology. Baltimore: William & Wilkins; 1969, p. 368.

Delay J. Intervention à propos de la terminologie et la classification des médicaments psychiatriques. In: Kline NS, editor. Neuropsychopharmacology Frontiers. New York: Little Brown; 1959a, pp. 426-9.

Delay J. Discussion: Fourth Symposium. In: Bradley PB, Deniker P, Radouco-Thomas C. Neuropsychopharmacology. Proceedings of the First International Congress of Neuro-Pharmacology. Amsterdam: Elsevier; 1959b, pp. 167-72.

Delay J, Deniker P. Méthodes Chimiothérapiques en Psychiatrie. Paris; Masson et Cie; 1961, p.14.

Janet P. The psycholeptic crises. Boston Med Surg J 1906; 152: 93-100.

February 27, 2014

Psychopharmacology by Thomas A. Ban

The term “psychopharmacology” was introduced in 1920 by David Macht, an American pharmacologist at Johns Hopkins University, in the title of his paper (“Contributions to psychopharmacology”), in which he studied the effects of ethanol, caffeine, bromine, opium alkaloids, and antipyretic analgesics on the “tapping speed test” (Berger 1976). Macht used the term as a synonym for pharmacopsychology, a term introduced by Kraepelin in 1892. Subsequently, the term was first used in psychiatry in 1935 by W.M. Thorner in the title of his paper “The psychopharmacology of sodium amytal”, published in the *Journal of Nervous and Mental Diseases*. The scope of psychopharmacology was gradually extended, first to research with psychomimetics (1940s), then to clinical investigations on the effects of psychotherapeutic drugs (end of the 1950s). In 1969, in *Ban’s Psychopharmacology*, it was defined as “a new scientific discipline which encompasses all the aspects and interactions between psychoactive drugs and biological systems”. In the years that followed, the all embracing concept of psychopharmacology was deconstructed. In *An Oral History of Neuropsychopharmacology*, a series on the first fifty years in the history of the field, based on peer interviews, psychopharmacology is separated from behavioral pharmacology, neuropharmacology and neuropsychopharmacology, and restricted (in *Volume Four - Psychopharmacology*) to the discipline that studies the effects of centrally acting drugs on psychopathology and psychiatric diagnoses (Ban 2011a, b).

Ban TA. Psychopharmacology. Baltimore: Williams & Wilkins; 1969, p. VII.

Ban TA, An overview of the series. In: Ban TA, editor. *An Oral History of Neuropsychopharmacology. The First Fifty Years. Peer Interviews. Volume One (Starting Up* , edited by Edward Shorter). Brentwood: American College of Neuropsychopharmacology; 2011, p. IX.

Ban TA. Preface. In: Ban TA, editor. *An Oral History of Neuropsychopharmacology. The First Fifty Years. Peer Interviews. Volume Four (Psychopharmacology*, edited by Jerome Levine). Brentwood: American College of Neuropsychopharmacology; 2011b, p. IX.

Berger A. History. In Usdin E, Forrest IS, editors. *Psychotherapeutic Drugs. Part I Principles*. New York/Basel: Marcel Dekker; 1976, pp. 11-57.

Kraepelin E. Über die Beeinflussung einfacher psychischer Vorgänge durch einige Arzneimittel. Jena: Fischer; 1892.

Macht DL. Contributions to psychopharmacology. *Bull Johns Hopkins Hospital* 1920; 31: 167-73.

Thorner MW. The psycho-pharmacology of sodium amytal. *Journal of Nervous and Mental Diseases* 1935; 81: 161 – 7.

December 12, 2013

Psychopharmacology Service Center by Martin M. Katz

The Psychopharmacology Service Center (PSC) was a program of the National Institute of Mental Health (NIMH). It was created by the National Institutes of Health (NIH) from the 2 million dollars appropriated by the U.S. Congress in 1956 to initiate a grants program and national effort to stimulate research and treatment in the application of new psychotropic drugs. Jonathon Cole, a young psychiatrist, was appointed to lead the Center with the guidance of a National Advisory Committee, chaired by Ralph Gerard (Cole 2011; Katz 2011). The Center initiated a basic research grants program, conducted a nationwide Collaborative Project to evaluate the new drugs (NIMH Collaborative Studies in Psychopharmacology), created the Early Clinical Drug Evaluation Unit (ECDEU) network to develop new drugs and published a new periodical, the *Psychopharmacology Bulletin*. The name of the Center was changed in 1965 and established at the NIMH as the Psychopharmacology Research Branch.

Cole JO interviewed by Ban TA in An Oral History of Neuropsychopharmacology - The First Fifty Years: Peer Interviews (Thomas A. Ban, editor), Volume 12- "History of the CINP" (Martin M. Katz, volume editor). Nashville: American College of Neuropsychopharmacology; 2011. p. 45-53.

Katz MM interviewed by Ban TA in An Oral History of Neuropsychopharmacology - The First Fifty Years: Peer Interviews (Thomas A. Ban, editor), Volume 12- "History of the ACNP" (Martin M. Katz, volume editor). Nashville: American College of Neuropsychopharmacology; 2011. p. 77-81.

October 30, 2014

Psychotropic Drugs by Thomas A. Ban

The term “psychotropic drugs” first appeared in 1957, in Ralph Gerard’s paper, “Dugs for the soul; the rise of psychopharmacology”, published in *Science* and in the title of the First International Symposium on Psychotropic Drugs held in Milan in May 1957 (Garattini and Ghetti 1957). In his paper, Gerard defined psychotropic drugs as substances which possess “psychic tropism” and are capable of modifying mental activity (Ban 1969). The term was adopted into French by Jean Delay (1959), who first referred to psychiatric dugs, as “drogues psychotropes”, in his discussion of the fourth symposium (“Comparison of Drug Induced and Endogenous Psychoses”) at the First Congress of The Collegium Internationale Neuro-Psychopharmacologicum (CINP), held in 1958 in Rome (Italy).

Ban TA. Psychopharmacology. Baltimore: Williams & Wilkins; 1969, p. 365.

Delay J. Discussion (Fourth Symposium). In: Bradley PB, Deniker P, Radouco-Thomas C. Neuropsychopharmacology. Proceedings of the First Congress of Neuro-Pharmacology. Amsterdam: Elsevier; 1959, pp. 167-72.

Garattini S, Ghetti V, editors. Psychotropic Drugs. Amsterdam: Elsevier; 1957.

Gerard R. Dugs for the soul; the rise of psychopharmacology. *Science* 1957; 125: 201-3.

February 20, 2014

Comments by Carlos R. Hojaj

The years succeeding the first use of chlorpromazine (1952) set the stage for “a rapid multiplication of drugs and psychic medications” with different actions. This observation by Jean Delay and his concern that a certain degree of confusion could have a negative impact on research and the clinic, led him to search for common terminology and classification. It was in 1957, during a Symposium of Psychopharmacology for the occasion of the 2nd International Congress of Psychiatry in Zurich, and not in the 1st Congress of the Collegium Internationale Neuro-Psychopharmacologicum, held in 1958, in Rome --as Tom Ban suggests-- that Jean Delay first used and adopted the term “psychotropic” and proposed a classification of these drugs based on their main effect in the “human clinic”. For Jean Delay (1957), the term psychotropic was valid since it was a general term to include all chemical substances, being natural or pharmaceutically made, which have a “psychological tropism”, capable of interfering in mental activity, not considering *a priori* the kind of modification to be promoted.

Delay J. Intervention à propos de la terminologie et la classification des médicaments psychiatriques. In: Kline NS, editor. Neuropsychopharmacology Frontiers. New York: Little Brown; 1959, pp. 426-9.

March 13, 2014

Stimulants of affect by Carlos R. Hojaij

“Stimulants of affect” are one of the two groups of “psychanaleptics” in Delay’s (1959a,b) classification of “psychiatric drugs”. They were defined in Delay and Deniker’s monograph published in 1961 as substances which regulate the oscillation of “mental tone” between “apathetic”, or under-responsive, and “pathetic” or over-responsive, with the potential by their action to replace an “apathetic tone” by a “pathetic” one. Included among the “stimulants of affect” are all antidepressants (Ban 1969).

Ban TA. Psychopharmacology. Baltimore: William & Wilkins; 1969, p. 368.

Delay J. Intervention à propos de la terminologie et la classification des médicaments psychiatriques. In: Kline NS, editor. Neuropsychopharmacology Frontiers. New York: Little Brown; 1959a, pp. 426-9.

Delay J. Discussion: Fourth Symposium. In: Bradley PB, Deniker P, Radouco-Thomas C. Neuropsychopharmacology. Proceedings of the First International Congress of Neuro-Pharmacology. Amsterdam: Elsevier; 1959b, pp. 167-72.

Delay J, Deniker P. Méthodes Chimiothérapiques en Psychiatrie. Paris; Masson et Cie; 1961, p.15.

January 9, 2014

Stimulants of vigilance by Carlos R. Hojaij

“Stimulants of vigilance” are one of the two groups of “psychoanaleptics” in Delay’s (1959a,b) classification of “psychiatric drugs”. They are defined in Delay and Deniker’s monograph, *Méthodes Chimiothérapiques en Psychiatrie*, published in 1961, as substances which increase alertness, intellect and noetic activity by stimulating arousal. Included among these substances are the “cortical stimulants”, as caffeine, and the “adrenergic activators”, as methylphenidate (Ban 1980).

Ban TA. Psychopharmacology for the Aged. Basel: Karger; 1980, pp. 42-7.

Delay J. Intervention à propos de la terminologie et la classification des médicaments psychiatriques. In: Kline NS, editor. *Neuropsychopharmacology Frontiers*. New York: Little Brown; 1959a, pp. 426-9.

Delay J. Discussion: Fourth Symposium. In: Bradley PB, Deniker P, Radouco-Thomas C. *Neuropsychopharmacology. Proceedings of the First International Congress of Neuro-Pharmacology*. Amsterdam: Elsevier; 1959b, pp. 167-72.

Delay J, Deniker P. *Méthodes Chimiothérapiques en Psychiatrie*. Paris; Masson et Cie; 1961, p. 15.

January 2, 2014

Symposia Medica Hoechst by Jules Angst

The Symposia Medica Hoechst was sponsored by the Medical Department of Hoechst Company, which also published the symposia proceedings. The meetings were organised by the chairmen of the symposia, usually a leading authority in a medical specialty, together with Dr Elke Lindenlaub from Hoechst. The venue was the Castle of Reinhartshausen on the Rhine. The first Hoechst Symposium, on Causal Factors of Myocardial Infarction, was held in 1968 and the report published 1969 (Schettler 1969). The 8th symposium (1973) was devoted to a psychiatric topic: Classification and Prediction of Outcome in Depression. It was organized by Jules Angst and attended by 33 experts from America, Europe and Australia. The presentations and discussions of this symposium were published in 1974 (Angst 1974). The last Hoechst Symposium, on the Biology of Memory, was held in 1988 and its report was published in 1990 (Squire and Lindenlaub 1990).

Angst J, editor. Classification and Prediction of Outcome of Depression. Stuttgart/New York: Schattauer; 1974.

Schettler G, editor. Causal Factors of Myocardial Infarction. Stuttgart/New York: Schattauer; 1969.

SquireLR, Lindenlaub E, editors. The Biology of Memory. Stuttgart/New York: Schattauer; 1990.

October 9, 2014

Tyramine oxidase by Joseph Knoll

Tyramine oxidase is the enzyme responsible for the oxidative deamination of tyramine. It was the first enzyme for oxidative deamination that was found to be present in the body. Research for the detection of the enzyme responsible for oxidative deamination began in 1877 with Oswald Schmiedeberg's findings that orally administered benzylamine, a monoamine, to dogs was deaminated and excreted in the urine as benzoylglycin (hippuric acid). It continued in 1910 by Ewins and Laidlaw's demonstration that endogenous monoamines, tyramine, a phenylalkylamine, and tryptamine, an indoleamine, were deaminated and excreted in the urine as p-hydroxyphenylacetic acid and indoleacetic acid, respectively. However, it was only 28 years later, in 1928, that Mary Hare showed the presence of "tyramine oxidase", the enzyme responsible for oxidative deamination of the monoamine, tyramine, in the liver. Today, the term "tyramine oxidase" is of historical significance only. In 1937, Blaschko, Richter and Schlossman discovered that tyramine oxidase, noradrenaline oxidase and aliphatic amine oxidase was the same enzyme, and in 1938, by Zeller's separation of diamine oxidase from "amine oxidase", tyramine oxidase became considered a part of the monoamine oxidase enzyme system.

Blaschko H, Richter D, Schlossmann H. The oxidation of adrenaline and other amines. *Biochemical Journal* 1937; 31: 2187-96.

Ewins AJ, Laidlaw PP. The fate of parahydroxyphenylethylamine in the organism. *Journal Physiology* 1910; 41:78-87.

Hare MLC. Tyramine oxidase I. A new enzyme system in the liver. *Biochemical Journal* 1928; 22:968-79.

Schmiedeberg O. Über das Verhältniss des Ammoniaks und der primären Monoaminbasen zur Harnstoffbildung im Thierkörper. *Archiv für experimentelle Pathologie und Pharmakologie* 1877; 8:1-14.

Zeller EA. Über den enzymatischen Abbau von Histamin und Diaminen. *Helvetica Chimica Acta* 1938; 21:881-90.

June 5, 2014

PHOTO HISTORY OF NEUROPSYCHOPHARMACOLOGY

**Photo History of Neuropsychopharmacology
(Photos)
Project Three
Coordinated by Edith Serfaty**

The Photo History of Neuropsychopharmacology was launched by the Introduction of Edith Serfaty on April 10, 2014. It documents in Individual Photos and Photo Collections the history of the field of neuropsychopharmacology through photographs of important participants.

Individual photos

Thomas A. Ban and Joseph Knoll (2002) – received fom Oakley S. Ray



Left to right: Thomas A. Ban and Joseph Knoll. Photo taken on January 23, 2002 in Budapest, Hungary after Knoll's interview by Ban for *An Oral History of Neuropsychopharmacology*.

Thomas A. Ban
June 12, 2014

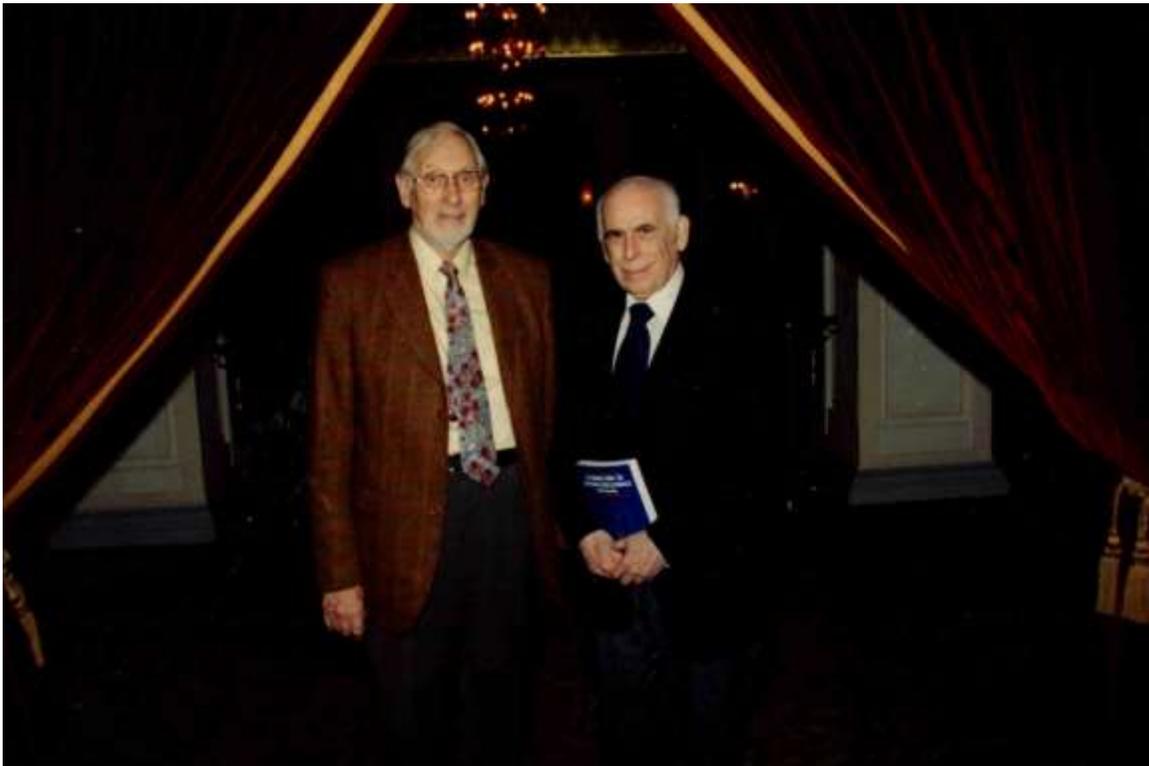
Thomas A. Ban and Alfred Pletscher (2002) – received from Thomas A. Ban



From left to right: Thomas A. Ban and Alfred Pletscher. Photo taken after Ban's interview of Pletscher for *An Oral History of Neuropsychopharmacology* in Riehen bei Basel, Switzerland on January 25, 2002.

October 9, 2014

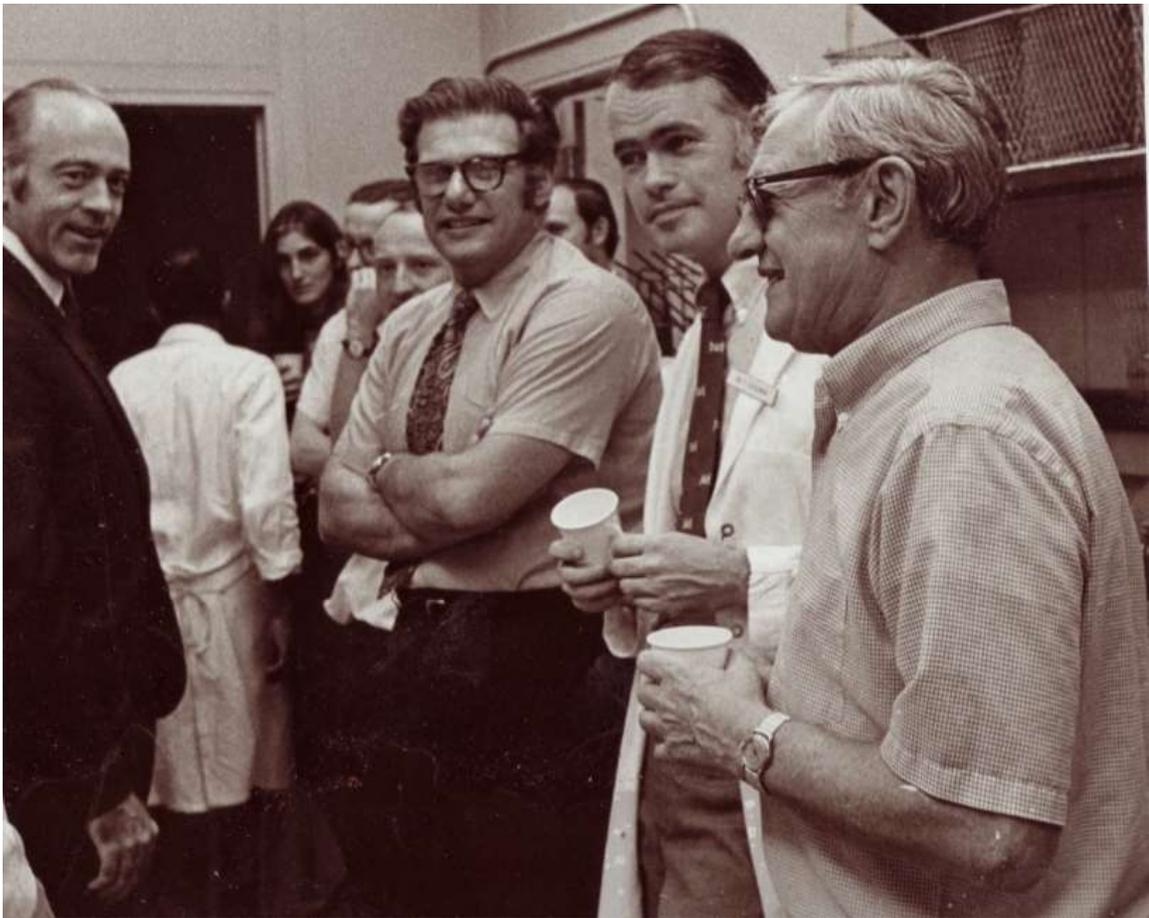
Philip B. Bradley and Thomas A. Ban (2002) – received from Thomas A. Ban



From left to right: Philip B. Bradley and Thomas A. Ban. Photo taken after Ban's interview of Bradley for *An Oral History of Neuropsychopharmacology* in London, England on January 21, 2002.

October 9, 2014

Roscoe Brady, Irwin J. Kopin, Frederick K. Goodwin and Julius Axelrod (1970)
– received from Irwin J. Kopin



Roscoe Brady, Irwin J. Kopin, Frederick K. Goodwin and Julius Axelrod in Axelrod's Laboratory at the National Institute of Mental Health, in Bethesda, Maryland, USA, on the day Axelrod was notified that he won a share with Ulf von Euler and Bernard Katz of the 1970 Nobel Prize in Medicine and Physiology.

July 17, 2014

Aitor Castillo and Pedro Ruiz (2012) – received from Aitor Castillo



From left to right: Aitor Castillo, President of Peruvian Psychiatric Association from 2010 to 2012 and Pedro Ruiz, President of World Psychiatric Association from 2010 to 2014. Photo taken at the XXIIth Peruvian Congress of Psychiatry in Trujillo, Peru on August 30, 2012.

October 9, 2014

Leonard Cook (1991) – received from Leonard Cook



Leonard Cook. Photo taken in 1991 in Wilmington, Delaware, USA.

December 11, 2014

Edmundo Fisher (1974) – received from Carlos R. Hojaij



Photo taken on April 28, 1974, at the Teatro del Centro Cultural General San Martín, during the opening session of the First World Congress of Biological Psychiatry, in Buenos Aires, Argentina.

June 5, 2014

Laurie Geffin, Alan Kopin, Lindor Brown and John Gillespie (1968) – received from Irwin J. Kopin



From left to right: Laurie Geffin, Alan Kopin (age: 12 years), Sir Lindor Brown and John Gillespie. Photo taken at the house of Rita and Irwin J. Kopin, in Bethesda, Maryland, USA, in July 1968, with some of the participants of an International Congress of Physiology in Washington.

August 14, 2014

Joseph Knoll and Daniel Bovet (1969) – received from Joseph Knoll



Left to right: Joseph Knoll and Daniel Bovet. Photo taken in Budapest, Hungary, in 1969 after Daniel Bovet was awarded the title of Honorary Doctor of the Medical University of Budapest (now Semmelweis University).

July 3, 2014

Irwin Kopin, Burroughs Mider and Louis Sokoloff (1980) – received from Irwin J. Kopin



From left to right: Irwin Kopin, Burroughs Mider and Louis Sokoloff. Photo taken at the National Institute of Mental Health, Bethesda, Maryland, USA, on Dec 10, 1980, after Louis Sokoloff delivered the annual Mider Lecture on "Metabolic Mapping of Local Functional Activity in the Central Nervous System." The annual G. Burroughs Mider Lectureship was established in 1968 in honor of the first director of laboratories and clinics of the National Institutes of Health.

August 21, 2014

Lorna Sandler, Barbara Pare, C. Michael Pare, Jane Pare, Rita Kopin and Merton Sandler (1964) – received from Irwin J. Kopin



From left to right: Lorna Sandler, Barbara Pare, C. Michael Pare, Jane Pare (daughter), Rita Kopin and Merton Sandler. (The children in gray are Pare's and the two others are Sandler's). Photo taken in the garden, back of Michael Pare's house, in Epsom, Surrey, England, circa summer of 1964.

September 18, 2014

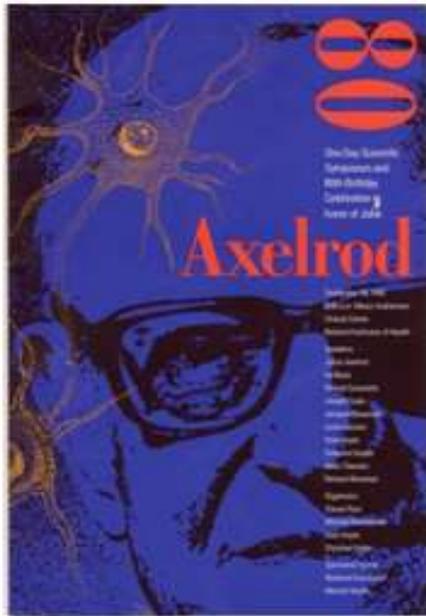
Jerzy A.J. Vetulani, Chaim R. Belmaker, Per Bech, Paul Kielholz, Monika Rief Rheme and Irwin J. Kopin (1983) – received from Irwin J. Kopin



From left to right: Jerzy A.J. Vetulani, Chaim R. Belmaker, Per Bech, Paul Kielholz, Monika Rief Rheme and Irwin J. Kopin on Sept 2, 1983 at the 9th Prize Awarding Ceremony of the Anna Monika Foundation in St. Moritz, Switzerland. There were four prizes for research on Depression, presented by Mrs. Monika Rief-Rheme. The first prize was awarded to Irwin Kopin (USA). There were two second prizes, awarded to Jerzy A.J. Vetulani (Poland) and Chaim R. Belmaker (Israel). The third prize was awarded to Per Bech (Denmark). Prof. Dr. Paul Kielholz was Chairman of the International Jury, which selected the prize winners.

July 24, 2014

Julius Axelrod's 80th birthday celebrations (1992) – received from Irwin J. Kopin



Julius Axelrod's 80th birthday celebrations (1992): dinner, guide to participants of dinner and poster of symposium. Photos (dinner and symposium poster) received from Irwin J. Kopin. Participants of dinner (see photo & guide) in alphabetical order: Julius Axelrod, Ira Black, Michael Brownstein, Roland Ciaranello, Joseph Coyle, Christian Felder, Jacques Glowinski, Frederick Goodwin, George Hertting, Leslie Iverson, Seymour Kety, Irwin Kopin, Louis Lemberger, Steven Paul, Solomon Snyder, Hans Thoenen, Richard Weinshilboom, and Richard Wurtman. Speakers of symposium: Julius Axelrod, Ira Black, Ronald Ciaranello, Joseph Coyle, Jacques Glowinski, Leslie Iversen, Irwin Kopin, Solomon Snyder, Hans Thoenen and Richard Wurtman. Organizers of symposium: Steven Paul, Irwin Kopin and Christian Felder. The 80th birthday celebrations were held, and the photos of the dinner and the poster were taken on September 18, 1992, at the National Institutes of Health in Bethesda, Maryland.

July 31, 2014

Photo collections

CINP COLLECTION: 1ST INTERNATIONAL CONGRESS (1958)

Leonard Cook and Joseph Brady – received from Leonard Cook



From Left to Right: Leonard Cook and Joseph Brady. Photo taken in 1958 at the the 1st CINP Congress in Rome, Italy.

December 4, 2014

2ND INTERNATIONAL CATECHOLAMINE SYMPOSIUM (1965)

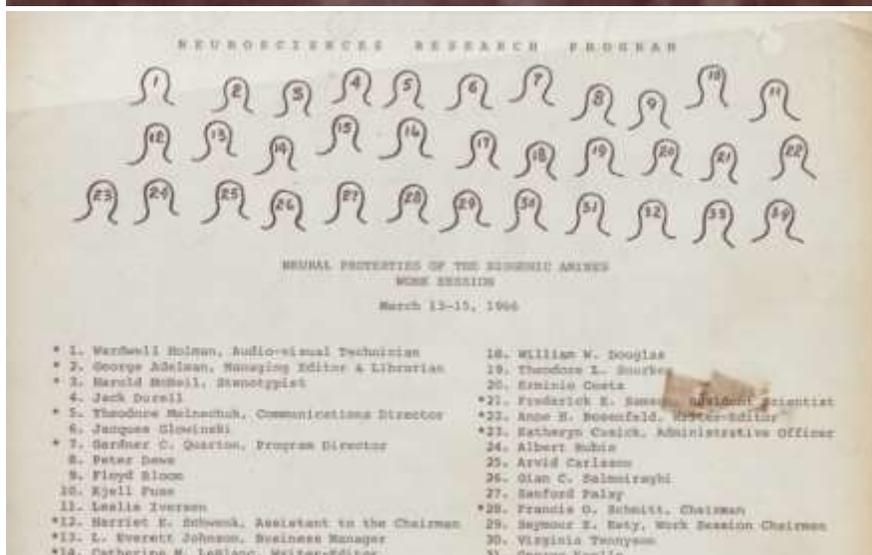
**Julius Axelrod, Rita Kopin, Irwin J. Kopin and George Hertting – received
from Irwin J. Kopin**



From Left to Right: Julius Axelrod, Rita Kopin, Irwin J. Kopin and George Hertting. Photo taken in Milan, Italy, in July 1965. Photo received from Irwin J. Kopin.

July 17, 2014

**AMERICAN ACADEMY OF ARTS AND SCIENCES - NEURAL PROPERTIES OF
THE BIOGENIC AMINES: NIMH NEUROSCIENCE RESEARCH PROGRAM
WORK SESSION (1966) – received from Irwin J. Kopin**



Group photo and guide to photo

Participants of “work session” (on photo) on the “Neural Properties of the Biogenic Amines”, in alphabetical order: Georg Adelman, Floyd Bloom, Arvid Carlsson, Erminio Costa, Catherine Cusick, Peter Dews, William W. Douglas, Jack Durell, Kjell Fuxe, Jacques Glowinski, Wardwell Holman, Lowell Hokin, Mabel Hokin, Leslie Iversen, L. Everett Johnson, Seymour S. Kety, George Koella, Irwin J. Kopin, Marin Larrabee, Catherine M. LeBlanc, Hugh Mc Lennen, Harold McNeil, Theodore Melnechuk, Sanford Palay, Gardner C. Quarton, Anne H. Rosenfeld, Albert Rubin, Gian C. Salmoiraghi, Frederick E. Samson, Francis O. Schmitt, Harriet E. Schwenk, Victor E. Sheshova, Theodore L. Sourkes, and Virginia Tennyson. Photo was taken in Brookline, Massachusetts in March 1966.

August 7, 2014

**INTERNATIONAL SYMPOSIUM ON PHARMACOLOGY, TOXICOLOGY
AND ABUSE OF PSYCHOTOMIMETICS (1968)**

Thomas A. Ban and Jacques Boissier – received from Simone Radouco-Thomas



From Left to Right: Thomas A. Ban and Jacques Boissier at the International Symposium on Pharmacology, Toxicology and Abuse of Psychotomimetics (Hallucinogens). Photo taken in Quebec City, Quebec, Canada, in September 1968.

November 20, 2014

Jacques Boissier – received from Simone Radouco-Thomas



Jacques Boissier at the International Symposium on Pharmacology, Toxicology and Abuse of Psychotomimetics (Hallucinogens). Photo taken in Quebec City, Quebec, Canada, in September 1968.

November 27, 2014

Pierre Deniker – received from Simone Radouco-Thomas



Pierre Deniker at the International Symposium on Pharmacology, Toxicology and Abuse of Psychotomimetics (Hallucinogens). Photo taken in Quebec City, Quebec, Canada, in September 1968.

November 20, 2014

Daniel X. Freedman – received from Simone Radouco-Thomas



Daniel X. Freedman presenting at the International Symposium on Pharmacology, Toxicology and Abuse of Psychotomimetics (Hallucinogens). Photo taken at the Symposium in Quebec City, Quebec, Canada in September, 1968. Photo received from Simone Radouco-Thomas.

July 10, 2014

Heinz E. Lehmann – received from Simone Radouco-Thomas



Heinz E. Lehmann at the International Symposium on Pharmacology, Toxicology and Abuse of Psychotomimetics (Hallucinogens). Photo taken in Quebec City, Quebec, Canada, in September 1968.

November 20, 2014

Vincenzo G. Longo – received from Simone Radouco-Thomas



Vincenzo G. Longo presenting at the Symposium on Pharmacology, Toxicology and Abuse of Psychotomimetics (Hallucinogens). Photo taken at the Symposium in Quebec City, Quebec, Canada in September, 1968.

July 10, 2014

**Vincenzo G. Longo, Daniel X. Freedman and Corneille Radouco-Thomas –
received from Simone Radouco-Thomas**



From left to right: Vincenzo G. Longo, Daniel X. Freedman and Corneille Radouco-Thomas, chairing session at the Symposium. Photo taken in at the Symposium on Pharmacology, Toxicology and Abuse of Psychotomimetics (Hallucinogens) in Quebec City, Quebec, Canada in September, 1968. Photo received from Simone Radouco-Thomas.

July 10, 2014

Theodore Sourkes – received from Simone Radouco-Thomas



Theodore Sourkes at the International Symposium on Pharmacology, Toxicology and Abuse of Psychotomimetics (Hallucinogens). Photo taken in Quebec City, Quebec, Canada, in September 1968.

November 27, 2014

Stephen Szara – received from Simone Radouco-Thomas



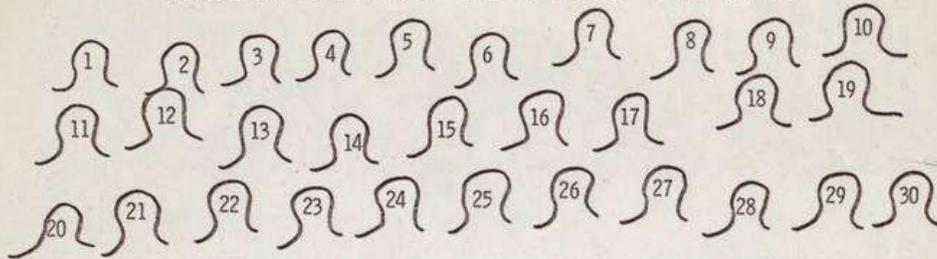
Stephen Szara at the International Symposium on Pharmacology, Toxicology and Abuse of Psychotomimetics (Hallucinogens). Photo taken in Quebec City, Quebec, Canada, in September 1968. Photo received from Simone Radouco-Thomas.

November 27, 2014

**WORKSHOP SECOND NEUROSCIENCE RESEARCH PROGRAM (1968) –
received from Irwin J. Kopin**



NEUROSCIENCES RESEARCH PROGRAM



THE MODE OF ACTION OF PSYCHOTOMIMETIC DRUGS WORK SESSION

November 17 - 19, 1968

- * 1. Wardwell Holman, Audio-Visual Technician
 * 2. George Adelman, Managing Editor & Librarian
 * 3. Arnold Leiman, Resident Scientist
 * 4. Richard Hirsh, Staff Scientist
 * 5. Theodore Melnechuk, Communications Director
 * 6. Jacques Mouret, Resident Scientist
 7. Helmut F. E. Neumann
 8. George Aghajanian
 9. Solomon H. Snyder
 10. David L. Beveridge
 11. Richard D. Morin
 12. Irwin J. Kopin
 *13. Yvonne Homsy, Writer-Editor
 *14. Catherine LeBlanc, Writer-Editor
 15. Arthur E. Heming
 *16. L. Everett Johnson, Business Manager
 17. Mac V. Edds
 *18. Gardner C. Quarton, Program Director
 19. Alexander T. Shulgin
 20. Daniel H. Efron
 21. Daniel X. Freedman
 22. Jack P. Green
 23. Spyridon G.A. Alivisatos
 24. Frederick Benington
 *25. Francis O. Schmitt, Chairman
 *26. John R. Smythies, Work Session Chairman
 27. Philip B. Bradley
 28. Joel Elkes
 29. Julius Axelrod
 30. Seymour S. Kety

*Staff

Participants of the Second Neuroscience Research Program (in alphabetical order): George Adelman, George Aghajanian, Spyridon G. A. Alivisatos, Julius Axelrod, Frederick Benington, David L. Beveridge, Philip B. Bradley, Mac V. Edds, Daniel H. Efron, Joel Elkes, Daniel X. Freedman, Jack P. Green, Arthur E. Heming, Richard Hirsch, Wardwell Holman, Yvonne Homsy, L. Everett Johnson, Seymour S. Kety, Irwin J. Kopin, Catherine LeBlanc, Arnold Leiman, Theodore Melnechuk, Richard D. Morin, Jacques Mouret, Helmut F. E. Neumann, Gardner C. Quarton, Francis O. Schmitt, Alexander T. Shulgin, John R. Smythies and Solomon H. Snyder. Photo taken in Boston, MA, USA, November 1968.

**CIBA FOUNDATION SYMPOSIUM: MONOAMINE OXIDASE AND ITS
INHIBITION (1975) – received from Joseph Knoll**



From left to right: Julie Knight, Ulrich Trendelenburg, Joseph Knoll, Thomas Singer, Merton Sandler, Dennis Sharman, Alfred Pletscher, C. Michael Pare, Herman van Praag, Dennis Murphy, Seymour Kety, Leslie Iversen, Norton Neff, Moussa Youdim, Ole Rafaelsen, Alec Coppen, Unidentified, Unidentified, Keith Tipton, Herman Blaschko, Lars Orelund, Laurent Maitre, Theodore Sourkes, Richard Green and Unidentified. Photo taken in London, England, in October 1975.

October 30, 2014

Hermann Blaschko, Joseph Knoll and Thomas Singer – received from Joseph Knoll



Left to right: Joseph Knoll, Thomas Singer and Hermann Blaschko at the 39th CIBA Foundation Symposium on Monoamine Oxidase and Its Inhibition, held in London, England, in October 1975. The Symposium was organized in honor of Mary L.C. Bernheim (née Mary Hare). Photo received from Joseph Knoll.

July 3, 2014

**KROC FOUNDATION CONFERENCE ON GABA (1975) – received from Irwin
J. Kopin**



From left to right: (1st row): Irwin Kopin and Erminio Costa; (2nd row): Eugene Roberts, Donald Tower, Masao Ito, Thomas Chase and Masanori Otsuka. Photo taken at the Kroc Foundation Conference on GABA in Santa Ynez, California, in February 1975.

July 17, 2014

ACNP COLLECTION: ACNP ANNUAL MEETING (1992)**Past Presidents of ACNP – received from Irwin J. Kopin**

From left to right, seated: Thomas Detre (1994), Herbert Meltzer (1985), Richard Shader (1990), Heinz Lehmann (1965), Eva Killam (1976), Roger Meyer (1993), Irwin Kopin (1992) and Floyd Bloom (1989). From left to right, standing: George Simpson (1991), Fridolin Sulser (1979), Arnold Friedhoff (1978), Leonard Cook (1982), Donald Klein (1981), Arthur Prange, Jr. (1987), Keith Killam, Jr. (1976), Eberhard H. Uhlenhuth (1986), William Bunney (1983), Jr. (1983), Daniel Freedman (1970), Alfred Freedman (1972), Richard Wittenborn 1973) and Oakley Ray. Photo taken in December 1992, at the Annual Meeting at the Caribe Hilton in San Juan, Puerto Rico.

September 4, 2014

FIFTH INTERNATIONAL AMINE OXIDASE WORKSHOP (1992)

Keith Tipton, Irwin J. Kopin and Moussa Youdim – received from Irwin J. Kopin



From Left to Right: Keith Tipton, Irwin J. Kopin and Moussa Youdim, organizers of the Fifth International Amine Oxidase Workshop, in Galway, Ireland, August 22-25, 1992.

August 28, 2014

**Rita Kopin, Peter Riederer, Irwin J. Kopin and Merton Sandler – received from
Irwin J. Kopin**



From Left to Right: Rita Kopin, Peter Riederer, Irwin J. Kopin and Merton Sandler at the Fifth International Amine Oxidase Workshop in Galway, Ireland, August 22-25, 1992.

September 4, 2014.

ACNP COLLECTION: ACNP ANNUAL MEETING (1997)**Presidents of ACNP – received from Irwin J. Kopin**

From left to right. First row: Oakley Ray, Eva Killam (1988), Thomas Detre (1994), Heinz Lehmann (1965), Benjamin S. Bunney (1996), David Kupfer (1995), Huda Akil (1998) and Floyd Bloom (1989); Second row: Keith Killam (1976), Roger Meyer (1993), Donald Klein (1981), Eberhard Uhlenhuth (1986), Arthur Prange (1987), Irwin Kopin (1992), Fridolin Sulser (1979), Leonard Cook (1982), Leo Hollister (1974) and William Bunney (1983). Photo taken in December 1997, at the Annual Meeting in San Juan, Puerto Rico.

September 4, 2014

CINP COLLECTION: XXIIND INTERNATIONAL CONGRESS (2000)**Thomas A. Ban and Julien Mendlewicz – received from Julien Mendlewicz**

From left to right: Thomas A. Ban and Julien Mendlewicz at the XXIInd International Congress of the CINP. Photo taken in Brussels, Belgium, in June 2000.

December 18, 2014

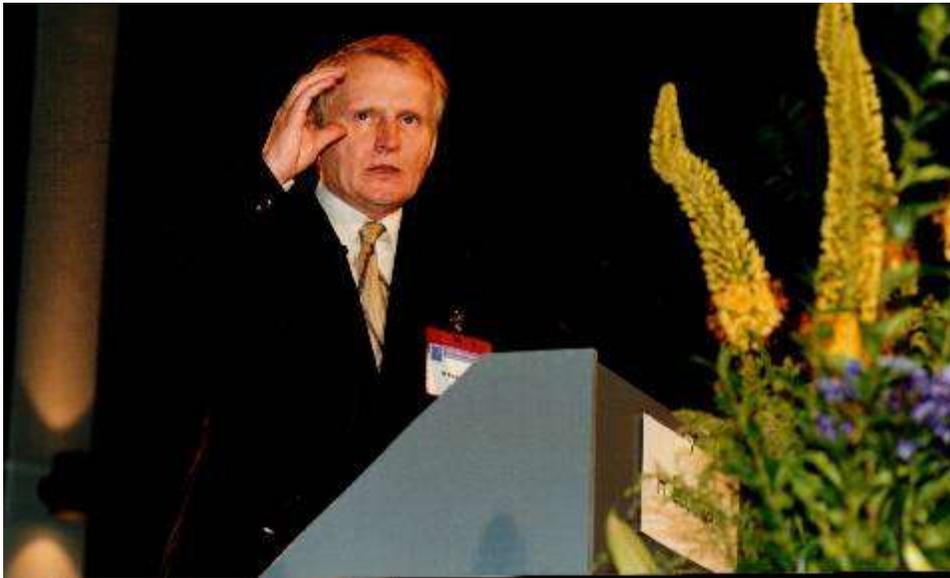
Thomas A. Ban and Julien Mendlewicz – received from Eugene S. Paykel



From Left to Right: Thomas A. Ban and Eugene S. Paykel. Photo taken in June 2000 in Brussels, Belgium at the XXIInd International Congress of the CINP.

October 16, 2014

Helmut Beckmann, President – received from Julien Mendlewicz



Helmut Beckmann, President XXIIInd CINP Congress. Photo taken in 2000, in Brussels, Belgium, at the premises of the Congress.

June 19, 2014

Helmut Beckmann – received from Julien Mendlewicz



Helmut Beckmann at the Opening Ceremony of the XXIIInd International Congress of the CINP.
Photo taken in Brussels, Belgium, in June 2000.

December 25, 2014

Helmut Beckmann and Julien Mendlewicz - received from Julien Mendlewicz



Helmut Beckmann and Julien Mendlewicz at the XXIIInd International Congress of the CINP. Photo taken in Brussels, Belgium, in June 2000.

December 25, 2014

Alec Coppen and Julien Mendlewicz – received from Julien Mendlewicz



From left to right: Alec Coppen (President 1988-1990) and Julien Mendlewicz (President 1990-1992) at the XXIIInd CINF Congress. Photo taken in 2000, in Brussels, Belgium, at the Congress.

June 19, 2014

Claude de Montigny – received from Julien Mendlewicz



Claude de Montigny at the XXIInd International Congress of the CINP. Photo taken in Brussels, Belgium, in June 2000.

December 25, 2014

Peter Gaszner – received from Julien Mendlewicz



Peter Gaszner at the XXIInd International Congress of the CINP.
Photo taken in Brussels, Belgium, in June 2000.

December 18, 2014

Solomon Langer and Julien Mendlewicz – received from Julien Mendlewicz



From left to right: Solomon Langer (Vice President 1992-1998) and Julien Mendlewicz (President 1990-1992) at the XXIIInd CINP Congress. Photo taken in 2000, in Brussels, Belgium, at the Congress.

June 26, 2014

Brian Leonard – received from Julien Mendlewicz



Brian Leonard at the XXIIInd International Congress of the CINP. Photo taken in Brussels, Belgium, in June 2000.

December 18, 2014

Julien Mendlewicz – received from Julien Mendlewicz



Julien Mendlewicz, Chair Local Organizing Committee, XXIIInd CINP Congress.
Photo taken in 2000, in Brussels, Belgium, at the premises of the Congress.

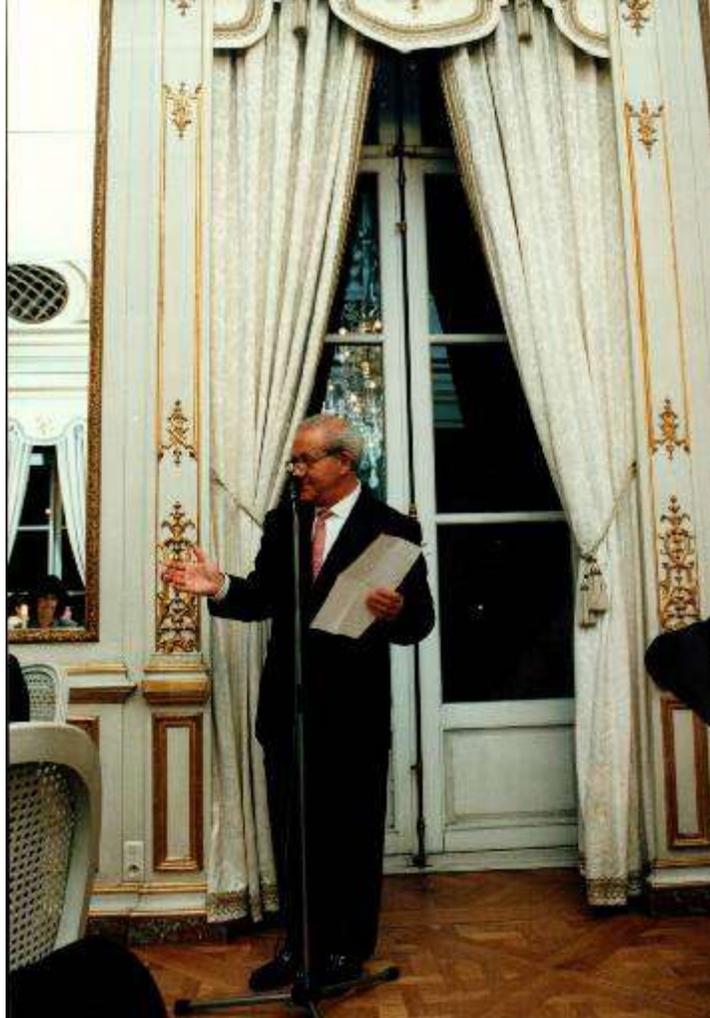
June 19, 2014

Julien Mendlewicz at the Opening Ceremonies – received from Julien Mendlewicz



Julien Mendlewicz (Chair Local Organizing Committee) at the Opening Ceremonies of the XXIIInd CINP Congress. Photo taken in 2000, in Brussels, Belgium, at the opening ceremonies of the Congress.

June 19, 2014

Julien Mendlewicz at the President's Dinner – received from Julien Mendlewicz

Julien Mendlewicz (Chair Local Organizing Committee) speaks at the President's Dinner of the XXIInd CINP Congress. Photo taken in 2000, in Brussels, Belgium, at the President's Dinner of the Congress.

June 26, 2014

Julien Mendlewicz and Hans-Jürgen Möller – received from Julien Mendlewicz



From left to right: Julien Mendlewicz (President 1990-1992) and Hans-Jürgen Möller (President 2008-2010) at the President's Dinner of the XXIIInd CINP Congress. Photo taken in 2000, in Brussels, Belgium, at the President's Dinner of the Congress.

June 26, 2014

Eugene Paykel – received from Julien Mendlewicz



Eugene Paykel (President 2000-2002) at the XXIInd CINP Congress. Photo taken in 2000, in Brussels, Belgium, at the premises of the Congress.

June 19, 2014

Eugene S. Paykel and Julien Mendlewicz – received from Eugene S. Paykel



From Left to Right: Eugene S. Paykel (President 2000-2002) receiving symbolic check from Julien Mendlewicz (Organizer of the XXIInd International Congress). Photo taken in June 2000 in Brussels, Belgium.

October 16, 2014

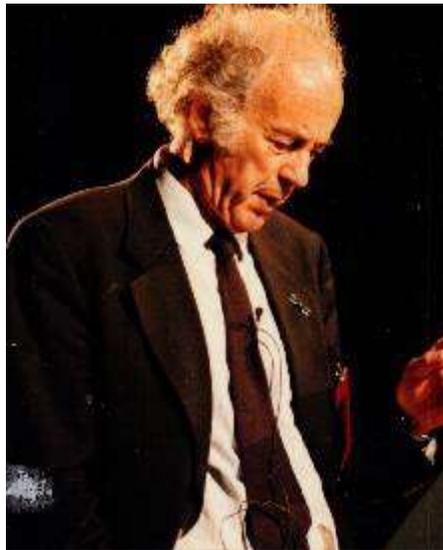
Eugene S. Paykel, Margaret Paykel and Herbert Meltzer – received from Eugene S. Paykel



From Left to Right: Eugene S. Paykel, Margaret Paykel and Herbert Meltzer. Photo taken in June 2000 in Brussels, Belgium at the XXIInd International Congress of the CINP.

October 16, 2014

Herman van Praag – received from Julien Mendlewicz



Herman van Praag at the XXIIInd International Congress of the CINP. Photo taken in Brussels, Belgium, in June 2000.

December 18, 2014

Herman van Praag, Julien Mendlewicz and Lewis Judd – received from Julien Mendlewicz



From left to right: Herman van Praag (Vice President 1976-1980), Julien Mendlewicz (President 1990-1992) and Lewis Judd (President 1994-1996) at the President's Dinner of the XXIIInd CINF Congress. Photo taken in 2000, in Brussels, Belgium, at the President's Dinner of the Congress.

June 26, 2014

**Peter Riederer, Moussa Youdim, Merton Sandler and Eric Wolten – received
from Moussa Youdim**



From left to right: Peter Riederer, Moussa Youdim, Merton Sandler and Eric Wolten. Photo taken in 2000 at the XXIIInd CINP Congress in Brussels, Belgium.

November 13, 2014

Torgny Svensson and Eugene S. Paykel – received from Eugene S. Paykel



From Left to Right: Torgny Svensson and Eugene S. Paykel. Photo taken in June 2000 in Brussels, Belgium at the XXIIInd International Congress of the CINP.

October 16, 2014

**WORLD PSYCHIATRIC ASSOCIATION THEMATIC CONFERENCE
HORMONES, BRAIN AND NEUROPSYCHOPHARMACOLOGY (2000)**

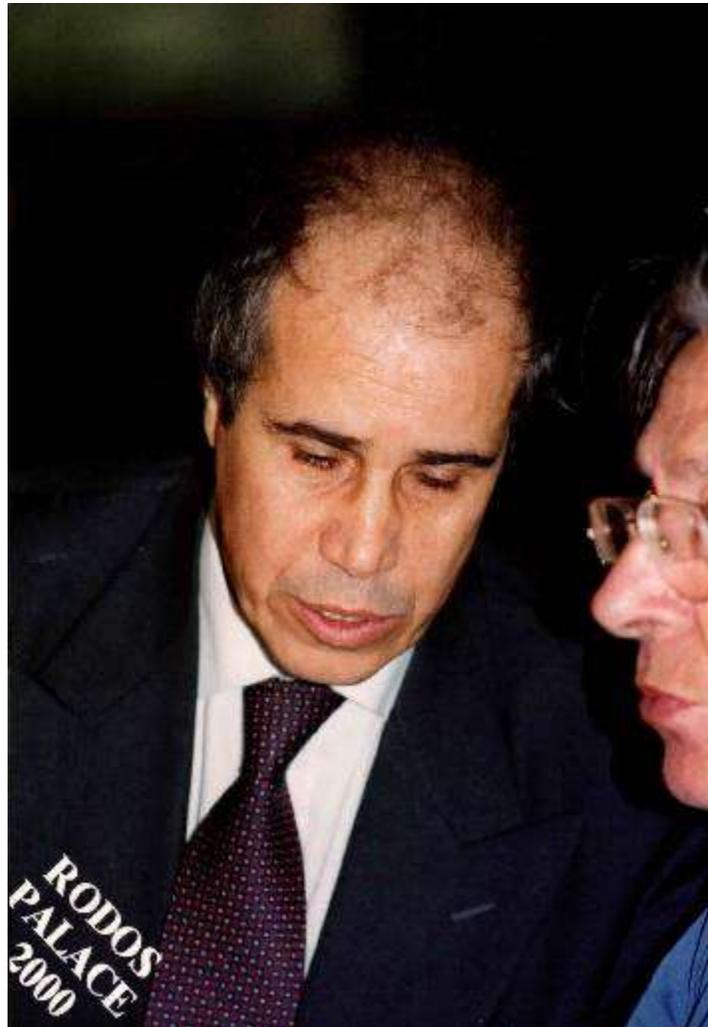
Eva Ceskova – received from Oakley Ray



Eva Ceskova at the World Psychiatric Association Thematic Conference on Hormones, Brain and Neuropsychopharmacology, organized by Oakley Ray and Uriel Halbreich. Photo taken in the Rodos Palace on Rhodes Island, in Greece, in July 2000.

Thomas A. Ban
December 11, 2014

Driss Moussaoui – received from Oakley Ray



Driss Moussaoui at the Thematic Conference on Hormones, Brain and Neuropsychopharmacology of the World Psychiatric Association organized by Oakley Ray and Uriel Halbreich. Photo taken in the Rodos Palace on Rhodes Island, in Greece, in July 2000.

Thomas A. Ban
December 4, 2014

Oakley Ray – received from Oakley Ray

Oakley Ray at the World Psychiatric Association Thematic Conference on Hormones, Brain and Neuropsychopharmacology, organized by Oakley Ray and Uriel Halbreich. Photo taken in the Rodos Palace on Rhodes Island, in Greece, in July 2000.

Thomas A. Ban
December 4, 2014

Robert C. Smith – received from Oakley Ray

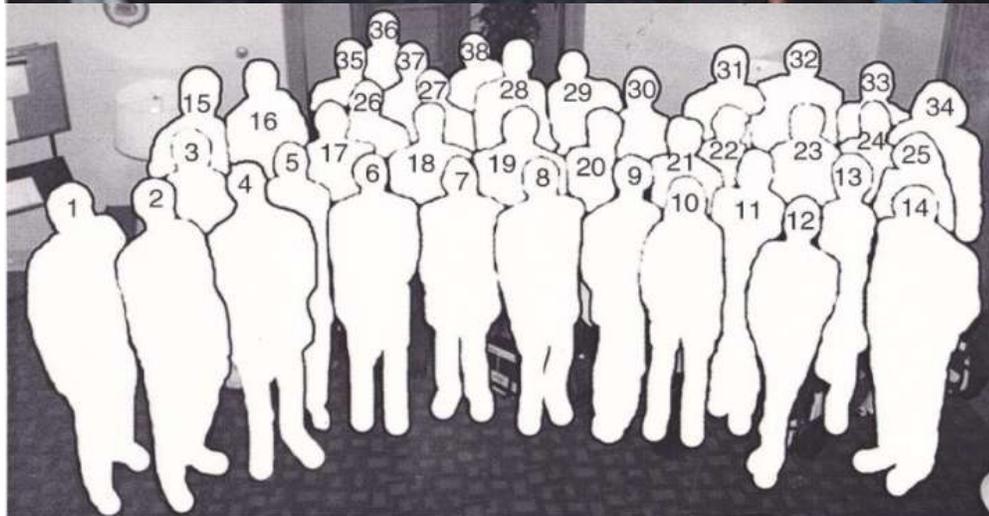


Robert C. Smith at the World Psychiatric Association Thematic Conference on Hormones, Brain and Neuropsychopharmacology, organized by Oakley Ray and Uriel Halbreich. Photo taken in the Rodos Palace on Rhodes Island, in Greece, in July 2000.

Thomas A. Ban
December 11, 2014

CINP COLLECTION: XXIIIrd INTERNATIONAL CONGRESS (2002)

Foreign Corresponding Organizations Luncheon – received from Eugene S. Paykel



1. Oakley Ray - USA 2. Brian Leonard - IRELAND 3. Trevor Norman - AUSTRALIA 4. Carlos Altamura - ITALY 5. Unknown 6. Eugene Paykel - UNITED KINGDOM
7. Jaime Monti - URUGUAY 8. Jaime Smolovich - ARGENTINA 9. Helena Calil - BRAZIL 10. Kathy Ray - USA 11. Unknown 12. Livia Vavrusova - SLOVAK REPUBLIC
13. Chan Kim - KOREA 14. Sergey Borisovich Seroderin - RUSSIA 15. Unknown 16. Humberto Nicolini - MEXICO 17. William E. Bunney - USA 18. Driss Moussaoui - MOROCCO 19. Ahmed Okasha - EGYPT 20. Herbert Meltzer - USA 21. Peter Gaszner - HUNGARY 22. Jun Horiguchi - JAPAN 23. Arvid Carlsson - SWEDEN
24. Eva Ceskova - CZECH REPUBLIC 25. Eva Palova - SLOVAK REPUBLIC 26. Sergei Mosolov - RUSSIA 27. Leonid Bardenstein - RUSSIA 28. Helmut Beckmann - GERMANY 29. Ronaldo Ucha - ARGENTINA 30. Masashi Sasa - JAPAN 31. Torgny Svensson - SWEDEN 32. William Potter - USA 33. Bernd Saletu - AUSTRIA
34. Zoltan Janka - HUNGARY 35. Gerardo Heinze - MEXICO 36. Unknown 37. Franck Bayle - FRANCE 38. Roger Porsolt - FRANCE

Group Photo and Map to Photo*

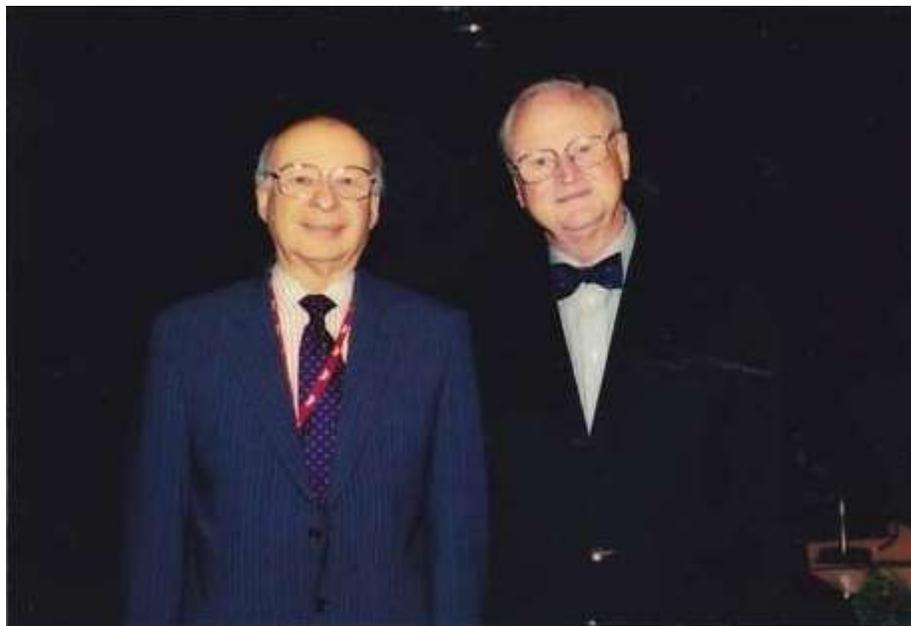
Thirty-five (35) of the thirty-eight (38) participants of the Foreign Corresponding Organizations Luncheon (in alphabetical order): Leonid Bardenstein, Franck Bayle, Helmut Beckmann, William E. Bunney, Helena Calil, Arvid Carlsson, Eva Ceskova, Peter Gaszner, Jaime Goncochea, Gerardo Heinze, Carlos Hojaj, Jun Homguchi, Zoltan Janka, Chan Kim, Brian Leonard, Herbert Meltzer, Jaime Monti, Sergey Mosolov, Driss Moussaoui, Humberto Nicolini, Trevor Norman, Ahmed Okasha, Eva Palova, Eugene Paykel, Roger Porsolt, William Potter, Kathy Ray, Oakley Ray, Bernd Saletu, Masashi Sasa, Sergey Borisovich Serodonin, Jaime Smolovich, Torgny Svensson, Ronaldo Ucha and Vivia Vavrusova. Photo taken, on June 27, 2002 at the XXIIIrd International CINP Congress in Montreal, Quebec, Canada.

*Number 4 is Carlos Hojaj and not Carlos Altamura as marked on the map

** Number 11 marked unidentified on the map is Jaime Goncochea from Colombia

October 2, 2014

Eugene S. Paykel and Arvid Carlsson – received from Eugene S. Paykel



From left to right: Eugene S. Paykel (President 2000 - 2002) and Arvid Carlsson (President 1978-1980). Photo taken, on June 27, 2002 in Montreal, Quebec, Canada.

September 25, 2014

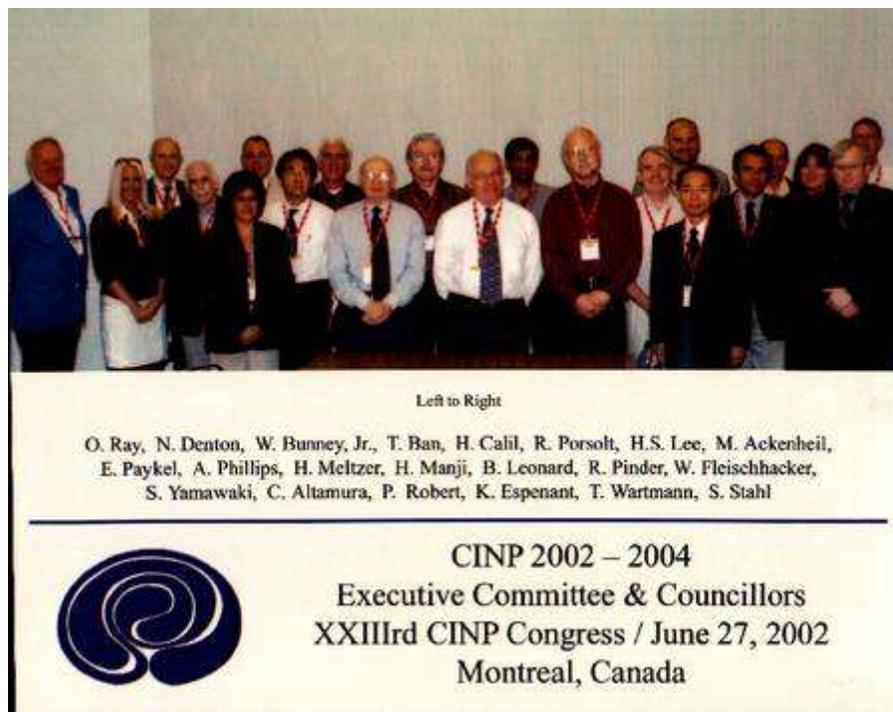
**Eugene S. Paykel, Monique de Montigny and Claude de Montigny – received
from Eugene S. Paykel**



From left to right: Eugene S. Paykel (President), Monique de Montigny and Claude de Montigny (Chair, Local Organizing Committee). Photo taken on June 27, 2002, in Montreal, Quebec, Canada.

September 25, 2014

CINP Executive Committee and Councillors – received from Oakley S. Ray



Left to right: O. Ray, N. Denton, W. Bunnet, Jr. T. Ban, H. Calil, R. Porsolt, H.. Lee, M. Ackenheil, E. Paykel, A. Phillips, H.Meltzer, H. Manji, B. Leonard, R. Pinder, W. Fleischhacker, S. Yamawaki, C. Altamura, P. Robert, K. Espenant, T. Wartmann and S. Stahl. Photo taken on June 27, 2002, at the XXIIIrd CINP Congress, in Montreal, Quebec, Canada.

Thomas A. Ban
June 12, 2014

**PROFILES OF DISTINGUISHED
NEUROPSYCHOPHARMACOLOGISTS**

**Profiles of Distinguished Neuropsychopharmacologists
(Profiles)
Project Four
Coordinated by Antonio Egidio Nardi**

This project was launched with an Introduction by Edith Serfaty on June 13, 2013. After posting twelve profile entries during 2013, coordination of the project was taken over by Antonio Egidio Nardi. An additional 17 profiles were posted during 2014.

Julius Axelrod by Irwin J. Kopin

Julius Axelrod (30 May 1912 – 29 December 2004) shared the 1970 Nobel Prize with Ulf von Euler and Bernard Katz for his discoveries related to catecholamine metabolism and termination of the actions of norepinephrine by reuptake into the nerve terminals from which it was released. In his Nobel lecture (Axelrod 1972), Julie cited over 50 of his papers that elucidated the regulation of norepinephrine biosynthesis, storage, release, metabolism, and inactivation in brain, as well as at peripheral sympathetic nerve terminals. Equally important, he showed that drugs, such as amphetamine, cocaine and antidepressants affect norepinephrine reuptake. This means of terminating actions of neurotransmitters has been verified for other neurotransmitters: serotonin, dopamine, glutamate and gamma-aminobutyric acid (GABA), providing an important target for drug development, particularly “serotonin-selective reuptake inhibitors” (SSRIs), e.g. fluoxetine (Prozac).

A short profile cannot adequately describe all of Julie’s many important other discoveries that help shape the development of Psychopharmacology and Neuroscience, fields that did not exist until the middle of the 20th century. Nor can it adequately reflect an appreciation of his mentorship of a host of young physician-scientists that have progressed to leadership roles in academia and the pharmaceutical industry. With regard to the Prize, those of us who were privileged to have worked with Julie concluded that “Nice guys do win ball games.” Sol Snyder, in a bibliographic memoir of Julie’s “most improbable” scientific success story (Snyder 1987) and Julie’s own chronicle of “Journey of a Late Blooming Biochemical Neuroscientist” (Axelrod 2003) relate the evolution of his earliest employment in a laboratory measuring vitamins in foods, the beginning of a research career in 1945, when Bernard Brodie invited him to work in his laboratory at Goldwater Memorial Hospital on the metabolism of analgesics, which led to their discovery of acetaminophen, the move to the National Institutes of Health (NIH) and the work for which he obtained his PhD from George Washington University, and his recruitment to the National Institute of Mental Health (NIMH), where he spent the rest of his career. At NIMH, he began studies on metabolism of psychoactive drugs, but in 1957, with the discovery of vanillylmandelic acid (VMA) as the major urinary excretion product of epinephrine, he embarked on a second major field, the series of studies on catecholamines, for which he was awarded the Nobel Prize. His ability to distinguish important from trivial questions, his elegantly simple design of experiments to provide clear results, his style of mentorship to bring out the best in his postdoctoral students, Julie’s contributions to chronobiology via melatonin and pineal function, his studies of methylation of phospholipids and a host of other accomplishments followed in the more than three decades after he received the Prize. After his death, a number of lengthy tributes to him by former postdoctoral fellows were published, e.g. Sol Snyder (2005), Leslie Iversen (2006), as well as his featured inclusion in Robert Kanigel’s “Apprentice to Genius: The Making of a Scientific Dynasty” (Kanigel 1986). There is also brief summary about Julie and his research in Wikipedia.

References:

Axelrod J. Noradrenalin: Fate and Control of its Biosynthesis, Nobel Lectures, Physiology or Medicine 1963-1970. Amsterdam: Elsevier Publishing Company; 1972.

Axelrod J. Journey of a late blooming biochemical neuroscientist. J. Biol. Chem. 2003; 278:1-13.

Iversen L. Julius Axelrod 2006 Biogr. Mems Fell. R. Soc. 87 (December)

Kanigel R. Apprentice to Genius: The Making of a Scientific Dynasty. Baltimore: The Johns Hopkins University Press; 1986.

Snyder SH. A Biographical Memoir of Julius Axelrod. 2005 Biographical Memoirs of the National Academy of Science; Volume 87

November 6, 2014

Hassan Azima by Antonio E. Nardi

Hassan Azima was born in Tehran, Iran, June 28, 1922, and received his M.D., in 1948, from the University of Kansas in the United States. He was trained in psychiatry in Paris, France and Montreal, Canada to receive his Diploma in Psychiatry, in 1955, from McGill University.

Azima became involved in the clinical evaluation of psychotropic drugs during his residency and, in 1954, he was among the first to publish on the effects of chlorpromazine (CPZ) on “mental syndromes” in North America (Azima and Ogle 1954). One year later, in 1955, he was also among the first to report on “jaundice” occurring during the administration of CPZ (Stacey, Azima, Huestis and Hoffman 1955). In the years that followed, Azima contributed to the clinical development of numerous psychotropic drugs. They included, among the neuroleptics, various phenothiazine preparations, e.g., chlorpromazine, promazine, thioridazine (Azima and Durost 1957; Azima, Durost and Arthurs 1959), Rauwolfia alkaloids (Azima, Cramer-Azima and DeVerteuil 1959) and haloperidol, a butyrophenone (Azima, Durost and Arthurs 1960); among the antidepressants, imipramine, a dibenzazepine (Azima 1959; Azima and Vispo 1958, 1959) and isocarboxazid, a hydrazine monoamine oxidase inhibitor (Azima, Durost, Arthurs and Silver 1959); and the anxiolytic meprobamate, a propanediol (Azima and Vispo 1960).

Azima conceptualized the therapeutic action of psychotropic drugs within a psychoanalytic frame-of-reference (Azima and Sarwer-Foner 1961; Azima and Wittkower 1957). He perceived the favorable effects of neuroleptics in patients with schizophrenia, a result of replacement of “psychic defenses,” such as “withdrawal” and “splitting” by “movement toward external objects,” with a shift from a “schizophrenic organization,” comparable to Melanie Klein’s “paranoid position” in infantile development, to a “manic-depressive-like organization,” comparable to Klein’s (1948) “depressive position,” that replaces the “paranoid position” in infantile development (Azima, Azima and Durost 1959; Azima, Cramer-Azima and DiVerteuil 1959; Ban 1969; Klein 1948). Similarly, he perceived the favorable effects of antidepressants in depression as a result of a shift of invested “psychic energy” from the “superego” to the “ego” and “id” (Azima 1959, 1961; Ban 1969); and of pharmacologically-induced sleep as a result of “ego split” with an inactivation of the “ego system” that allows a return from “pathological fixation points” (Azima 1955; Azima and Vispo 1960).

Azima stayed at McGill, throughout his professional career. He died in Montreal, on June 26, 1962, at age 39.

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September 25, 2014

Hans Berger by Antonio E. Nardi

Hans Berger was born on May 21, 1873, in Neuses, Germany. He received his medical degree from the University of Jena, in 1897. Subsequently, he joined Otto Ludwig Binswanger's Department of Psychiatry and Neurology at the University of Jena to become his successor as Professor and Director of the Clinic, in 1919 (Millett 2001). During this period of over 20 years, through an opening made by trephination on the skull, he investigated blood circulation and brain temperature (Berger 1904-7; 1910); studied the influence of heartbeat, respiration, vasomotor functions and position of the head and body on brain pulsations; and explored the effects of medications, such as camphor, digitoxin, caffeine, cocaine, and morphine on brain pulsations (Berger 1921).

In 1924, Berger was first to record brain electrical activity (rhythms) in man by electrodes placed on the scalp of human volunteers. He referred to the record obtained as the Elektroenzephalogram and the procedure was to become known as electroencephalography (EEG). By the time he first published his findings, in 1929, Berger recognized that the dominant oscillations in normal subjects were 10 cycles per second ("alpha"-waves to be referred to later as "Berger's waves") with lesser amount of waves of lower voltage and faster frequencies ("beta" waves) and higher voltage slower rhythms ("theta" waves and "delta" waves); as well as that the electrical waves were best defined when subjects were at rest with eyes closed; that eye opening produced "alpha" blockade", i.e., replacement of "alpha" waves by "beta" waves; and that the waves changed with mental activity, e.g., by doing simple calculations (Fink 2004). Pursuing further his research, in the early 1930s, Berger had shown the effects of drugs on the EEG and by the late 1930s, he also demonstrated relationships between EEG changes and behavior (Berger 1931, 1938). Thus, after subcutaneous administration of 30 mg cocaine, the amplitude of alpha waves increased at the time the pupils were dilated, pulse rate was rapid and alertness enhanced; in chloroform-induced anesthesia, EEG amplitudes progressively decreased as narcosis deepened and then increased, when narcosis waned; in scopolamine-induced delirium, the frequency of beta waves increased, whereas in scopolamine-induced sedation, the frequency of alpha waves decreased; and during the time of behavioral control in agitated psychotic patients with 20 mg morphine and 1 mg scopolamine, the EEG was desynchronized with a loss of rhythmic alpha activity (Fink 1998).

By the end of the 1930s, the EEG was recognized as a diagnostic tool in neurology. Hans Berger died in Jena on June 1, 1941 at age 68.

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June 26, 2014

Hermann Blaschko by Joseph Knoll

Hermann (Hugh) Felix Blaschko was born January 4, 1900 in Berlin, Germany, and received his medical degree, in 1922, from the University of Berlin. Subsequently he worked at the Medical Clinic of the University Hospital in Göttingen, before embarking on a research career, in 1925, in Otto Meyerhof's laboratory in Berlin (Born and Banks 1962).

In 1933, Blaschko moved from Germany to England and on the encouragement of Professor Joseph Barcroft, began with his studies on adrenaline metabolism at the Institute of Physiology in Cambridge. This led to his discovery that it was the same enzyme, he referred to as amine oxidase, and not substrate specific enzymes, as many believed at the time, which metabolized tyramine, dopamine, noradrenaline, adrenaline and aliphatic amines, in general (Blaschko, Richter and Schlossman 1937a; Hare 1928). They also demonstrated the presence of the enzyme in the liver (Blaschko, Richter and Schlossman 1937b). In 1938, after Zeller's separation of diamine oxidase from amine oxidase, the name of Blaschko's enzyme was changed to monoamine oxidase to indicate that its function is restricted to the oxidative deamination of monoamines. Extending his research from the metabolism of adrenaline to the synthesis of catecholamines, in 1939, Blaschko described l-DOPA decarboxylase and discovered that it is the enzyme involved in the decarboxylation of levodopa to dopamine. Furthermore, by the mid-1940s, Blaschko recognized that tyrosine converts into levodopa, levodopa into dopamine, dopamine into noradrenaline and noradrenaline into adrenaline (Blaschko 1952).

In 1943, Blaschko moved from Barcroft's Institute of Physiology in Cambridge, to J.H. Burns' Department of Pharmacology in Oxford. He continued his research with adrenaline and catecholamines, and about 10 years later, in 1953, he demonstrated that adrenaline is stored in cytoplasmic particles in vesicles, localized in the membrane of cells which produce it in the adrenal medulla (Blaschko and Welch 1953). He also recognized that in case of need, adrenaline is driven out from its storage vesicles by an inner force, referred to as "exocytosis" (Blaschko and Muscholl 1972).

In 1962, in recognition of his contributions, Hermann Blaschko was elected a Fellow of the British Royal Society (FRS). On April 18, 1993, at age 93, Blaschko died, in Oxford.

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July 17, 2014

Philip B. Bradley by Marina Dyskant Mochovitch

Philip B. Bradley was born in Bristol, England, in 1919. He graduated from Bristol University in Zoology and Chemistry, in 1948, and received his PhD in Pharmacology and DSc in Neuropharmacology from the University of Birmingham, in 1952 and 1958, respectively (Bradley 2000).

In 1951, while still a postgraduate student, Bradley joined Joel Elkes's newly founded Department of Experimental Psychiatry at the University, and in the early 1950s, he developed a technique for studying electrical activity in the brain in conscious animals (Bradley 1952; Bradley and Elkes 1953a). With the employment of the new technique, he studied the effects of several centrally acting drugs on the electrical activity of conscious cat (Bradley and Elkes 1954). His findings with atropine and physostigmine provided further substantiation of Abraham Wikler's (1952) finding of a dissociation between the effect of anticholinergic drugs, such as atropine, on behavior and on the electroencephalogram (EEG) in dog (Bradley and Elkes 1953b). This "lack of correlation" was not present with the other drugs they studied, such as amphetamine, lysergic acid diethylamide (LSD) and chlorpromazine (Bradley 2000; Bradley and Elkes 1953b).

In the mid- and late-1950s, Bradley extended his research to the study of the effects of drugs on the brainstem reticular formation (reticular activating system) by recording, in collaboration with Brian Kay, the arousal response produced by direct electrical stimulation of the brainstem reticular formation or by peripheral auditory stimulation. Findings in these studies indicated that drugs, which produced an effect on the EEG that was correlated with behavioral effects, acted either directly, as the barbiturates and amphetamines, or indirectly, as chlorpromazine and LSD, on the brainstem reticular formation, whereas drugs which produced an effect on the EEG that was not correlated with behavior, as atropine or physostigmine, acted more diffusely (Bradley 1957b; Bradley and Kay 1957, 1959; Moruzzi and Magoun 1949).

After defining the role of the brainstem reticular formation in the action of different psychotropic drugs, Bradley, with the adoption of a floating microelectrode technique, still in the 1970s, studied the effect of adrenaline and acetylcholine on single unit activity of the decerebrate cat, and subsequently with the employment of microiontophoresis, a technique he pioneered with John Wolstencroft, he began mapping neurons of the brainstem reticular formation on the basis of their response to putative neurotransmitters (Bradley 1957a, 2000, 2011; Bradley and Mollica 1958). Continuing with his research on the effect of drugs on the brain, in 1970, he demonstrated with his associates that LSD antagonized the action of 5-hydroxytryptamine, not only in the periphery, as shown by Gaddum, in 1953, but also in the brain (Boakes, Bradley, Briggs, Dray 1970; Gaddum 1953).

By the 1980s, Bradley research shifted to the study of receptors and his findings with the employment of microiontophoresis, reported in 1984 and 1986, contributed to the

classification of opioid and serotonin receptors, respectively (Bradley and Brooks 1984; Bradley et al 1986; Dhawan et al 1996). One year later, in 1987, Bradley published his *Introduction to Neuropharmacology*.

Philip Bradley died in 2009.

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April 24, 2014

Alfred M. Freedman by Sergio Machado

Alfred M. Freedman was born in Albany, New York, in 1917. He received his medical degree from the University of Minnesota Medical School in 1941, and completed his training in general and child psychiatry at Bellevue Hospital, in Manhattan, in the early 1950s (Freedman 2000, 2011).

During his residency, Freedman became involved in studying the effects of psychotropic drugs, as they appeared on the psychiatric scene, in psychiatric disorders in children. He continued with this research at Downstate Medical Center, in New York, throughout the 1950s, and over a decade, he explored the effects of diphenhydramine, mephenesin, meprobamate, promethazine, chlorpromazine in disturbed children with psychiatric disorders (Freedman et al 1955), and of iproniazid and lysergic acid diethylamide in “schizophrenic autistic children” (Freedman 1958; Freedman, Ebin and Wilson 1962). In the course of this research, he found diphenhydramine and promethazine effective in controlling disturbed behavior in children and recognized that as a “tranquilizer”, chlorpromazine was superior to all other drugs he tried (Freedman 2000). He found chlorpromazine effective also in controlling vomiting in children with familial dysautonomia (Freedman et al. 1957). None of the drugs he tried had therapeutic effect in “schizophrenic autistic children” (Freedman 1958; Freedman, Ebin and Wilson 1962).

In 1960, Freedman was appointed chairman of the Department of Psychiatry at the New York Medical College, and during the 1960s, in collaboration with Max Fink, he contributed to the clinical development of the first series of opiate antagonists: cyclazocine, naloxone, and naltrexone (Freedman et al 1968, 1970). His collaboration with Fink continued, and in a study conducted with Costas Stefanis, in Greece, they were among the first, in the mid-1970s, to demonstrate that there was no clinically detectable brain damage in heavy chronic hashish users over a decade (Fink et al. 1976; Freedman 2000; Stefanis et al. 1976). Freedman was also a member of the team that reported favorable effects with an extract of *Gingko biloba* in dementia (Le Bars, Katz, Berman, Itil, Freedman and Schatzberg 1997).

Independent of his contributions to neuropsychopharmacology, Freedman conceived and co-edited with Harold Kaplan, *Comprehensive Textbook of Psychiatry*, the first edition of which was published in 1967. Subsequently, he served as president of the American Psychopathological Association, in 1971; of the American College of Neuropsychopharmacology, in 1972; and of the American Psychiatric Association, in 1973-1974.

Alfred M. Freedman died in 2011, in New York City, at age 94.

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July 31, 2014

J. Christian Gillin by Bruno Nazar

J. Christian Gillin was born, in 1938, in Columbus, Ohio, USA. He received his medical degree from Case Western Reserve School of Medicine, in 1966, and completed his psychiatric residency training at Stanford University Medical School, in 1971. In 1982, after 11 years within the Intramural Research Program of the U.S. National Institute of Mental Health, Gillin moved to the Veterans Administration Medical Center in San Diego, California, affiliated with the Department of Psychiatry, University of California San Diego, as professor of psychiatry. He stayed in this position for the rest of his life (Gillin 2011).

In the late 1970s, Gillin became involved in studying the sleep EEG in depressed patients. His early findings, in 1978, provided further substantiation of Kupfer and his associates reports that an early onset of the first period of rapid eye movement (REM) sleep was an indicator of “primary depression” (Kupfer 1976; Kupfer and Foster 1972; Kupfer, Hanin, Spiker, et, al 1978) and that an increase in the latency time of the onset of the first REM period was after the administration of 50 mg of amitriptyline was a predictor for a favorable outcome of treatment with the drug (Gillin, Wyatt, Fram and Snyder 1978). He hypothesized that amitriptyline’s effect on the onset of the first REM period (REM latency) was linked to its anticholinergic properties, and his findings that intravenous administration of the cholinesterase inhibitor, physostigmine (Gillin, Sitaram, Mendelson and Wyatt, 1978), and of the direct muscarinic agonist, arecoline (Sitaram, Nurnberger, Gershon and Gillin, 1980), decreased REM latency, whereas the infusion of a muscarinic receptor antagonist, scopolamine prolonged it (Sitaram, Moore, & Gillin, 1978), were supportive of his hypothesis.

Throughout the 1980s and 1990s, Gillin studied the effects of putative antidepressants on the sleep EEG. In one of his first studies, conducted in the early 1980s, he found that both pargyline, a nonselective monoamine oxidase inhibitor (MAOI), and clorgyline, the prototype Type-A MAOI, suppressed REM sleep (Cohen, Pickar, Garnett, et al 1982); and in his last study conducted in the late 1990s, he revealed that fluoxetine, a selective serotonin re-uptake inhibitor, delayed the onset of the first REM period, whereas nefazodone, a serotonin modulating antidepressant did not (Rush, Armitage, Gillin et al. 1998). To pursue further his research on the biochemical regulation of REM sleep, he developed the “cholinergic rapid eye movement induction test” (CRIT) (Gillin, 1992) and his findings with the employment of this test indicated that patients with primary depression have a supersensitive induction of REM sleep in response to the administration of the muscarinic acetylcholine receptor agonist, arecoline (Gillin et al. 1991). Supplementing the CRIT by using a “tryptophan free drink”, he revealed that while muscarinic acetylcholine receptor stimulation increased, serotonin (5HT) depletion decreased latency of the first REM period (Bhatti, Gillin, Seifritz, et al. 1998). The same study also indicated that 5HT depletion lowered mood and decreased vigor. Finally, in one of their last reports, Gillin and his associates indicated that the decrease of REM latency by 5HT depletion was mediated by 5HT_{1A} receptors and the increase

REM latency by acetylcholine was mediated by M₂ muscarinic receptors (Seifritz, Gillin, Rapaport, et al. 1998).

In 1987, Gillin became founding editor of *Neuropsychopharmacology*, the journal of the American College of Neuropsychopharmacology and served in that position for seven years, until 1994. Christian Gillin died in San Diego, in 2003, at age 65.

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September 11, 2014

Turan M. Itil by Antonio E. Nardi

Turan Itil was born in Bursa, Turkey in August 12, 1924. He received his MD from the Medical College, University of Istanbul in 1948, and completed his training in neurology and psychiatry in the early 1950s at the University of Tübingen in Germany. Subsequently, he joined Fritz Flügel's Department of Neuropsychiatry in Erlangen, Germany (Itil 1998, 2011).

Itil became involved in studying clinical and electroencephalographic changes with centrally acting drugs in collaboration with Dieter Bente, in the mid – 1950s. It was in the course of their first study, in which they tested the therapeutic effect of promethazine on phantom pain that he learned that drugs which affect human behavior also produce effects on the human electroencephalogram (EEG) (Bente and Itil, 1954; Itil 1998). Pursuing further the same line of research, they reported on the clinical and electroencephalographic effects of chlorpromazine in 1954 and of reserpine, methamphetamine and lysergic acid diethylamide in 1957 (Bente and Itil 1954, 1957 a & b). In 1957, at the First CIMP Congress in Rome, Bente and Itil (1959) reported on the differences in chlorpromazine-induced and natural sleep; and in 1960, at the Second CIMP Congress in Rome, Flügel, Bente, Itil and Molitoris reported their findings with acylated piperazine phenothiazines that was allegedly instrumental in the clinical development of butaperazine (Bente and Itil 1959; Flügel, Bente, Itil and Molitoris 1961). It was also in 1961 that Itil published first on the differential effects of neuroleptics and thymoleptics on the EEG.

In 1963, Itil joined Max Fink at the Missouri Institute of Psychiatry, where they developed a digital computer analysis of the human EEG that they referred to as quantitative EEG, or pharmaco-EEG (Fink, Itil and Shapiro 1967); and he set up a laboratory for the screening, early clinical evaluation and monitoring psychotropic effects (Fink, Shapiro, Hickman and Itil 1968; Itil 1966, 1968; Itil, Shapiro and Fink 1968). It was in this laboratory in the mid-1960s that he found that the pentothal-induced change in the EEG could be used as a prognostic index in drug therapy of psychotic patients (Itil 1965); and demonstrated, in collaboration with Samuel Gershon and Max Fink that tetrahydroamino acridine could reverse not only the delirium, but also the EEG changes associated with delirium induced by anticholinergic drugs (Itil 1966; Itil and Fink 1966). It was also in this laboratory, in collaboration with Polvin and Hsu, he revealed that Org GB 94 (mianserin), a tetracyclic substance has antidepressant properties (Itil, Polvin and Hsu 1972). In 1974, Itil moved from the University of Missouri to the New York Medical College and established, in Terrytown, HZI Research Center Laboratory for using pharmaco-EEG in the identification of psychoactive properties of drugs and in the prediction of their therapeutic activity, i.e., whether they had characteristics of antipsychotics, antidepressants, cognitive enhancers or anxiolytics (Itil 1972). Among the early drugs studied at the center were lisuride, an antiparkinson drug related to dopaminergic ergoline compounds, and mestrolone, a synthetic androgen preparation (Itil, Herrmann and Akpınar 1978a; Itil, Herrmann, Blasucci and Freedman 1978b); and among the last

was ginkgo biloba, a plant extract with central nervous system effects, he reported on, in 1996 (Itil, Eralp, Tsambis, Itil and Stein 1996).

In the late 1990s, Itil moved back to Turkey and died in Mersin, Turkey, April, 29, 2014, at age 89.

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August 21, 2014

Hitoshi Itoh by Hajime Kazamatsuri

Hitoshi Itoh was born in Yokohama, Japan, on September 21, 1925. He received his medical degree from the Ciba University School of Medicine, in 1950. After graduation from medical school, he spent five years at the Institute of Infectious Disease Research, Tokyo University and worked for about five years in immunology and neurochemistry. Subsequently, he began with his training in psychiatry at the Keio University Hospital in Tokyo, in 1955.

Itoh was appointed associate professor of psychiatry at the Keio University School of Medicine in 1973 and became Director of the Psychopharmacology Research Group. He translated many European and American books related to neuropsychopharmacology into Japanese and wrote many papers on topics related to the field (Itoh 1981; Itoh, Ichimaru, Kawakita, Kudo, Kurihara, Satoh and Takahashi 1971; Itoh, Miura, Yagi, Sakurai, and Ohtsuka 1977; Itoh, Ohtsuka, Ogita, Yagi, Miura and Koga 1977; Itoh, Yagi, Fujii, Iwamura and Ischikawa 1984). He also edited several books on psychotropic drugs (Itoh & Miura 1973).

Itoh was councilor of the CINP from 1984-1988. He is regarded as one of the pioneers of clinical psychopharmacology in Japan.

Itoh died on April 30, 1985 at the age of 60.

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November 20, 2014

Paul Kielholz by Antonio E. Nardi

Paul Kielholz was born November 15, 1916, in Brugg, Switzerland, and received his MD, in 1943, from the Faculty of Medicine, University of Zurich. In 1947, Kielholz joined John Eugen Staehelin's Department of Psychiatry at the University of Basel and 12 years later, in 1959, succeeded Staehelin as head of the Department and Director of the University Clinic. He remained in the same position until his retirement in 1985.

Kielholz began his research in the late 1940s by exploring the use of narcosis and muscle relaxants in electroconvulsive therapy (ECT) (Heuscher and Kielholz 1949; Kielholz and Heuscher 1949) and of the "perfusion method" in the treatment of "acute catatonia" (Kielholz 1949). In the early 1950s, he extended his research to the study of "chronic morphinism" (Kielholz 1952). Then, in 1953, he co-authored with Staehelin the first paper on the therapeutic effect of chlorpromazine (CPZ) published outside of France (Staehelin and Kielholz 1953). Pursuing his research further with CPZ, in 1954, he reported on the therapeutic effects of the substance in depression, mania and drug (morphine and barbiturate) withdrawal (Kielholz 1954). The turning point in Kielholz's research was the publication of his report, in 1958, with Raymond Battagay, in which they provided further substantiation of Roland Kuhn's (1957) discovery of the therapeutic effect of imipramine (IMI) in some depressed patients (Kielholz and Battagay 1958). Subsequently, he was a member of the team which, in 1961, recognized that desmethyylimipramine (DMI) was an active metabolite of IMI and implicated the major role of DMI in IMI's antidepressant effect (Brodie, Dick, Kielholz, et al 1961). In the early 1970s, Kielholz was chairman of two influential symposia ("Depressive Illness" and "Masked Depression"), which were instrumental in establishing the place of pharmacotherapy in the treatment of depression (Kielholz 1972, 1973). By the late 1970s, there were several drugs available for the treatment of depression and, in 1979, Kielholz was among the first to relate the pharmacological activity of these drugs to their therapeutic profile (Kielholz 1979). During the 1970s, Kielholz was also involved in studying the effects of "pharmacotherapy of toxicomania" (Kielholz 1974); the effects of alcohol and other drugs on "driving behavior" (Kielholz and Hobl 1977); and in developing treatment strategies, e.g., intravenous administration of antidepressants, for therapy refractory depression (Kielholz, Terzani and Gastpar 1979). Exploring possible treatments for therapy of refractory depression dominated Kielholz's research during the 1980s (Kielholz 1986, 1990; Kielholz et al 1982).

Paul Kielholz died on May 25, 1990. He was 73 years old.

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October 9, 2014

Heinz E. Lehmann by Antonio E. Nardi

Heinz Lehmann was born in Berlin, Germany, in 1911, and received his MD from the University of Berlin, in 1935. In 1937, he immigrated to Canada and in the same year, he took a post at the Verdun Protestant (later Douglas) Hospital, a psychiatric inpatient facility in the suburbs of Montreal (Quebec), with which he remained affiliated for 60 years. In 1948, he was appointed lecturer in the Department of Psychiatry, McGill University, in Montreal and became actively involved in teaching. He rose on the academic ladder to full professor and served as the Chairman of the Department from 1970 to 1974 (Shorter 2011).

Lehmann became involved in psychiatric research with drugs in the early 1940s. In his first project, the findings of which were published only in 1979, he studied the differential effect of pentobarbital on yawning in psychiatric patients (Lehmann 1979, 1993). Subsequently, in 1944, he published a report on the therapeutic effect of massive doses of nicotinic acid on post-traumatic confusional state (Lehmann 1944) and in the late 1940s, developed a short-lived hypnotic, containing nicotinic acid, a barbiturate, scopolamine, and apomorphine (Lehmann 1949).

In 1954, Lehmann was propelled into dominance by being the first in North America to publish his findings on the effect of chlorpromazine in psychomotor excitement and manic states (Lehmann and Hanrahan 1954). The impact of his paper was so profound that in 1957, he was presented with the prestigious Lasker Award (Ban 2011). Lehmann was also the first in North America, in 1958, to report on the effects of imipramine in the treatment of depression (Lehmann, Cahn & DeVerteuil 1958), and among the first in the same year, to report on findings in a clinical trial with iproniazid in depressed and apathetic patients (DeVerteuil & Lehmann 1958). During the 1960s, he was also involved in developing one of the first rating scales for the assessment of changes in the treatment of depression (Lehmann, Cahn and DeVerteuil 1958) and methods for the evaluation of psychoactive drug effects that were based on psychological performance tests (Lehmann and Knight 1961). As the Principal Investigator of a grant from the US Public Health Service to support the operation of an Early Clinical Drug Evaluation Unit of the network organized by the Psychopharmacology Service Center of the United States, Lehmann was also involved during the 1960s and 1970s in the clinical evaluation of numerous new psychotropic drugs in development (Lehmann & Ban 1963).

In recognition of his contributions, in 1976, he became an Officer of the Order of Canada; and in 1998, he was recipient of the Pioneers in Psychopharmacology Award of the Collegium Internationale Neuro-Psychopharmacologicum. There are also several awards honoring his name: The Heinz Lehmann Award of the Canadian College of Neuropsychopharmacology, the Heinz Lehmann Award of Excellence of the Quebec Psychiatric Association, and the Heinz Lehmann Research Award, established by the New York State Office of Mental Health, where he served in the last decade of his life as Deputy Commissioner in the Research Division.

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April 17, 2014

Laszlo J. Meduna by Antonio E. Nardi

Lászlo Meduna was born on March 27, 1896, in Budapest, Hungary and received his MD, in 1921, from the Medical Faculty of Pázmány Péter University. Subsequently, in 1922, he joined Károly Schaffer, a psychiatrist and neurohistologist, in his Interacademic Institute for Brain Research in Budapest. After Schaffer's appointment, in 1927, as professor (chair) of the Department of Psychiatry at the University, he became a member of his faculty (Shorter and Healy 2007).

Meduna began research in histopathology in the mid-1920s. While studying microglia cells in the rabbit, he found disease dependent differential changes, i.e., atrophy, in some diseases and swelling in others (Meduna 1927). Extending his research to autopsied material from psychiatric patients, in the early 1930s, he noted a marked decrease of microglia cells in the brains of patients with schizophrenia and a marked increase in patients with epilepsy (Fink 1985; Meduna 1932). Considering the findings of Nyirö and Jablonsky (1929) that the incidence of seizures decreased in those epileptics who developed schizophrenia, the observations of Glaus (1931) that schizophrenic psychopathology was transiently alleviated in schizophrenic patients with epilepsy and the report of Müller (1930) that two patients with schizophrenia "recovered" when they developed epilepsy, Meduna, in 1934, introduced pharmacologically-induced convulsions in the treatment of schizophrenia, with camphor first, then with pentylenetetrazol (Meduna 1935, 1937). In the late 1930s, Meduna emigrated from Hungary to the United States (Kuncz 1993). He became professor of Neurology at Loyola University and became settled for the rest of his life at the Illinois Psychiatric Institute. In the mid-1940s, he coined the term "oneirophrenia" for a small group of "atypical psychoses" conventionally diagnosed as schizophrenia (Meduna and McCulloch 1945, 1946) and in the late 1940s, he introduced carbon dioxide therapy, a "pharmacodynamic treatment of psychoneuroses" (Meduna 1947, 1948). In 1950, he published a monograph on both, with the title, Oneirophrenia and Carbon Dioxide Therapy (Meduna 1950). In 1958, Meduna became founding editor of the journal *International Neuropsychiatry*. Finally, in 1959, Meduna in collaboration with Abood, was one of the first to explore Ditrán (1-ethyl-3 piperidyl cyclopentylphenylglycolate), an anticholinergic substance with atropine-like actions, in the treatment of depression (Meduna and Abood 1959).

Meduna died in Chicago on November 30, 1964, at age 68.

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November 27, 2014

Dionisio Nieto Gómez by Antonio Torres-Ruiz

Dionísio Nieto Gómez was born in Madrid, Spain on March 13 1908. In 1929, he received his MD from the Faculty of Medicine, Complutense University in Madrid. Subsequently, he spent five years, from 1931 to 1935, in Germany studying neuropsychiatry. After returning to Spain, he worked from 1935 to 1937 at the Psychiatric Clinic of the General Hospital of Madrid and in the Cajal Institute.

Nieto left Spain in 1939 after the Civil War, and arrived in Mexico via France and Santo Domingo, in April 1940. In Mexico City, he worked first at the National Psychiatric Hospital, commonly known as "La Castañeda" and was instrumental in establishing the foundation of the Laboratory of Medical and Biological Research that was to become UNAM's (Universidad Nacional Autónoma de México) Institute of Biomedical Research.

In 1964, Nieto joined the National Institute of Neurology and Neurosurgery in Mexico City, and soon after he became head of the Department of Psychiatry and Research of the Institute. In the mid-1950s, he was involved in studying copper metabolism in the CNS (Escobar and Nieto 1957) and its effect on mental disorder. He also developed a chemical reaction, the "Nieto Reaction", for the diagnosis of neurocysticercosis in the cerebrospinal fluid (Nieto 1956).

In the late 1950s, Nieto's interest turned to psychopharmacology and he was among the firsts to explore the psychopathology induced by *stropharia cubensis*, a potent species of psychedelic mushroom, whose principal active compounds are psilocybin and psilocin (Nieto 1959, 1962). In the 1960s, he contributed with his research to the treatment of epilepsy with methaminodiazepoxide (chlordiazepoxide) (Nieto, Escobar, Castro and Roldan 1960) and to the prophylactic treatment of manic-depressive psychosis with lithium carbonate (Nieto 1963, 1969). In the 1970s, he studied the effects of Prussian blue, ferric hexanocyanate ferrate, a substance in use at the time in heavy metal poisoning and in 1980, he reported his findings with the substance in schizophrenia and in the treatment of thallium, arsenic, lithium, etc. poisoning (Nieto 1980).

In 1970, Nieto was appointed head of the Mexican National Reference Center of the International Reference Center Network of Psychopharmacology of the World Health Organization. He was instrumental in setting a foundation of psychopharmacological research in Mexico and will be remembered as the beloved teacher of the first generation of psychopharmacologists in this country.

Nieto died on January 2, 1985, in Mexico City.

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April 3, 2014

Juri Saarma by Jaanus Harro

Jüri Saarma was born on October 24, 1921, in Viljandi, Estonia. He received his medical degree from the University of Tartu, in 1945. He joined the University's Department of Psychiatry as a volunteer assistant, in 1943, as a doctor and lecturer, in 1945 and was appointed as professor, in 1965. Jüri Saarma served as head of the department during 1975-1983 and also held other influential administrative positions throughout his career (Saarma 2000).

In 1952, Jüri Saarma founded a laboratory for research on higher nervous activity at the department. This and the subsequent formation of the laboratory of experimental and clinical psychopharmacology in 1967 were pivotal to the development of one of the most prolific medical research schools in the region, as this endeavor seamlessly complemented the psychopharmacological investigations of Lembit Allikmets and his disciples in the Department of Pharmacology of the University of Tartu.

In 1973, Saarma was a visiting professor at McGill University, in Montreal. He also lectured at the universities of Helsinki, Oulu, Toronto and Turku.

Jüri Saarma's early research was devoted to the effects of insulin therapy on autonomic nervous system (Saarma 1966). The laboratory he led contributed to characterization of the actions of a large variety of antipsychotic and antidepressant drugs (Saarma 1963, 1970, 1974). Saarma was an excellent teacher and superb clinician, who published a series of textbooks in Estonian and Russian. He advanced his own variant of a nosological system of psychiatric syndromes. He aimed at personalized psychiatry by developing the highly complex Tartu Psychometric Test Battery to delineate the diagnostic profile of schizophrenias, affective and anxiety disorders and to differentiate therapeutic profiles of prototype psychotropic drugs (Saarma 1976).

Jüri Saarma died on February 7, 2001 in Tartu.

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October 30, 2014.

Sydney Spector by Fridolin Sulser

Sydney Spector was born in 1923 in New York, NY. He received his PhD in 1956 from the Jefferson Medical College, Philadelphia, PA. After graduation, he joined Bernard B. Brodie's Laboratory of Chemical Pharmacology at the National Heart Institute of the National Institutes of Health (NIH). Sydney Spector was part of the Laboratory that became the Mecca of Biochemical Pharmacology and gave birth to Biological Psychiatry. His studies on monoamine oxidase (MAO) and MAO inhibitors and on the action of reserpine and biogenic amines in brain contributed significantly to the scientific basis of the heuristic catecholamine hypothesis of affective disorders.

In 1961, he started collaborating with Al Sjoerdsma and Sydney Udenfriend at the NIH. His kinetic studies on catecholamine synthesis demonstrated that the rate-limiting step in the biosynthesis of catecholamines is tyrosine hydroxylase (Levitt, Spector, Sjoerdsma and Udenfriend 1965). He then discovered α -methyltyrosine (α -MT) as an inhibitor of tyrosine hydroxylase (Spector, Sjoerdsma and Udenfriend 1965). Because of its specificity, α -MT provided researchers in psychopharmacology with an important tool for the elucidation of the mechanism of action of psychotropic drugs (e.g., the tricyclic antidepressants failed to "reverse" the reserpine-like syndrome in rats whose brain norepinephrine was selectively depleted by α MT, indicating that catecholamines were involved in the antidepressant action). These studies on catecholamines are one of the most frequently quoted papers.

In 1968, Sydney Spector moved to the Roche Institute of Molecular Biology in Nutley, New Jersey. There, after a sabbatical with Herman Eisen at Washington University, he moved into a new research area: Immunopharmacology. He provided clinicians and basic researchers with tools to measure drug levels in a quantitative way in plasma, brain tissue and cerebrospinal fluid: The "Spector Monoclonal Antibodies" to barbiturates, morphine, reserpine, desmethylimipramine (DMI), naloxone, chlorpromazine, haloperidol, etc. (Spector 1974). Then came the most exciting discovery: the discovery of endogenous morphine in brain. In meticulously designed studies, Sydney Spector demonstrated that brain morphine was endogenous in nature, located in neurons and released by depolarization (Gintzler, Lewy and Spector 1976). The potential of these studies is just beginning to be unravelled.

Sydney Spector received numerous awards for his research accomplishments, including the Paul K. Smith Award of Washington University School of Medicine, the ASPET Award for Experimental Therapeutics and the Julius Axelrod Award. In 1987, he was elected President of the American Society of Pharmacology and Experimental Therapeutics. Sydney Spector excelled in his dedication to nurturing and developing scientific talent. His scientific legacy will live on in the cadre of scientists who trained under his mentorship and subsequently established their own distinguished career all over the world, occupying leadership positions in government, universities and industry.

Sydney Spector, age 88, passed away October 26, 2012.

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March 27, 2014

Joseph Wortis by André B. Veras

Joseph Wortis was born, in 1906 in Brooklyn, New York, in the United States, and graduated in medicine, in 1932, at the University of Vienna, in Austria. He was trained in psychiatry at the Bellevue Hospital, in New York, spending 1934-1935, as a Havellock Ellis Fellow in Vienna. It was during this year that he met Manfred Sackel and became familiar with his insulin coma therapy of schizophrenia (Shorter 2011).

After returning to the United States in the mid-1930s and translating Sakel's monograph on insulin coma therapy, Karl Bowman set up an insulin ward for Wortis at Bellevue Hospital. In 1937, with the publication of their experiences on that ward in the *American Psychiatric Association Journal*, insulin coma therapy was launched in the USA (Wortis and Bowman 1937). In the same year, Wortis was part of Harold Himwich's team that was first to study and report on "brain metabolism during hypoglycemic treatment of schizophrenia" (Himwich, Bowman, Wortis and Fazekas 1937). In the five years that followed, he remained involved in studying "biochemical changes occurring in the cerebral blood" (Himwich, Bowman, Wortis and Fazekas 1939) and exploring the availability of substances, such as lactic acid and sodium pyruvate for brain metabolism during insulin coma treatment (Wortis and Goldfarb 1940). He also developed a simple method for prolonging coma (Wortis and Korr 1942).

In 1935, soon after his return from Europe, Wortis was invited by Clarence Farrar, at the time editor of the *American Psychiatric Association Journal*, to write a review article on insulin coma therapy in the Annual Reviews of Progress of the journal. Instead, Wortis wrote an "Annual Review of Progress in Physiological Treatments", which became a regular feature in the journal for about 20 years, from about 1935 to 1955 (Wortis 2011). It was in his annual review that the first reference to chlorpromazine in the English language appeared (Wortis 1954).

In the late 1950s and early '60s, Wortis explored the effect of chlorpromazine on brain metabolism, using minced rat brains with the employment of a Warburg respirometer. He observed that chlorpromazine had a biphasic effect on brain respiration, in the first phase, lasting about 16 hours, inhibiting, and in the second, lasting for about four days, enhancing it. He also noted that chlorpromazine depressed brain metabolism in the lower, and enhanced it in the higher cortical structures (Wortis and Jackim 1962).

In June 1973, Wortis became the founding editor of *Biological Psychiatry*, the journal of the Society of Biological Psychiatry. He continued in this position until 1992.

Joseph Wortis died, in 1995, at age 88 (Gelder 1995).

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July 3, 2014

**CONTROVERSIES IN THE HISTORY OF
NEUROPSYCHOPHARMACOLOGY**

**Controversies in the History of Neuropsychopharmacology
(Controversies)
Project Five
Coordinated by Barry Blackwell**

This project was launched with an Introduction by Barry Blackwell on May 30, 2013. However, only one essay (Thomas A. Ban: Conflict of interest in neuropsychopharmacology: Marketing vs. education, December 26, 2013) was posted in this project during 2013.

Thomas A. Ban: Conflict of interest in neuropsychopharmacology: Marketing vs. education

This essay by Thomas A. Ban was the first posting in Controversies in the History of Neuropsychopharmacology on December 26, 2013 (see *INHN 2013*, pp. 71-78). The following are comments and replies that ensued and were posted during 2014 as a consequence of the essay:

Comments by Barry Blackwell

The picture your essay portrays accurately and elegantly is not so much an ethical "conflict of interest" as a conflict between a homogeneous (specific) approach to drug discovery and clinical treatment versus a heterogeneous (DSM) one. I think it is a mistake to view this as a difference between "education" and "marketing" for the following reasons:

1. You omit all mention of safety and concentrate on efficacy. But the Hippocratic ideal of "First do no harm" surely applies equally to both industry and education and was the foundation of the Kefauver Amendments that set FDA policy. Risk is increased to the extent that large homogeneous populations are used to "prove" efficacy and should be of interest to both educators and industry, especially since the etiology of a side effect may have nothing to do with the mechanism of therapeutic efficacy.
2. Your thesis demands a narrow definition of who is an educator. As clinical psychopharmacology evolved, it moved from asylums, the VA and private practice to academic medical centers - the heart of medical education after the Flexner revolution. And this is where the DSM and double blind methodology flourished, precisely because they had a false aura of scientific integrity, serving as an antidote to psychoanalytic ideology. Educators are as much, perhaps more, to blame as is industry for developing and endorsing the tools that led to a heterogeneous approach. The subsequent fact that industry bribed education and its professional associations (APA, ACNP) to support the approach long after its falsehood became clear to a few wise individuals (like you) makes any distinction between "education" and "industry" dubious at best.
3. There is an extent to which making the distinction as you do dilutes the moral implications. So educators are not responsible for what industry does (even as they endorse it), while industry is only trying to make an honest profit (even as it stifles research findings, raises false hopes and kills people). Meanwhile they both foster the heterogeneous approach to clinical efficacy.

In short, I am far less concerned with what I believe to be a weak "straw man" definition of "conflict of interest" than I am about the mutual harm both "educators"

and "industry" have wrought by endorsing the heterogeneous approach to efficacy while downplaying side effects.

January 30, 2014

Reply to Barry Blackwell by Thomas A. Ban

Thank you for your comments. If the recognition that the objectives of marketing (to get a particular product prescribed to the widest possible population) and education (to guide the judicious and discriminate use of drugs) are in conflict would imply approval of illegal marketing practices, you would be correct that I “dilute moral implications“, and provide a ”straw-man definition” of “conflict of interest”. But this is not the case. I consider those practices you condemn, such as bribing, overstating benefits, covering up adverse effects of drugs, etc., just as distasteful, and even criminal, if they violate the law, as probably you do. True, I have not addressed in my essay these well-known concerns because they are quite apparent, already voiced, and rightfully attacked by many, including you. Instead, I was trying to focus attention on a less obvious and unrecognized issue. It is the excessive promotion by some educators the prescribing of psychotropic drugs to an artificially enlarged population by the replacement of prototype-based diagnoses by consensus-based diagnoses in which in some diagnoses, e.g., major depression, more patients are exposed to the risk of potential side effects than would expect to benefit from treatment. Pointing fingers at individuals or blaming industry in this situation does not help to resolve the issue. It may even distract attention from the need to develop a methodology that would allow the delineation of pharmacologically more homogeneous diagnostic populations than those currently in use and make possible a more discriminate use of psychotropic drugs

March 13, 2014

Response to Thomas Ban's reply by Barry Blackwell

The nub of our disagreement lies in your concluding assertion that "pointing fingers at individuals and blaming industry ... does not resolve the issue." On this we agree except for the implications. Blame is an impotent strategy unless it is accompanied by consequences and sanctions. If the FDA, Law courts and Congress required industry to be honest (and scrupulously scientific) and academic institutions fined or fired faculty who are well-funded false prophets, then "conflict of interest" would disappear. This is why I called your definition a "straw man" - it leads to no solution.

June 12, 2014

Comments by Jose de Leon

If one comments on the issue of conflict of interest in neuropsychopharmacology, a very “conflictive” issue, one should acknowledge his/her own conflicts and those of other discussants who are commenting.

In that spirit of openness regarding the issue of conflict of interest, I would like to acknowledge that I do not agree with all of David Healy’s writings but I usually recommend his book, *The Creation of Psychopharmacology* (Cambridge, MA: Harvard University Press, 2002) to my residents. One suspects that many neuropsychopharmacology experts might disagree with my admiration of some of Healy’s writings.

Regarding Dr. Blackwell, I have never met him in person but I am very familiar with his book, *Discoveries in Biological Psychiatry* (Lippincott, 1970), to the point of recently ordering a second copy. I know his claim to fame, the “cheese” effect associated with MAO inhibitors. I am also familiar with one of his letters on lithium prophylaxis (*Br J Psychiatry* 1971; 118: 131-2), in which he made Dr. Schou very unhappy by comparing him with a religious fanatic. In summary, I am neutral regarding Dr. Blackwell (I credit him for the cheese effect, but diminish him for criticizing Schou) besides admiring him as being one of the “elders” who started psychopharmacology.

Regarding Dr. Ban, I am afraid that I am very positively biased in a way that I may have made my words too critical. (If I were to believe in psychoanalysis, which I do not, I would accuse myself of suffering from a reactive formation in this comment.) I have never met Dr. Ban in person but I have always admired: 1) his involvement in the AMDP English version; 2) his schizophrenia treatment response studies using the Leonhard classification; and 3) his crucial role as main CINP historian. In November 2013, Dr. Ban contacted me by e-mail. Since then, we have had several wonderful e-mail and phone conversations. We discovered that among other things, we share a love for: 1) the history of psychiatry; 2) descriptive psychopathology; and 3) conceptual issues. Moreover, I have discovered he is a very nice and gentle “elder”. He impresses me as more of a “Franciscan monk” than a psychopharmacologist. I am a psychopharmacologist in my 50s; if one conducted a personality study on me and my colleagues in this age group, high mean scores in arrogance and meanness would be expected, making Dr. Ban an absolute statistical outlier.

Unfortunately, Dr. Ban’s kind nature complicates his ability to criticize conflict of interest in psychopharmacology. Lenzer and Brownlee’s comment in *BMJ* (2008; 337:206-208) entitled, “Is there an (unbiased) doctor in the house?” described corrupt doctors, using psychiatrists as an example. This is not a good thing to be known for. In this context, having Dr. Ban talk about conflict of interest is probably not a good idea; he would be naturally prone to be too soft. I am afraid that I agree 100% with Dr. Blackwell, who may have become a very nice gentleman with age but was less so in the

1970s. As Dr. Blackwell describes, I believe that Dr. Ban missed the point completely in his comment. In that sense, I found Dr. Healy's discussion on conflict of interest much more illuminating (Medical partisans? Why doctors need conflicting interests. *Aust N Z J Psychiatry* 2012; 46:704-7) despite the fact that I found some areas somewhat offensive. I have never met Dr. Healy but I suspect current psychopharmacologists deserve someone like him as a critic, instead of somebody as kind as Dr. Ban. I also found Dr. Maj's article illuminating (Financial and non-financial conflicts of interests in psychiatry. *Eur Arch Psychiatry Clin Neurosci.* 2010 Nov; 260 Suppl 2:S147-51).

March 20, 2014

Reply to Jose de Leon by Barry Blackwell

I enjoyed and appreciated Professor Jose de Leon's perceptive and (mostly) generous comments in response to my own concerning Tom Ban's posting on "Conflict of Interest in Neuropsychopharmacology". In doing so, he declared his own "conflicts of interest" towards Tom and I based on his prior knowledge of our accomplishments.

Jose expresses some ambivalence about my credibility based on a letter I wrote to the British Journal of Psychiatry 43 years ago, questioning Dr. Schou's credibility in regard to his previous research on lithium prophylaxis. We seem to have a court full of credibility issues!

The origin of that controversy stems from 1968 (46 years ago), when I had just completed residency training at the Maudsley Hospital and was working as a research fellow with Professor Michael Shepherd. We published an article (I was first author) in the Lancet, "Prophylactic Lithium: Another Therapeutic Myth?" [Lancet 1968 (1) 968-971]. This article did two things; it provided a rigorously critical analysis of Schou's study methodology (for which the Maudsley was renowned under Sir Aubrey Lewis) and it employed the same methodology to show that imipramine could produce similar results.

In 2012, (54 years later), I published my memoir, "Bits and Pieces of a Psychiatrist's Life" in which I devote 14 pages (215-229) to the topic, "Learning from Lithium". In it I state "we reached the wrong conclusion for all the right reasons" (p.220). By this I meant that over a half century of clinical practice has clearly proven Schou's claim was accurate and a great boon to the profession and our bipolar patients. What is also true, however, is that the scientific method Schou chose was seriously flawed for a variety of reasons discussed in the original Lancet article and it failed to distinguish lithium from imipramine – controversies about trial design and outcomes in bipolar disorder that continued for several decades.

I challenge Professor de Leon to resurrect and carefully read our original 1968 article, review the subsequent research and also read the appropriate section in my 2012 memoir before submitting his own contribution to the "Controversies" section of inhn.org on the subject of Prophylactic Lithium. I am confident from the tenor of his current comments that he is a fair-minded scientist and that doing so will eradicate any doubts he still has in assessing my own motives in the lithium controversy. I will be happy to provide him with a free (autographed) copy of my book.

April 24, 2014

Reply to Jose de Leon by Thomas A. Ban

Thank you very much for your comments. If conflict of interest issues could be restricted to financially motivated actions contrary to fiduciary interest, i.e., to the legal-ethical definition of the concept, I would agree with you to leave it to those currently involved with them. But this is not the case and my essay addresses a “conflict of interest” issue that has not been addressed to date, in so far as I know. It is the “conflict of interest” that arises from the “conflict” between “marketing” with the objective to get a particular psychotropic product prescribed for the widest possible population and “education” with the objective to provide a guide for the judicious and discriminate use of psychotropic drugs. Introduction of psychotropic drugs during the 1950s focused attention on the pharmacological heterogeneity within psychiatric diagnoses. To meet educational and also research objectives in neuropsychopharmacology, there was a need to resolve this heterogeneity. Yet, in keeping with marketing interests, the randomized clinical trial was adopted for the demonstration of therapeutic efficacy in pharmacologically heterogeneous diagnostic populations. There has been virtually no effort for well over half a century to develop a clinical methodology for identifying the treatment responsive subpopulations. Compromising the objective of education for marketing interests interfered with the development of neuropsychopharmacology. It also encouraged the indiscriminate use of psychotropic drugs. Addressing “conflict of interest” issues, which qualify for the legal-ethical definition of the concept, may assist in capturing crooks; whereas addressing conflict of interest issues, which arise from the conflict between marketing and education by adopting or developing a methodology that would provide pharmacologically more homogeneous diagnostic populations than current consensus-based classifications, may open the path for the development of more selective and thereby more effective psychotropic drugs.

December 11, 2014

Comments on Barry Blackwell's reply to Jose de Leon by Larry Stein

Barry Blackwell concedes that Mogens Schou was right about lithium as an effective bipolar intervention, but that Schou's methodology was wrong. I did not know Schou, but it seems obvious that he was an unusually insightful clinician with extraordinary case material. True, it was an N=1 situation, but that N=1 happened to be his brother, whom he had been trying to cure, or at least to treat, for many years. So when the brother responded to lithium, after so many failed attempts with other agents, Schou knew! Furthermore, were not the other early major psychiatric drug discoveries also serendipitous? Large double-blind clinical experiments have their place and may be fine for final confirmation, but they probably slow down and even discourage discovery. For the FDA, responsible for safety and sensitive to politics, this is not the biggest problem. Safety demands caution, but discovery requires boldness –a delicate balance.

May 15, 2014

Comments by Donald F. Klein

The discussion between Ban and Blackwell misses crucial current issues. “Conflict of interest” rose to public interest when it became apparent that Pharma publications were regularly more outcome positive than independent studies. This led to the suspicion of bias but with no way to prove it, since data were sacrosanct. Therefore, suspicion was diverted onto the basically problematic, ad hominem approach of authors declaring income sources. This miscarried repair diverted from the basic issue “Is there really data bias?”

This issue can only be met by independent data analysis at the patient level. If a therapeutic claim is made, shouldn't the data supporting that claim be available for independent analysis? Otherwise, peer review is helpless, since it only has data summaries and inferential statistics and implicit trust in their relevance and accuracy.

That is exactly the highly charged debate going on with regard to the initially forward looking policies of the European Medicines Agency. Their website yields worthwhile, detailed access to the EMA positions.

However, the move to demand public access to patient level data is now stymied in court by firms claiming that such disclosure causes economic loss. The European Ombudsman has already declared that public health issues trump questionable economic losses. Recently, it looks like EMA is backtracking. Still ambiguous regarding decisions but the concerns of Pharma may prove decisive. Stay tuned.

Ira Glick and I have also addressed these issues in our paper, Klein DF, Glick ID: Conflict of interest, journal review, and publication policy, published in *Neuropsychopharmacology*. 2008 Dec; 33 (13): 3023-6. My point is that both Ban and Blackwell could have improved their rather abstract discussions by reference to the current legal and judicial struggle for and against open access, as well as citing the various activist groups.

July 10, 2014

Reply by Barry Blackwell to Donald F. Klein's comments

I agree with Don Klein's point concerning Pharma's current stranglehold on data and the consequent absence of independent peer review to which he and Ira Glick have drawn attention.

This is certainly the contemporary focus of concern but both Tom Ban and my comments were embedded in a more historical and fundamental analysis of conflict of interest. My own focus which, while it may appear "rather abstract", goes to the roots of a problem that involves far more than industry and its latest maneuvers.

It includes trial study clinicians who relinquish their data for analysis and publication in return for money without critical oversight; academics who provide paid for endorsements of industry claims; professional and advocacy organizations that accept funding for meetings or organizational support in return for access to the public and spurious legitimacy; practicing physicians of all stripes who accept lavish dinners, golf outings and office paraphernalia in return for prescribing a company's products; journal editors who publish flawed articles and print dubious advertising claims; Presidents and Department Chairs of prestigious universities who accept million dollar grants to support faculty stipends and research with the naiveté of a Robin Hood robbing the rich to help the poor; the FDA and Congress for turning a blind eye to flawed products and over the top television advertising to the public which drown out bad news with distracting visual images. In its broadest sense conflict of interest is about how greed and money suborn scientific integrity.

Contemporary opinions about "conflict of interest" continue to debate its meaning and implications as recently as the current issue of JAMA, "Potential Conflicts of Interest for Academic Medical Center Leaders" (JAMA. 2014; 312(5): 558). My sentiments echo those of Arnold Relman, long time former editor of the *New England Journal of Medicine*, expressed in his final letter to JAMA, submitted a few short sad weeks before his death: "Academic medical centers and pharmaceutical companies are quite different social functions. The companies are obligated to maximize profit for its owners and shareholders. In contrast, AMC's have a moral commitment to serve the public interest before their own. No individual can simultaneously serve as a leader in both these institutions without compromising obligations to one or both."

While these caveats are directed to leaders at the apex of the most involved and prestigious organizations, my own concerns, expressed above, cover a wider range.

September 11, 2014

Barry Blackwell: Adumbration: A history lesson

“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)

Over 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 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 & 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 6 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 combined 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 while taking Parnate; taking a drug history in every patient admitted in such cases was mandatory but unproductive. Until, several months later, 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 flan 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 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 9 months of my original letter to the Lancet, I had collected 12 patients taking an MAOI, mostly Parnate, of whom 8 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), 4 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 & 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 & 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 twentieth century physiologists discovered it was a hypertensive agent (Dale & 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 50mm 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 MAOIs, 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 & Taylor, 1967), it was the most often prescribed and most effective of the MAOIs 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 norepinephrine, 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 influence by dosage, duration of treatment and proximity to an antecedent dose of the drug (Blackwell, Marley, Price & 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 3 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 removed an offending organ, the “nuciform sac”. The controversy surrounding this topic became the subject of a conference, convened by the Royal Society of Medicine in 1913, during

which headaches were among the offending symptoms and cheese 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, 1968 a & 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 & 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 fifteen 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 5 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 (McCable 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 tranlycypromine 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 neurotransmitter 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.

POSTSCRIPT

“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 anti-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 cyclooxygenase-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 twenty 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 rofecoxib (Vioxx) from the market. The story is told by NPR on the internet (Prakash & Valentine 2007).

In 1999, Merck, concerned that Vioxx, like other NSAIDs, might cause gastrointestinal bleeding, launched an 8000 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 \$5000 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 3 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, Massachusetts) 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 & 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 fuller discussion of "Conflict of interest" see the "Controversies" program on the INHN.Org website.

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Barry Blackwell: 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 fifty 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” belong mainly from the twentieth 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 drug to treat anxiety. 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 (1970-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 manufacture of “Carter’s Little Liver Pills.” It was their only product. Here Frank worked to develop a longer acting congener of mephenesin. This was meproamate, 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*, the novel that 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 meproamate 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).

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 (Oxford English Dictionary, “*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. This decision was based entirely on a traumatic experience caring for a pregnant woman, anxious and terrified of childbirth in the care of an obstetrician, who declined to discuss my request for a psychiatric consultation or the possibility of a Caesarian section in favor of a Pitocin drip. I sat by her bedside as she screamed through labor and then wrote a letter, published in the *Lancet* on *Human Relations in Obstetrics* (Blackwell 2012).

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. My chief resident and mentor had described, in a letter to the *Lancet*, a patient who suffered a subarachnoid hemorrhage while taking tranlylcypromine (Parnate). He drilled into me the importance of taking a drug history in such cases, knowledge that formed the impetus for my future work as a first year psychiatry resident on the MAO inhibitors and interactions with tyramine containing foods.

More 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 brainstem stimulants, keeping them alive until recovery. This study won the hospital's annual research award and the results were published (Blackwell 1964). This experience 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).

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, but after six months, due to my early work on the MAOI-cheese interaction, was promoted to the Professorial Unit at the Maudsley, where we wore white coats and worked under the eagle eye of Sir Aubrey Lewis. 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.” 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 Oxford English Dictionary.

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 (*mental or emotional strain*, OED) 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 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 an unusual study designed and carried out with my fellow resident and lifelong friend, David Taylor. In 1964, the gold standard and perhaps the only standard for clinical evaluation of a therapeutic claim was a meticulously designed, preferably double blind, controlled study with a well-crafted null hypothesis. My untidy mind thought this was slightly daft. How could one discover anything new or what was happening in the real world if you were already single-minded or certain about the outcome? Immersed in animal experiments on rats injected with MAO inhibitors and administered cheese or tyramine via a duodenal tube, I was eager to discover why my mentors were using these drugs and with what results. Perhaps such a study would generate new hypotheses. So David and I designed a study of all the patients prescribed these drugs by the five consultants working in the Maudsley outpatient clinic. We called it “An Operational Evaluation” but, in retrospect, it was a very early effectiveness study – a primitive, unfunded, CATIE study (Blackwell and Taylor 1967). Outcome was determined not by the usual diagnostic and demographic variables but by whom and how the drugs were prescribed. The enthusiasts prescribed the MAOI earlier, more often and got better results. 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 eighty five 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:

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).

Further results are pertinent; Parstelin (a combination of tranylcypromine and low dose trifluoperazine) obtained statistically better outcomes than three other MAOIs, alone and overall, the addition of a benzodiazepine improved outcomes from half to two thirds. Two thirds of patients treated with MAOI took them for only 6 months, by which time, 50% had achieved a good outcome.

At the completion of my psychiatric residency (1967), I had published over twenty 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 a fortuitous decision; though my time in the practice was brief, it was productive and educational. Not only did it broaden my horizons by exposing me to the mild and early manifestations of affective disorders in primary care but my contemporary and fellow resident, David Goldberg, 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 was 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 metaphors; feeling “rundown”, “fighting off flu”, “low blood pressure”, often coupled with requests for vitamins, iron tablets or a tonic. Closer enquiry revealed symptoms often present in both 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, B., 2011), Leo Hollister, asked about his classification of depression replies as follows, “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 comorbidity 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, J, 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.”

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 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 Merrell'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, as a consultant. A devout Catholic and father of twelve children, Frank had lived in the Vatican and served as advisor to the Pope on ethical and psychiatric matters. He was also a founding member of both the CINP and the ACNP. Frank took me under his wing and introduced me to most of the leading psychopharmacologists in America. We made presentations to the ACNP and published together (Blackwell and Ayd, 1971) on research in prison volunteers and Frank sponsored me as a member of the ACNP, in 1970. 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 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 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 (see 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. Following Frank's death, in 2005, at age 95, his wife Christine compiled and published a lifetime of his written philosophical reflections in the book *A Man of Understanding: A noted Scientist's Guide to Happiness and Success* (see my review; Blackwell, 2014b). This remarkable book contains only a single comment about Frank Berger's famous discovery. "*There are misunderstandings about tranquilizers, about what they can and cannot do, who should use them and why use them. They may make you feel normal again, able to cope again, but they are no substitute for philosophy.*" This statement is

on the book's back cover but while the pages are divided alphabetically into 60 topics, including Frank's own ideas and those of others, "Anxiety" and "Tranquilizers" are not among them.

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 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 2000 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 Chair, Maury Levine, a psychoanalyst 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, was 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 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-seventies, many such patients were also being treated, with little success, by minor tranquilizers.

The new treatment we developed evolved from David Mechanic’s 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, namely 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 tranquilizers 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 (Blackwell 1987).

“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 Lucinda 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 'alexithymia' – 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, *Psychotropic Drugs in Use Today: the Role of Diazepam in Medical Practice*, published in *JAMA* (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 1960’s had shown that diazepam was five times more potent as a tranquilizer and muscle relaxant than 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 eighteenth century, it was opium, in the nineteenth, bromides and in the early twentieth century, barbiturates. The 1960’s 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 withholders. 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 1970’s, 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, in Britain, poured fuel on the fire in a *Lancet* article titled, *Benzodiazepines; Opium of the Masses*. His subsequent *mea culpa* (Lader 1998), over twenty 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), 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 anticholinergic side effects 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.

Over 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 diagnosis or use of other psychiatric drugs.

Extensive use of antianxiety drugs might be reduced by prescribing them “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 1970’s 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 was effective in some types of anxiety disorder, this takes time, therapists are in short supply 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 drug’s 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 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 GlaxoSmithKline (\$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 twentieth 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 on) with ‘psychosomatic’ implications.

At the mid-point of the twentieth century, minor tranquillizers entered the picture at the beginning of the creative psychopharmacology era (1950-1970) 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, comorbid 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 interpret fever charts and to define ten 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 indifférence*), 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 generics 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 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 percent of patients were symptom free within six weeks at the relatively low cost of under \$1500 for an average of thirteen 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 teenagers 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 creative 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 twenty 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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October 30, 2014

Barry Blackwell: The lithium controversy: An historical autopsy

I am delighted Larry Stein has joined Jose de Leon in expressing interest and concern about aspects of an ancient controversy that may have contemporary relevance. Perhaps it is time to engage in a more detailed and complete analysis of the issues raised, many of which are dealt with in my memoir, *Bits and Pieces of a Psychiatrist's Life*, and will be cited in this essay (Blackwell 2012).

It is now almost 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 will be 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 later). 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 (Sargent 1968). Sargent'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 twentieth 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 1949, the identical year 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 (*Thioxanthines*). 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 all 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 twenty years, until the definitive studies, in 1984, by the Medical Research Council in Britain (Glen et al) and the NIMH study group in the USA (Prien et al). 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 one 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 1960's, 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. Twenty-seven 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. The "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 3 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 3 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 3 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 or testing as a hypothesis. The problem arises in how to remove this bias towards the new idea from the outcome of an investigation. Sometimes it is more difficult than others, and in my own initiation into research, I was fortunate.

As a first year resident, I became involved in the interaction of MAOI and tyramine containing foods. The first clue to the possible cause of a sometimes fatal hypertensive crisis came when a hospital pharmacist (GEF Rowe) read a letter I wrote to the *Lancet* describing the syndrome and its symptoms – predominantly a sudden severe pounding headache. He recognized and described this process in his wife on two consecutive occasions after she ate cheese; “Could there be something in the cheese?” So a fellow resident and I took an MAOI for two weeks, before eating cheese from the hospital cafeteria. Nothing happened. Nevertheless, I subsequently obtained data from twelve cases in less than 9 months, some including measures of blood pressure and one produced under experimental conditions (Blackwell 1963). Nobody suggested my interest and potential bias was artificially elevating a patient’s blood pressure or causing a headache. But the research director of the pharmaceutical company making the MAOI did write a letter to the *Lancet* stating that my conclusions were “unscientific and premature”. Within weeks, researchers at another hospital had isolated tyramine in their body fluids after eating cheese. The issue was no longer moot. Physiological and physical parameters are less subject to observer bias than emotional and behavioral outcomes but finding a glib reason to disparage either is easy.

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, in 1954, 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 over ten 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 immigrated 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 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 of 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 twenty years after our *Lancet* article, Michael Shepherd asked me to review the book, *The History of Lithium Therapy* (F.N. Johnson, Macmillan Press: 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 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.” (Grof 1998). 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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Samuel Gershon: The trazodone controversy and its potential fatal consequences

In mid-September 2013, 12 people were murdered in a rampage of violence at the Washington Navy Yard by Aaron Alexis, a US Navy veteran. As one learns from an article in the Toronto National Post by Dr. Charles Krauthammer, one month prior to the incident, Alexis had called police for protection from “three people” he thought “were following him, sending microwaves through walls, making his skin vibrate and preventing him from sleeping”; he had also twice visited during the month the emergency room of the Veterans Administration Hospital, and was prescribed “trazodone”, an “antidepressant”, known to be effective for some patients with insomnia. Dr. Krauthammer, a trained psychiatrist, who became a syndicated columnist, recognized that Alexis’ diagnosis was missed and had he been given an “antipsychotic” instead of an antidepressant, the incident could have probably been prevented.

The Washington Navy Yard incident was also noted without any details in the September issue of RxISK website’s Newsletter by Dr. David Healy, a professor of psychiatry. For Healy, the simple fact that Alexis had been on trazodone, at the time of the incident, “re-emphasized the adverse effects all prescription drugs can have and why it is so inappropriate for companies to hide effects that might have contributed to this and other tragedies.”

Trazodone, the substance under scrutiny, is an old drug. It was synthesized, in 1966, by G. Palazzo (1973) and it was primarily on the basis of pharmacological studies by Bruno Silvestrini (1967) that it was qualified as a psychotropic. The First International Symposium on Trazodone was held in Montreal, Canada, in 1973 (Ban and Silvestrini 1974).

Working with trazodone, I have not seen or experienced any such violent behavior in any patient on any dose, and there is no good evidence in its pharmacology that could explain it. Further, I concur with Dr. Krauthammer that the incidence may have been prevented by proper pharmacological treatment.

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July 31, 2014

Martin M. Katz: Onset of clinical action of antidepressants

Time of onset of clinical actions induced by antidepressants (ADs) is critical for uncovering basic mechanisms underlying their efficacy, for developing further understanding of the nature of the depressive disorder and for predicting, early in treatment, whether a drug is likely to be effective. The criticality of the onset issue has been recognized since the discovery of the new drugs. It was initially observed by Kuhn (1958) that the clinical effect in most responsive patients occurred within the first week. The controversy was then ignited by the Quitkin et al. (1984) study, showing that clinical actions of the antidepressants “lag” several weeks behind the drug’s initial effects on central neurotransmitter systems. The latter study resulted in the “onset lag” becoming a commonly accepted “textbook” notion. Conversely, the National Institute of Mental Health (NIMH) Collaborative Depression Study group (CDS) reported in Katz et al. (1987), based on a large sample of severely depressed, hospitalized patients, that in treatment-responders, significant changes in major components of the disorder occurred within the first two weeks. Neither of the two studies was aimed directly at the “onset” issue; the results on onset were the product of secondary analyses. Neither study was, therefore, able to provide a definitive answer to the question of clinical-onset. What the studies did accomplish, however, was to highlight the onset question, critical to determining sequence of drug actions and to uncovering relationships between drug-induced neurochemical and clinical actions. At the practical level, knowledge of timing also determines when the clinician can expect to see the first drug-induced changes, and whether the presence or absence of early changes can predict the nature of the patients’ clinical response to drug treatment.

Following these early reports, technical papers aimed at the methodology required to achieve definitive answers on timing appeared, and a series of independent meta-analyses targeting the problem in large drug trials, were conducted. A body of literature on the issue has been developed since 1990 that many now believe have resolved the issue.

An abbreviated set of references, including papers which analyze this area of the literature, and which report the more definitive results from the meta-analytic studies, is listed below. The list includes the published earlier exchange on the two conflicting views in the journal *Neuropsychopharmacology*.

The general consensus as it exists today can be summarized in the following statements drawn from several of these recent publications:

1. “One-third of the total (clinical) effect of selective serotonin re-uptake inhibitors (SSRIs) after six weeks of treatment is seen in the first week” (Taylor et al. 2005, based on literature review and meta-analyses).
2. “Among responders the onset of improvement occurs in more than 70% of cases within the first three weeks of treatment with an AD” (Stassen et al. 1997 based on

analysis from a multihospital study and survey of results).

3. “Drug specific types of behavioral response in the first one or two weeks of treatment with desipramine or paroxetine are highly predictive of six week outcome” (Katz et al. 2004 based on drug-placebo comparison study).

4. Absence of behavioral changes during first two to three weeks indicates little chance of positive response at outcome (Szegedi et al. 2009; Katz et al. 2011; Stassen et al. 1997 based on finding that >90% of patients who show no improvement during the first two weeks show non-response at outcome).

References:

I. Technical: How to measure onset

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3. Leon AC, Blier R, Culpepper L et al. An ideal trial to test differential onset of antidepressant effect. *J Clin Psychiatry* 2001; 62: 34-6.

4. Stassen HH, Angst J, Delini-Stula A. Time course of improvement under antidepressant treatment: a survival-analytic approach. *Eur Neuropsychopharmacol* 1993; 3: 127-35.

II. Clinical Studies and Reviews

1. Kuhn R. The treatment of depressive states with G22355 (imipramine hydrochloride). *American Journal of Psychiatry* 1958; 115: 459-64.

2. Quitkin F M, Rabkin JG, Ross D, Stewart JW. Identification of true drug response to antidepressant. *Arch Gen Psychiatry* 1984; 41: 782-6.

3. Katz MM, Koslow SH, Maas JW, Frazer A, Bowden CL, Casper R, Croughan J, Kocsis J, Redmond E. The timing, specificity, and clinical prediction of tricyclic drug effects in depression. *Psychol Med* 1987; 17: 297-309.

4. Stassen HH, Angst J, Delini-Stula A. Delayed onset of action of antidepressant drugs? Survey of recent results. *Eur Psychiatry* 1997; 12: 166-76.
5. Katz MM, Tekell J, Bowden CL, Brannan S, Houston JP, Berman N, Frazer A. Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression. *Neuropsychopharmacology* 2004; 29: 566-79.
6. Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. Early onset of SSRI antidepressants: Systematic review and meta-analysis. 2006; 63: 1217-23.
7. Posternak MA, Zimmerman MD. Is there a delay in the antidepressant effect? A meta-analysis. *J Clin Psychiatry* 2005; 66: 148-58.
8. Papakostas GI, Perlis RH, Scalia MJ. A meta-analysis of early sustained response rates between antidepressants and placebo for the treatment of major depressive disorder. *J Clinical Psychopharmacol* 2006; 26: 56-60.
9. Robinson DS. Antidepressant drugs: Evidence for onset of therapeutic effect. *Primary Psychiatry* 2007; 14: 21-3.
10. Machado-Vieira R, Luckinbaugh DA, Manji HK, Zarate CA. Rapid onset of antidepressant action: a new paradigm in the research and treatment of major depressive disorder. *J Clin Psychiatry* 2008; 69: 946-58.
11. Szegedi A, Jansen WT, van Wugenburg AP. Early improvement in the first two weeks as predictors of treatment outcome in patients with major depressive disorder: a meta-analysis including 6,562 patients. *J Clin Psychiatry* 2009; 70: 344-53.
12. Katz MM, Berman N, Bowden CL, Frazer A. The componential approach enhances the effectiveness of 2-week trials of new antidepressants. *J Clin Psychopharmacology* 2011; 37: 193-218.

III. Earlier Controversy: Conflicting Views on the Evidence

Can the effects of antidepressants be observed in the first two weeks of treatment?

Quitkin et al. *Neuropsychopharmacology* 1996; 15: 390-4.

Katz MM et al. *Neuropsychopharmacology* 1997; 17:110-1.

January 9, 2014

Comments by Donald F. Klein

Martin Katz stated in the Controversy section of INHN that Fred Quitkin started a controversy by claiming that the clinical actions of antidepressants lag several weeks behind the drug's initial effects on the CNS. It might be helpful to recall the background of that particular study (Quitkin et al., 1984).

Each of 185 patients were administered weekly Global Improvement Scores, while receiving placebo or medication double-blind. The question was whether there was some trajectory peculiar to drug treatment. It seemed simplest to dichotomize these scores, to either zeroes or ones. This meant frank remission or unimportant symptomatology without dysfunction was rated zero, and all other scores, rated one. Since there were five weeks of scoring during treatment, there were 32 conceivable patterns of consecutive ones and zeros.

Remarkably, certain patterns never appeared in the placebo group, but were relatively common during drug treatment. Further, they were markedly similar to each other. Within this group, each string was initiated by a zero, at any week, and was also rated zero for all subsequent weeks. The only exception was that this series never started at week one. There were patients whose initial score was zero but these inevitably went downhill. We were quite pleased with this result, since it confirmed our clinical impressions - especially the persistence of benefit.

Note that this is overstated by Katz, who cites, the "Quitkin et al. (1984) study showing that clinical actions of the antidepressants 'lag' several weeks behind the drug's initial effects on central neurotransmitter systems".

What is the subtext here? We guess that a certain model of pathophysiology and repair of neural functioning during depression is at stake. It was discovered that imipramine rapidly blocks the synaptic reuptake mechanism, delaying the exit of the neurotransmitters from the synaptic cleft. It was initially assumed that this excessive synaptic stimulus would relieve the brain of the functional decrement that underlay depression. (It was never quite clear why the excess neurotransmitter did not lead to receptor desensitization. Inhibitory afferent autoceptors were not part of the machinery yet). It followed that the antidepressant effect should be very rapid since the hypothesis was that the neurotransmitter deficit was directly manifested as depression. This fit well with simplistic advertising that strongly implied that a depression was due to a neurotransmitter deficit so that you had norepinephrine and serotonin depressions, as well as norepinephrine and serotonergic therapies.

If there was a lag between drug administration and antidepressant effect, it conceptually demoted these neurotransmitters into being, at best, the first domino initiating a complex cascade involving who knows what.

Strangely this heuristic question relating the initial impact of medication to eventual

clinical repair has gotten twisted into studies arguing for a quick medication effect, as if that corrected some misapprehension Quitkin had generated. After all, Quitkin had not claimed a “several week delay” was necessary.

The supposed opinion difference regarding onset gap has been further twisted to rest upon whether it can be shown that there is statistically significant drug superiority to placebo within the first week.

Now we can get into a highly technical, mathematical exposition concerning the power that would allow detection of a small drug - placebo difference at week one, the necessity for a multisite study, the increase in diagnostic error, deterioration of reliability, etc. However, fortunately, all of that is completely unnecessary.

Even if it were true that under some circumstances medication was substantially better than placebo, during the first week of administration, it is certainly not the usual situation.

The majority of drug responsive patients, even in all the cited studies that Katz believes affirms his position, achieve remission after several weeks - just as Quitkin et al. affirmed. The heuristic question has been answered - the gap exists. The immediate effects of antidepressants on neurons are insufficient for understanding the process of recovery.

Perhaps there are practical issues that hinge on whether there is an early therapeutic response or not. Katz has made three suggestions that depend upon the supposed ability of a small improvement during the first two weeks being highly related to a good eventual outcome. Further, if during the first two weeks there is not even slight evidence of improvement, it is extremely unlikely that this treatment will work. Therefore, switching treatments is a real option early during an unsatisfactory treatment. Also, since early response is so closely tied to the eventual outcome, there is no reason why the clinical trial cannot be radically shortened to say two and one half weeks, and enormous savings incurred.

One strange aspect of these studies is the lack of inclusion of a placebo group in these analyses, which are essentially within drug group predictive analyses. This, of course, is highly problematic. Further, the numerical basis for many claims in this area is often obscure. We are fortunate that Katz has provided relevant data in Katz et al. (2011).

TABLE 1. Predictive Accuracy of 2-Week Improvement Values: Percentage of Correct Component Predictions at Treatment Outcome (Modified)
Desipramine (n = 26) Paroxetine (n =24)

	TP	TN	C	TP	TN	C
Depressed mood	62	100	68	58	89	71
Anxiety	55	33	52	25	100	43
Motor retardation	76	100	80	40	64	52
Hostility	53	63	56	46	88	62
Anx-Agit	69	67	68	33	91	67
DM-MR	67	100	72	64	80	52
Hamilton total	64	50	62	64	90	75

Table 1 is a direct transcript of the text, removing significance signs.
TP is the proportion of $\geq .5$ outcomes correctly called.
TN is the proportion of $< .5$ outcomes correctly called.
C=TP +TN

From the above data, the basic 2 X 2 table relating early small ($\geq 20\%$) gains to later findings of substantial ($\geq 50\%$) gain can be definitively reconstructed. [See Table 2](#) (without rounding to nearest integer) or [Table 2a](#).

TABLE 2. Basic 2X2 table relating early small ($>20\%$) gains to later substantial ($>50\%$) gains in mood measures without rounding to nearest integer.

PAROXETINE			PREDICTION UNDERSHOOT		DMI			PREDICTION OVER SHOOT	
	$\geq 20\%$	$< 20\%$	POS OUTCOMES	NEG OUTCOMES		$\geq 50\%$	$< 50\%$	POS OUTCOMES	NEG OUTCOMES
DEP MOOD	$\geq 20\%$	0.08 1.11 5.19	0.34	0.47	DEP MOOD	$\geq 20\%$	13.57 0.00 13.57	0.38	2.03
	$< 20\%$	5.85 8.96 14.81 13.94 10.06 24.00				$< 20\%$	8.32 4.11 12.43 21.89 4.11 26.00		
ANX	$\geq 20\%$	4.58 0.00 4.56	0.75	2.58	ANX	$\geq 20\%$	12.35 2.38 14.73	0.34	2.18
	$< 20\%$	13.68 5.76 19.44 18.24 5.76 24.00				$< 20\%$	10.10 1.17 11.27 22.45 3.55 26.00		
MOT RET	$\geq 20\%$	4.80 4.32 9.12	0.24	0.24	MOT RET	$\geq 20\%$	16.47 0.00 16.47	0.24	1.20
	$< 20\%$	7.20 7.68 14.88 12.00 12.00 24.00				$< 20\%$	5.20 4.33 9.53 21.67 4.33 26.00		
HOST	$\geq 20\%$	6.52 1.18 7.70	0.46	0.66	HOST	$\geq 20\%$	9.65 2.89 12.53	0.31	0.73
	$< 20\%$	7.05 8.65 16.30 14.17 9.83 24.00				$< 20\%$	8.35 4.01 13.47 18.20 7.80 26.00		
ANX AGIT	$\geq 20\%$	3.28 1.27 4.54	0.54	0.38	ANX AGIT	$\geq 20\%$	8.97 4.29 13.26	-0.02	-0.02
	$< 20\%$	6.65 12.80 19.46 9.93 14.07 24.00				$< 20\%$	4.09 8.71 12.74 13.00 13.00 26.00		
DM-R	$\geq 20\%$	8.64 2.10 10.74	0.20	0.26	DM-R	$\geq 20\%$	14.78 0.00 14.78	0.33	1.85
	$< 20\%$	4.86 8.40 13.26 13.50 10.50 24.00				$< 20\%$	7.28 3.94 11.22 22.06 3.94 26.00		
HAM TOT	$\geq 20\%$	8.86 1.02 9.88	0.29	0.39	HAM TOT	$\geq 20\%$	14.26 1.86 16.12	0.28	1.66
	$< 20\%$	4.98 9.14 14.12 13.85 10.15 24.00				$< 20\%$	8.02 1.86 9.88 22.29 4.71 26.00		

TABLE 2a. Basic 2X2 table relating early small (>20%) gains to later substantial (>50%) gains in mood measures rounding to nearest integer.

PAROXETINE				DMI					
VARIABLE		>=50%	<50%		>=50%	<50%			
DEP MOOD	>=20%	8,08	1,11	9,19	DEP MOOD	>=20%	13,57	0	13,57
	<20%	5,85	8,96	14,81		<20%	8,32	4,11	12,43
COL SUM			10,06	24	COL SUM		21,89	4,11	26
ANX	>=20%	4,56	0	4,56	ANX	>=20%	12,35	2,38	14,73
	<20%	13,68	5,76	19,44		<20%	10,1	1,17	11,27
COL SUM		18,24	5,76	24	COL SUM		22,45	3,55	26
MOT RET	>=20%	4,8	4,32	9,12	MOT RET	>=20%	16,47	0	16,47
	<20%	7,2	7,68	14,88		<20%	5,2	4,33	9,53
COL SUM		12	12	24	COL SUM		21,67	4,33	26
HOST	>=20%	6,52	1,18	7,7	HOST	>=20%	9,65	2,89	12,53
	<20%	7,65	8,65	16,3		<20%	8,55	4,91	13,47
COL SUM		14,17	9,83	24	COL SUM		18,2	7,8	26
ANX AGIT	>=20%	3,28	1,27	4,54	ANX AGIT	>=20%	8,97	4,29	13,26
	<20%	6,65	12,8	19,46		<20%	4,03	8,71	12,74
COL SUM		9,93	14,07	24	COL SUM		13	13	26
DM-R	>=20%	8,64	2,1	10,74	DM-R	>=20%	14,78	0	14,78
	<20%	4,86	8,4	13,26		<20%	7,28	3,94	11,22
COL SUM		13,5	10,5	24	COL SUM		22,06	3,94	26
HAM TOT	>=20%	8,86	1,02	9,88	HAM TOT	>=20%	14,26	1,86	16,12
	<20%	4,98	9,14	14,12		<20%	8,02	1,86	9,88
COL SUM		13,85	10,15	24	COL SUM		22,29	3,71	26

Several findings then appear. The positive outcome proportions predicted are substantially less than those obtained. The proportion of subjects who do well is usually about 30% greater than the proportion predicted to do well. The claim that those who do well initially, will also do well later, is true but misleading. The undershoot invalidates the claim for a short clinical trial since the drug would be undervalued.

The claim that if the patient does poorly on all initial variables, they will do poorly later, cannot be evaluated since only individual variables are available. However, for these individual variables, the chance of doing well despite poor initial performance is substantial for paroxetine but looks even better for DMI. Here the drugs are predictively devalued, which casts doubt on the value of early treatment change, given initial disappointment. It would also seem likely that those who do poorly on all

initial variables are only a small proportion of the sample and may also be quite atypical on other grounds.

It should be noted that a focus on the immediate effects of medication on neurotransmitters yields a supposedly promising, fairly narrow, pathway to the development of agents that will improve the process, and thereby, act therapeutically. On the other hand, if one has to deal with a complex cascade, our theory of depression becomes quite obscure and the directions that one can take in pursuing remediation appear all too many. As the development of antidepressants has been almost exclusively a matter of serendipity, it is plain that understanding pathophysiology and repair is still well beyond us. It seems unlikely that translational thrashing about, using limited current knowledge, will prove profitable.

To sum up, Katz has made a heuristic and several practical suggestions relating to clinical trials. These suggestions are not supported by his data. Similar re-analyses of data, whose current analyses claim to support Katz's views, would be very worthwhile.

References:

Katz MM, Berman N, Bowden CL, Frazer A. The componential approach enhances the effectiveness of 2-week trials of new antidepressants. *J Clin Psychopharmacology* 2011; 37: 193-218.

Quitkin FM, Rabkin JG, Ross D, Stewart JW. Identification of true drug response to antidepressants. Use of pattern analysis. *Arch Gen Psych* 1984; 44: 259-64.

February 20, 2014

Martin M. Katz: Component-specific vs. diagnosis-specific clinical trial in depression

Research indicates that the central neurotransmitter systems most highly associated with the pathophysiology of depression are the serotonin and noradrenergic systems. Basic research links these systems with the regulation of different behaviors and moods, serotonin with impulsive aggression and anxiety and norepinephrine with “arousal” and motor activity (Katz and Maas 1994).

Antidepressant drugs have been found to be equally effective for anxiety, phobic and obsessive-compulsive disorders. Thus, their therapeutic effects in depression are more likely based on the changes they effect in the components of anxiety, hostility and motor functioning, components not necessarily in the “core” pathology of depression. The most effective methods for measuring drug actions are methods for measuring the principal behavioral, mood and cognitive components of the disorder (Katz, Bowden and Frazer 2010).

In 2013, in his book, *Depression and Drugs: The Neurobehavioral Structure of a Psychological Storm*, Katz reports findings that the “component specific clinical trial” model is more informative about the range of drug actions and suggests that it is “more efficient” than the traditional, diagnosis-centered clinical trial model, in the study of depression.

References:

Katz MM. Depression and Drugs. The Neurobehavioral Structure of a Psychological Storm. Berlin: Springer; 2013, pp. 61-71.

Katz MM, Bowden CL, Frazer A. Rethinking depression and the actions of antidepressants: Uncovering the links between the neural and behavioral elements. *J Affective Disorders* 2010; 120: 16-23.

Katz MM, Maas JW. Psychopharmacology and the etiology of psychopathological states: Are we looking in the right way? *Neuropsychopharmacology* 1994; 10: 139-44.

February 27, 2014

Martin M. Katz: Multivantaged vs. conventional assessment method

The Multivantaged Assessment Method (MVAM) of clinical evaluation was adopted to describe an approach to the measurement of the diverse patterns of psychopathology displayed in the various forms of mental disorder and to measure changes in the patterns before and after treatment. The approach assumes that most disorders are comprised of dimensions, components of disturbed affect, behavior and cognition, which interact to define their structure. It is further assumed that no one vehicle of measurement, whether the observations of the experts or the subject's report of the experience, is capable of fully or accurately describing the complex nature or the critical facets of the disorder. Because of the many ways that the disorder can be expressed, it requires more than one "vantage" on its expression to achieve accurate measurement. To achieve a more "objective" picture of the behavior, the multivantaged assessment method (MVAM) involves combining such perspectives to achieve a consensual estimate of the type and severity of the behavior or emotion at issue. In the case of serious emotional disorders such as "depression", a collection of valid clinical methods are recommended exemplifying the multivantaged approach to measure the facets and severity of the disorder and to assess the impact of various interventions on the disorder. This is called the "Multivantaged Assessment Method". The currently established method for clinical trials of antidepressants relies on a sole method of evaluation, the Hamilton Depression Scale, which measures change in overall severity of the disorder, but which provides no further validated information on the specific clinical actions of the experimental drug. The MVAM was designed to extend and enhance the conventional assessment by providing, in addition to a measure of overall severity, a profile of the clinical and psychological actions of the trial treatment.

FURTHER ELABORATION OF MVAM

Accurate measurement of the various facets of psychopathology cannot be accomplished through any one vehicle of measurement. It requires combining the observational ratings, the report of the subject, and the subject's performance on cognitive and psychomotor tasks. The term, "multivantaged", takes on important meaning, particularly where observation of behavior and physical expression is concerned, since it is known that the perspectives of observers of emotionally charged incidents can vary widely. The author of the term refers in his book (Katz 2013) to the "Rashomon" effect, best demonstrated in a classic Japanese film, showing how the emotional aspects seriously influence the perceptions of different observers, but in different ways. To achieve a more "objective" picture of the behavior, the MVAM involves combining such perspectives to achieve a consensual estimate of the type and severity of the behavior or emotion at issue. In the case of serious emotional disorders, such as "depression", a collection of valid psychological methods are recommended exemplifying the MVAM, to measure the facets and severity of the disorder and to assess the impact of various interventions on the disorder. These methods include the Schedule for Affective Disorders and Schizophrenia-Change version (SADS-C), the Hamilton Depression Rating Scale, the Symptom Checklist (SCL-90), NIMH Mood

Scale, Video Interview Behavior Evaluation scales (VIBES) and selected psychomotor tests. This is called the “Multivantaged Assessment Method”.

References:

Katz MM, Koslow SH, Berman N, Secunda S, Maas JW, Casper R, Kocsis J, Stokes P. A multivantaged approach to the measurement of behavioral and affect states for clinical and psychobiological research. *Psychological Reports Monograph* 1984; 55, 619-73.

Katz MM, Houston JP, Brannan S, Bowden CL, Berman N, Swann A, Frazer A. A multivantaged behavioral method for measuring onset and sequence of the clinical actions of antidepressants. *International Journal of Neuropsychopharmacology* 2004; 7: 471-9.

Katz MM. *Depression and Drugs: The Neurobehavioral Structure of a Psychological Storm*. New York: Springer; 2013.

May 22, 2014

**BOOKS IN NEUROPSYCHOPHARMACOLOGY:
CLASSIC AND CURRENT**

Introduction by Carlos Morra

I am writing to introduce myself as the new coordinato for BOOKS (Project 8). I am succeeding Samuel Gershon, who launched this project, in which we post reviews of classic and recent books relevant to neuropsychopharmacology. I will continue to work with Tom Ban, but contrary to my predecessor, who worked alone, my intention is to have a small team working with me. I am pleased to inform you that Walter Brown has accepted my invitation to join our team and help us with editing and other matters.

We intend to shorten the time between receipt of communication and posting by a new arrangement that will allow us to post at least one communication weekly on the website and we intend to facilitate discussion on posted communications by inviting colleagues to comment on them. Furthermore, by reviewing the “books” listed in our project from time to time, we intend to also provide educational material that we hope will help place the information covered in these books in a historical perspective.

I am looking forward to working with you on this project and I would like to take this opportunity to invite you to comment on any of the books already posted on our website and to participate in ongoing interactions related to these books. I invite you to send me directly (carlosmorra@hotmail.com) “reviews” of books you have written or edited for consideration for posting. Please ascertain that in your submission you follow our standard format (Contents and Author’s/Editor’s/Reviewer’s Comment).

September 18, 2014

**Jules Angst: Classification and Prediction of Outcome of Depression (1974) –
reviewed by Jules Angst
F.K. SchattauerVerlag, Stuttgart/New York (313 pages)**

INFORMATION ON CONTENTS: This book reports the proceedings of a symposium with the same title, chaired by Jules Angst. It was held in Schloss Reinhartshausen on the Rhine from September 23 to 26, 1973 and was the 8th of the Symposia Medica, organized and published by Hoechst AG. The material is organized according to the symposium's five sessions, with discussion either after the single presentations or at the end of the session. The book opens with the editor's (chairman's) Introductory Remarks and ends with his Conclusions.

In Session One, two classifications of depressive disorders are presented, one by P. Kielholz and the other by M. Roth, R. Garside and C. Gurney. These are followed by a review of R.E. Kendell, P.Pichot and M. Von Cronach on the *Differences in concepts of affective disorders amongst European psychiatrists*.

Session Two deals with the "unipolar" and "bipolar" distinction. Two papers are presented: in one, G.L. Klerman reviews, *Theoretical and empirical issues in establishing the validity of nosological concepts in the classification of affective disorders* and in the other, C. Perris addresses, *The heuristic value of a distinction between bipolar and unipolar affective disorder*.

In Session Three, the emphasis shifts from diagnosis and classification to the course, long-term treatment, prophylaxis and prognosis of depression. Six papers are presented in this session: following W.E. Bunney's Introduction, A. J. Coppen's review of *The morbidity of recurrent affective disorder and the effect of long-term lithium treatment*, and R.F. Prien's *Observations from a multihospital collaborative study and Prophylactic treatment of recurrent depression*, three papers deal with the course of depression. In the first, B. Davies and T. Blashki present findings from their study comparing the course of depression in general practice and in hospital. In the second, P. Grof, J. Angst and T. Haines discuss practical issues related to the clinical course of depression, and in the third, T.Tashev gives an account of *The course and prognosis of depression on the basis of 652 deceased patients*.

Pharmacokinetics and the dependence of the effect of treatment on variables related to the metabolism of the drug used in treatment are dealt with in Session Four, which comprises eight papers. In the first, G.D. Burrows, B.A.Scoogins and B. Davies present findings on a relationship between *Plasma nortriptyline and clinical response*, and in the second, M. Asberg, P. Kragh-Sorensen, L. Bertillson, B. Cronholm, Ch. Eggert-Hansen, F. Sjöquist and J.R. Tuck discuss methodological problems in *Studies of relationship between plasma level and clinical effects of nortriptyline*. In the third paper, A.J. Coppen provides support for the *Clinical significance of plasma levels of tricyclic antidepressant drugs (amitriptyline and nortriptyline) in the treatment of depression*, and in the fourth, N.S. Kline and T.B. Cooper propose, *Methods for the*

evaluation and interpretation of drug (doxepin) plasma levels. In the remaining four papers, B.K. Shah and N.S. Kline draw attention to, *Data analysis problems in the area of clinical response, plasma levels and kinetic parameters*; J. Angst and R. Rothweiler report on, *Blood levels and clinical effects of maprotiline*; O.J. Rafaelsen and L.F. Gram review, *Interactions between antidepressants and other psychopharmacaca*; and D.S. Robinson, A. Nies, C.L. Ravaris, J.O. Ives and R. Lamborn present findings on the *Relation to depressive typology and blood platelet MAO inhibition* in the treatment response to MAO inhibitors.

Finally, in Session Five, M. Hamilton discusses *Prediction of response to ECT in depressive illness*; D.F. Klein introduces the diagnostic concept of *Endgenomorphic depression*; and J. R. Wittenborn presents findings supporting the hypothesis of depression-prone personality (in women).

As mentioned, the volume includes the participants' discussion of the presentations. In alphabetical order the 33 participants, including the speakers, were: J. Angst, W.E. Bunney, A. Coppen, B. Davies, R.R. Fieve, P. Grof, M. Hamilton, K. Heinrich, H. Helmchen, H. Hippus, R.E. Kendell, P. Kielholz, L.G. Kiloh, D.F. Klein, G.L. Klerman, N.S. Kline, P. Kragh-Sorensen, J. Levine, N. Matussek, M. Perel, C. Perris, R.F. Prien, O.J. Rafaelsen, D.S. Robinson, M. Roth, R. Rubovits, N. Sartorius, M. Schou, B.K. Shah, G.M. Simpson, T. Tashev, G. Winokur and J.R. Wittenborn.

EDITOR'S COMMENT: This symposium was an example of the fruitfulness of gathering together experts from different continents, which at the time posed very considerable organizational and financial difficulties.

September 25, 2014

Thomas A. Ban: Conditioning and Psychiatry (1964) – reviewed by Thomas A. Ban
Aldine, Chicago (244 pages)

INFORMATION ON CONTENTS: The monograph is divided into five parts. The first, *From Overt Behavior to Neurophysiology*, begins with an account of the developments that lead from Bidder and Schmidt's observation, in the mid-19th century that teasing a dog with food led to gastric secretion, to Pavlov and his associates' demonstration of the same, in the early years of the 20th century by sham-feeding of an esophagotomized dog. It continues by a description of the 31 experiments in Pavlov's laboratories, in which the behavioral properties of this "psychic secretion" that was to be referred to as, "conditional reflex", were defined; and then, Pavlov's conceptualization of his findings in his "brain model" are discussed. It concludes with information about the role of various cerebral structures in conditional reflex formation and of the electroencephalographic correlates of conditioning. In the second part, *Pavlovian Psychiatry*, Pavlov's conceptualization of his findings is extended from his "brain model" to psychiatric symptoms (general psychopathology) and diagnoses (clinical psychopathology) with implications for treatment. Special considerations are given to "sleep therapy". In the third, *From Animal Experiments to Human Test Procedures*, the emphasis shifts from Pavlov's original experiments in animals and deductions, to the study of conditional reflex variables in normal subjects and patients with mental pathology. The different conditioning techniques used in human, e.g. galvanic skin resistance, plethysmography and defensive finger withdrawal are described, and procedures for studying anomalies (qualitative and quantitative) in conditional reflex variables (properties) are presented. In part four, findings in diagnostic and therapeutic (including pharmacological) research with the employment of conditioning are reviewed. The monograph ends with a "critical evaluation" in part five, in which Pavlovian conditioning is examined in the light of learning theory and the information on "classical" conditioning is complemented with information on "instrumental" or "operant" conditioning. By the time of the 1960s, when this monograph was written, Pavlov's deductions became of historical interest only, while both classical and instrumental conditioning were increasingly used in behavioral pharmacological research and in the study of mental pathology in psychiatric patients with different diagnoses and the effect of treatment with psychotropic drugs.

AUTHOR'S STATEMENT: This monograph is based on my "thesis" to fulfill requirements for obtaining a diploma in psychiatry at McGill University (Montreal, Canada), in 1960. It was first published, in 1964, in Chicago by Aldine Publishing Company with a Foreword by W. Horsley Gantt, at the time one of the last living direct disciples of Pavlov. It was reprinted two years later, in 1966, for distribution in the UK by George Allen & Unwin Limited in London. In 2008, Transaction Publishers rendered it available again under the title, *Conditioning Behavior and Psychiatry*.

January 30, 2014

**Thomas A. Ban: Schizophrenia: A Psychopharmacological Approach (1972) –
reviewed by Thomas A. Ban
Charles C. Thomas, Springfield (134 pages)**

INFORMATION ON CONTENTS: This monograph is divided into five chapters including: Introduction (chapter 1), Drugs (chapter 2), Patients (chapter 3), Schizophrenias (chapter 4), and Concluding Remarks (chapter 5). They are preceded by a Preface and Acknowledgments and followed by a Bibliography and two Indexes (Authors and Subjects). In Chapter 1 (Introduction), a brief, enthusiastic account is given for the introduction of chlorpromazine, the first neuroleptic, in the treatment of schizophrenia around the world, from 1952 to 1955. In Chapter 2 (Drugs), the neuroleptics, introduced in the treatment of schizophrenia during the 18 subsequent years and their clinical effects, are discussed. During these years, the number of neuroleptics rapidly grew and by 1970, there were over 20 neuroleptics in clinical use, with more or less equal overall therapeutic efficacy but without any clearly defined differential therapeutic indications.

In Chapter 3 (Patients), the emphasis shifts from drugs, to the effect of neuroleptics on patients. Thus, information is presented on the effects of neuroleptic treatment on psychiatric hospitalization (population changes, duration of hospital stay, prevention of hospitalization) and on the behavior of patients in hospital; the effects of neuroleptics are compared to other available treatments (psychotherapies, physical therapies) for schizophrenia; and the changes affected by neuroleptics on the different psychiatric syndromes and psychopathological symptoms encountered in schizophrenic patients, are discussed. A special section is dedicated to the characterization of schizophrenic patients in the community, the primary site of treatment after the introduction of neuroleptics.

Finally, in Chapter 4 (Schizophrenias), the effects of neuroleptics on the schizophrenias are examined. In view of the pharmacological heterogeneity of responsiveness and the recognition that a patient refractory to treatment with one drug may respond to another, the possibility is raised of using pharmacological responsiveness for classifying patients. However, attempts for grouping patients in a clinically meaningful way on the basis of their pharmacological responsiveness, have invariably failed. The same applies to the testing of biochemical hypotheses of schizophrenia, which have emerged during the 1960s and 1970s, such as anomalies of tryptophan metabolism, phenylalanine metabolism and transmethylation.

The monograph concludes with the sobering statement that in spite of all the changes which have been encountered during the two decades after the introduction of chlorpromazine, schizophrenia in all civilized countries have remained a major public health problem; neuroleptics have helped but did not cure schizophrenic patients. Yet, the introduction of neuroleptics brought about a new way of thinking about schizophrenia that has generated testable biochemical hypotheses about the pathomechanism of the illness.

AUTHOR'S COMMENTS: This monograph is an expansion of my Hoffman-LaRoche Lecture at the Clarke Institute of Psychiatry, presented on January 15, 1971. It is also available in Japanese in Hayime Kazamatsuri's translation.

May 29, 2014

**Thomas A. Ban: Recent Advances in the Biology of Schizophrenia (1973) –
reviewed by Thomas A. Ban
Charles C. Thomas, Springfield (119 pages)**

INFORMATION ON CONTENTS: This monograph is divided into two parts (Part One: Etiology and Part Two: Treatment) and eleven chapters: Descriptive Classifications (chapter 1), Conditional Reflex Correlates (chapter 2), Neurophysiological Findings (chapter 3), Biochemical Hypotheses (chapter 4), Genetic Factors (chapter 5), Present Status (chapter 6), Pharmacotherapy with Neuroleptics (chapter 7), Prediction of Neuroleptic Effects (chapter 8), Neuroleptics Versus Other Treatments (chapter 9), Other Pharmacological Treatments (chapter 10) and Present Status (chapter 11). Chapter 1 is preceded by a Preface and Acknowledgements, and chapter 11 is followed by Concluding Remarks, Bibliography and two Indexes (Authors and Subjects).

In Chapter 1 (Descriptive Classifications), the controversy of the 1950s is addressed, namely whether the different forms of schizophrenia are progressive stages of one generalized disorder of the brain, as perceived by Klaus Conrad, or distinct, localized disorders of the brain, affecting one or more neurological system simultaneously, as perceived by Karl Kleist and Karl Leonhard.

In Chapter 2 (Conditional Reflex Correlates), findings with conditioning test batteries, in the 1960s, are presented. It was noted that in 1962, Christian Astrup described the differential conditional reflex profiles of Carl Schneider's three different forms of "acute schizophrenia" and Karl Leonhard's eighteen different forms/sub-forms of "chronic schizophrenia".

In Chapter 3 (Neurophysiological Findings), findings with surface electroencephalography (EEG) and averaged evoked potentials (AEP) are discussed. It was noted that no "exclusive EEG signs" of schizophrenia could be identified, but there was a relative excess of fast activity (EEG) and a greater variability in auditory evoked potentials (AEP) in schizophrenic patients than in normal subjects.

In Chapter 4 (Biochemical Hypotheses), numerous biochemical theories and speculations about the "cause" of schizophrenia are reviewed. They include: (1) normal products of phenylalanine metabolism, such as norepinephrine (NE) and dopamine (DA); (2) abnormal products of phenylalanine metabolism, such as 3, 4-dimethoxyphenylethylamine (DMPEA), adrenochrome and adrenolutin; (3) psychotoxic dimethylated products of tryptophan metabolism, such as bufotenin and dimethyltryptamine; (4) transmethylation, i.e., the metabolic process itself; (5) nicotinamide adenine dinucleotide deficiency; and (6) a plasma protein factor that interferes with the conversion of glucose into pyruvic acid (in vitro). While none of these hypotheses were borne out by evidence, supportive of the role of dopamine in the pathogenesis of schizophrenia, or at least, in the pathogenesis of some of the symptoms or syndromes of schizophrenia, are findings which indicate that all neuroleptics with

demonstrated therapeutic efficacy in the treatment of schizophrenia antagonize some of the central effects of dopamine.

In Chapter 5 (Genetic Factors), the role of heredity in schizophrenia is examined. Findings in traditional twin studies, in studies in adopted away children of schizophrenic parents and in biochemical genetic investigations are reviewed. It was noted that in Pollin's biochemical genetic investigation, urinary excretion levels of catecholamines were higher in both members of monozygotic twins discordant for schizophrenia than in normal subjects, whereas 17-OH steroid levels were higher only in the schizophrenic members of the pairs.

In Chapter 6 (Present Status), Part One concludes as follows: "There is sufficient evidence to believe that schizophrenia is a genetic disease, although neither the nature of the genetic disturbance, nor the mode of transmission has been demonstrated to date. Similarly, there is sufficient evidence to believe that there are biochemical disturbances in schizophrenia, but whether they are the causes or the effects of the psychopathological manifestations is not known".

In the remaining five chapters, the focus in the monograph shifts from "etiology" to "treatment".

In Chapter 7 (Pharmacotherapy with Neuroleptics), the status of pharmacotherapy in schizophrenia with neuroleptics in the early 1970s is reviewed; findings related to neuroleptic dose requirements in the treatment of schizophrenia are presented; and information on neuroleptic dependence, toxicity and teratogenicity is discussed.

In Chapter 8 (Predictors of Neuroleptic Effects), possible predictors of treatment outcome with neuroleptics are examined, without success of identifying any. It was noted that early relapse after neuroleptic withdrawal might be predicted by the absence of a startle response.

In Chapter 9 (Neuroleptics Versus Other Treatments), findings in efficacy studies in the treatment of schizophrenia in which neuroleptics are compared with other non-pharmacological treatments are reviewed. It is shown that neuroleptics compare favorably in the treatment of schizophrenia to milieu therapy, psychotherapy, insulin coma and electroshock.

In Chapter 10 (Other Pharmacological Treatments), findings in the Canadian Mental Health Association Collaborative Studies on nicotinic acid in the treatment of schizophrenia are reviewed. It is shown that treatment with nicotinic acid in megadoses has no therapeutic effect in schizophrenia.

In Chapter 11 (Present Status), Part Two (Treatment) concludes as follows: "In the foregoing modern biological treatments of schizophrenia were reviewed. It was noted

that since the introduction of chlorpromazine at least 50 neuroleptics had been clinically investigated. While most of these new drugs...are successful pharmacological agents in the control of psychopathological manifestations of schizophrenia, the fact remains that neuroleptics may alter the course but cannot cure the disease”.

AUTHOR’S COMMENTS: This monograph is an expansion of my presentation at a Symposium on Schizophrenia, organized and chaired by Nathan S. Kline that was held at the Arizona State Hospital in Phoenix, on November 12, 1971. The material was also presented in my lectures on the Biology of Schizophrenia to postgraduate students in psychiatry, McGill University, at the Douglas Hospital in Verdun, Quebec, during the month of January, 1972.

June 5, 2014

**Thomas A. Ban and Heinz E. Lehmann: Experimental Approaches to Psychiatric Diagnosis (1971) – reviewed by Thomas A. Ban
Charles C. Thomas, Springfield (119 pages)**

INFORMATION ON CONTENTS: This monograph is based on experiments carried out from 1962 to 1968 in the Research Department of Douglas Hospital, a psychiatric inpatient facility in Verdun, Quebec, Canada. The studies employed different methods of assessment, the findings of which complemented the clinical information on patients. The book is divided into five chapters: I. Experimental Approaches to Geriatric Diagnosis; II. Psychometric Tests and Psychiatric Diagnosis; III. Conditioning and Psychiatric Diagnosis; IV. Psychopharmacology and Psychiatric Diagnosis; and V. Direction of Future Research: A Comprehensive Test Battery. The monograph opens with the authors' Preface (and Acknowledgments) and closes with the authors' Concluding Remarks (and a Name and Subject Index).

Chapter I (Experimental Approaches to Geriatric Diagnosis) is based on a study with 107 geriatric patients, in which prediction of treatment outcome with six drugs (methylphenidate, meprobamate, amitriptyline, thioridazine, nicotinic acid and fluoxymeterine) was compared in diagnostic subpopulations derived by psychopathological symptom clusters (arousal, mood, affectivity, integration and organicity, based on the Modified Verdun Target Symptom Rating Scale), psychometric test performance (tapping speed, auditory reaction time, critical flicker fusion frequency, word association time, digit span forward, digit span backward and counting test) and psychopharmacological load tests (normal saline, 10 mg of methamphetamine, 250 mg of sodium amobarbital and the inhalation of a 95% oxygen and 5% carbon dioxide mixture).

Chapter II (Psychometric tests and psychiatric diagnosis) is based on three studies in which the psychometric correlates of psychiatric diagnosis were studied with 14 tests measuring 19 variables with the employment of a specially devised psychometric test battery. The battery includes three "afferent-perceptual tests" (Critical Flicker Fusion Frequency, Chromatic After-Image Disappearance Limen and Achromatic Spiral After Effect); six "central-intrinsic tests", measuring nine variables (Word Association Speed, Digit Span Forward and Backward, Stroop Color Word Test Time and Error, Time Estimation Production and Reproduction, Paired Associate Learning and Ideational Recall); and five "efferent-psychomotor tests" measuring seven variables (Simple Auditory Reaction Time, Tapping Speed, Track Tracer Test Time and Error, Cancellation Test Time and Error and Body Sway Test). The first study included 10 normal subjects and twenty patients (chronic schizophrenia, chronic organic brain syndrome); the second, 129 patients (personality disorders, psychoneurotic reactions, manic-depressive manic reactions, acute schizophrenic reactions, chronic schizophrenic reactions and organic brain syndromes); and the third, 20 normal subjects and 100 patients (personality disorders, neurotic depression, psychotic depression, schizophrenia, organic brain syndrome).

Chapter III (Conditioning and psychiatric diagnosis) is based on two sets of studies, in which conditional reflex (CR) variables were used in the differentiation among psychiatric diagnostic groups (2 studies) and in the differentiation of subpopulations within diagnoses (2 studies). In all these studies, the Verdun Conditioning Procedure (VCP), based on measuring responses to stimuli by changes in galvanic skin resistance (GSR), was employed. The VCP provides information in terms of latency and amplitude in eight psychophysiological functions: startle response, orienting reflex, unconditional reflex, acquisition, extinction, disinhibition, differentiation, and reversal. The population of the first set of two studies focused on differentiation among diagnostic groups. One of these studies was conducted in 20 normal subjects and 100 psychiatric patients (personality disorder, neurotic depression, psychotic depression, schizophrenia, chronic organic brain syndrome) and the other, in 15 normal subjects and 25 psychiatric patients (schizophrenia, chronic organic brain syndrome). The population of the second set of two studies focused on differentiation within diagnoses. One of these studies was conducted in 7 normal subjects and 21 depressed (neurotic, endogenous and schizophrenic) patients; and the other, in 147 schizophrenic patients belonging to six different forms of schizophrenia: paranoid, simple, undifferentiated, hebephrenic, catatonic and schizoaffective.

Chapter IV (Psychopharmacology and psychiatric diagnosis) is based on four studies, from which three were conducted in patients with a diagnosis of schizophrenia and one in patients with the diagnosis of depression. In all these studies, prediction of treatment outcome was explored with the employment of the VCP00: in the first three studies to neuroleptics and in the fourth to tricyclic antidepressants. The four studies included a total of 105 patients: 30 patients in the first study, 20 in the second, 30 in the third and 25 in the fourth.

Findings in the studies reviewed in chapter IV generated hypotheses but did not identify any predictive variable of treatment outcome. Hence, in Chapter V (Direction of future work: A comprehensive test battery), the last chapter of this monograph, the VCP, was extended to measure CR variables, also with the employment of other than the GSR technique. They included variables derived with the employment of "salivary secretion", "eyelid closure", "defensive finger withdrawal", Ivanov-Smolenskys's technique for studying the transmission from first (non-verbal) to second (verbal) signal system activity, a modification of Astrup's "word association technique" for studying second signal system activity, and Lehmann's "active avoidance technique" for studying voluntary interference with a skeletomuscular CR. Chapter V also includes findings of a test-retest reliability study of the extended procedure conducted in 30 normal subjects and 30 chronic psychotic patients.

AUHOR'S COMMENT: In this monograph, three different "approaches" (pharmacological loads, psychometric performance tests and conditioning procedures), are presented for complementing clinical (subjective) diagnostic information with experimental (objective) measures. The underlying assumption was that employment of these approaches might provide cues for the detection of the pathophysiology

(pathology in the processing of signals) in the diagnoses studied and/or help to identify pharmacologically more homogenous psychiatric populations than derived by clinical diagnoses.

November 20, 2014

Thomas A. Ban and Bruno Silvestrini: Proceedings of the First International Symposium on Trazodone (1974) – reviewed by Thomas A. Ban S.Karger, Basel/Munchen/Paris/London/New York/Sydney (210 pages)

INFORMATION ON CONTENTS: This volume is the Proceedings of the First International Symposium on Trazodone, held in Montreal (Quebec, Canada), on October 5 and 6, 1973. The book opens with an Introduction by Bruno Silvestrini, the pharmacologist who was instrumental in developing the drug; and is divided into seven sections, corresponding with the sessions of the symposium. The first section, composed of three papers, deals with the pharmacology of the substance, including possible mechanism of action; the second, of five papers, with biochemistry, including drug metabolism; and the third, of two papers with toxicology, including, teratogenicity and placental transfer. In the fourth section, the emphasis shifts from preclinical to clinical information. It includes two papers: a review of literature on the substance and a report on comprehensive clinical studies with trazodone in Canada, in patients with organic brain syndrome, schizophrenia, and depression. In the fifth section, findings in two clinical studies with trazodone, one conducted in Italy and the other in Japan, in the treatment of neurosis are discussed. The sixth section is dedicated to seven free communications from which in one, findings in psychophysiological studies, in another, in polygraphic sleep studies, and in the third, in electroencephalographic studies are reported. The remaining four clinical papers in this section include a special study with trazodone in patients with total or partial ventilatory insufficiency and a study of intravenous administration of the substance to patients with severe depression. The final, seventh session, has three papers that include two clinical studies with trazodone in depression and the concluding remarks to the symposium. The volume is complemented with a subject index and a list of participants of the symposium. The 25 papers included in the volume were authored by 49 contributors. They are (in alphabetical order): A. Agnoli, M.M. Amin, F. Antonelli, L. Angelucci, T.A. Ban, M. Blenim, J. R. Boissier, B. Bolle, M. Casacchia, G.B. Cassano, P. Castrogiovanni, G. Coccagna, L. Conti, M. De Gregorio, A. Dionisio, E.F. Domino, F. Engelsman, C. Fazio, J. Fichelle, T. Fujita, S. Garattini, G.L. Gatti, M. Guazzelli, G. Gunella, A. Kitahara, V.G., Longo, A. Lopez-Zanon, C. Maggini, S. Miura, R. Montanini, A. Muratorio, N.P.V. Nair, S. Ohtake, F. Pariante, D. Peruzu, M. Piccione, E. Portmann-Cristesco, K.F. Rivett, J. Saarma, D. Schwarz, Y. Shibahara, A. Scotti de Carolis, B. Silvestrini, P. Soubrie, Y. Suzuki, T. Takahashi, Y. Yamanishi, C. Yamato, and K. Yamatsu.

EDITOR'S STATEMENT: Trazodone, 2-(3-(4-(3-chlorophenyl)piperazin-1-yl)propyl-1-2-4-triazolo(4,3-a)pyridin-3(2H)one hydrochloride, is a phenylpiperazine derivative of triazolopyridine. It was synthesized, in 1966, by Palazzo in the laboratories of F. Angelini, an Italian pharmaceutical company. The initial pharmacological studies with the substance were carried out by Silvestrini, in the mid-1960s. In 1968, preliminary data on trazodone were presented at a session of a meeting of the World Psychiatric Association in Milan (Italy), co-chaired by Thomas Ban. He became interested in the substance and conducted with his associates a series of studies with it in the early years of the 1970s, in the Division of Psychopharmacology, McGill University, Montreal

(Canada). Findings of these studies provided further substantiation of the therapeutic potential of trazodone, in depressive manifestations. The accumulating clinical information on trazodone, in the early 1970s, was first reviewed at a round table discussion, in June 1972, in Amsterdam (The Netherlands). The international symposium, the proceedings of which are presented in this volume, was held in 1973, about one year later.

February 27, 2014

Per Bech: Clinical Psychometrics (2012) – reviewed by Per Bech
Wiley-Blackwell, John Wiley & Sons, Ltd, Oxford (202 pages)

This book review by Per Bech was first posted in Books in Neuropsychopharmacology: Classics and Current on July 11, 2013 (see *INHN 2013*, pp. 129-130). The following interactions are comments and replies that ensued and were posted during 2014 as a consequence of this book review:

Reply to Donald F. Klein by Per Bech

When reviewing my *Clinical Psychometrics*, Donald F. Klein recalls the massive criticism put forth by psychoanalysts against measurement-based therapies. With reference to the randomized double-blind trials introduced in the 1950's in clinical medicine, the psychoanalysts found it a meaningless procedure to use rating scales in psychiatry; adding up very different symptoms to give a total score was considered impossible.

When the Danish statistician Georg Rasch introduced his Item Response Theory (IRT) model in the 1960's, he used the term "specific objectivity" as a general scientific principle in trials of antidepressants when comparing patients from baseline to endpoint by rating scales that fulfilled his criteria of unidimensionality. As outlined by Klein, the Rasch model for specific objectivity is based on Guttman's model of scalability, which implies that scorings on lower prevalence items presupposes scorings on higher prevalence items.

Klein refers to his "widely unnoticed" paper from 1963, in which he demonstrates the great discrepancy between global judgment of change and factor-analytically derived rating scales in placebo-controlled clinical trials of antidepressants or antipsychotics. This is actually a problem of transferability, which is the degree to which a scale continues to measure the same thing psychologically across the different rating occasions during a clinical trial. Responsiveness to change is not a separate dimension, but an aspect of validity for which factor analysis is not able to test. However, because item difficulty is a parameter in the Rasch model, the same difference between two levels of depressive states will be given in the Rasch confirmed rating scales whether the individual item covers mild, moderate or severe depression. This is crucial for measuring changes in placebo-controlled trials of antidepressants or antipsychotics.

It is on the other hand important to point out that Rasch himself was always very careful to examine the nature of the items that did not fulfill his model of measurement. Klein's chapter from 2001 on causal thinking for objective psychiatric diagnostic criteria actually includes the Rasch reasoning in clinical psychometrics. We need to have a clinically based observation about the dimension we are examining before the psychometric analysis is performed. This holds both for dimensions of depression severity like Klein's 1963 paper and for predictors of clinical response. The sub-

syndrome of panic attacks within anxiety disorder as a predictor of the response to imipramine is such an example (Klein DF, *Psychopharmacology* 1964; 5: 397-408). Another is the sub-syndrome of atypical depression within major depression. In this case, increased appetite and hypersomnia are symptoms that are both excluded from the Rasch model of depression severity, but both have predictive validity when showing the superiority of phenelzine over imipramine.

This subsyndromal distinction of atypical depression has not been captured in the antidepressant trials performed over the past decades by the industry because the goal of these placebo-controlled trials is primarily to obtain FDA marketing approval. As concluded by Klein, the group average outcomes on more or less validated ratings scales in these FDA oriented trials do not determine which patients actually require medication for a positive response. We are forced by the fact of more and more patients with treatment-resistant depression to prevent this development by an early recognition of specific sub-syndromes. It is to be hoped that this specific issue will be discussed in more detail in this INHN framework.

January 16, 2014

Response by Donald F. Klein to Per Bech and Martin M. Katz

Katz's comments are useful in clarifying issues. For instance, he states regarding factor analysis, "it was because we first sought measures of the facets of psychopathology".

I do not think that factor analysis can effectively resolve mixtures. That has been a major problem for statistical diagnosis from Lazarsfeld to Meehl. I refer to this problem in my first text. Bech appears to agree, "We are forced more and more (to)...an early recognition of specific sub-syndromes".

Bech also states, "Responsiveness to change is not a separate dimension, but an aspect of validity which factor analysis is not able to test for. However, because item difficulty is a parameter in the Rasch model, the same difference between two levels of depressive states will be given in the Rasch confirmed rating scales whether the individual item covers mild, moderate or severe depression".

I would appreciate it if Bech could refer me to studies where differences in Rasch scores provided effective comparative measures. A comparison to standard techniques, such as ANCOVA, would be valuable.

Katz agrees that, "Separating the placebo from the drug effect in a patient is an important problem" and that currently we cannot distinguish patients who require medication from those who got better while on placebo. However his suggestion, "utilizing 'early response' to treatment as a predictor,...an approach that can help reopen the issue", seems to have the same problem with mixtures as factor analysis.

I would appreciate knowing the views of Katz and Bech about "intensive analysis" as such an approach. If it succeeds in isolating patients who require a medication to maintain gains, it seems a step towards homogeneity. Using a number of medications, that seem to differ in their proposed mechanisms of action, might further elicit subsyndromes--although it may require very large samples.

Katz states, correctly, that scales loaded with items that respond differentially to drug A and placebo, might fail in a study of drug B. However, if therapeutic drug action requires a normalizing interaction with the dysfunction underlying the manifest disorder--then if on this loaded scale, drug A works but drug B does not--but drug B has been shown effective, using a different scale-- I believe this amounts to a mixture reduction.

March 27, 2014

Questions regarding Donald F. Klein's response by Martin M. Katz

In trying to respond to your critique regarding whether factor analysis or the Rasch approach can resolve the “mixture” problem, I find it unclear about what meaning of “mixture” you are using in this context. Are you asking, e.g, whether the wide range of symptoms that we observe in depression is the result of a mixture of the underlying syndromes of major depressive and generalized anxiety disorders, as against in the other case, the results of the interaction of independent dimensions uncovered through factor analysis?

Also, on a related issue, what do you mean by “intensive analysis”?

It would be useful if you could clarify these concepts so that I can try to provide an intelligible reply. One problem in regard to discussing the mixture issue may be the several meanings we encounter in psychometrics for factor analysis. When using Hotelling's principal components, I would restate that of the factor analytic techniques involved, principal components is characterized as a strictly mathematical approach, based on deriving dimensions generated by the intercorrelations of the factored variables, with investigators confined to minimal interpretation, i.e., interpreting the meaning underlying the most highly “loaded” variables of an extracted component. Factor analysis, in general, in psychometrics can, however, take several forms, several of the techniques relying more heavily on the investigator's choice of the form and on his interpretations at several stages of the procedure. So that the role of factor analysis in relation to the mixture problem may differ as a function of the specific factor analytic approach referred to.

April 17, 2014

Answers by Donald F. Klein to Martin M. Katz's questions

Marty Katz sensibly raises a central problem in scientific discussion. A word may derive its precise meaning from a particular mathematical or well defined psychological context. However, in verbal discussion there can be semantic slippage so that terms are misused because in a different context they are now inappropriate.

Katz gives examples, "One problem in regard to discussing the mixture issue may be the several meanings we encounter in psychometrics for factor analysis. When using Hotelling's principal components, I would restate that of the factor analytic techniques involved, principal components is characterized as a strictly mathematical approach, based on deriving dimensions generated by the inter-correlations of the factored variables, inappropriately requires no maintenance investigators confined to minimal interpretation, i.e., interpreting the meaning underlying the most highly "loaded" variables of an extracted component."

However, each loaded variable is a composite of correlated variables, each with a somewhat ambiguous label. Labeling the composite is not due to "minimal interpretation". Rather, it affords ample grounds for disagreement and misunderstanding.

Katz continues, "Factor analysis, in general, in psychometrics can, however, take several forms, several of the techniques relying more heavily on the investigator's choice of the form and on his interpretations at several stages of the procedure".

"I find it unclear about what meaning of "mixture" you are using in this context. Are you asking, e.g., whether the wide range of symptoms that we observe in depression, is the result of a mixture of the underlying syndromes of major depressive and generalized anxiety disorders, as against in the other case, the results of the interaction of independent dimensions, uncovered through factor analysis?"

Also a good example of communication difficulty, Katz clearly raises the mixture issue, "whether the wide range of symptoms....are due to a mixture of the underlying syndromes...as compared to...the results of the interaction of independent dimensions, uncovered through factor analysis?"

I do not understand this last clause. Can dimensions be independent, but nevertheless have interactions? How can we resolve this? My general conclusion is that a complex verbal statement is best illuminated by a simple concrete example. I believe Katz is arguing that some form of factor analysis would produce results equivalent to a model of latent categories. An example would help.

Katz asks what is meant by inclusive design. This fits very well with the mixture model discussion. The term "mixture" is well defined within modern statistical analysis.

Muthen, in his online notes states: “M plus Class Notes Analyzing Data: Latent Class Other Mixture Models. Mixture models are measurement models that use observed variables as indicators of one or more latent categorical (diagnostic) variables. One way to think about mixture models is that one is attempting to identify subsets or ‘classes’ of observations within the observed data. The latent variable (classes) is categorical, but the indicators may be either categorical or continuous”.

It is often unclear how to model the relationship of outcome to baseline data. For instance, in the 1950’s, NIMH and the VA hoped that multiple regression analysis might find different treatment relevant diagnoses within an overall diagnosis by using outcome as a validity criterion. Unfortunately, these promising investigations failed on replication and the approach was abandoned.

Perhaps this was due to the heterogeneity of treatment outcome. This remained unclear in such studies. For instance, a study might find that 60% of medication-treated patients remitted, whereas only 30% of those on placebo did so. Given statistical significance, this was sharp evidence, sufficient for the FDA, that the medication was causally effective. However, identifying the responders who required medication for benefit had not been solved.

In 1967, J. B. Chassan extensively discussed the issue of how to identify drug responders in “Research Design in Clinical Psychology and Psychiatry” (The Century Psychology Series). However, this concern fell out of fashion, probably because the FDA sufficient successes of the parallel group extensive model design made it seem trivial.

Chassan’s ideas were revived and extended (Klein D.F.: Causal Thinking for Objective Psychiatric Diagnostic Criteria: A Programmatic Approach in Therapeutic Context, in the monograph, *Causality and Psychopathology: Finding the Determinants of Disorders and their Cures*, Eds. Patrick Shrout, Katherine Keyes, Katherine Ornstein, American Psychopathological Association, 2010).

Chassan recommended “intensive design”, that is repeated periods of intervening and non-intervening, judging whether benefit synchronized with intervention. This concept suggests a different clinical trials design. Openly treat all relevant patients with the study medication program, titrating for optimal dose. Patients, who clearly did not respond to treatment, are set aside. Responders would be divided randomly into two double blind groups; either to be weaned onto placebo or to remain on medication. All would be closely followed, double blind, for defined signs of worsening. Sufficient worsening would restart medication. Those who both worsened on placebo substitution and then improved on blind medication retreatment are very likely specific drug responders. In contrast, those switched to placebo, who continued to do well, would probably not be specific medication responders.

A higher worsening rate among those switched to placebo than those maintained on medication would be clear evidence of medication efficacy, quite comparable to the inference established by the parallel groups, extensive design.

But better, the intensive design dissects the initial latent mixture into three response specific categories: likely medication specific responders, likely non-specific responders and non-responders. Each group's meaningful outcome homogeneity, as well as increased heterogeneity between groups, may illuminate the drug's specific benefit on pathophysiology.

April 24, 2014

Response to Donald F. Klein's answers to Martin M. Katz's questions by Martin M. Katz

Don Klein cites a valid concern about “semantic slippage” when moving from one context to another with various statistical approaches. So, he believes that despite the selection of the most mathematically based factor analysis technique, principal components, there is “ample grounds for disagreement” about the extent of interpretation involved. Although it can be true that “each loaded variable is a composite of correlated variables, each with....an ambiguous label”, it is also true that with certain techniques, the labels or items involved can be unambiguous and straightforward in content.

In support of my earlier statement that interpretation was minimal with the principal components procedure, I was referring to such examples generated from observational and self-reported mood inventories as “depressed mood-motor retardation”. That title was for a component from our own work, that had in its high loading clusters such items as “looks sad”, “reports feeling down”, “blue”, “motor movements slowed down”, etc., where the additional variables in the component add reliability but no further conceptual complexity to the component. Nevertheless, the dimensions derived with principal components can get somewhat more complicated in concept, so he has a basis for requiring more attention to the degree of interpretation involved in any example, even of this type.

He then questions in regard to the mixture issue, “Can dimensions be independent but nevertheless have interactions?” To answer this query, one has to step back and examine how the “dimension” is derived. It is originally composed of parts that are shown to be highly linked, with each part having a similar pattern of relationships with other variables that may be part of other dimensions. For example, despite forming the parts of the “anxiety-agitation-somatization” dimension in our work, we note that each part has its own pattern of relationships with variables that make up the composition of other independent dimensions, e.g., anxiety, in itself, a component of psychopathology across most all mental disorders, is known from many studies to correlate significantly (>0.50) with “depressed mood” and with “hostility” (>0.40), items representative of other dimensions. The opportunities for interaction of key parts of different independent dimensions are, therefore, multiple. That is what we found in our studies and was elaborated on in the “Depression and Drugs” book.

The interactions in those studies were clear and led to the “opposed emotional states” hypothesis. We believe that the interactions of these states helped to explain, in great part, the psychological turmoil and general stress undergone by the patient. Note that there was no attempt with the principal components analysis to “produce results equivalent to a model of latent categories”. The aim in that study was not to uncover new “diagnoses”, new subcategories of illness, but to identify and describe the dimensions of psychopathology that structure the “major depressive disorder”.

Klein provides an interesting discussion of Chassen's intensive research design. It reminds us that earlier there were alternative approaches to the currently established model for clinical trials. It is a much more satisfying approach to drug evaluation for the experienced investigator than the mechanical quality associated with the current established model, which relies less on the expert, more on the trained rater. This alternative approach was not taken up by many and is now rarely used because of the intense monitoring and the expertise required of the clinical investigators in the conduct of such studies. He also notes that we were still unable to predict response to any of the drug classes, i.e., which patients respond to which drugs. Despite its scientific advantages, the expense to conduct the intensive trial makes the current established model look more feasible and more modest in its overall costs. Others have advanced ideas to improve the current model.

The Depression book provides another alternative, also applied in earlier trials. The "componential" model of antidepressant clinical trials includes the use of the established trial's Hamilton Depression Rating method for evaluating overall "efficacy", but goes further to profile the specific clinical and psychological actions of the experimental drug. The latter step, which requires little additional expense greatly expands the amount of information that can be retrieved from the study of a new treatment, and makes possible the uncovering of actions that although not applicable to the target disorder, may uncover drug actions that are applicable in the treatment of mental disorders, other than depression, e.g., anxiety or phobic disorders. The "intensive design" has a distinct place in the clinical evaluation of new drugs. It still, however, does not achieve what is even more essential when carrying out a major drug trial, that is, the uncovering and quantifying of the specific clinical and psychological actions of the new drug, something that none of the current approaches, including the established model endorsed by the FDA, make a serious attempt to accomplish.

June 5, 2014

Reply to Donald Klein's response by Per Bech

Two very important issues are raised by Donald F. Klein in our dialogue based on my *Clinical Psychometrics*, namely the recognition of sub-syndromes in major depression and the dimension of severity on which the clinical effect is measured in trials of antidepressants.

The research question concerning sub-syndromes is: "On what basis may the experienced psychiatrist say that this person has a type of depressive illness for which a specific treatment is needed?" The research question about the measurement of clinical effect is: "Which symptoms may the experienced psychiatrist assemble when making a global assessment of depression severity?"

We have previously answered the second question (Bech, Gram et al. 1975) and identified the following Hamilton items used by experienced psychiatrists: Depressed mood, work and interest, general somatics (fatigability), psychic anxiety, guilt feelings, and psychomotor retardation (HAM-D6). Using Rasch analysis, we showed that this rank order was maintained from week to week in trials of antidepressants (Bech, Allerup et al. 1984, Licht, Qvitzau et al. 2005, Bech, Allerup et al. 2014).

In our re-analysis of the STAR*D study, we showed that the remission rate for Level 1 on citalopram with the HAM-D6 was 45% (HAM-D6 < 4) versus 36% on the HAM-D17 (HAM-D17 < 7), $P < 0.01$ (Ostergaard, Bech et al. 2014). On Level 2 in the STAR*D study, using HAM-D6 but not using HAM-D17, we showed that bupropion was significantly superior to buspirone as citalopram augmentation in non-responders from Level 1 (Bech, Fava et al. 2011). When demonstrating dose-response relationship of antidepressants, we found HAM-D6 superior to HAM-D17 (Bech 2010).

Concerning the other research question on sub-syndromes, use of factor analysis is appropriate to classify the sub-types without any basic measurement operation. Thus, the universe of symptoms behind DSM-5 major depression can indeed be combined in many different ways (Ostergaard, Jensen et al. Dec 2011). Sub-syndromes such as atypical depression (hyperphagia and hypersomnia), apathetic depression (tiredness, lack of interests, concentration problems, insomnia) have been identified by principal component analyses. In such sub-syndromes the Rasch model's requirement of rank ordering or item difficulty is beyond the scope of the psychometric analysis. Here it is the confirmative validity of the items that is in focus.

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May 29, 2014

**Samuel Gershon and Baron Shopsin, editors: Lithium Its Role in Psychiatric Research and Treatment (1973) – reviewed by Samuel Gershon
Plenum Press, New York (358 pages)**

INFORMATION ON CONTENTS: The material in this book is organized into 16 chapters. In the first, a “narrative account” is given about the discovery and uses (nonmedical and medical) of lithium, with special reference to its use in psychiatry; and in the second, the chemistry and biochemistry of the substance is reviewed. These two introductory chapters are followed by seven chapters on the pharmacology of the substance from which the first (chapter three) deals with “lithium absorption, distribution, renal handling, and effect on body electrolytes”, the second (chapter four) with lithium’s effect on “biogenic amines” (catecholamines and indoleamines), and the third (chapter five) with its effect on cyclic adenosine monophosphate (AMP), membrane transport and cholinergic mechanisms. Included under “pharmacology” are chapters on the “neurophysiology” (chapter six), “toxicology” (chapter seven), “teratology” (chapter eight) and “biology” (chapter nine) of lithium. There is a separate chapter (chapter ten), dedicated to “lithium preparations, dosage, and control”. The book culminates in six clinical chapters, from which in the first (chapter eleven) “clinical and epidemiological aspects” of affective disorders are presented, and in the second, third, fourth and fifth (chapters twelve, thirteen, fourteen and fifteen) findings in clinical studies with lithium in “mania”, “depression”, “recurrent endogenous affective disorders” (prophylactic and maintenance treatment), and in “other psychiatric disorders” are discussed. The book concludes with chapter sixteen in an “overview” of therapeutic and prophylactic trials with lithium in psychiatric patients. The 21 chapters are authored by 21 contributors (alphabetically): Leslie Baer, James E. Barrett, John M. Davis, Michael H. Ebert, Khaled El-Yousef, Ronald R. Fieve, Eitan Friedman, Samuel Gershon, Michael D. Goldfield, Frederick K. Goodwin, David S. Janowsky, Gerald L. Klerman, Nathan S. Kline, J. Mendels, Joseph J. Schildkraut, Mogens Schou, Baron Shopsin, Iver S. Small, Joyce G. Small, Morton R. Weinstein, and E.J.P. Williams.

EDITOR’S STATEMENT: This book, published in 1973, 40 years ago, was the first textbook on lithium therapy and research. It was edited by Samuel Gershon, MD, and Baron Shopsin, MD; but it included important contributions from the whole group that made up Gershon’s Neuropsychopharmacology Research Unit in the department of psychiatry, New York University School of Medicine. It also included findings of lithium research conducted by members of the Unit in collaboration with members of other departments of the University. There was participation from medicine and endocrinology in studying kidney function, thyroid function and the strange response of leucocytosis that had no untoward effects but was posited eventually, as a treatment for low white blood cell count associated with cancer treatment. A series of studies were undertaken with neurology. Dr. Gordon Johnson, a research fellow from Australia with Gershon’s Unit, was primarily responsible for these studies and particularly for some interesting electroencephalography studies, which could detect early onset of toxicity. The Unit already had set up a Lithium Clinic, which treated outpatients and provided the follow up for discharged inpatients. In the early 1970s, there was a burgeoning interest in using lithium therapy, so this text was an attempt to provide some of the

available information on findings in treatment and research with the substance to that date. Editors felt that it contributed to generation of interest for using lithium by clinicians. We are pleasantly surprised that this may indeed be the case, as it has been reprinted twice and the latest reprint was in 2013.

January 30, 2014

**Lothar B. Kalinowsky and Paul Hoch: Shock Treatments and Other Somatic Procedures in Psychiatry (1946) – reviewed by Carlos Morra
Grune & Stratton, New York (294 pages)**

CONTENT: This book is divided into eight chapters, preceded by Nolan D.C. Lewis' *Introduction* and authors' *Preface*. To set the stage for their review of the status of physical therapies, the authors present an overview of *Historical Development* of organic treatments in psychiatry. It includes bloodletting, emetics, purgatives, removal of the clitoris, turpentine oil produced abscess, sulfosin-induced fever, etc.

The three central chapters of this book are devoted to physical therapies. In chapter two, the status of *Insulin Shock Treatment* is reviewed in terms of indications, contraindications, complications, and prognostic indicators. In chapter three, a similar review of *The Convulsive Therapies* are divided into pharmacologically induced (camphor, metrazol) and electrically induced convulsive treatments (ECT). And in chapter three, the status of *Combined Insulin-Convulsive Treatments* is presented.

In chapter five, the focus shifts from “physical therapies” to *Other Somatic Nonsurgical Treatments and Their Relation to Shock Treatments*, such as Sodium Amytal, Benzedrine, Dilantin, Continuous Sleep, Fever Therapy, Nitrogen Inhalation, Vascular Shock, Faradic Shock, Refrigeration Therapy and Electric Narcosis. These treatments are perceived as alternative therapies to ECT, or modifiers of its effectiveness, or safety. A special chapter (chapter six) is dedicated to *Prefrontal Lobotomy and Its Relationship to Shock Therapy*, in which the authors argue that with the availability of effective physical therapies, surgical interventions, such as lobotomy, have no longer a place in the treatment of psychiatric disorders. Finally, in the concluding chapter (chapter seven), *Theoretical Considerations*, is a discussion of the mechanism of action of ECT, from psychological to biological.

REVIEWER'S STATEMENT: The authors were particularly attracted by ECT. Yet they recognized in their conclusions that they are “treating empirically disorders whose etiology is unknown with shock treatments whose action is also shrouded in mystery”.

December 25, 2014

**Martin M. Katz: Depression and Drugs: The Neurobehavioral Structure of a Psychological Storm (2013) – reviewed by Martin M. Katz
Springer International: New York (92 pages)**

This book review by Martin M. Katz was first posted in Books in Neuropsychopharmacology: Classics and Current on August 8, 2013 (see *INHN 2013*, pp. 138-139). The following interactions are comments and replies that ensued and were posted during 2014 as a consequence of this book review:

Introductory Comment by Donald F. Klein

Martin Katz' early entry into clinical psychopharmacology, his career at NIMH, his collaboration with Jim Maas in the ambitious National Institute of Mental Health (NIMH) Collaborative Psychobiology of Depression Program, followed by the Texas Study, provides the industrious background for this book.

Katz recognizes that therapeutic drug mechanisms remain unclear and that drug discovery efforts by pharmaceutical companies have stalled. He believes that his collaborative studies provide a way out of these doldrums.

Katz states, "In this book I describe the research approach, and the new findings that led to: (1) identifying the major mood, cognitive, and behavioral components of the multifaceted depressed state; (2) uncovering the dimensional structure of the disorder; (3) further elaboration of the psychological turmoil that defines the experiential state of depression; (4) proposing a new theory about its conflictual nature detailing the interaction of neurochemistry and behavior which comprise the state; and (5) describing the impact of the antidepressant (AD) drugs on behavior and chemistry, that is, the drug-specific actions on behavior, and the onset and sequence of clinical actions that precede recovery".

This would be a remarkable accomplishment for a 92 page book.

However, this reviewer found it problematic attempting to comment on the book because he could not clearly understand some of the text and he did not agree with some of the contents. Since clarification that is not clear and exposition of disagreements is of general interest, it was agreed that instead of making one general comment, the reviewer will present a series of comments, in the form of 12 critical questions prompted by the book that would open up an interactive scientific discussion between the reviewer and the author. Such a discussion with possible participation of INHN membership could get down to details and continue until each “critical question” is clarified or interaction becomes unproductive.

January 23, 2014

Reply to Donald F. Klein by Martin M. Katz

As a proponent of viewing depression as a “psychobiological”, dimensional disorder, and the antidepressants as having multiple clinical actions associated with differential impact on its neurobehavioral components, I realize that a number of technical and methodological concerns are raised in my book about how research is conducted on these issues. Don Klein is aware of these issues and their application to clinical research, generally. He apparently plans to identify them and to open them for discussion. I look forward to a useful interchange on these matters and trust that other members of the Network will participate in the discussion.

February 13, 2014

First Comment (Sample size) by Donald F. Klein

Katz states, “In this book I describe the research approach, and the new findings that led to: (1) identifying the major mood, cognitive, and behavioral components of the multifaceted depressed state; (2) uncovering the dimensional structure of the disorder; (3) further elaboration of the psychological turmoil that defines the experiential state of depression; (4) proposing a new theory about its conflictual nature detailing the interaction of neurochemistry and behavior which comprise the state; and (5) describing the impact of the antidepressant (AD) drugs on behavior and chemistry, that is, the drug-specific actions on behavior, and the onset and sequence of clinical actions that precede recovery” (p. viii).

Katz believes that adequate description of depression requires contributions from doctor observations, patient self-reports, psychomotor performance, nurse observations and video interviews coded by behavioral evaluation scales (p. 26-8). These observations are linked, in part, by factor analyses.

Katz’s “constructs of the depressive disorder are based partly on phenomenological analyses from Grinker et al [4] and Kendell [7], and partly, on the result of factorial analyses of data assembled from the one hundred four moderately to severely ill patients sampled across the six hospitals in the CDS [1]. The constructs encompass affect or emotional components such as depressed mood, anxiety and anger, disturbed psychomotor performance, thinking, somatic functioning and social behavior elements. There are 11 components inter-correlated in various degrees that were factor-analyzed to derive fewer dimensions, independent in quality that could be applied to understanding the structure of the psychopathology underlying this class of disorder” (p. 26).

My general concern is that the sample sizes, a total of 106 patients, derived from six sites, are very small to serve as the bases for stable, generalizable factors. Further, the sample sizes seem to fluctuate. For instance, on p. 29 the sample is stated as 130.

Do you believe that this sample size is adequate for your purposes?

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Kendell RE. The Classification of Depressive Illnesses. London: Oxford University Press; 1968.

January 30, 2014

Reply to Donald F. Klein's First Comment by Martin M. Katz

Sample size is always an issue in clinical research. The target sample in clinical studies is usually patients suffering from one of a range of mental disorders. When investigating a causal or structural factor in the makeup of the disorder or the effect of a treatment, the investigator strives to assemble a representative sample of the disorder – not easy to accomplish. Whatever the study results, however, they must be limited in their generality to the kinds of patients represented in the study. Second to representativeness of the sample, in accord with the study aims, is the consideration of sample size. Certain technologies to be applied to analyzing the data require a minimum number of subjects so that not achieving a required size does not allow the statistical techniques appropriate to the problem to be applied. Factor analysis or principal components analyze the relationships among multiple variables. Depending on the precision with which these variables are measured, and the sheer number of variables at issue, factor analytic procedures require rather large samples to produce stable solutions. So, clinical research more so than basic research is burdened because of the complexity of its human subjects, the need to assemble large, diversified samples and to usually follow them over extended lengths of time. In evaluating the factors (dimensions), the viewer must take into account the content and quality of the methods utilized to derive them, and note, that in the end, their value is dependent on how well they meet the aims of the overall study.

The viewer will note that in the NIMH Collaborative Depression Study (CDS) (Maas et al 1980), the factors made possible the testing of neurobehavioral hypotheses and refined analyses of the drug actions upon the disorder. Their application resulted in new information about the composition of the disorder, about the timing and specificity of clinical actions of the drug, and of their associations with the underlying neurochemical changes affected by these drugs.

The problem initially confronting investigators in that study, based on the aims in the CDS of testing neurobehavioral hypotheses and the effects of treatment, referred to by Klein was to assemble a “representative” sample, diverse enough to cover the variations across the most severe of depressed patients. If such a group could be assembled and sound, psychometrically tested methods applied to the analysis of their psychopathology, it should be possible to uncover the essential mood, behavior and cognitive components that comprise the disorder. And then, through principal components analysis, identify the underlying dimensions that describe this structure.

How large and diverse a sample must be assembled to meet these aims? We note, as background, that because of the practical difficulties in this field noted, clinical studies usually progress on the shoulders of very small samples. So theoretical ideas, like the “catecholamine hypothesis” or the “dexamethasone test”, were developed from relatively small samples. The CDS sample in this area of research was designed to be especially large and diverse in order to generate more definitive tests of these hypotheses, originally developed on small samples.

Six hospitals in diverse areas of the country were recruited and representative samples of unipolar and bipolar depressives, selected utilizing the research diagnostic criteria (RDC), operational definitions of the disorders, resulted in 130 patients for this study, a “very large” sample in this sphere of research.

It was possible to use 73 of these patients for the second-order factor analysis of the behavioral components. The sample size requirements for factor analysis are based, as noted, on the number of variables, the soundness of the methods, so that 5 to 10 patients per variable is required for “exploratory” or confirmatory factor analyses (Floyd & Widaman 1995). The sample size used in the CDS study is not large for factor analysis (conducted with 11 variables) but adequate in accord with technical requirements. Probably more telling is that the variables included are not simply items, known to have dubious reliability, but are previously validated clusters of item score sub-factors already tested for reliability. The methods were selected based on prior factor and other analyses involving proposed dimensions of the disorder, uncovered in earlier research, and room was left in the analysis for the derivation of new 2nd order dimensions to appear in the new sample.

The principal components analysis is the most used, most precise technique available for such analyses. In evaluating the factors (dimensions), the viewer must take into account the quality of the methods used and note that in the end, the validities of the methods are dependent on prior psychometric analyses, and then on how well they do in meeting the aims of the overall study.

The viewer will note that the factors make possible the testing of the hypotheses, the refined analyses of drug actions on the disorder, resulting in new information about composition of the disorder, about the timing and specificity of clinical actions of the drugs, and their associations with the immediate neural changes effected by the drugs.

Of most importance, however, is that the analyses have made “visible” a conflict of opposed emotional dimensions in this disorder, which provides the basis for a new theory of its neurobehavioral dynamics. I expect, in the future, further elaborations on these dimensions and understanding of the “psychological storm” underlying the tumult and severity associated with this range of disorders.

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March 6, 2014

Second Comment (Concept of depressive disorder) by Donald F. Klein

Katz states: “The constructs of the depressive disorder...encompass affect or emotional components such as depressed mood, anxiety and anger, disturbed psychomotor performance, thinking, somatic functioning and social behavior elements” (p. 26).

The goal was to “devise methods for measuring the psychological facets as separate elements”. Eleven constructs were described, then boiled down by principal component analysis to three dimensions, referred to as (1) Anxiety-agitation-somatization-sleep disorder, (2) Depressed mood-motor retardation and (3) Hostility-interpersonal sensitivity (p. 35).

Katz argues that major depressive disorder should be viewed as multifaceted, rather than as a “whole disorder”. The disorder comprises opposing central nervous system states...(p. 37).

Katz should clarify if he considers the term “depression” to refer to some single distinct class with multiple independent manifestations, like measles? Or perhaps to several symptomatically overlapping classes, like typhoid and typhus?

The Galenists saw the manifestations of illness as the particular, but entirely variable, combination of the four humors. Is that like the independent interactions of the opposing neurotransmitters? In contrast, Sydenham viewed disease as distinct in terms of phenomenology and course.

In particular, can Katz's primary statistical approach, factor analysis, resolve or deny the mixture problem: whether there are overlapping but distinct syndromes as opposed to a single syndrome with varying manifestations? Or, more drastically, whether both the mixture and syndrome concepts are ill-advised? Is the proposed alternative that the conflictual interplay of independent components, neurotransmitters rather than humors, that generates symptomatic variety?

March 13, 2014

*Third Comment (Variations in neurotransmitter systems and supervening syndrome)
by Donald F. Klein*

In Katz's view, do the several component neurotransmitter systems vary independently, producing all possible combinations and manifestations? In that case, there should be no recognizable syndromes or courses. Alternatively, are certain neurotransmitter deviation combinations particularly likely, thus giving the appearance of syndromes?

But if certain combinations of deviances are somehow favored, how does that differ from the diagnostic syndrome formulation, which accepts multi-causal impairments of a particular evolved adaptive function, as modified by adaptive backups, yielding a particular somewhat variable, syndrome?

June 12, 2014

Reply to Donald F. Klein's Third Comment by Martin M. Katz

The questions (Klein's Third Comment, above):

"In Katz's view, do the several component neurotransmitter systems vary independently producing all possible combinations and manifestations? In that case, there should be no recognizable syndromes or courses. Alternatively, are certain neurotransmitter deviation combinations particularly likely, thus giving the appearance of syndromes?"

"But if certain combinations of deviances are somehow favored, how does that differ from the diagnostic syndrome formulation which accepts multi-causal impairments of a particular evolved adaptive function, as modified by adaptive backups, yielding a particular somewhat variable, syndrome?"

Dr. Klein raises basic questions concerning the neural mechanisms underlying the mental disorders, e.g., specifically, the depressive disorders and their relationships to our system of diagnosis. In responding, one has to acknowledge that such an analysis at this point in our progress is required at two levels, one, the presumed neurochemical basis for the mechanisms involved, and two, the observable behavioral and somatic manifestations of the disorders, which represent the sole indicators of the presence of the clinical syndromes. We understand that at this point in time, despite our knowledge of the role of genetics in the susceptibility to certain of these disorders, e.g., the bipolar disorder, we still have no "biological markers" for the diagnosis of any of the mental disorders.

Regarding the interaction of the central neurotransmitter systems at the first level, raised in Klein's opening questions, there is evidence of strong linking in functioning among the dopaminergic, serotonergic and adrenergic systems, described earlier by Sulzer (1985) and later demonstrated in several studies, including in our own collaborative research program (Maas et al 1991). The intercorrelations are substantial, but do not approach unity, indicating that they do not vary together or completely independently, and thus, are not likely to "produce all possible combinations". Evidence also exists that in attempting to link the dysfunction in the neurotransmitter systems to specific behaviors, as reported in the book by Katz (Katz 2013) and as summarized in the review by Morilak and Frazer (2005), the functioning of the serotonin system is significantly associated with "impulsive aggression" and anxiety and the norepinephrine system with motor retardation and depressed mood. There is no evidence that we are aware of what links a specific pattern of neurotransmitter dysfunction to a specific diagnosis. Progress along this line must await further advance in the capacity to link "diagnosis" on one side, to patterns of neurotransmitter dysfunction, on the other. Until then, Carlsson (2013) summed up our dilemma with his classic comment, "drugs don't care about the boundaries between one diagnosis and another."

I cannot adequately answer Klein's second question, except to indicate that, at present, we do not appear to have the proper capacity. We are not able to link the two levels, that is, the neurochemical basis and an overt syndrome, directly. We are, however, part of the way, having established that the various neurotransmitter systems have distinct patterns of relationships with behavioral variables, such as anxiety, that are core aspects of most syndromes.

Basic clinical research that will adopt this behavioral componential approach in parallel with the elemental neurotransmitter systems, an approach discussed in detail in the "Depression" book, requires abandoning in this critical search, the established DSM diagnostic system. It is, however, more likely to enhance progress in uncovering the underlying biological patterns of the major dimensions of psychopathology.

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July 17, 2014

Fourth Comment (Mental syndromes and neurotransmitters) by Donald F. Klein

If the neurotransmitters each control a particular behavioral domain, then particular distinctive arrays of behavior, such as melancholia, panic disorder, animal phobia, etc. (generally called syndromes), should each be mapped onto a particular complex of neurotransmitters. However, we are told that neurotransmitters vary without regard to any supervening syndrome. Does this imply that syndromes are due to some other non-neurotransmitter processes? Or, is it an argument for the lack of utility of the syndrome notion? Or, does it indicate that stating neurotransmitters vary without regard to supervening syndrome may be sometimes correct and sometimes wrong. I don't see, given our current limited knowledge, how to decide. Perhaps, simply deferring judgment is the best option.

September 4, 2014

Reply to Donald F. Klein's Fourth Comment by Martin M. Katz

Don Klein's question is: "if each neurotransmitter system controls a particular behavioral domain, then, distinctive arrays of behaviors (or syndromes) should each be mapped onto a particular complex of neurotransmitters?" But he says, "if neurotransmitter systems vary without regard to any supervening syndrome then syndromes are either due to other non-neurotransmitter processes or the syndrome notion is useless."

To respond to his question it is necessary to reexamine the background evidence of the relationships of the monoaminergic systems and behavior. There is no evidence currently that diagnostic syndromes are associated with any specific underlying pattern of dysfunctional neurotransmitter systems. The evidence shows, however, that each of the monoaminergic systems, dopaminergic, serotonergic (5-HT), and noradrenergic (NE) are associated with or regulate different, but potentially, overlapping patterns of behavior and mood. As summarized in the 2004 paper by Morilak and Frazer, 5-HT, is primarily associated with anxiety and impulsive aggression and NE with "arousal", mood and motor activity. Further, the neurotransmitter systems do not operate independently, but interact with each other, thus, complicating the nature of specific neurotransmitter-behavioral associations. There is no current evidence that neurotransmitter systems vary in accord with any clinical syndromes or diagnoses but disturbed patterns of behavior and mood that are identified as syndromes may yet be found to be associated with a pattern of dysfunctions in several of the neurotransmitter systems (Katz and Maas 1994).

Applying this evidence to treatment issues, we note that because patients vary in their clinical profiles of the disorder, some, e.g., with peaks in anxiety, others with feelings of anger, it is possible and now done with some success, to select drug(s) in any given case based not on the diagnosis, but on the agent's targeted action on major behavioral component(s) of the disorder, i.e., the drug is selected because of its action on a specific neurotransmitter system or systems and that system's evidenced association with that behavioral component, e.g., an SSRI or a selective NE agent, a dual action, or possibly, an agent with a new pattern of specific clinical actions, expecting, through this pattern of associations, to achieve the most effective therapeutic result.

So, it is not yet clear whether a particular complex of neurotransmitters underlies any of the clinical syndromes. The evidence regarding the interactions of the neurotransmitter systems and behavior generally, and the soundness of the syndrome concept, however, point to the strong possibility that such patterns may well be eventually uncovered. What is needed to achieve an answer is to set aside the syndrome concept and to first apply in future neurobehavioral studies the same level of precision in describing the profile of psychopathology, i.e., the disturbed behavior, affect, and cognition associated with the syndrome that is applied to the measurement of the neurochemistry. Until then, we will have to, as Klein suggests, defer judgment on this important issue.

References:

Katz MM. Depression and Drugs: The Neurobehavioral Structure of a Psychological Storm. Springer, New York: Springer; 2013.

Katz MM, Maas JW. Psychopharmacology and the etiology of psychopathologic states: Are we looking in the right way? *Neuropsychopharmacology* 1994; 10: 139-44.

Morilak D, Frazer A. Antidepressant brain monoaminergic systems: A dimensional approach to understanding their effects in depression and anxiety disorders. *International Journal of Neuropsychopharmacology* 2004; 7:193-218.

October 23, 2014

Donald F. Klein's response to Martin M Katz's reply to fourth Comment

Katz and I agree that it is best to defer judgment on the knotty area of syndromes, neurotransmitters, and distinct neurotransmitter behavioral effects while awaiting relevant findings.

During theoretical mysteries, various approaches are tried, hoping, as researchers do, that there may be a payoff.

Nonetheless, Katz clairvoyantly states "What is needed...is to set aside the syndrome concept...first apply...the same level of precision in describing...psychopathology, applied to the measurement of the neurochemistry".

How can Katz be so sure about "What is needed"?

November 13, 2014

Martin M. Katz's response to Donald F. Klein's response to his reply to Klein's fourth comment

Don Klein states that we agree about “the need to defer judgment on syndromes, neurotransmitters and distinct behavioral effects while awaiting relevant findings.” We agree to a point. I, however, believe that we are further along on these issues than Don Klein may be ready to accept. The evidence is stronger regarding the differential associations the neurotransmitter systems have with behavior than many investigators acknowledge. Specific relationships of the functioning of the serotonin system and the regulation of anxiety and of “impulsive aggression” are strong, as are the norepinephrine system and its association with “arousal” and dopamine with motor activity (see Morilak, Frazer’s 2004 summary of this basic research). True, the interaction among these neurotransmitter systems are, in themselves, complicated, so that there is still much to learn about how the regulatory activities on various moods and behaviors play out in the functioning organism. But I believe that one aspect of the issue is very clear and that is that decades of attempting to find direct, straightforward linkages of neurochemical systems with classical mental disorders, as defined in the DSM, or even with syndromes as more commonly defined, has been unsuccessful, leading to many blind alleys. As Arvid Carlsson put it earlier, in another investigatory framework, “Drugs don’t care about the boundaries between one diagnosis and another”.

This is not to deny the values of the diagnostic system or that disorders such as schizophrenia or the affective disorders are not real. Decades of study make clear that these syndromes clearly exist in much the same form as they are described in the established literature. The problem is that they are as conceptions, too complex in nature, and too difficult to quantitate reliably, to be of any great value in uncovering the neurobehavioral mechanisms underlying abnormal behavior and the impact of drugs on these mechanisms. The late James Maas and I encountered this “diagnostic” obstacle in early work on the psychobiology of depression attempting to relate drug-induced neurochemical changes to changes in the composition of the disorders (Maas et al. 1991). Our solution then, when seeking to uncover underlying neurobehavioral mechanisms, was to adopt a more elemental approach in measuring the behavioral side, i.e., to substitute the use of behavioral components and the dimensions that structured the disorders, for the disorders themselves, rather than attempting to find links between the neurochemical systems and the “whole” disorders. This line of thinking and the evidence for it was elaborated in more detail in my book.

So, Klein is correct that I feel strongly that a major “drag” on progress is our over reliance on diagnosis and syndromes in clinical investigations as against improving the precision of our measures of anxiety, anger, apathy in order to further chart the network of associations of the neurotransmitter systems and behavior. Uncovering parts of this network has already improved our capacity to resolve issues about the underlying mechanisms of psychopathology and broadening our knowledge about the nature and timing of specific actions of antidepressants. It is the evidence utilizing this

dimensional approach that has stimulated new thinking and theory about how the depressive disorders are structured and how the drugs work to achieve clinical response. That evidence supports my view that efforts should continue to be concentrated on further elaborating the characteristics of these all important neurochemical-behavioral networks and their functions in the various mental disorders.

References:

Katz MM, Depression and Drugs: The Neurobehavioral Structure of a Psychological Storm. New York: Springer; 2013.

Maas JW, Katz MM, Frazer A et al. Current evidence regarding biological hypotheses of depression and accompanying pathophysiological processes: A critique and synthesis of results using clinical and basic research results. *Integrative Psychiatry* 1991; 7:155-69.

Morilak D, Frazer A. Antidepressant brain monoaminergic mechanisms: A dimensional approach to understanding their effects in depression and anxiety disorders. *International Journal of Neuropsychopharmacology* 2004; 7: 193-218.

December 11, 2014

**Martin B. Keller: Clinical Guide to Depression and Bipolar Disorder (2013) –
reviewed by Martin B. Keller
American Psychiatric Publishing Inc, Arlington, Virginia (218 pages)**

INFORMATION ON CONTENTS: Conceived in the early 1970s to study the phenomenology, diagnosis, genetics, and clinical course of depression, the National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS) has influenced research and practice since its inception. Prior to the CDS, there had been no longitudinal study of this scope and clinical focus. This book summarizes key findings from the study and the related literature to provide comprehensive and up-to-date knowledge on the course and outcome of illness in mood disorders. The first chapter of the book, the *Introduction*, outlines the epidemiological findings underscoring the importance of the CDS, the inception of the collaborative program on the psychobiology of depression, the transformation of the CDS into an extended longitudinal study, and topics covered in the book, as well as a summary of the effect of the CDS. The second chapter, *Collaborative Depression Study Procedures and Study Design*, reviews the assessments, procedures and study designs of the CDS. Chapters 3 and 4, titled *Dimensional Symptomatic Structure of the Long-Term Course of Unipolar Major Depressive Disorder* and *Dimensional Symptomatic Structure of the Long-Term Course of Bipolar I and Bipolar II Disorders*, put forth a dimensional method of studying the severity of symptoms in unipolar Major Depressive Disorder and bipolar disorders. Chapter 5, *Risk Factors for Suicide Attempts and Completions*, covers risk factors, with attention to the symptoms and temperament measures that were consistent for short and long term attempts and completions. Chapter 6, *Psychotic Features in Major Depressive and Manic Episodes*, describes the boundaries between psychotic mood disorders and schizophrenia and summarizes the effects of psychotic features on manic and depressive episode prognoses. Chapter 7, *Development of Mania or Hypomania in the Course of Unipolar Major Depression*, speaks to the incidence and determinants of progression to bipolar disorder. Chapter 8, *Comorbidity of Affective and Substance Use Disorders*, analyzes the importance of the CDS to research regarding the comorbidity of affective and substance use disorders. Chapter 9, *Treatment Effectiveness and Safety in the Longitudinal Course of Mood Disorders*, highlights the CDS studies which looked into somatic treatments' effectiveness and safety for mood disorders. Chapter 10, *Personality and Mood Disorders*, describes CDS contributions to existing knowledge regarding the relationship between depression and personality. Chapter 11, *Family History and Genetic Studies in Mood Disorders*, assesses findings when diagnoses in relatives were analyzed, including the results of a second blind reassessment six years after the first assessment. Chapter 12, "Clinical Course and Outcome of Unipolar Major Depression", describes information on time to recovery, time to recurrence and various predictors. Chapter 13, *Predictors of Course and Outcome of Bipolar Disorder*, shows typical phase lengths and risk factors for change, as well as symptom morbidity. Chapter 14, *Under-treatment of Major Depression*, notes the finding that about two-thirds of patients who entered the study with Major Depressive Disorder (MDD) did not receive antidepressants for an adequate time (with even fewer at an adequate dose). Chapter 15, *Impact of Anxiety Severity on Mood Disorders*, demonstrates how ratings enabled the measurement of anxiety

symptoms with major affective disorders. Chapter 16, *Contributions of the NIMH Collaborative Depression Study to DSM-5*, discusses key contributions, such as a spectrum view of mood disorders and the comorbidity of anxiety. An *Index* rounds out the volume.

EDITOR'S STATEMENT: The Clinical Guide to Depression and Bipolar Disorder is the culmination of over 30 years of semi-annual and annual interviews with almost 1000 patients and a series of interviews with more than 4000 first degree relatives, spouses, and mates. To date, there have been more than 280 peer reviewed original articles published in leading psychiatric and general medical journals. The findings of the CDS, have led to the most meaningful changes in the field's understanding of the clinical course and outcome of mood disorders and co-morbid conditions since the writings of Kraepelin at the end of the nineteenth century.

During the 1950s and 1960s, descriptive and biological psychiatry were challenging the prevailing approach of psychodynamic psychiatry. The swirling controversy was fueled by limited clinical assessments and the lack of reliable and valid diagnostic criteria sets. The NIMH's recommendation for intensive research focusing on nosology, genetics, and pathophysiology resulted in establishment of the biological studies and clinical studies components of the CDS. Initiated in 1977, the findings from the early data of the clinical studies component were stunning; showing the clinical course of depression was worse than what was previously known. Findings of longer durations of episodes, higher relapse and recurrence rates and higher rates of chronicity led to the transformation of the CDS from a two year follow up into a longitudinal study with the largest sample, shortest interval interview prospective study of mood disorder in the history of psychiatry. The findings of the CDS conceptualized unipolar depression as a lifelong illness. Results showed subsyndromal symptoms as the second most common symptomatic state during follow up of unipolar and bipolar depression and are associated with significant dysfunction in 7 out of 9 domains of psychosocial functioning. The presence of residual symptoms is associated with early relapse and a worsening of future course of these disorders. The findings were essential in the development of treatment goals for both bipolar disorder and unipolar major depression. The findings of the CDS led to identification of risk factors, such as comorbid anxiety or substance use, double depression, and long duration of episodes and improved treatments for those long suffering from mood disorders.

The specific data on the timing and predictors of long term outcomes and comorbidities from the CDS inspired the motivation and design of numerous continuation and maintenance studies of depression and bipolar disorder, which led to improved treatments for those long suffering from mood disorders. The CDS data also inspired massive advocacy efforts to significantly increase funding for research on mood disorders by the NIMH, National Alliance of Mental Illness (NAMI), National Alliance for Research in Schizophrenia and Depression (NARSAD) and other foundations and served as the impetus for numerous advocacy campaigns by non-profit (The National Depressive and Manic Depression Association, The Depression and Bipolar Support

Alliance, NAMI and others) and government organizations to reduce the stigma of depression, bipolar disorder and mental illnesses, which have had major success, although there is still much work to be done. The CDS data on suicide also contributed to the creation of organizations, such as the American Foundation for Suicide Prevention and the JED foundation and efforts by the NIMH and Substance Abuse and Mental Health Services (SAMSA) to raise awareness about suicide risk and efforts to reduce this risk through public education and new research.

Each chapter in the Clinical Guide to Depression and Bipolar Disorder provides a summary of the findings, focusing on various aspects of the research, including the dynamic and fluctuating severity levels of symptoms of unipolar and bipolar depression, the course and outcome of the disorders, and treatment implications in relation to effectiveness, safety, and the ongoing gaps between research and practice. Genetics, psychotic symptoms, substance use, and anxiety severity were explored through the decades of research. With each chapter, summarized with clinical implications, the authors provide practical and evidence-based guidelines for clinicians.

January 16, 2014

Comments by Martin M. Katz

The authors' description of the inception, results and impact on psychiatry and psychopharmacology of the NIMH Collaborative Depression Study, as presented in this recent book, is sharp and greatly informative. The study was started by the Institute's Clinical Research Branch, in 1970, to deal with essential unresolved problems in nosology, genetics and pathophysiology. It was to expand greatly over the years, resulting in major contributions to the understanding of long term course in depression and to the development of the Research Diagnostic Criteria (RDC). The RDC was to serve later as the basis for the radical revision of the diagnostic system, the creation of the operationally defined DSM III. The Study's successes resulted in receiving grant support for several decades, so that by 2010, it was still in operation recruiting new investigators and producing important findings on the longitudinal course of the disorder, leading to several scientific awards. Notably, it was conducted alongside an equally ambitious Biological Collaborative component, initiated at the same time, to test the then, new hypotheses concerning the nature of the disorder, e.g., the "catechol amine hypothesis", and to uncover the specific relationships of neurochemistry and behavior that are presumed to represent underlying mechanisms of the disorders.

Between them, the two Collaborative efforts have resulted in several hundred publications, produced by a range of authors, representing several disciplines in neuropsychopharmacology. Keller, in his emphasis on description of the book's content, omits discussion of the contributors who participated over the decades in the conduct of the study. Regarding its initiation, as he states, an outgrowth of the NIMH 1969 Williamsburg Conference (Williams, Katz, Shield [eds], *Recent Advances in the Psychobiology of the Depressive Disorders*. GPO, Washington DC, 1972) the planning group for the Study included such historical figures as Eli Robins and George Winokur and was chaired by James W. Maas. Bob Hirschfeld, who was later to become coordinator of the Clinical Study, describes well this history in the Introductory Chapter. Of critical importance to its beginning were the roles of Gerald Klerman, Bob Spitzer and Jean Endicott. Gerry and I, as Chief of the Clinical Research Branch, co-chaired the Clinical Committee, but it was Klerman, who sparked the effort and with his unequalled administrative skill, managed to keep it on track for many years. Alongside him, monitoring every element was Jean Endicott, a co-editor of the volume. The early "young" co-investigators included such notable figures in our fields as Jan Fawcett, John Davis, Nancy Andreason, Bill Coryell (a co-editor), Tom Williams, Joe Mendels, Robert Shapiro, Jack Croughan, Paula Clayton, Regina Casper, John Rice and Ted Reich.

In addition to its contributions to the research literature and to clinical practice, generally, the Collaborative studies made a major contribution to the training of young, primarily, psychiatric investigators in the methodology of clinical research and helped to prepare them for careers in research. Little is more important for advancing the field and elaborating on its history than these kinds of accomplishments.

A word should be said for the contribution of the NIMH to this long term, complex program of research. The Institute is looked to primarily, almost solely, for its financial support of independent research. In the case of the Collaborative Studies, it deserved credit for recognizing that clinical, unlike basic research, requires a more active role, that is, mechanisms to identify critical unresolved obstacles in order to move forward in this important area of research. In that case, having a national conference to identify the problems, it was then able to move ahead and actively organize strategic studies to solve the focal problems. Fortunately, today, the current Director has a comparable vision and has shown his respect for the role of history in current efforts to resolve similar problems in clinical research.

July 3, 2014

**Donald F. Klein, Rachel Gittelman, Frederic Quitkin and Arthur Rifkin:
Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children
(1983) – reviewed by Donald F. Klein
Williams & Wilkins, Baltimore (849 pages)**

INFORMATION ON CONTENTS:

Foreword: Jonathan O. Cole.

Introduction: Brief historical summary of somatic psychiatric care, “We may be fortunate to be entering a period in which rational comparative study will become the standard for therapeutic decision...”, “We are looking forward to the publication of the American Psychiatric Association Diagnostic and Statistical Manual III”.

I. *Diagnosis, the Diagnostic Process, and Common Errors*; II. *Psychotropic Drug Management, General Principles*; III. *The Concept of Psychosis* - This was a unique, we think, still fruitful, hypothesis developing the term, psychosis, as due to a flaw in inferential processes, yielding an unwarranted sense of certainty through the failure of innate skepticism; IV. *Diagnosis of Schizophrenia*; V. *Review of Nosological Schemes in Schizophrenia*; VI. *Review on the Pharmacotherapy and Psychotherapy of Schizophrenia: A Review of the Literature*; VII. *Clinical Management of the Various Stages and Subtypes of Schizophrenia*; VIII. *Side Effects of Antipsychotic Drugs and their Treatment*; IX. *Antipsychotics in non-schizophrenic conditions*; X. *Diagnosis of Affective Disorders: Clinical Considerations*; XI. *Diagnosis of Affective Disorders: Review of Nosological Schemata*; XII. *Review of the Literature on Mood-Stabilizing Drugs*; XIII. *Clinical Management of Affective Disorders*; XIV. *Side Effects of Mood Stabilizing Drugs and Treatments*; XV. *Diagnosis of Anxiety, Personality, Somatoform, and Factitious Disorders*; XVI. *Review of the Literature on Antianxiety Drugs*; XVII. *Treatment of Anxiety, Personality, Somatoform and Factitious Disorders*; XVIII. *Assessment and Treatment of Childhood Disorders: General Considerations*; XIX. *Diagnosis and Drug Treatment of Childhood Disorders*; XX. *Critique of Treatment Studies*; XXI. *Theoretical Inferences Concerning Clinical Groupings and Psychotropic Drugs*.

Author Index; Subject Index; Glossary of Drugs.

EDITOR’S STATEMENT: This second edition of this book is organized somewhat differently from the first edition, which was co-authored by John M Davis M.D. (First edition: Donald F. Klein and John M. Davis: *Diagnosis and Drug Treatment of Psychiatric Disorders*. Williams & Wilkins, Baltimore, 1969 – See, INHN “Books”, November 28, 2013). In 1969, there was still considerable doubt within the psychiatric profession concerning the scientific basis for the uses of antipsychotics, antidepressants and antianxiety agents. It was not unusual to hear the firm assertion that there were more studies proving that these drugs do not work than demonstrating that they were effective. We felt, at that time, that the presentation of extensive tabulated reviews of

studies of drug efficacy would be a worthwhile contribution. In fact, the evidence of drug efficacy was well-nigh overwhelming. This work had been done largely through the efforts of John Davis, who has since continued to contribute brilliantly to systematic critical reviews of psychopharmacological studies.

For this edition, we decided this tactical goal had been accomplished and that it didn't pay to belabor what had become the obvious, although a recent spurt of lay books have endeavored to muddy the waters. Unfortunately, these efforts have been reinforced by the recent evidence concerning the deletion of important negative clinical data by industry. We believe that only release of the raw patient level data will restore the public's justified confidence.

Therefore, for the Second Edition, critical reviews and tabulations focused on narrower specific questions that were, circa 1983 (and still are), controversial.

Yet another change is a unique section on pediatric psychopharmacology, ably managed by Rachel Gittelman. Negative feelings towards the use of psychiatric medication reach their apogee in the treatment of children. Our review dealt systematically with realistic concerns. It should help dispel largely irrational fears. The section on affective disorders was largely the work of the late Frederick Quitkin. The section on schizophrenia was based on the efforts of Art Rifkin.

It is recognized that many of the descriptions of psychiatric syndromes are abstract and the reader might well have benefited from representative case illustrations. This proved impractical. The reader is referred to Klein DF. *Psychiatric Case Studies: Treatments, Drugs and Outcomes*, Williams & Wilkins, Baltimore, 1972 (see, INHN "Books", January 2, 2014), which remains the only set of full case presentations addressing the long-term effects of the range of psychopharmacological treatments.

February 6, 2014

**Donald F. Klein with Alfreda Howard: Psychiatric Case Studies: Treatment,
Drugs and Outcome (1972) – reviewed by Donald F. Klein
Williams & Wilkins, Baltimore (491 pages)**

INFORMATION ON CONTENTS:

Forward - Jonathan O. Cole: "..... the only text in which theories and principles of psychopharmacological therapy are illustrated by good examples of their application to individual patients".

The Psychiatric Case Study - Discussion

Schizophrenia-Diagnostic Issues

- Schizoaffective - 6 Cases with Comments
- Childhood Asocial - 3 Cases with Comments
- Fearful Paranoid - 2 Cases with Comments

Recurrent Affective Disorders -Diagnostic Issues

- Retarded Depression - Two Cases with Comments
- Agitated Depression - Three Cases with Comments
- Dysphoric States - Two Cases with Comments
- Bipolar Type = Manic States - Two Cases with Comments

Late Life Onset

- Schizoid Personality with Depressive - Paranoid Exacerbation - One Case with Comment
- Paranoid Personality with Involutional Psychosis - One Case with Comment
- Agitated Depression during Involutional Period - One Case with Comment

Neuroses and Character Disorders - Diagnostic Issues

- Phobic Anxiety Reaction (Agoraphobia) - Three Cases with Comments
- Emotionally Unstable Character Disorder - Two Cases with Comments
- Passive - Aggressive Character Disorder - Two Cases with Comments
- Hysterical Character Disorder - Two Cases with Comments
- Pseudo-Schizophrenic Neurosis - Two Cases with Comments

Diagnoses & Prevention of Diagnostic & Medication Treatment Errors

References

This text is partly derived from a double-blind, randomized, placebo-controlled clinical trial of imipramine, chlorpromazine and placebo, conducted during 1960-1961 at

Hillside Hospital. The psychiatric inpatients were at the 200-bed long term psychoanalytic inpatient facility of the Federation of Jewish Philanthropies. Uniquely, there was a Department of Experimental Psychiatry, the Director of which was Max Fink M.D. Just as uniquely, the new Director of the Hospital was Lew Robbins M.D., an open minded training analyst from the Topeka School, who recognized the clinical importance of psychotropic drugs, as well as the necessity of properly conducted, placebo controlled, clinical trials to evaluate their pluses and minuses. This required randomization without regard to the very shaky psychiatric diagnoses, since two years of pilot work indicated that remarkable errors, based on these clinical, observational beliefs were often incurred.

The Principal Investigators were Max Pollack Ph.D. and Max Fink M.D. (USPHS MH-2715). This study was replicated by Donald F. Klein M.D. (USPHS MH 08004), in 1964-1966. This remains probably the largest single clinical trial carried out at a single inpatient facility. A number of useful discoveries were made. These included the utility of imipramine for spontaneous panic attacks, which led to formulations of panic disorder and agoraphobia. Other findings were the equivalence of chlorpromazine to imipramine for the normalization of the mood of severely depressed patients, as well as the lack of utility of chlorpromazine for schizophrenics with childhood in asociality.

Both groups were systematically followed for up to three years by Sidney Levenstein D.S.W. (USPHSMH-10191). Many had somewhat more unsystematic, follow-up evaluations, up to eleven years after treatment.

AUTHOR'S COMMENTS: The anonymized material was used in a didactic course for psychiatric residents. The residents received the information up to the point of hospitalization and asked to predict the likely course. For many, this was a humbling, if illuminating, experience. The point was that even a detailed well-written case study is often insufficient to serve as a solid, predictive, causal document. Post hoc ergo propter hoc remains a key critical principle for psychiatry. However, the course was not repeated.

The motivation to put this material into a book (effectively facilitated by Alfreda Howard) was largely to flesh out the somewhat abstract descriptions given by the Klein and Davis text. Also, it demonstrated the complex, often obscure, demands placed on attempting to systematically formulate descriptive diagnoses.

It cannot claim to be a success, since it sold poorly and was infrequently referred to, although I confess a paternal fondness. At least, it casts some light on the psychiatric attempts of the 1960s to deal with the revelations of the paradigm destroying psychotropic drugs.

January 2, 2014

Joseph Knoll: The Theory of Active Reflexes: An Analysis of Some Fundamental Mechanism of Higher Nervous Activity (1969) – reviewed by Joseph Knoll
Publishing House of the Hungarian Academy of Sciences, Budapest and Hafner Publishing Company, New York (131 pages)

INFORMATION ON CONTENTS: This monograph was an attempt to analyze drive-motivated goal-directed psychic activity, perceived as a special “active reflex”. It is divided into seven chapters.

Chapter I. *The basic principals of the theory of the active reflexes.* A special stimulus (A) induces and maintains an “excitatory focus” (“active focus”) (A’), which is regulating and programming general activity, a chain of “orientatory-searching reflexes”, elicited and maintained by the given environment. This chain persists until the goal (B) is reached, which results in the disappearance of the “active focus” as well as all of its consequences.

Chapter II. *Experimental proof of food-seeking activity being an unconditioned active reflex.*

Chapter III. *Experimental analysis of an avoidance reaction being an unconditioned “active reflex”.*

Chapter IV. *Experimental analysis of “cylinder-seeking” activity being a conditioned active reflex.* The technique of how to fix into the brain of rats a special acquired urge, the “glass-cylinder-seeking drive”, is presented in this chapter. Based on an unconditioned avoidance reflex (escape from a hot plate) and using the sound of a shrill bell, to play the role of conditioned stimulus, rats were trained to search for a 30-cm-high glass-cylinder and jump to the rim of it. The cylinder was open at the bottom and top with diameters of 16 cm and 12 cm, respectively, and with a side opening through which a rat (up to 350-400 g body weight) could manage to get inside the cylinder. In the training procedure, the rat was ushered through the side opening of the glass-cylinder to a metal plate heated to 60°C, and the jumping reflex was elicited for a couple of weeks, three times daily on 10-50 occasions at 10s intervals with bell and heat stimulation. An extinguishable conditioned reflex (ECR) is transiently developing and after a short training period, a chain of inextinguishable conditioned reflexes (ICRs) developed and the rat displayed indefatigably the jumping reflex without heat stimulation, even as much as 100 times in succession. This was a transient stage, which led to the manifestation of the glass-cylinder-seeking drive. The rats that performed best in this study, acquired the glass-cylinder-seeking drive in a stable manner, thereafter maintaining this unnatural urge for a lifetime. The rats showed the same high-grade adaptability and readiness in overcoming different obstacles during goal-attainment as the ones influenced by innate drives, such as hunger or sexual desire. In the most efficiently trained, best performing rats, the acquired drive was so powerful that it prevailed over life among other important innate drives. When such a rat has been deprived of food for 48 hours, and then food was offered within the usual setup

that contained the glass-cylinder, the rat looked for the glass-cylinder and left the food untouched. Similarly, when a receptive female was offered to a fully sexually active glass-cylinder-seeking male rat in the usual setup, the male looked for the glass-cylinder and neglected the receptive female. The mouse, a rodent closely related to the rat, trained under the same experimental conditions as the rat, was unable to acquire the glass-cylinder-seeking drive.

Chapter V. *Temporary connections in the light of the active reflex.* The main novel finding in this Chapter was the demonstration of the difference between EEG records of untrained rats and rats trained using the sound of a bell as a conditioned stimulus, to build an extinguishable or an inextinguishable conditioned reflex (ECR or ICR respectively). The effect of 20 min continuous bell ringing on the EEG arousal reaction was examined. In the untrained rat, when the bell ringing started – a new stimulus! – desynchronization, i.e., excitation of the non-specific activation system, set in. This state lasted for a short period; after habituation to the stimulus, synchronized cortical activity was restored. In the rats with ECR, habituation after EEG arousal, set in at practically the same rate as in the untrained controls. However, in the rats with ICR, the bell had a lasting capacity to cause excitation in the non-specific activation system.

Chapter VI. *Inhibitory processes in the light of the active reflexes.* In our studies with glass-cylinder-seeking rats, we saw that once the animals manifested the acquired drive, they searched for the glass-cylinder repeatedly, and for long periods of time without any signs of trouble. As time passed, however, tedious repetitions of glass-cylinder search efforts in an unchanged environment led to a peculiar behavioral modification. The phenomenon, strikingly reminiscent to boredom, appeared in rats that were compelled, after the acquisition of the glass-cylinder-seeking drive, to search for the glass-cylinder at least 20 times a day in an unchanged environment for a longer period of time. As a consequence of this form of training, the characteristic change in behavior was already observable in some of the well-performing rats within 3-4 weeks, though with the others, months passed until the phenomenon appeared. As soon as we changed the environment where the animal lingered a long time, the rat started immediately working with the highest intensity. We never observed the phenomenon reminiscent of “boredom” in connection with innate drives, where the inexhaustible mesencephalic neurons keep the cortical neurons active. It, therefore seems that tedious repetitions of glass-cylinder searches with 30s intervals, in an unchanged environment, sooner or later, lead to the decline of the specific stimulation-induced enhanced excitability in the sensitive group of cortical neurons (active focus), responsible for regulating and programming general activity of the glass-cylinder-seeking behavior, until the goal is reached.

Chapter VII. *Influence of drugs on the activation process of the central nervous system.* We found conspicuous differences in sensitivity to drugs between the extinguishable and inextinguishable conditioned reflexes. The ECR was readily inhibited by sedative-hypnotics and neuroleptic agents, the ICR displayed selective sensitivity to neuroleptics. On the other hand, we found that 2 mg/kg amphetamine enhances

significantly the ability of the rat to build a conditioned reflex.

AUTHOR'S STATEMENT: In the late 1950s, the careful analysis of the nature and physiological significance of the acquired drives called my attention to the catecholaminergic brain engine, which plays the key role in the activation of the cortex. In case I needed to stimulate the catecholaminergic neurons, I used necessarily the best disposable experimental tools, the long-acting b-phenylethylamine (PEA)-derivatives, amphetamine and methamphetamine. My problem with the amphetamines was that as soon as the dose surpassed the 1-2 mg/kg level, the drug-induced continuous, irresistible release of catecholamines from their intraneuronal stores in the brainstem neurons arrives to an intensity resulting in aimless hypermotility, which blocks purposeful behavior. In the early 1960s, monoamine oxidase (MAO) inhibitors represented a new type of central stimulation, so I decided to start the structure-activity-relationship study with methamphetamine, containing a propargyl-group, attached to the nitrogen. This group was known to form a covalent binding with the flavin in MAO and block the enzyme irreversibly. Out of a series of newly synthesized, patentable methamphetamine derivatives, E-250 (later named deprenyl) was selected as the most suitable. (-)-Deprenyl (Selegiline) is now a drug used worldwide to treat Parkinson's disease (PD), Alzheimer's disease (AD) and major depressive disorder (MDD).

February 27 2014

Joseph Knoll: The Brain and Its Self. A Neurochemical Concept of the Innate and Acquired Drives (2005) – reviewed by Joseph Knoll
Springer, Berlin (176 pages)

INFORMATION ON CONTENTS: The Introduction and Chapter 1 recapitulates the main conclusion of the 16-year research period summarized in a monograph (Knoll: *The Theory of Active Reflexes*, 1969). The first monograph was based on the discovery that the manipulability of the behavior of highly developed mammals depends on the ability of their cortex to fix acquired drives, unusual urges that, in contrast to the innate drives, are unnecessary to the survival of the individual or the species. The present book is a summary of the results and conclusions of the following 36-year research period. Chapter 2 is a brief summary of the conception that whatever humans achieved derives from the unrestricted capacity of their brain to acquire drives. Chapter 3, an analysis of the operation of the enhancer regulation, is a summary of the results of a neurochemical approach to the innate and acquired drives. Section 3.1., defines the enhancer regulation; describes b-phenylethylamine (PEA) and tryptamine as endogenous enhancers of the catecholaminergic and serotonergic neurons; shows the role of (-)-deprenyl in the discovery of the enhancer regulation in the catecholaminergic neurons; analyses (-)-deprenyl as the PEA-derived enhancer substance and R-(-)-1-(benzofuran-2yl)-2-propylaminopentane [(-)-BPAP] as the tryptamine-derived enhancer substance. Section 3.2., describes (-)-BPAP as the specific experimental tool to detect the specific and non-specific form of enhancer regulation. Section 3.3., is a consideration about enhancer receptors. Section 3.4., is an assumption about the physiological significance of cortical enhancer regulation; thoughts about its role in the modification of behavior through exercise, training or practice; and a brief summary of an experiment supporting the concept that learning is a cortical enhancer regulation dependent function. Section 3.5., is a summary of therapeutic aspects of the synthetic enhancer substances. Chapter 4 approaches old problems from a new angle. Section 4.1., is a new interpretation of the substantial individual differences in behavioral performances. Section 4.2., is a new interpretation of forgetting, remembering, and boredom. Chapter 5 analyses theoretical aspects of the enhancer regulation approach. Section 5.1., describes the simultaneous coexistence of determinants of order and chaos in the human brain and its role in the origin of science and art. Section 5.2., emphasizes the timeliness of the conception of the enlightenment: *sapere aude* (dare to go independently).

AUTHOR'S STATEMENT: The purposeful manipulation of the human brain (domestication) is the *sine qua non* for the establishment and maintenance of a community. The billions, who remained during the history of mankind untouched by their wartime killings of masses of their innocent peers and were ready to die in the name of "God", "fatherland" and so on, illustrate the consequences of the practically unlimited capacity of the human brain to fix acquired drives. Even in the dark history of mankind, the Holocaust – the extermination of millions within a few years with unprecedented success, due to a systematically planned and executed evil mass manipulation of a whole nation – was a unique event. This horrifying recent example testifies to the fact that the potential to misuse the physiological endowments of the human cortex is practically unlimited. Since the human being, a building block in the

creation of the most gigantic product on earth: human society, was born with a brain capable to create a non-existing world, Homo sapiens created necessarily a myths-directed society, which is still in the trial-and-error phase of its development and seeks to arrive at the final state a rationally organized human society. Only a global change of education, based fully on the exact knowledge of the brain mechanisms that enable the manipulation of individuals, can lead, at some point in the future, to the desired rationally directed society.

January 23, 2014

Joseph Knoll: How Selegiline Slows Brain Aging (2012) – reviewed by Joseph Knoll
Bentham Science Publishers (195 pages)

This book, review by Joseph Knoll, was first posted in Books in Neuropsychopharmacology: Classics and Current on September 5, 2013 (see *INHN 2013*, pp. 145-146). The following interactions are comments and replies that ensued and were posted during 2014 as a consequence of this book review:

Comment by Donald F. Klein

The title of this book, *How Selegiline Slows Brain Aging*, certainly stirs my interest. However, as indicated above, this book is really a summary of Professor Knoll's distinguished career relating selegiline to depression, Alzheimer's disease and Parkinson's disease. This is in the context of his ingenious basic work.

In particular, the idea that selegiline, alias ((-)-deprenyl), this specific MAO B inhibitor, has an even more important role as a Catecholamine Activity Enhancer was news to me. However, a PubMed review indicates that for the past 20 years, this notion has been the exclusive property of the Hungarians and the Japanese, but has little intellectual traction in the USA. Peculiar.

Obviously, conducting a life extending trial in humans is a far from easy task. Almost all of the longevity studies that Knoll lists use rats or mice, although there is a study each of Syrian hamsters, Beagle dogs, and *Drosophila*.

Interestingly, the early studies were primarily devoted to studies of sexual functioning, using this as a surrogate for striatal functioning. The effects on longevity seem quite substantial. "In the saline-treated group (n=66) the last signs of sexual activity vanished to the 33rd week of treatment. (-)-deprenyl treatment restored full scale sexual activity in 64 out of 66 rats. The longest living rat in the saline-treated group lived 164 weeks. The average lifespan of the group was 147.05 ± 0.56 weeks. The shortest living animal in the (-)-deprenyl-treated group lived 171 weeks and the longest living rat died during the 226th week of its life. The average lifespan was 197.98 ± 2.36 weeks, i.e. higher than the estimated maximum age of death in the rat (182 weeks). This is the first instance that by the aid of a well-aimed medication, members of a species lived beyond the known lifespan maximum." Other studies showed that rodents with a naturally low sexual drive do not live as long as the high functioning group, but that this difference is remedied by selegiline.

There is some peculiar problem here, probably due to economics and patent rights, although I don't rule out the endemic narrow focus on molecular biology. One would think that a group of drugs that possibly lead to living longer, while preserving sexual

potency, would have substantial appeal. Certainly, the lack of clinical sexual investigation of Selegiline—which has the virtue of being on the American market is surprising—in fact, dumfounding.

April 3, 2014

Reply by Joseph Knoll

I would like to thank Dr. Donald Klein for his comments and questions. It seems to me that the catecholaminergic activity enhancer (CAE) effect of selegiline, discovered in the mid 1990's, remained unknown because I introduced the compound in 1972 as the first selective inhibitor of B-type MAO, and in humans a daily 10 mg dose is needed to completely inhibit the enzyme in the brain. Thus, selegiline, now registered in more than 60 countries, marketed under more than 100 trade names to treat Parkinson's disease (PD), Alzheimer's disease (AD) and major depressive disorder, cited in thousands of papers and described in textbooks as the selective inhibitor of MAO-B, is used in this high dose, whereas its main, CAE effect is exerted at a low dose. In addition, the dose-effect relation regarding the CAE effect is unusually complicated. In the rat, for example, the peak dose of the 'specific' CAE effect is 0.001 mg/kg, and 0.25 mg/kg blocks the activity of MAO-B in the brain. In this high dose, selegiline exerts its 'non-specific' CAE effect. As a matter of fact, the share of the 'non-specific' CAE effect of selegiline in the therapeutic benefits observed in patients treated with the usually used 10 mg daily dose remains to be clarified in the future. It is clear by now that selegiline is primarily a β -phenylethylamine (PEA)-derived CAE substance and blocks MAO activity in high doses only.

The catecholaminergic brain engine is the most rapidly aging system in our brain. We lose 13% of our striatal dopamine in the decade after age 45. The aging of the brain engine is primarily responsible for the decay of behavioral and sexual performances over time, and plays a role in the manifestation of neurodegenerative diseases. I wrote this book to put facts and arguments together, which highlights that selegiline, due to its CAE effect, slows the aging of the catecholaminergic brain engine, and as a consequence of this effect, selegiline significantly prolongs the life of different mammalian species. Experimental and clinical studies with selegiline strongly support the proposal that preventive administration of a synthetic CAE substance during post-developmental life could significantly slow the decay of behavioral and sexual performances with the passing of time, prolong life and prevent or delay the onset of aging-related neurodegenerative diseases. In humans, the maintenance from sexual maturity on 1 mg selegiline daily is currently the only feasible preventive measure with a promising chance to accomplish this aim. However, a proper trial on healthy volunteers is still missing. Let us hope all is not lost that is delayed. Since INHN published the "Information on Contents" and "Author's Statement" of my three monographs (inhn.org., Publications: September 5, 2013; January 23, 2014; and February 27, 2014) and also "The history of selegiline/(-)-deprenyl the first selective inhibitor of B-type monoamine oxidase (MAO) and the first catecholaminergic activity enhancer (CAE) substance" (inhn.org. Archives: Miklya Collection), there is now available the summation of my research started in the early 1950's which ultimately led to the discovery of the enhancer regulation in the mammalian brain. At present, we see only the tip of the iceberg. We learned that PEA and tryptamine are native CAE substances and developed a PEA-, and a tryptamine-derived synthetic CAE substance, selegiline and (-)-BPAP, respectively. We use them to study the enhancer regulation in the brain. Selegiline is at present the available drug to test exactly the preventive anti-

aging effect of a safe synthetic CAE-substance. Klein's remark "...conducting a life extending trial in humans is a far from easy task....." is only too true, but the stakes are tremendous. In the Epilogue of my book (p 92), I mention that though "never marry your hypothesis" was and has remained my leitmotif, the outcome of the first longevity study (Knoll J., The striatal dopamine dependency of lifespan in male rats. Longevity study with (-)-deprenyl. *Mechanisms of Aging and Development*, 1988, 46:237-262) fascinated me so greatly that I decided, at age 64, to undertake a self-experiment. I am on 1 mg (-)-deprenyl daily since January 1, 1989. After the lapse of 25 years, my self-experiment so far augurs well. I wish to thank Dr. Donald Klein again for his comments, which coming from a leading expert in our field might be helpful in disseminating the CAE problem to a wider audience and foster additional interest.

May 1, 2014

Comment by Larry Stein (on all three books by Joseph Knoll)

At the approach of Professor Joseph Knoll's 90th birthday next year – and honored to be asked to add a few words to the detailed commentaries of Dr. Miklya and others who worked with him – I wish to underscore the contributions of this brilliant and courageous Jewish-Hungarian scientist to neuropsychopharmacology.

Why the emphasis on “Jewish-Hungarian scientist”? I am recalling the five extraordinary Jewish-Hungarian scientists – von Kármán, Szilard, Wigner, von Neumann, and Teller – whose remarkable insights changed twentieth-century physics and made vital contributions to the defense of the free world in World War II (see I. Hargittai, *Martians of Science*, Oxford University Press, 2006). In neuroscience, too, Hungarian researchers have made historic contributions. Following University of California Irvine neurobiologist Ivan Soltesz (*Trends Neurosci.* Oct 2011; 34(10): 501–503), I could mention “Károly Schaffer (of ‘Schaffer collaterals’), Mihály Lenhossék (who introduced the term ‘astrocyte’), and János Szentágothai (whose numerous contributions include the recognition of the basis of lateral inhibition in the cerebellar cortex) and others” (p. 501). Might there be a special Hungarian gene pool which favors the scientific enterprise, one wonders, marked perhaps by a surplus of alleles for creativity and imagination?

Why “courageous”? First, there is Knoll's personal life story. As Dr. Miklya briefly indicates, he is an indomitable survivor of Auschwitz and Dachau. Secondly, I salute his intellectual valor. It must have required unusual courage for Knoll – in communist Hungary in the 1960's – to depart from the traditions of Pavlovian reflexology and focus instead on the American behaviorist approaches of Thorndike and Skinner. At an early point, Knoll thus recognized that goal-directed (operant) behavior provides a more fruitful target than the conditioned reflex for the scientific investigation of neurological and psychiatric illnesses and for therapeutic drug discovery. In describing his neurobehavioral hypotheses, Knoll prefers the conceptual term “drive” to “reinforcement” (the term favored by Olds and myself, and later Crow, Koob, Wise and others, in our related work on brain self-stimulation and drug self-administration reward), but there is a common emphasis on brain catecholamines as decisive neurochemical facilitators of goal-directed actions. Interestingly, Knoll and I apparently conceived our catecholamine-facilitation hypotheses from the same pharmacological fact: i.e., serendipitous observation of markedly augmented goal-directed behavior in rats following moderate doses of amphetamine or methamphetamine. (Curiously, because his drug doses and current levels always were too high, Olds initially reported only suppression of self-stimulation with amphetamine.)

Finally, Professor Knoll and I share a rare speculative interest in a potential role for the largely-neglected “trace” amine, β -phenethylamine (PEA). In typically daring fashion, Knoll hypothesizes that PEA serves as a critical “mesencephalic enhancer substance” for the regulation of many functions, including mood, learning and memory, sexual behavior, and even longevity (*The Brain and Its Self*, Springer, 2005, pp. 27-90). And

indeed, consistent with his hypothesis, Knoll finds significant life-extending effects in rats chronically treated with selegiline [(-)-deprenyl], a drug he himself invented, which selectively inhibits the oxidative metabolism of PEA and dopamine. My own involvement with PEA is more empirical. In 1964, I found that PEA, largely without effect by itself on brain self-stimulation or other operant behaviors, exerted a strong stimulant action indistinguishable from that of amphetamine when rats were pretreated with iproniazid or other inhibitors of monoamine oxidase (L. Stein, Fed. Proc.23, No. 4, 836-850). This key observation, together with complementary experiments utilizing the amine-depleter reserpine, established that the central actions of amphetamine are not exerted directly on brain catecholamine or serotonin receptors, as then was generally believed, but rather are mediated indirectly via the release “of a phenethylamine derivative (such as a catecholamine)” (p.850).

September 18, 2014

Reply to Larry Stein by Joseph Knoll

I am thankful for your comments so rich in ideas. Let me just pick out the PEA problem, which still deserves special attention. Thousands of papers have described and analyzed this trace amine in the mammalian brain, classified as a releaser of catecholamines. Owing to the synthesis of amphetamine and methamphetamine, the long-acting PEA-derivatives in the 1930's, these compounds played a key role as special stimulants of the catecholaminergic brain engine. However, light was thrown only in the mid 1990's on the fact that PEA is primarily an endogenous catecholaminergic activity enhancer (CAE) substance and in very high concentrations, only a releaser of catecholamines. Amphetamine and methamphetamine are PEA-derived CAE substances which, like their parent compound, are releasers of catecholamines. The CAE effect of PEA and the amphetamines remained undetected for decades because the catecholamine releasing effect concealed their detectability. Only the synthesis of (-)-deprenyl, the first PEA-derivative devoid of the catecholamine releasing property, made the CAE effect clearly visible. (-)-Deprenyl, still known as the first selective inhibitor of B-type MAO, blocks this enzyme in the brain of rats in a subcutaneous dose of 0.25 mg/kg and exerts its specific CAE effect in a subcutaneous dose of 0.001 mg/kg. (-)-Deprenyl paved the way for the development of (-)-BPAP, the most selective and most potent synthetic enhancer substance known, which stimulates enhancer-sensitive neurons in femto/picomolar concentrations and is the ideal pharmacological tool to detect, hitherto unknown, enhancer regulations in the mammalian brain. It is my ardent wish to provoke discussion of enhancer regulation, considering all angles of the question, and to move scientists to examine closely the soundness of the available data. I count upon your aid in this undertaking and I thank you for your appreciation of my work.

November 6, 2014

Heinz E. Lehmann: Non-Tricyclic and Non-Monoamine Oxidase Inhibitors (1982)
 – reviewed by Carlos Morra
Modern Problems of Pharmacopsychiatry (Volume 18)
Karger, Basel (212 pages)

CONTENT: This book is divided into five sections, preceded by the Editor's Foreword. Section One, *Neurotransmitter Modifiers*, includes six papers. It opens with a paper on *Monoamine Uptake Inhibitors (MAUI)* by T.A. Ban, in which he reviews the status of ten structurally different groups of non-tricyclic antidepressants that belong to this category. Then come four reviews on specific drugs: *Maprotiline* by W. Grüter and W. Pöldinger; *Trazadone* by F.J. Ayd and E.C. Settle Jr; *Mianserin* by R.M. Pinder and M. Fink; and *Iprindole* by C. de Montigny. In the last paper of Section One, H.M. van Praag discusses the *Significance of serotonin precursors as antidepressants*.

Section Two, *Ion Transport Modulators* comprises two papers. In the first, J. Mendels addresses the *Role of lithium as an antidepressant* and in the other, R.R. Fieve and K.R. Jamison provide an "overview" and "clinical perspective" on Risperidone. Each of the remaining three sections includes only one paper. In Section Three, a chapter on neuropeptides, by A.J. Prange and P.T. Loosen, examines the status of *Neuropeptides as novel antidepressants*; in Section Four, J.R. Wittenborn presents information on *Antidepressant use of amphetamines and other psychostimulants*; and in Section Five, J.P. Feighner discusses the use of *Benzodiazepines as Antidepressants* with special reference to alprazolam, "a triazolo-benzodiazepine used to treat depression".

REVIEWER'S COMMENT: This volume reflects the status of antidepressant development in the early 1980s. It was a period in which, as Heinz Lehmann, the editor of this volume said in his, *Foreword*, there was, "a whole new generation of antidepressants available for clinical use" and "many more agents of this type were in various stages of pharmacological and clinical investigation". In concluding the volume, Lehman wrote that it was a period in which it seemed, "that antidepressant therapy has broken out of its mold and that future development in the field will be based more on rational search than on empirical trial".

October 30, 2014

Heinz E. Lehmann and Thomas A. Ban: The Butyrophenones in Psychiatry (1964)
– reviewed by **Thomas A. Ban**
Quebec Psychopharmacological Research Association, Montreal (164 pages)

INFORMATION ON CONTENTS: *The Butyrophenones in Psychiatry* is based on the proceedings of the First North American Symposium on the butyrophenones that was held on January 12, 1964, in L'Annociation, Quebec, Canada. The book opens with a *Preface*, in which, the editors give a brief account of the story of the first clinically-introduced butyrophenones, haloperidol and triperidol, from the time of their synthesis, in 1956, to the time of the symposium. By 1964, haloperidol was extensively prescribed in Europe, but in North America, its introduction and use was lagging behind.

The book is divided into two parts, corresponding with the two sessions of the symposium: *Basic Science Session* and *Clinical Session*. From the five papers of the *Basic Science Session* in the first, the pharmacology of butyrophenones was reviewed. It was pointed out that all phenothiazine, thioxanthene and butyrophenone drugs with therapeutic effect in psychoses/schizophrenia are potent “cataleptogens”, antagonize psychostimulants, potentiate barbiturates and general anesthetics and contain a three carbon chain between a tertiary nitrogen and the rest of the molecule (Aurée Beaulnes). The similarities between these drugs are extended, in the second paper, to their effect on capillary permeability in Sprague Dawley rats (Laszlo Kato, Bela Gozsy, Marcel Lemieux, and Andre St. Jean) and in the third, to their effect on the surface electroencephalogram in schizophrenic patients (Herbert Mueller and Hector Warnes). In the fourth paper, the differential effects of haloperidol, chlorpromazine and chlorprothixene were presented on a battery of psychometric performance tests in a group of male schizophrenic patients (St. Jean, Arnold Lidsky, Thomas A. Ban and Heinz E. Lehmann); and in the fifth, the differential effects of the same drugs on spider web formation were discussed (George Groh and Marcel Lemieux).

From the seven reports in the clinical session, in the first, carried out in 84 patients with mixed diagnoses, haloperidol, in an average daily dose of 6 mg for three weeks, was effective in twice as many patients with a diagnosis of “schizophrenia” than with a diagnosis of “neurosis” (Henri Durost, Hilary Lee and Dorothy Arthurs). In the second report, carried out in an open psychiatric setting in a general hospital, haloperidol was not tolerated because it caused severe extrapyramidal side effects (Gerald Sarwer-Foner). In the third, a comparative clinical study of haloperidol, chlorpromazine and chlorprothixene in 30 acute schizophrenic patients, all three drugs produced favorable changes in symptoms related to arousal and affect, with haloperidol affecting a wider range of symptoms than the other two drugs (Heinz E. Lehmann, Thomas A. Ban, Valerie Matthews, and T. Garcia Rill); and in the fourth, based on two open clinical trials with a total of 28 patients, in one, haloperidol was effective in controlling agitation in the daily dose range from 7.5 mg to 15 mg, and in the other, in controlling hallucinations and delusions in the daily dose of 4.0 mg (Yves Rouleau and Bernard Jean). In the fifth report, based on a study that followed a latin-square cross-over design with haloperidol, triperidol, and floropipemide in 15 chronic psychotic patients, all

three butyrophenones decreased psychotic symptomatology, with triperidol most, floropipemide least, and haloperidol in between (Warnes, Lee and Ban); and in the sixth, carried out in a total of 30 chronic schizophrenic patients, haloperidol was more effective than fluphenazine in excited, agitated patients, whereas fluphenazine was more effective than haloperidol in inactive and withdrawn patients (Ban and Edgar Stonehill). The final, seventh presentation of the clinical session, was an overview of the symposium. It concluded: “the butyrophenones are valuable drugs which contribute to our present (1964) therapeutic armamentarium in psychiatry” (Ban).

REVIEWER’S STATEMENT: The First North American Symposium on The Butyrophenones in Psychiatry was also the first symposium of the Quebec Psychopharmacological Research Association (QPRA), founded in the summer of 1963, by a small number of psychiatrists in the Province of Quebec, Canada, who were interested in improving the standards of research in psychopharmacology and communication of new findings in pharmacotherapy in psychiatry. The material presented in this book, with the exception of the papers on the pharmacology of butyrophenones by Beaulnes and on the aborted clinical study with haloperidol by Sarwer-Foner is based on studies carried out by members of QPRA from the Verdun Protestant (now Douglas) Hospital and from Hopital des Laurentides at L’Annonciation, Quebec. There was close research collaboration in psychopharmacology between these two hospitals that led to systematic clinical investigations with potential new psychotropics. In case of the butyrophenones, this collaboration included studies on the effects of these drugs on the surface electroencephalogram and psychometric performance tests, exploratory investigations in patient with different diagnoses and comparative studies with drugs already in use for psychoses/schizophrenia.

March 27, 2014

**Heinz E. Lehmann and Thomas A. Ban: Toxicity and Adverse Reaction Studies with Neuroleptics and Antidepressants (1965) – reviewed by Thomas A. Ban
Quebec Psychopharmacological Research Association, Montreal (184 pages)**

INFORMATION ON CONTENTS: *Toxicity and Adverse Reaction Studies with Neuroleptics and Antidepressants* is based on papers presented at three meetings of the Quebec Psychopharmacological Research Association. The first, on Toxicity (chaired by E. Kingstone), was held on March 22, 1965, at the Allan Memorial Institute, in Montreal, Quebec, Canada; the second, on Skin Pigmentation and the Phenothiazines (chaired by A.S. McPherson), on April 30, 1965, at the Douglas Hospital, in Verdun, Quebec; and the third, on Electroencephalographic Changes with Psychoactive Drugs (chaired by A. St. Jean), on June 4, 1965, at Hôpital des Laurentides, in L'Annonciation, Quebec. Accordingly, the book is divided into three corresponding parts: *Toxicity*, edited by Kingstone; *Skin Pigmentation and the Phenothiazines*, edited by McPherson; and *Electrocardiographic Changes with Psychoactive Drugs*, edited by St. Jean.

In Part One, “toxicity study requirements” prior to the introduction of a psychoactive drug into clinical investigations and use are reviewed, from the *Pharmacologists Viewpoint* (J. Brodeur), the *Clinical Pharmacologists Viewpoint* (L. Joubert) and the *Legal Aspects* (R.W. Shepherd and W. Murphy). The three papers of Part One are preceded by an *Introduction* (McPherson) and followed by a *General Summary* (McPherson) and a *Bibliography* that lists 11 references.

In Part Two, skin pigmentation encountered during chronic phenothiazine (primarily chlorpromazine) treated patients are discussed. From among the 17 papers, the first deals with the *Incidence* of skin pigmentation in phenothiazine treated patients (G. Marier) and the second reviews *Experience at Douglas Hospital* (DH) with skin pigmented patients (T. Ban). All patients with skin pigmentation at Douglas Hospital were studied by a team of medical specialists and the findings of these studies were presented in nine reports: (1) *Dermatological Aspects* (W. Gerstein); (2) *Ophthalmological Aspects* (K. Adams); (3) *Neurological Aspects* (M. Vulpe); (4) *“Electroencephalographic Aspects* (H.F. Muller); (5) *Electrocardiographic Aspects* (J. Ballon); (6) *Hematological Aspects* (J. Blustein); (7) *Gastroenterological Aspects* (H. Warnes); (8) *Bronchopulmonary, Genito-urinary and Endocrinological Aspects* (D. Findlay); and (9) *Clinical Aspects* (H.Lee, H.E. Lehmann and T.A.Ban). From the remaining six papers, one is a *Psychiatrist's Comment* (D.R. Gunn) on skin pigmentation, another deals with *Chlorpromazine metabolism* (I.S. Forrest), a third reports on a possible *Therapy* (B.A. Gibard) of skin pigmentation, a fourth, presents *Post-mortem findings* (N. Kerenyi), a fifth addresses the *Histogenesis* (G. Rona) of increased melanin production, and the sixth describes findings on the *Distribution of chlorpromazine in animal eyes* (H.Green and T.Ellison). The 17 papers are preceded by an *Introduction* (McPherson) and followed by a *General Summary* (McPherson) and a *Bibliography* that lists 52 references.

In Part Three, *Electrocardiographic changes with psychoactive drugs*, with special emphasis on thioridazine-induced conductance changes in the ECG are discussed. From the nine papers of Part Three, two are literature reviews: *Neuroleptic drugs and the ECG* (E. Kingstone), and *Antidepressants and the ECG* (B. Lavallee); three are reports on ECG findings in *Studies with phenothiazines* (P.B. Roy, A. St. Jean, S. Desautels), *Studies with Thioridazine* (A. St. Jean, S. Desautels, J. Ballon and T.A. Ban) and *Experiments with Thioridazine*; two are notes on ECG changes with *Amitriptyline, haloperidol and thioproperazine* (A. St. Jean and T.A. Ban), and with *butaperazine and haloperidol* (H.E. Lehmann, T.A. Ban, H. Warnes and H. Lee); and one is an account of *A pharmacological study* on the possible anti-arrhythmic effect of some phenothiazine drugs (J. Brodeur). In addition, *The cardiologist's viewpoint* about the psychoactive drug induced ECG changes, and especially, about thioridazine-induced conductance, was discussed by J. Ballon, and *The pathologist's viewpoint* by G. Rona. The nine papers are preceded by an *Introduction* (St. Jean), and followed by a *General Summary* (St. Jean) and a *Bibliography* that lists 40 references.

EDITOR'S STATEMENT: This is the third volume of a series published by the Quebec Psychopharmacological Research Association. In the first, the proceedings of the first North American symposium on *The Butyrophenones*, and in the second, on *Trimipramine*, were presented. This, third volume, provided an opportunity to discuss findings in our studies published, in 1964, in which we demonstrated dose-dependent cardiac conductance changes with thioridazine (Ban TA, St. Jean A. The effect of phenothiazines on the electrocardiogram. *Canadian Medical Association Journal* 1964; 91: 537-41) and in 1965, in which we reported on skin pigmentation in schizophrenic patients treated with large doses of chlorpromazine over a long period of time (Ban TA, Lehmann HE. Skin pigmentation, a rare side effect of chlorpromazine. *Canadian Psychiatric Association Journal* 1965; 10: 112-24).

June 19, 2014

**Heinz E. Lehmann and Thomas A. Ban: Pharmacotherapy of Anxiety and Tension (1970) – reviewed by Thomas A. Ban
Charles C. Thomas, Springfield (129 pages)**

INFORMATION ON CONTENTS: *Pharmacotherapy of Tension and Anxiety* is divided into seven chapters, including *Introduction* and *Conclusions*. It opens with an exposition of the “clinical and conceptual uncertainties” about anxiety and its pharmacological treatment. The first paragraph of the *Introduction* reads: “Americans are now spending over \$500 million each year for sedative drugs --commonly called tranquilizers-- to combat a wide variety of conditions gathered loosely together under the name of anxiety. Virtually all of this money is spent on doctor’s prescriptions; one out of ten prescriptions is for this type of drugs. This is despite the fact that the very conditions for which the drugs are being ordered are still often poorly understood by the clinicians, that they defy still a widely acceptable scientific definition, and despite the fact that there still is no general agreement as to the mechanism of action of tranquilizers or even their clinical effectiveness”. The *Introduction* (Chapter I) continues with the definition of “anxiolytic sedatives”; the tracking of the term “tranquilizer” to 1822; the definition of the term “anxiety” from existential, clinical and experimental standpoints; and the differentiation of “anxiety” from stress, tension, arousal, excitement and depression.

In Chapter II, the different “types of drugs” used in the past and present to control anxiety, psychomotor restlessness and insomnia introduced during the second part of the 19th century, are reviewed, including the bromides, chloral hydrate and paraldehyde; and the barbiturates, propanediols, benzodiazepines, carbinols, piperidinediones, quinazolones and dipenylmethanes, brought into clinical use, subsequently, in the first seven decades of the 20th century. The information on barbiturates, popanediols and benzodiazepines, the three groups of drugs that dominated prescribing for anxiety, in this order chronologically, includes details about their chemical structure; absorption, metabolism and excretion; neurochemistry and neurophysiology; behavioral pharmacology; and adverse effects, including toxicity and dependence.

In Chapters III and IV, the common and differential “behavioral effects” (Chapter III) of anxiolytic sedatives, as well as their “interaction with conditioning”(Chapter IV) are discussed. Special attention is paid to their effect on perceptual, cognitive and psychomotor performance in humans, and to their property of increasing conflict tolerance in both animal and human experiments.

In Chapter V, the “possible mechanism of action” of anxiolytic sedatives is entertained. It is suggested that traditional sedatives, like the barbiturates, inhibit the entire feedback network that plays a role in anxiety, i.e., the reticular activating system (RAS), the limbic lobe and the neocortex, whereas the newer anxiolytic sedatives, like propanediols and benzodiazepines, have less inhibitory effect on the RAS and neocortex than on limbic structures. In so far as biochemical changes are concerned, most anxiolytic sedatives either decrease catecholamines or antagonize their effects:

meprobamate decreases catecholamine excretion, chlordiazepoxide blocks stress-provoked rise of catecholamines, diazepam antagonizes the central stimulant effect of noradrenaline, and barbiturates lower both noradrenaline and adrenaline excretion in humans. Furthermore, both chlordiazepoxide and diazepam suppress the somatotrophic hormone, while increasing the output of 7-ketosteroids.

The book culminates in Chapter VI, in which “clinical applications” of anxiolytic sedatives are discussed with consideration of some “general principles” about their use. This is followed by identification of their “general indications” that includes anxiety, a subjectively distressing symptom, somatic (autonomic) and behavioral manifestations of tension states, behavioral excitement and insomnia, perceived as a functional disorder of a biological rhythm. The chapter also includes information on “specific indications” for some of the anxiolytic sedative drugs; findings in “comparative studies” with anxiolytic sedatives; and a discussion of their “limitations and dangers”, such as “suicide”, “dependence and withdrawal” and “effects on driving”.

In the final, concluding chapter (chapter VII), characteristics that the authors believe would be an ideal anxiolytic sedative are described, and some leads for developing new anxiolytic sedatives drugs are entertained. One such lead is the finding that the spinal fluid of sleeping animals contains an unidentified substance that induces sleep when transfused into other animals.

The book is complemented with a *Bibliography*, a *Compendium of Anxiolytic Sedatives* and an *Author and Subject Index*.

REVIEWER’S STATEMENT: At the time *Pharmacotherapy of Tension and Anxiety* was written, benzodiazepines dominated prescription practices for anxiety and tension in the United States. Originally prepared for a chapter in a multi-authored text, *Pharmacotherapy of Tension and Anxiety*, found its place in W. Horsley Gantt’s series on *American Lectures in Objective Psychiatry*.

March 20, 2014

**H.E. Lehmann, M. Berthiaume and T.A. Ban: Trimipramine: a New
Antidepressant (1964) – reviewed by Thomas A. Ban
Quebec Psychopharmacological Research Association, Montreal (105 pages)**

INFORMATION ON CONTENTS: Trimipramine was synthesized, in 1956, by Jacob and Messer with the hope that it will combine the effect of imipramine on dysthymic mood and psychomotor inhibition with those of levomeprazine on states of anxiety and sleep disturbances. The synthesis resulted in trimipramine, a substance that differed pharmacologically from imipramine in that it reduced epinephrine-induced hypertension, while increasing the hypertensive effect of norepinephrine. The psychotropic properties of the substance were recognized and first evaluated in France, where the preclinical and clinical aspects of the drug were studied by Julou, Dutertre, Lambert, Sigwal, Vidal, Géraud, Millon and Pommé.

The material in this book is divided into two parts (Basic Science Session and Clinical Session), preceded by a *Preface* and followed by a *Bibliography* of publications on the drug. The *Basic Science Session* opens with Heinz E. Lehmann's *Introduction*, in which he notes that the "issue of antipsychotic versus antidepressant pharmacotherapy has recently (1964) come under scrutiny" because there are psychotic non-depressed patients who improve when they receive antidepressant medication, and there is a certain proportion of depressed patients who benefit from antipsychotic medication. He also expressed concerns about the lack of indicators for identifying those patients who will derive the greatest benefit from a particular psychoactive drug. Lehmann concludes his introduction as follows: "A more sophisticated diagnostic classification of our psychiatric patients has become an urgent requirement if we want to become closer to the ideal of good physicians who treat their patients as individuals and not statistical probabilities." From the five papers that follow, in the first, the pharmacology of trimipramine is reviewed by Aurèle Beaulnes; in the second, the effects of trimipramine on capillary permeability alterations induced by dextran in the rat are presented by L. Kato, B. Gozsy, M. Lemieux and A. St. Jean; in the third, the effects of the substance on the human electroencephalogram are discussed by Maurice Coulombe; in the fourth, the effects of trimipramine, levomepromazine and chlorpromazine on a battery of "psychophysical test performance" are compared by A. St. Jean, T.A. Ban and W. Noe; and in the fifth, the differential effects of trimipramine and chlorpromazine on spider web formation are described by G. Groh and M. Lemieux.

The Clinical Session opens with Pal Rajotte's *Introduction*, in which he emphasizes the importance of establishing clearly the effectiveness of potential new antidepressants, in view of the experience that some of these drugs in clinical investigation had failed to fulfill expectations in terms of therapeutic effects. From the eight papers that follow, in two, one conducted by R. Legault and the other by R. Côté, the effects of trimipramine are described in 81 and 19 patient with anxiety and depression, respectively; and in another two, one conducted by Y. Rouleau, and the other conducted by I. Erutku, T.A. Ban and H.E. Lehmann, the effects of the substance are discussed in 100 and 20 newly admitted depressed patients, respectively. In one paper, findings in two studies, both

conducted in geriatric patients by H.E. Lehmann, V.A. Kral, T.A. Ban, H. Ast, C. Barriga and A Lidsky, are presented. From these two studies, in one, the substance was used as add-on medication in 10 patients, whereas in the other, a placebo-controlled study, the substance was used in 12 patients as sole medication. Finally, in two studies, one conducted by A. Scarlato, W. Jacob and L. Kelen in 129 patients, and the other by W. Jacob in 102 patients, the effects of the substance were described in general practice.

The book concludes with a chapter by Thomas A. Ban on *Trimipramine in psychiatry*, in which the history of trimipramine is briefly reviewed and the findings presented in the *Basic and Clinical Sessions* in this volume are integrated with the published literature.

EDITOR'S STATEMENT: *Trimipramine: A New Anti-Depressant* is based on the proceedings of the first North American Colloquium on Trimipramine, organized by the Quebec Psychopharmacological Research Association (QPRA) at St. Jean-de-Dieu Hospital, in Montreal-Gamelin, Quebec, Canada, on May 28, 1964. This was the second meeting of the QPRA. The first, held in January 1964, attempted to place a new group of drugs with anti-psychotic properties, the butyrophenones, in the proper place in the therapeutic arsenal of psychiatry. The goal of the second meeting was to introduce trimipramine, a substance already in clinical use in the treatment of depression in Europe, at the time, in North America.

June 26, 2014

Peter R. Martin, Bennett A. Weinberg and Bonnie K. Bealer: Healing Addiction: an Integrated Pharmacopsychosocial Approach to Treatment (2007) – reviewed by Peter R. Martin

John Wiley & Sons Inc., Hoboken, New Jersey (248 pages)

INFORMATION ON CONTENTS: *Healing Addiction: an Integrated Pharmacopsychosocial Approach to Treatment* is divided into five parts, complemented by a *Foreword* (written by Patrick J. Carnes) and *Prefaces* by the authors: Part 1, entitled *Out of Control: The Biopsychosocial Model of the Causes of Addiction* deals with various clinical presentations and the progression of addictive disorders, epidemiology and changing attitudes about these disorders, brain changes and complications associated with drug use and biopsychosocial underpinnings of addiction; Part 2, *The Integrated Approach: Pharmacopsychosocial Treatment of Addiction as a Bona Fide Mental Illness*, with identification, diagnosis and the treatment process; Part 3, *Gaining Understanding: Treating Drug Addictions*, with different drug use disorders, including alcohol, opioids, central nervous system depressants, stimulants and marijuana and tobacco; Part 4, *Gaining Understanding: Treating Behavioral Addictions*, with the neurobiological mechanisms of behavioral addictions, such as problematic hypersexuality, pathological gambling, food-related disorders and the fundamental role of learning in these behaviors; and Part 5, *Recovery as an Ongoing Process: Control is Never Complete*, with definitions of treatment success and strategies for managing recovery over a lifetime. The volume is complemented by a *Glossary of Terms*, *Helpful Websites*, *Epidemiological Tables*, *Pharmacological Treatment of Withdrawal Syndromes*, *Pharmacological Maintenance Strategies for Substance Dependence after Detoxification Is Completed*, and a *Bibliography*.

AUTHOR'S STATEMENT: The central concept of this book is the "Pharmacopsychosocial Treatment Triangle", which represents the integrated delivery to the addicted patient of treatment which includes (A) pharmaceutical therapies for primary addictive disorders and co-occurring other psychiatric conditions, as indicated; (B) psychological therapy and counseling specifically adapted to substance use and/or behavioral addiction disorders; and (C) social support incorporating a network of the patient's family, friends and members of the appropriate mutual support groups, e.g., 12-Step programs.

If appropriately delivered, the pharmacopsychosocial treatment of addictive disorders resonates with, and specifically addresses, each of the elements of the biopsychosocial model of drug use disorders and behavioral addictions. This book underlines that these are *bone fide* mental illnesses whose treatment outcomes equal those of other chronic illnesses encountered in medical practice and present similar challenges to the treating physician. The greatest obstacle to success is recognizing that drug use and other addictive disorders may masquerade as other psychiatric and medical conditions, which in fact, are not the underlying problem, but rather represent clinical complications of the primary disorder.

The reason that drug use and other addictive disorders are so often not correctly identified by psychiatrists has to do with limited training received in residency, the associated stigma and therapeutic nihilism, the belief that not much can be done for these patients. Thus, it seems easier to label the patient's signs and symptoms as an affective or thought disorder, for which the psychiatrist has many psychopharmacologic tools in his armamentarium. However, these tools are mostly ineffective if the appropriate diagnosis is not made. Rather, the problem that must be addressed is the addictive process, not simply its complications. Recent advances in developing pharmacologic strategies for treatment of the addiction *per se* is a conceptual advance that has become a major component of the Pharmacopsychosocial Treatment Triangle and is discussed in this book.

Another theme in the book is that some of the same neurobiological mechanisms involved in drug use disorders come into play in repetitive and out-of-control behaviors that are self-destructive, e.g. problematic hypersexuality, gambling and over-eating associated obesity or food restriction. An especially important implication of this notion is that it might be feasible to utilize the Pharmacopsychosocial Treatment Triangle in management of disorders, heretofore considered "medical" in nature, such as obesity-induced type 2 diabetes mellitus. Individuals with this form of diabetes, which constitutes a major healthcare challenge in the developed world, might well benefit from focusing on the behavior of over-eating, much as the treatment approach for addictive disorders. This would be a significant advance over simply controlling blood glucose or addressing insulin resistance, the currently-practiced and mostly ineffective approach to treatment (unless of course lifestyle change is also achieved).

The major points in the book are underlined using relevant case studies, which provide an integrative guide to understanding and treating addiction that draws on advances in neuroscience, pharmacology, social sciences, and psychological research. It presents a model of addiction as a mental illness involving physiological changes in the brain, and addiction treatment as requiring both medical and psychosocial components. It is intended as a resource for physicians, professionals in the addiction community, for social scholars and policy makers, and for the interested general reader.

February 13, 2014

Bertalan Pethö and Thomas A. Ban: DCR Budapest-Nashville in the Diagnosis and Classification of Functional Psychoses (1988) – reviewed by Thomas A. Ban Karger, Basel: *Psychopathology* 21(4-5):152-240

In collaboration with Andras Kelemen, Gabor Ungvari, Istvan Karczag, Istvan Bitter, Judith Tolna (Semmelweis Medical University, Budapest), Marek Jarema, Francois Ferrero, Eugenio Aguglia, Giovanni Luca Zuria, Olaf K. Fjetland (Vanderbilt University, Nashville)

Based on Pethö B, Ban TA, Kelemen A, Ungvari G, Karczag I, Bitter I, Tolna J: Kutatasi Diagnosztikai Kriterionok functionalis psychosisok korismeresehez. Ideggyogyaszati Szemle 1984; 37: 102-31. (In Hungarian).

INFORMATION ON CONTENT: Recognition of the inadequacy of diagnostic categories in Kraepelin's classification for psychiatric research led to the development of the KDK Budapest and its English adaptation, the DCR (Diagnostic Criteria for Research) Budapest-Nashville. The DCR is based on a linear disease model; a socio-medical concept of psychosis; and psychopathology-based diagnoses. In the DCR, an attempt was made to synthesize the experience of different psychiatric schools (German, Scandinavian, French, American, English), and for the identification of pathognomonic and holistic characteristics of psychiatric illness. Karl Leonhard's classification of endogenous psychoses, based on clinical syndromes described by Carl Wernicke and Karl Kleist, was chosen as the framework, because it is a more detailed and subtle classification than Kraepelin's or Bleuler's. However, the DCR is not a replica of Leonhard's classification even with regard to endogenous psychoses. It differs from Leonhard's system by its emphasis on the characteristics of the form (Gestalt) and overall clinical picture, and by its shift of emphasis from the end state to the first or index psychosis. The central component of the DCR is its Diagnostic Assessment Scale (DAS), a diagnostic decision tree that consists 524 variables, organized into 179 diagnostic decision clusters yielding to 213 (including tentative, provisional, working, final, atypical and undifferentiated) diagnoses. It separates "minor psychiatric disorders" from the "psychoses" and "symptomatic-organic psychoses" and "mental retardation with psychoses" from the "functional psychoses," before entering into differentiation within the "functional psychoses". Thus, in the DCR, "functional psychoses" are divided into "reactive" ("psychogenic") and "endogenous" with "delusional development" in between; "endogenous psychoses" into "affective" ("phasic") and "schizophrenic" with "cycloid psychoses" in between; "affective psychoses" into "bipolar" and "unipolar", and "schizophrenic psychoses" into "nonsystematic" and "systematic." The DCR includes a glossary of all DAS items, in which definitions are primarily based on John (Jan) Hoenig and Marion Hamilton's translation from German into English, the 7th edition of Karl Jaspers' *General Psychopathology*, and on William Guy and Thomas A. Ban's translation from German into English, the 3rd edition of the *AMDP (Association for Methodology and Documentation in Psychiatry) System Manual*. It also includes definition of DCR diagnoses, a display of DCR's diagnostic process and a list of 72 original references.

AUTHOR'S STATEMENT: The KDK Budapest was developed by a team of Hungarian psychiatrists in the Department of Psychiatry, Semmelweis University, involved in research in "endogenous psychoses" under the leadership of Bertalan Pethö. Instrumental to its development was Pethö's adoption of Jasper's contention that in nosology one is guided by the "idea of disease" in order to isolate "relative disease entities" that would provide "useful orientation points" for research; his definition of "psychosis" as a nonspecific syndrome, characterized by lack of insight and sufficient severity to disrupt everyday functioning with collapse of customary social life that may call for psychiatric hospitalization; and his findings in a six-year follow-up study that supplementation of psychopathological and personality variables with social adjustment variables lowered predictive validity of diagnoses made at the time of the index psychoses. The DCR Budapest-Nashville, the English adaptation of the Hungarian KDK with some minor modifications, was developed in collaboration between Pethö's team in Budapest, Hungary, and Ban's team at Vanderbilt University, in Nashville, Tennessee, USA. Ban's research was focused on resolving the pharmacological heterogeneity of "consensus-based diagnoses". He considered identification of treatment responsive subpopulations within consensus-based diagnoses, a "prerequisite," for breaking the impasse in neuropsychopharmacology research, and in the pharmacotherapy of psychiatric illness with psychotropic drugs. His observations and findings with Leonhard's classification and the German-AMDP System indicated that pursuing research in psychiatric nosology and psychopathology might yield to pharmacologically sufficiently homogeneous populations to meet clinical and research needs. At the time of its publication in the late 1980s, it appeared that DCR diagnoses provide pharmacologically more homogeneous populations than consensus-based diagnoses. Today, almost three decades later, the concept of "functional psychoses" is no longer in the vocabulary of psychiatry, but DCR diagnoses still seem to provide pharmacologically more homogeneous populations than consensus-based diagnoses.

From the 12 co-authors of the DCR, four were to become professors and chairs of university departments in psychiatry: Eugenio Agulia in Trieste, Italy; Istvan Bitter in Budapest, Hungary; Francois Ferrero in Geneva, Switzerland; and Marek Jarema in Warsaw, Poland.

January 9, 2014

**David R. Rosenberg, John Holttum and Samuel Gershon: Pharmacotherapy of Child and Adolescent Psychiatric Disorders (1994) – reviewed by Samuel Gershon
Brunner/Mazel, New York (554 pages)**

INFORMATION ON CONTENTS: *Pharmacotherapy of Child and Adolescent Psychiatric Disorders* opens with a *Foreword* by David Kupfer and a *Preface* by the authors. The text is presented in two sections. In Section I, an *Introduction to Psychopharmacology* in child and adolescent psychiatry is given; and in Section II, *Classes of Medication* used in child and adolescent psychiatry are reviewed. The first section consists of two chapters: one that provides a *Historical Perspective on Child and Adolescent Psychopharmacology*, and another, written by Robert A. Branch, that describes *Characteristics of Drug Disposition* (distribution and elimination) during childhood. The second section consists of 12 chapters, from which 12 (chapters 3 to 12) deal with different classes of drugs, one (chapter 13), with *Pharmacologic Approaches to Consult-Liaison Psychiatry* in child and adolescent psychiatry, and the last (chapter 14), with *Pharmacologic Treatment of Substance Abuse Disorders in Children and Adolescents*. The 12 classes of drugs reviewed from chapter 3 to 12 are: *Psychostimulants*, *Tricyclic Antidepressants*, *Novel (Atypical) Antidepressants* (fluoxetine, sertraline, paroxetine, trazodone, bupropion, and thyroid hormones), *Monoamine Oxidase Inhibitors*, *Antipsychotic Agents*, *Lithium*, *Anticonvulsants*, *Anxiolytics*, and *Adrenergic Agents in Child and Adolescent Psychiatry*. Each chapter includes *References*, and the volume is complemented with an *Appendix*, *Name Index*, *Subject Index*, and *Information on the Authors*.

EDITOR'S STATEMENT: At the time this volume was written, psychopharmacology in children and adolescents was in its infancy. This volume was the first textbook published on the topic of *Pharmacotherapy of Child and Adolescent Psychiatric Disorders*. By the time it was published, adult psychopharmacology had developed to the point where there was already a range of therapeutic agents being prescribed for a variety of psychiatric disorders. It seemed that child psychiatry would inherit a large stock of potential therapeutic agents. Imipramine, for example, by that time was established as an antidepressant in adults and considered as a significant therapeutic advance. Hence, child psychiatry approached this compound as having an excellent possibility of transferring it from adults for use in children and adolescents with depression. This, of course, required dosage adjustments in keeping with weight and age of the patient. It seemed we had all of the potential for a dramatic start in child and adolescent psychopharmacology with this agent. This, however, was not to be the case. Its introduction was followed by a number of positive therapeutic reports in the literature. After several years, the positive reports dwindled and a new question arose...is it actually having a beneficial effect in this population? This question was put to the test of a randomized control trial by Puig Antich and his associates, in 1987, in Pittsburgh. The results, when published caused quite a disappointment for this new field. The reason being, it was shown to be ineffective in the control study. Thus,

preparation of the first edition taught us all that the stockpile of pharmaceuticals in the adult armamentarium could not necessarily be transferred to the child population.

February 20, 2014

**David R. Rosenberg, Pablo R. Davanzo and Samuel Gershon, editors:
Pharmacotherapy of Child and Adolescent Psychiatric Disorders, 2nd Edition
(2002) – reviewed by Samuel Gershon
Marcel Dekker, New York (754 pages)**

INFORMATION ON CONTENTS: The second edition of *Pharmacotherapy of Child and Adolescent Psychiatric Disorders* was published by Marcel Dekker, in New York. It opens with an *Introduction* to the series by William A. Frosch, that is followed by two *Forewords*, one by David J. Kupfer, and the other by Charles B. Nemeroff, a *Preface* by the editors, and the list of its' contributors.

The text is presented in two parts, the first with the title, *Introduction to Psychopharmacology*, and the second, with the title, *Classes of Medication*. Part One includes six chapters, from which in the first a *Historical Perspective on Child and Adolescent Psychopharmacology* is given; in the second, *Ethical Issues in Pediatric Psychopharmacology* are addressed; and in the third, *Pharmacoepidemiology of Psychotropic Medications in Youth* is discussed. Chapter four deals with *Child and Adolescent Psychopharmacology: A Call for Pharmacoeconomics Research*; chapter five reviews *Clinical Pharmacology of Psychoactive Drugs*, and chapter six, describes *Cardiac Side Effects of Psychoactive Drugs in Children and Adolescents*.

Part Two, includes fourteen chapters from which eleven, is dedicated to different classes of medications: *Psychostimulants*, *Tricyclic Antidepressant*, *Selective Serotonin-Reuptake Inhibitors*, *Novel (Atypical) Antidepressants*, *Monoamine Oxidase Inhibitors*, *Antipsychotic Agents*, *Lithium*, *Anticonvulsants*, *Anxiolytics*, *Adrenergic Agents*, and *Atypical and Adjunctive Agents*. From the remaining three chapters, one deals with *Pediatric Psychopharmacology in the Consultation Liaison Setting*, another with *Pharmacological Treatment of Substance Abuse Disorders*, and the third with *Combination Pharmacotherapy* in children and adolescents. The volume is complemented with an *Index*.

REVIEWER'S STATEMENT: The first edition of this text, authored by David Rosenberg, John Holttum and Samuel Gershon was converted into an edited volume (Rosenberg, Davanzo and Gershon) with 17 contributors: Beth Bower, Oskar K. Bukstein, John V. Campo, Pablo A. Davanzo, Mellissa P. DelBello, David J. Edwards, Samuel Gershon, Junius J. Gonzalez, Joseph Kitkas, Robert A. Kovatch, James M. Perel, David R. Rosenberg, Daniel J. Safer, Jess P. Shatkin, Benedetto Vitiello, Vikram K. Yeragani and Julie Magno Zito. The addition of seven chapters extended the scope of information covered in the volume to ethical issues, pharmacoepidemiology, pharmacoeconomics, clinical pharmacology, cardiac side effects, selective serotonin reuptake inhibitors and combination pharmacotherapy in children and adolescents.

April 3, 2014

David R. Rosenberg and Samuel Gershon, editors: Pharmacotherapy of Child and Adolescent Psychiatric Disorders, 3rd edition (2012) – reviewed by Samuel Gershon
Wiley-Blackwell, United Kingdom (453 pages)

INFORMATION ON CONTENTS: This is the third edition of this textbook. The first edition, written by D.R. Rosenberg, J. Holtum and S. Gershon, was published in 1994 by Brunner/Mazel in New York (554 pages), and the second, edited by D.R. Rosenberg, P.R. Davanzo and S. Gershon, in 2002 by Marcel Dekker in New York (745 pages). The historical evolution of the field (1994, 2002 and 2012) is presented in these three volumes. The material in this volume is organized into seventeen chapters. In the first, a historical perspective on child and adolescent psychopharmacology is given; in the second, pharmacoepidemiology of the use of psychotropic medications in youth is reviewed; in the third, off-label prescribing of drugs in child and adolescent psychiatry is presented; in the fourth, the use of generic drugs in pediatric psychopharmacology is discussed; and in the fifth, basic concepts in clinical pharmacology in children with special reference to pharmacokinetics and dosing, are elaborated. These five introductory chapters are followed by ten chapters on the different conventionally used groups of psychotherapeutic drugs in children in the first decade of the 21st century. They include psychostimulants (chapter 6), tricyclic antidepressants and monoamine oxidase inhibitors (chapter 7), selective serotonin reuptake inhibitors (chapter 8), novel (atypical) antidepressants (chapter 9), antipsychotics (chapter 10), lithium (chapter 11), anticonvulsants (chapter 12), anxiolytics (chapter 13) and adrenergic agents (chapter 14). There is a chapter on “atypical psychopharmacologic strategies” (chapter 15) that deals with opiate antagonists, memantine, riluzole, secretin, topiramate, herbal medications and dietary supplements, melatonin, omega -3-fatty acids, St. John’s wort and valerian. The volume concludes with an overview of psychopharmacology in preschool children (chapter 16), and a chapter on combination pharmacotherapy for psychiatric disorders in children and adolescents (chapter 17). It is complemented with an index. The 17 chapters are contributed by 33 authors (in alphabetical order): David A. Axelson, Boris Birmaher, Heidi R. Bruty, Barbara C. Coffey, Paul Croarkin, C. Lindsay DeVane, David J. Edwards, Robert L. Findling, Graham J. Emslie, Anna M. Georgiopoulos, Samuel Gershon, Karim D. Ghalib, Charlotte M. Heleniak, John L. Herzer, Aron Janssen, Gagan Joshi, Tajal Kaur, Joan Luby, Tushita Mayanil, Christopher - Paul Milne, Mani Pavuluri, Steven R. Pliszka, Brieana M. Rowles, Moira A. Rynn, Daniel J. Safer, Dara Sakolsky, Lawrence David Scahill, Richard I. Shader, Jess Shatkin, Garrett M. Sparks, Mini Tandon, Julie Magno Zito, and Amanda L. Zwilling,

EDITOR’S STATEMENT: These three volumes were an educational and historical experience for the editors and we hope, for the readers. The first volume was written when psychopharmacology in children and adolescents was in its infancy. This volume was the first textbook published on the topic of Pharmacotherapy of Child and Adolescent Psychiatric Disorders. By the time of its publication, adult psychopharmacology had developed to the point where there was already a range of therapeutic agents being prescribed for a variety of psychiatric disorders. Thus, it

seemed that child psychiatry would inherit a large stock of potential therapeutic agents. For example, imipramine had been introduced as an antidepressant in adults and was established as a significant therapeutic advance. Child psychiatry approached this compound as an excellent example of the possibility of transferring it for use in children and adolescents with depression. This, of course, required dosage adjustments in keeping with weight and age of the patient. So it seemed we had all of the potential for a dramatic start in child and adolescent psychopharmacology with this agent. Imipramine was, thus, widely used in this new population for the treatment of depression. Its introduction was followed by a number of positive therapeutic reports in the literature. After several years, the positive reports dwindled and a new question arose...is it actually having a beneficial effect in this population? This question was put to the test of a randomized control trial by Puig Antich et al., in 1987, in Pittsburgh. The results when published caused quite a disappointment for this new field. The reason being, it was shown to be ineffective in the control study. Thus, the first edition taught us all that the stockpile of pharmaceuticals in the adult armamentarium could not necessarily be transferred to the child population. We, therefore, undertook an educational update in preparing the second edition to correct this and other findings that had accrued over the intervening years. Then, with the additional information that was being discovered in related fields of drug metabolism, genetics, adverse effects etc., we undertook the third edition.

Rather than expand on our own thoughts about the third edition we are taking advantage of a review of this volume by Theodore A. Petti, M.D., M.P.H. in the *Journal of Clinical Psychiatry*, in July 2012 and quote some excerpts from this review: "The past decade has witnessed the coming of age of child and adolescent psychopharmacology.....Each chapter provides sufficient information about basic properties, the available neuroscience, actions, indications, adverse effects and the evidence base for their use...(it) provides a developmental perspective and considers the hierarchy of responses when treating psychiatrically ill...children with regard to the critical role of psychotherapy and psychosocial interventions...and consider(s) situations when psychopharmacology may be considered as a first line, how to administer and monitor medications... and off-label prescriptions".

May 15, 2014

**Charles Shagass: The Role of Drugs in Community Psychiatry (1971) – reviewed
by Carlos Morra**

**Modern Problems of Pharmacopsychiatry (Series Editors: F.A. Freyhan, N.
Petrilowitsch and P. Pichot), Volume 6
Karger, Basel (128 pages)**

CONTENT: This book is divided into twelve chapters, including an *Introduction* by the volume editor. In chapter two, *The Scope and Limits of Community Psychiatry*, David Goldberg focuses on the rapid expansion of the demand for psychiatric services in the mid-1960s. He points out that community mental health services are “satisfying a part of that need”. From the two chapters that follow, in one, *Drugs in Psychiatric Hospitals*, Jonathan Cole discusses the role that drug treatment has played in the move of psychiatric patients from hospitals into the community; and in the other, *Emergency Pharmacotherapy – the Role of Drugs in Psychiatric Crises*, Anthony Panzetta points out that “crisis intervention is very much a part of the community psychiatric orientation” and “early case detection and treatment is within the preventive concern of the community psychiatry philosophy”. Three chapters (numbers five, six and seven), deal with drugs in different settings: *Drugs in Outpatient Practice*, by Karl Rickels; *Psychiatric Drugs in General Hospitals*, by Albert S. Norris; and *The Role of Drugs in Aftercare, Homecare and Maintenance*, by Else B. Kris. Max Fink provides a special chapter on *Long-acting (Depot) Phenothiazines in Emergency and Maintenance Therapy of Psychoses* and Hunter H. Comly contributes a chapter on, “*Drugs in Child Psychiatric Care*. For the remaining two chapters, James Anthony and Adolfo Rizzo give us *The Effect of Drug Treatment on the Patient’s Family* and Frederick Glaser offers, “*The Abuse and Misuse of Psychopharmacological Agents* and the “relevance of the problem to community psychiatry”.

REVIEWER’S COMMENT: Several authors in this volume express uncertainty about the significance of pharmacotherapy in community psychiatry. They seem to be of the opinion that drugs alone do not provide an adequate solution to “major psychiatric problems” and “may create new difficulties”. Hence, they advocate, along with Charles Shagass, the editor of the volume, a “need to maintain a high level of psychological and social sophistication in clinical situations that may involve drug treatment”.

December 4, 2014

**BIOGRAPHIES, AUTOBIOGRAPHIES AND SELECTED
WRITINGS OF NEUROPSYCHOPHARMACOLOGISTS**

Introduction by Barry Blackwell

Welcome to Project Nine, *Biographies* on the INHN.org website. My name is Barry Blackwell and my contact information is: blackwellbarry@hotmail.com (email) and 414 940 0844 (cell). As coordinator of this program, feel free to contact me at any time (USA, Central Time Zone).

We seek to publish several types of biographies in any one of the following formats:

1. Authors may submit a review of their own *Autobiography* or *Memoir*. This should include a synopsis of both the format and brief comments on the contents. To view an example of this format, see on the INHN website Barry Blackwell: *Bits and Pieces of a Psychiatrist's Life*.
2. An author may mail their book to the coordinator for an independent review either by a colleague they name or by the coordinator. Examples of the latter are Jean Delay, Karl Rickels, Enoch Calloway (*Asylum*), and Frank Berger.
3. Any member of the INHN may submit a biography they have written of an outstanding contributor to our field. These differ from the program *Profiles*, which document only a person's scientific contributions, supported by specific citations. The purpose of a biography is to portray an interesting picture of the individual's persona, including their scientific, organizational, administrative, literary or other contributions. The length may vary considerably, either covering the entire trajectory of a career or focusing on selected highlights. Controversial aspects or issues are acceptable, but if these are prominent, the biography may be placed in the *Controversies* project. For an example, see *A Distinguished but Controversial Career: Jose Delgado*". Citations are acceptable but not always necessary. For examples of shorter more succinct biographies, see *Hassan Azima* (by Hector Warnes) and *Turan Itil* (by Martin Katz). Other examples of varying lengths and styles can be found in the *Dramatis Personae* sections in various volumes of the *Oral History of Neuropsychopharmacology* (Series Editor TA Ban), Volumes 3 thru 7 are particularly illustrative.

The INHN website does not currently have staff to provide detailed editorial assistance. Therefore, it is helpful and desirable if submissions are made in the format for authors provided in the Appendix to the Table of Contents on the Home Page. The completed biography should then be e-mailed to the coordinator (see above) as an attachment in Word. If there are concerns or questions about a potential contribution, please e-mail or call me for advice on how best to proceed.

The *Biographies* section already documents the accomplishments of a number of pioneers in our field and I look forward to collaborating with members to enlarge that archive from your own colleagues, friends, mentors and acquaintances.

November 13, 2014

Hassan Azima by Hector Warnes

Dr. Hassan Azima had a most distinguished career in the field of neuropsychopharmacology during the golden era at McGill University, in the fifties and early sixties, when the fields of neurosurgery, neuropsychology, experimental psychology, neurophysiology, neurobiochemistry, transcultural psychiatry and psychoanalysis blossomed.

Azima was born in Iran, in 1922, and died in Montreal at the Royal Victoria Hospital at the age of 39, in 1962. He obtained his B.A. from the University of California and his M.D. at the University of Kansas, in 1948. After two years' residency at the University of Paris, working particularly with Jean Delay, he joined the McGill Diploma Course in Psychiatry and completed his studies, in 1955, and his M.Sc. a year later. His wife, Dr. Fern J. Cramer Azima, was instrumental in several of the research methodologies during his dazzling career. She was an outstanding psychologist, who was, as was her husband, of international standing. She died in Montreal in 2013. Their many research and clinical contributions were conducted at the Allan Memorial Institute of Psychiatry, where the Chair of the Department of Psychiatry of McGill University, D. Ewen Cameron, was located.

In my contribution to *Reflections of twentieth century psychopharmacology*, edited by T.A. Ban, D. Healy and E. Shorter, published by Animula Publishing House in Budapest (2004), I wrote of my experience of Hassan Azima's brilliant career with an abrupt and untimely ending at the peak of his creativity.

I shall limit myself to his contributions to the field of neuropsychopharmacology, in particular, to his clinical research on two paradigmatic drugs: chlorpromazine and imipramine. He introduced psychodynamics in the interpretation of the positive changes brought about by the newer compounds, including reserpine. His psychoanalytic bent did not cloud at all his clinical research objectivity. Along with his friend, G. L. Sarwer-Foner, who wrote a memorial on the demise of Azima, published in *Recent Adv Biol Psychiatry* (6: 214-216, 1963), he was of the opinion that drugs had a placebo, or symbolic effect based on the doctor-patient relationship; the psychodynamic shifts and the purely pharmacological effects, which Azima described regarding reserpine, each interacting with the other. He goes further to explore this domain in the book edited by G. Sarwer-Foner, *Dynamics of Psychiatric Drug Therapy* (Thomas, Springfield, Illinois 1960). Azima attempted to focus on the alteration of psychological structure with the administration of drugs, which would have psychotherapeutic or psychoanalytic influences. Though he, himself, used statistical methods, he believed that longitudinal follow-up would shed light on these issues. Freud himself was of the persuasion: "...But here we are concerned with therapy in so far as it works by psychological means; and for the time being we have no other. The future may teach us to exercise a direct influence, by means of particular chemical substances on the amount of energy and their distribution in the mental apparatus" (*An Outline of Psychoanalysis*—The Hogarth Press and the Institute of Psychoanalysis- vol.

XXIII, reprinted 1973, page 182).

In his paper on *Anaclitic Therapy*, presented at the Third World Congress of Psychiatry (4-10 June, 1961), he took a stand against: “the use of regressive ECT with or without prolonged sleep is the least satisfactory because of the organic confusion induced, the inaccessibility of the patient to verbal contact, and the incomprehensibility of the events occurring owing to the organic vicissitudes” (vol. II, p. 1074).

His pioneering research on the effect of chlorpromazine (Largactil) followed those of Laborit’s observations in *Hibernation* and introduction by Jean Delay et al. of the drug in the clinical field of mental disorders. H. Azima and W. Ogle (*Can. Med. Assoc. J.* 71(2):116-121, 1954) recognized that Lehmann and Hanrahan were the first to use Largactil in North America and confirmed the observations of the French authors regarding its usefulness in psychomotor excitement.

One hundred unselected patients with mental syndromes were treated with an average dose of 400 mg of Largactil daily for an average period of 3 weeks. The sample consisted of 44 neurotics, 27 schizophrenics, 25 manic depressives, one patient with paranoid psychosis and 3 with organic brain syndromes. It is of interest that the drug moderately helped the cases of neurotic anxiety but not those with obsessional neurosis. Among the schizophrenics, there was a reduction of symptoms associated with better socialization. Among the five cases of manic excitement, 3 recovered and 2 were refractory and had to receive ECT. Azima and Ogle noted the sympatholytic and neuroleptic effects, along with a tendency to hypometabolism and hypotension in most cases. The side effects reported, including somnolence or apathy, the potentiation of barbiturates, the increase of weight and appetite, maculo-papular rash on the skin, plus hepatotoxic potential and Parkinson-like symptoms were noted in a few cases.

Azima’s research on imipramine (Tofranil) was published in the *Can. Med. Assoc. J.* 80(7):535-540, 1959. I shall quote from his introduction, “Following R. Kuhn, observations concerning the therapeutic efficacy of an iminodibenzyl compound in a preliminary trial of 65 depressed patients and a clinical and psychodynamic study proved this substance to have a potent antidepressant capacity and very little or any effect on other mental syndromes. Concomitantly, Lehmann, Cahn and De Verteuil reached similar conclusions” (p. 535). Approximately half of the 100 depressed patients were neurotic and half were psychotic depressives (agitated, non agitated and involuntal)...“Psychotic depression showed twice as great improvement as neurotic depression” (p.540). Azima was of the opinion that there was a continuum between neurotic and psychotic depression, based on the level of regression:

- a) the severity of the feeling of depression and guilt;
- b) the degree of regression and of ego disorganization;
- c) the intensity of self-destructiveness;

- d) the intensity of agitation;
- e) the involuntional age; and
- f) the presence or absence of depression or manic attacks in the past or in their relatives.

The dose of Tofranil started with 75 mg up to a maximum of 200 mg daily in a few cases. Generally, there was a lapse of 30 days before the optimal therapeutic response was seen. About 50% of patients responded in 10 days and 70 % in two weeks. He noted that the treatment should continue for at least 3 months and the discontinuation of the drug should be gradual within 10 days...“many patients will require long term maintenance therapy for from 6 to 12 months or more” (p. 537). In 10 patients, there was a shift to a manic state and Azima recommended the use of chlorpromazine or promazine to control the symptoms. Regarding the side effects, they were the usual atropinic side effects, including more difficult to control tremors (20%). Lowering the dose was sufficient to overcome the side-effects. I must cite an amazing observation: “about 80% of patients requiring ECT may no longer require this treatment” (p.539) and he recommended that the drug could be used in ambulatory care and by general practitioners or other specialists, not only in the treatment of depressive disorders but in the treatment of premenstrual disorders, skin disorders and addictions.

Azima investigated several compounds, including the use of Mellaril in the treatment of 75 patients (44 schizophrenics, 6 manic depressive, 2 organic psychotics and 23 neurotics) with an average dose of 400 mg for 3 weeks in acute cases and 3 months in chronic cases, using a single blind method compared longitudinally in 3 groups of 40 patients, each with chlorpromazine and promazine (*The effect of thioridazine [Mellaril] on mental syndromes - comparison with chlorpromazine and promazine*, H. Azima, H. Durost and Dorothy Arthurs, *Can. Med. Assoc. J.* 81 (7): 549-553, 1959). They reported that the response to thioridazine was similar to that of chlorpromazine, except for the fewer side effects of Mellaril, particularly the lack of extrapyramidal and liver complications.

It would be beyond the scope of this paper to discuss each of the many studies and publications carried out by H. Azima on consciousness, on homeostasis in schizophrenic patients, anaclitic therapy, perceptual and sensory isolation, on the effects of meprobamate in sustained high dosage, on sleep treatment and on basic science and psychiatry.

September 4, 2014

**Frank M. Berger: A Man of Understanding: A Noted Scientist's Guide to
Happiness and Success (2013) – reviewed by Barry Blackwell
ACB Publishing LLC, New York (268 pages)**

Frank Berger's posthumously assembled book of short writings, *A Man of Understanding*, 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."

Readers should realize the who, the how and the 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 break-through 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, 1955-1956, 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: Series Editor Thomas A. Ban: Volume 3, Editor Fridolin Sulser and Volume 9, Editor Barry Blackwell).

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 his 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 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 and 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; and 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, scientist, 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.”

August 21, 2014

**Enoch Callaway: ASYLUM: A Mid-Century Madhouse and its Lessons about
Our Mentally Ill Today (2007) – reviewed by Barry Blackwell
Praeger, Westport, Connecticut (187 pages)**

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 & 2) using them as a metaphor (Parts 3 & 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.

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).

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 till 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 with Clark University Physiology Department in laboratory space provided by the hospital. This collaboration 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 neuroscience era. To Noch, the environment mirrored the image of the 1947 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 3000 patients, 1000 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 forty year decline in prestige and influence of psychoanalysis 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 sixty 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, Thomas A. Ban, which together detail an 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 fifty 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 “back-wards” 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.” None the less, 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 give the impression that one knows what one is talking about. They not only mask the mystery of the disease but give the impression 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 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 against 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 enquired 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 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 Noch’s “misguided” advice, Tom 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 residents 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. 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 (see *An Oral History of Psychopharmacology*, ACNP 2011, Series Editor Thomas A. Ban, Volume 7, Volume editor Barry Blackwell).

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.

Part Three: *Leader's of the Vision* (Chapter 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." John Rosen 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.

Chapter 41, *The Psychoanalytic Innovator*, examines the fate of psychoanalytic theory, current during Noch's 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 and 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”. This 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.

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 deinstitutionalization 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 Deinstitutionalization* (Chapter 52). It identifies the events that invoked the end of asylum care; the libertarian zeitgeist of the 1960's, 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 Alliance* (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 1970's 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. 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 patient’s 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.

April 10, 2014

Driss Moussaoui: A Biography of Jean Delay (2002) – reviewed by Barry Blackwell
Excerpta Medica (112 pages)

This short volume of 112 pages plus references, 8 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 Paris University, a close collaborator with 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". Neglecting this advice he nevertheless began to write and publish short stories at the age of 20, while an intern at the Salpêtrière 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 was the environment in which he created his major accomplishments, 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 World Health

Organization (WHO).

During his scientific career, Jean Delay published over 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 3 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 1980's, 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 received 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, of which he served as President, were the French language Congress of Neurology and Psychiatry (1954), the Society 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 2 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 on 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 VII). 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 jeunesse d'Andre Gide*. Out of his total of 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 4am 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.

February 27, 2014

Turan M. Itil by Martin M. Katz

Turan Itil was born in Bursa, Turkey, on August 12, 1924. He was educated in Turkey and received his basic medical training at Istanbul Universitesi Cerrahbasa (1948). He then obtained advanced training as a neuropsychiatrist in Germany at the Universities in Tübingen and Erlangen, under the guidance of such historical figures as Kretschmer and Flügel, becoming an expert in neurology, in clinical psychiatry and in the analysis of brain wave activity through electroencephalography. Advancement in academia in Germany was, however, very limited for non-Germans, so at the invitation of Max Fink, in 1964, he immigrated to the U.S. where he was offered a Professorship at the University of Missouri School of Medicine. He formally began his academic career there, moving some years later to the New York Medical College and then, in 1991, to the New York University School of Medicine.

Contributions:

Max Fink, a pioneer in encephalography and a lifelong collaborator, gives Turan Itil the majority of the credit for (1) development of computerized approaches to the EEG (Itil 1968) and (2) its use in profiling the distinct brainwave patterns induced by the various classes of psychotropic drugs.

In merging his skills in neurology and psychiatry for the new field of neuropsychopharmacology, Itil brought a distinct form of expertise to the field. Grounded in his new technology, he advanced brain wave analysis, supported by grants from the National Institute of Mental Health and from pharmaceutical companies: he (3) generated distinct profiles of the various classes of psychotropic drugs (Itil et al 1968) and (4) developed early tests of promising new drugs through his studies of their actions on brain wave activity (Itil et al 1972). His studies led to the detection of antidepressant properties in Organon's mianserin (GB-94), which he then patented, and which has now become an established treatment for the depressive disorders (Itil et al 1972).

In his role as a clinical methodologist, he collaborated in the design of studies testing new treatments for mental disorders and helped develop a new type of drug evaluation, e.g., (5) the new VIBES, a method that utilizes video to assess clinical changes (Katz, Itil 1974). (5) In the allied field of neurology, he innovated in the early detection and treatment of Alzheimer's disorder (Itil et al 1996). He was valued for his active role in the NIMH Early Clinical Drug Evaluation program as a consultant for several pharmaceutical companies and was particularly helpful in the conduct of cross-national drug studies, an area in which he had distinct sensitivity. Aside from his academic role, he continued to see patients throughout his career and took special pride in his capacity as a clinician, a skill he valued above all others.

Turan Itil was a pioneer in the field of neuropsychopharmacology and an innovative

and creative investigator. As a person and collaborator, he was especially valued for the energy and enthusiasm he brought to every project on which he worked.

He touched the lives of many colleagues and patients, was a joy to work with, and brought a unique “light” into a very complicated field of clinical and research activity.

Turan Itil passed away at his home, in Mersin, Turkey, on April 29, 2014, at the age of 89. The scientific and clinical community, his friends, and especially, his family, his son, Kurt and daughter, Yasmin Leland, and the many relatives who were fortunate enough to know him during his long and eventful life, will miss him greatly.

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Paul Kielholz by Raymond Battegay

Paul Kielholz, the son of the medical director of the psychiatric hospital of Königsfelden, Switzerland, was born on November 15, 1916. The family lived in a house near the buildings of the patients. The young Paul was recognized as very intelligent and ambitious. On the one side he identified with his father, a psychiatrist, but at the same time, he was interested also in other branches of medicine. So, after he acquired some experience, in several branches of medicine, he definitely chose psychiatry as his domain.

Paul Kielholz was always a person who, whenever he made a decision in his life, stuck firmly to that decision. He was much interested on one side in deeply understanding psychiatric patients and on the other, to search for the origins of psychic diseases and to find the psychopharmacologic approach with which the patient may be treated and cured.

Because of the wide recognition of his merits, he provided leadership to psychiatrists with whom he worked and other co-workers so as to advance research, diagnosis and treatment of the psychoses, depressive disorders and addictions. In 1959, he was elected as Professor of Psychiatry of the University of Basel and Director of the Basel Psychiatric University Hospital. Paul Kielholz was an excellent Director of the Psychiatric Clinic; he knew very well how to lead his staff. In 1967, he became Dean of the Basel University Medical Faculty.

Several important medical societies named Paul Kielholz as an honorary member. He was recognized internationally for scientific merit and as member or leader of organisations with the mission to develop psychiatric nosology. He was recognized for his wide experience in psychiatry and psychopharmacology throughout the world and was invited in 1968 to join the World Health Organization (WHO) Expert Advisory Panel.

Since 1960, he has been an active member of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) and was chosen as one of the councilors of its 10th Executive. From 1982 to 1984, he was President of CINP. Paul was an excellent leader, with clear opinions that he expressed skillfully and was highly esteemed because of his humanism.

Paul Kielholz, together with J.E. Staehelin, was among the first psychiatrists who recognized that Largactil (chlorpromazine) was an essential drug for the therapy of schizophrenia. Patients in the Basel University Psychiatric Hospital under this treatment became healthy over time and regained their capacity of reality testing. Paul Kielholz with Raymond Battegay also played a significant role in implementing treatment of patients with depression with imipramine (Tofranil). Paul Kielholz was also interested in patients with masked depression and burnout. Not only was he occupied with the treatment of patients, but also with giving lectures at Congresses and also teaching

psychiatrists and general physicians to recognize all sorts of depressive states, specifically, those with the risk of suicidality. He was very active in Switzerland, but also in International bodies, e.g., the Council of Europe, which is focused on investigating the development of drug use disorders. He published many papers and was often invited to present lectures in universities, congresses of psychiatry in Switzerland and other countries such as Germany, Austria, England, France, United States, among others.

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October 2, 2014

**Karl Rickels: A Serendipitous Life: From German POW to American Psychiatrist
(2011) – reviewed by Barry Blackwell
Noting Hill Press, Evergreen, CO (215 pages)**

Karl Rickel's memoir, *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 it.

The contents are almost equally divided between personal and family affairs (Chapters 1-4, Chapter 10, 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 book end an intervening piece on *Research and Discovery*. Throughout the book, the warp and weft of family and work mingle 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 ten, 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” 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 by the time he was in the ninth grade, World War II 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 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 1500 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 twenty two, 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 not 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 a hundred 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 1200 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 fifteen 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. Karl describes the scene thus; "It was still a time when barbiturates and bromides, the only sedatives available, did not work and straightjackets, 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 that 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 on the wards where these violent patients lived disappeared. It was truly a wonder.”

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 1995 and remains there today, fifty nine 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 was located at the University hospital but the hub and heart of the program was at the Institute, a large private practice located on “large 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. 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 fifty minute therapy session, Dr. Appel intervened. In a brief fifteen 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. 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 eighty five. 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 by NIMH). 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 thirteen nations included 6 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* (Editors: 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 early 1980’s, 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 fiftieth 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 forty four years and established another spousal alliance that successfully merged domestic with professional life.

In his lengthy and prolific career, Karl has published almost six hundred reviews, articles and book chapters, as well as editing nine books beginning with the classic *Non Specific Factors in DrugTherapy* (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 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 5, *The Era of Psychopharmacology*). Much of the concern emanated from Britain, where one psychiatrist 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 anti-anxiety 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 anti-anxiety drugs are appropriately used and that dependence is seldom a severe problem. 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 Adolescents 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 twenty-five years.

Karl has also spent his abundant energies in many additional directions not mentioned in his memoir. (See *Dramatis Personae* in *An Oral History of Neuropsychopharmacology* (OHP), Series Editor, Thomas A. Ban, Volume 4 editor, Jerry Levine, ACNP, 2011). 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 over half a century. It provides a cautionary tale of troubled times echoing and elaborating on concerns of many of his contemporaries (see OHP, Series Editor, Thomas A. Ban, Volume 9, Update, editor Barry Blackwell). 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 Xanax. He notes that academia is highly represented on lucrative industry speakers' bureaus or advisers to marketing departments. In an earlier chapter, Karl reminds us that he consulted only to research and never to marketing and even there, he 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 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, *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.

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. Third, and last, is titled, *Advice of a Husband and Father to his Children and Grandchildren*. It is 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 her 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.

Karl chose to title his memoir, *A Serendipitous Life*, which is surely an understatement of the forces governing his career. The word serendipity was coined by Horace Walpole in a letter to a friend, in 1754, describing a Persian fairy tale, *The Three Princes of Serendip*, (formerly Ceylon, now Sri Lanka). This tells how one of the princes deduced that a mule, blind in the right eye had travelled the same path because the grass was only eaten on the left side. The tale does not reveal if the link between the cause (blindness) and the outcome (the shorn grass) was made by someone who knew the mule was impaired in some way beforehand or by an unformed observer. In the former instance, serendipity might be closer to Pasteur's aphorism that "Chance favors the prepared mind." But by common usage, the dictionary definition (Oxford English Dictionary) of serendipity focuses only on chance, "The occurrence and development of

events by chance in a happy and beneficial way". 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.

May 29, 2014

**ELECTRONIC ARCHIVES AND EDUCATIONAL E-BOOKS IN
NEUROPSYCHOPHARMACOLOGY (2013 and 2014)**

**Electronic Archives in Neuropsychopharmacology
(Archives)**

Project Eleven

Coordinated by Gregers Wegener

and

**Educational E-Books in Neuropsychopharmacology
(e-books)**

Project Twelve

Coordinated by Peter R. Martin/Aitor Castillo

**Individuals with a Collection in Electronic Archives of
Neuropsychopharmacology:**

1. Thomas A. Ban
2. Frank M. Berger
3. Charles C. Cahn
4. Samuel Gershon
5. Laszlo Gyermek
6. William Guy
7. Heinz E. Lehmann
8. Ildiko Miklya

List of Educational E-Books posted in 2013 and 2014:

1. Thomas A. Ban: CODE-SD Composite Diagnostic Evaluation of Schizophrenic Disorders
2. Thomas A. Ban: DAS Diagnostic Assessment Scale for Diagnostic Criteria for Research
3. Thomas A. Ban: Dementia: Differential Diagnosis
4. Thomas A. Ban: From Melancholia to Depression. A History of Diagnosis and Treatment
5. Thomas A. Ban: History of Psychiatry & General Psychopathology
6. Thomas A. Ban: Neuropsychopharmacology and the Forgotten Language of Psychiatry. Madness: From Psychiatry to Neurology
7. Thomas A. Ban: Psychopharmacology and the Classification of Functional Psychoses (Monograph 1985)
8. Thomas A. Ban: Psychopharmacology of Anxiety Disorders CODE-AD
9. Thomas A. Ban and Ronaldo Ucha Udabe: Classification of Psychosis
10. Frank M. Berger: My Biography
11. Barry Blackwell: Jose Delgado: A Case Study. Science, Hubris, Nemesis and Redemption
12. Martin M Katz, editor: An Overview of the First Fifty Years. Oral History of Neuropsychopharmacology. Synopses by the 10 Volume Editors with Concluding Remarks by the Series Editor
13. Peter R. Martin, editor: Recollections of the History of Neuropsychopharmacology through Interviews Conducted by Thomas A. Ban
14. Peter R. Martin and Thomas A. Ban, editors: Recollections of the History of Neuropsychopharmacology Through Interviews Conducted by Leo E. Hollister
15. Peter R. Martin, editor: Thomas A. Ban, Barry Blackwell, Samuel Gershon, Peter R. Martin and Gregers Wegener International Network for the History of Neuropsychopharmacology (INHN 2013)
16. Gregers Wegener and Thomas A. Ban, editors: Celebration of the 100 Years Birthday of Joel Elkes

POSTSCRIPT

In 2014, INHN began to set standards for operating projects and to develop guidelines for the preparation of postings. In the course of this process, it became evident that the Network could not achieve its objectives by simply coordinating activities but needed firm direction.

While the operating committee (Thomas A. Ban, Barry Blackwell, Samuel Gershon, Peter R. Martin and Gregers Wegener) and project coordinators were retained, each member of the Committee was given a different and specific role and coordinators were no longer expected to carry out their function without considerable central input.

The transformation was rapid and spontaneous with Tom Ban assuming responsibility for directing activities of the Network and Peter Martin for copy-editing each posting for the website. Barry Blackwell took responsibility for developing Biographies with an extended scope that includes autobiographies, biographies, reviews of autobiographies and biographies and selected writings of neuropsychopharmacologists. The role of Sam Gershon evolved into reading and commenting on each document when received and reading each document again, after edit before posting. The role of Greg Wegener remained unchanged.