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 educational material in the history of the field. About a year later, on May 23, 2013, the Network launched its website and began posting material on the history of the field. In INHN 2013, some of the material posted in 2013 is assembled in a volume and presented as an electronic E-Book. With the exception of this Preface and subsequent Table of Contents, INHN 2013 includes material exclusively posted on the INHN website. Even the Introduction that follows the Table of Contents is the Introduction to the Network, posted with the launching of the website under the title "Welcome to INHN", and not an Introduction to this volume.

Instrumental to the founding of INHN was the publication of two major series of source books on the history of the field. One of these series, The History of Psychopharmacology and the CINP as Told in Autobiography, sponsored by the Collegium Internationale N|europsychopharmacologicum and edited by Thomas A. Ban, David, Healy and Edward Shorter, was published with the volume titles, The Rise of Psychopharmacology and the Story of CINP (Volume One), The Triumph of Psychopharmacology and the Story of CINP (Volume Two), From Psychopharmacology to Neuropsychopharmacology in the 1980s (Volume Three) and Reflections on Twentieth-Century Psychopharmacology (Volume Four), in 1998, 2000, 2002 and 2004, respectively. The other series, An Oral History of Neuropsychopharmacology The First Fifty Years Peer Interviews, sponsored by the American College of Neuropsychopharmacology and edited by Thomas A. Ban, was published in 2011. This ten volumes series was co-edited by Edward Shorter, as editor of Volume One (Starting Up); Max Fink, of Volume Two (Neurophysiology), Fridolin Sulser, of Volume Three (Neuropharmacology); Jerome Levine, of Volume Four (Psychopharmacology); Samuel Gershon, of Volume Five (Neuropsychopharmacology); Herbert Kleber, of Volume Six (Addiction); Barry Blackwell, of Volume Seven (Special Areas); Carl Salzman, of Volume Eight (Diverse Topics); Barry Blackwell, of Volume Nine (Update); and Martin M. Katz, of Volume Ten (History of the ACNP). In INHN 2013, information on these two source books and information on two other available source books follow the Introduction under the heading, "First Hand Accounts". The two other "First Hand Accounts" are: Discoveries in Biological Psychiatry, edited by Frank Ayd and Barry Blackwell, published in 1970, and The Psychopharmacologists: Interviews with David Healy, a three volumes series, published respectively, in 1996, 1998 and 2000.

In INHN 2013, each posted vignette (Dictionary, Drug Inventory and Profiles), essay (Controversies), chapter (Textbook) or review (Books and Biographies) initially posted on the INHN website is assigned to one of seven sections of the book, corresponding with seven of the nine ongoing projects of the Network. The seven INHN projects, the postings of which are included in this E-Book with the corresponding Sections in the E-Book, are: Historical Dictionary of Neuropsychopharmacology (Dictionary) – Project One and Section One; Historical Drug Inventory (Drug Inventory) – Project Two and Section Two; Profiles of Distinguished Neuropsychopharmacologists (Profiles) – Project Four and Section Three; Controversies in the History of Neuropsychopharmacology (Controversies) – Project Five and Section Four; Textbook on the History of Neuropsychopharmacology

(Textbook) – Project Six and Section Five; Information on Books in Neuropsychopharmacology Classic and Current (Books) – Project Eight and Section Six; and Biographies, Autobiographies and Selected Writings of Neuropsychopharmacologists (Biographies) – Project Nine and Section Seven.

Section One, Historical Dictionary of Neuropsychopharmacology, has no entry other than an Introduction by Carlos R. Hojaij, the coordinator of the project.

Section Two, Historical Drug Inventory, has three entries (vignettes), in addition to the Introduction by Eric Konofal, the project coordinator. The entries in this section are presented in alphabetical order of drugs: Bromides by Thomas A. Ban, Methylphenidate by Eric Konofal and Thyrotropin Releasing Hormone by Andrew Winokur.

Section Three, Profiles of Distinguished Neuropsychopharmacologists, has 12 entries, in addition to Edith Serfaty's Introduction. The entries (vignettes) in this section are presented in alphabetical order of the distinguished neuropsychopharmacologists: Frank Ayd by Barry Blackwell, Frank Berger by Thomas Ban, Charles Bradley by Walter Brown, Bernard Brodie by Fridolin Sulser, John Cade by Samuel Gershon, Jean Delay by Driss Moussaoui, Edmundo Fischer by Edith Serfaty, Horsley Gantt by Thomas Ban, Nathan Kline by Barry Blackwell, Roland Kuhn by Thomas Ban, Alfred Pletscher by Fridolin Sulser, and Leo Sternbach by Thomas Ban.

Section Four, Controversies in the History of Neuropsychopharmacology, is based on five essays presented in alphabetical order of the authors and in case of two essays by the same author, in alphabetical order of the titles. The five essays in order of presentation are: Thomas A. Ban: Conflict of Interest in Neuropsychopharmacology Marketing vs. Education; Barry Blackwell: A Distinguished but Controversial Career: Manuel Rodriguez Delgado; Paul Devenyi: Addictions Are Not Treatable Diseases; Paul Devenyi: Pharmacotherapy of Addiction Not a Success Story; and Edward Shorter: The Q-T Interval and the Mellaril Story. In this Section there are nine entries in addition to Barry Blackwell's Introduction. From the nine entries, four are the original essays; three are Peter Martin's comments on both Devenyi essays and on Shorter's essay; one is Devenyi's reply to Martin's comment on his first essay; and one is Martin's response to Devenyi's reply.

Section Five, Textbook on the History of Psychopharmacology has four entries in addition to Peter Martin's Introduction (Aitor Castillo has now taken over the task of coordinating the textbook). It includes two chapters from the prospective text presented in order of the table of contents: one by Thomas A. Ban, on The Birth of Neuropsychopharmacology, and the other, by Edward Shorter, on Endocrine Psychiatry in a Historical Perspective. It also includes two comments on Shorter's chapter, one by Andrew Winokur and the other by Walter Brown.

Section Six, Books in Neuropsychopharmacology, has 18 entries (reviews) in addition to Samuel Gershon's Introduction. It includes reviews of six books by their authors and 12 comments or replies to comments on these books. The books reviewed are presented in

alphabetical order of authors and in case of more than one book by the same author, in order of year of publication. The books reviewed are: Thomas A. Ban: Psychopharmacology (1969); Thomas A. Ban: Psychopharmacology and the Tricyclic Antidepressants (1974); Per Bech: Clinical Psychometrics (2012); Martin M. Katz: Depression and Drugs: Neurobehavioral Structure of a Psychological Storm (2013); Donald F. Klein and John M. Davis: Diagnosis and Drug Treatment of Psychiatric Disorders (1969); and Joseph Knoll: How Selegiline [(-)-Deprenyl] Slows Brain Aging (2013). From the 12 comments/replies four are based on interaction between Martin M. Katz, Donald F. Klein and Per Bech, in relationship to Bech's monograph; four are based on interaction between Samuel Gershon, Donald F. Klein and Martin M. Katz in relationship to Katz's monograph; and four are based on interaction between Ildiko Miklya, William M. Petrie and Joseph Knoll in relationship to Knoll's monograph.

Section Seven, Biographies, Autobiographies and Selected Writings of Neuropsychopharmacologists, the final section has only one entry, in addition to Barry Blackwell's Introduction. This entry is a review by Barry Blackwell of his autobiography, Bits and Pieces of a Psychiatrist's Life, published in 2013.

We hope that further edit of the vignettes, essays, chapters and reviews 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, rendered the vignettes, essays, chapters and reviews more readily accessible for educational and other purposes. Undoubtedly, the presentation of the vignettes, essays, chapters and reviews as parts of a book, made proper referencing of individual contributions possible.

Peter R. Martin

December 25, 2014

INTRODUCTION

The International Network for the History of Neuropsychopharmacology (INHN) was first proposed in early 2012. It evolved from discussions among several editors involved in previous efforts to document the history of the field. An important impetus derived from these efforts has been the recognition of the lack of predictive success in psychotropic drug development and the need for education in the history of neuropsychopharmacolog in order to facilitate communication between neuropsychopharmacolgists of different generations.

Objectives: The Network, through its members, is committed to documenting, preserving and disseminating all contributions relevant to the history of neuropsychopharmacology. It will also analyze material relevant to contemporary research, education and mental health care to generate new information and educational material related to the history of the field. The raison d'etre of the Network is to facilitate communication between neuropsychopharmacologists of different generations and professional backgrounds, and thereby provide a more solid foundation for future development of the field.

We will be using our website for posting educational - historical information and for establishing a continuous interaction with our membership.

Currently, you will find on our website information "About Us," our membership, and about first hand accounts (Publications) of the first 50 years in the history of our field:

- *Discoveries in Biological Psychiatry,* the proceedings of a symposium in which some of the original discoveries in the pharmacotherapy of psychiatry (and biological psychiatry) are recounted by those who made them;
- *The Psychopahrmacologists*, a series of three volumes of interviews by David Healy with some founders of psychopharmacology;
- *The History of Psychopharmacology and the CINP As Told in Autobiography,* a series of five volumes, sponsored by the Collegium Internationale Neuro-Psychopharmacologicum (CINP); and
- *An Oral History of Neuropsychopharmacology – The irst Fifty Years –Peer Interviews,* a series of ten volumes, sponsored by the American College of Neuro-Psychopharmacology (ACNP).

As a member of our Network, you will be informed when any new information is posted on our website and we would like to encourage you to comment on and discuss this material. We are asking you also to provide us with historical material to be posted on our website and/or stored in our electronic archives`

We are looking forward to working with you.

May 22, 2013

FIRST HAND ACCOUNTS

Frank J. Ayd, Jr. and Barry Blackwell, editors:
Discoveries in Biological Psychiatry
J.B. Lippincott Philadelphia/Toronto, 1970

Discoveries in Biological Psychiatry was first published in 1971, and re-published in 1984. The book reports the proceedings of a unique international symposium sponsored by the Taylor Manor Hospital in Baltimore, in 1970. It includes first person accounts by those who discovered the original drugs in each of the major categories of psychotropic medications.

The book's senior editor, Frank Ayd, was a psychiatrist in private practice whose prolific publications reported on the benefits and side effects of the earliest medications used to successfully treat mental illness. The junior editor, Barry Blackwell, reported the cheese reaction to MAO inhibitors, while a first year resident at the Maudsley Hospital in London, later immigrated to America, and at the time of the conference, held joint appointments in pharmacology and psychiatry at the University of Cincinnati and as Group Director of Psychiatric Clinical Research at the Wm. S. Merrell Company.

The first and final chapters are by the editors; Blackwell used his original research in animals and humans as the template to review the literature on the process of scientific discovery and the matrix of variables that influence that outcome. Ayd reviewed the impact of biological psychiatry on everyday practice, what had been accomplished in the first fifteen years, what had been learned and concluded with present and future needs. It is a brilliant synopsis, viewed retrospectively, from today's awareness of the successes and failures of the ensuing forty years.

Between these two bookends, is a library of personal testimony by the pioneers of psychopharmacology, each describing his own discovery and the framework within which it was made. Joel Elkes relates the beginnings of the new science of Neuropsychopharmacology and his personal involvement in creating among the first programs in Britain and America, with the ensuing emergence of national and international organizations to promote interdisciplinary collaboration, including the CINP and the ACNP (of which Joel was the first President). Two following chapters record the evolution of the discipline; Irvine Page traces its scientific development and Luther Kalinowsky describes the first biological treatments to emerge, including fever therapy, insulin coma, ECT and psychosurgery. Next, Chauncey Leake traces the long road in drug development, from original idea through animal research to successful or unsuccessful outcomes in humans.

What follows this groundwork is the detailed descriptions of the first discoveries in each category of psychotropic medication. This includes Tracy Putnam (Anticonvulsants), Albert Hoffmann (Hallucinogens), John Krantz (Anesthesia and Convulsants), Frank Berger (Meprobamate), Irv Cohen (Benzodiazepines), Hugo Bein (Reserpine), Pierre Deniker (Phenothiazines), Paul Janssen (Butyrophenones), Jorgen Ravn (Thioxanthines), Nathan Kline (MAO Inhibitors), Roland Kuhn (Tricyclic Antidepressants) and John Cade

(Lithium).

This book, containing the remarkable roll call of pioneers and their unique discoveries, is now out of print. Copies of the 1984 hardback edition are available at a reasonable cost on Amazon but copies of the original 1971 soft back are rare and sell for around five hundred dollars!

Barry Blackwell
May 23, 2013

David Healy, interviewer and editor: The Psychopharmacologist
(Three Volumes)
Altman, London 1996, 1998; Arnold UK, 2000

The Psychopharmacologists is a three volume series, published in 1996, 1998 and 2000, respectively. It includes 78 edited audio-taped interviews by David Healy with 85 "psychopharmacologists," including many of the pioneers in the field. According to Healy, a major impetus that led to the publication of this series was that after writing the history of the British Association of Psychopharmacology, he wanted to "branch out" because it was clear to him that if the "pioneers in the field (of psychopharmacology) were ever going to be interviewed, it had to be done now or never."

In the interviews in these volumes, Healy sees the interviewer as the instrument through which the actors in an historical drama, in this case psychopharmacology, reveal themselves. Therefore, it is important that readers know, "how the gain on the instrument they are using has been set at least insofar as biases have been consciously registered." To meet this need, one year after the release of volume I, in 1997, he published his monograph, "The Antidepressant Era," and two years after the release of the third volume, in 2002, he published his book on "The Creation of Psychopharmacology." (Both were published by Harvard University Press, Cambridge, Massachusetts and London, England).

Each interview in the series is presented with a title given by Healy or extracted from the interviewee, and each volume is complemented with Dramatis Personae of the interviewees, in a vignette that reflects the most important contribution(s) of the interviewee to development of the field.

New and old hardcover copies of the three volumes of The Psychopharmacologists are available via AMAZON.

Thomas A. Ban
May 23, 2013

Thomas A. Ban, David Healy and Edward Shorter, editors: The History of Psychopharmacology and the Story of CINP As Told in Autobiography
(Four Volumes)
Budapest: Animula; 1998, 2000, 2002 & 2004

Volumes

1. The Rise of Psychopharmacology and the Story of CINP
2. The Triumph of Psychopharmacology and the Story of CINP
3. From Psychopharmacology to Neurosychopharmacology in the 1980s and the Story of CINP
4. Reflections on Twentieth-Century Psychopharmacology

Content

This series covers in autobiographical accounts the first fifty years in the history of neuropsychopharmacology. The autobiographies in Volume I (*The Rise of Psychopharmacology and the Story of CINP*) are from psychopharmacologists who began their professional careers in the 1950's and 1960's; in Volume II (*The Triumph of Psychopharmacology and the Story of CINP*), from those who started in the 1970's; in Volume III (*From Psychopharmacology to Neuropsychopharmacology in the 1980s and the Story of CINP*), who started in the 1980's; and in Volume IV (*Reflections on Twentieth-Century Psychopharmacology*), who started in the 1990's.

At the core of each volume, are personal accounts in which the contributions of the scientists are at the center of the reflections, but also include several sections in which the reflections are focused on the mainstream of events, particular areas of research, individuals and organizations.

The series was the extension of an effort by CINP's History Committee, during the chairmanship of Tom Ban, to document both the history of the College and the enire field. It was co-edited by Ban, David Healy and Edward Shorter. Its publication was supported by the College primarily from non-restricted publication grants received from Pierre Fabre, Janssen Pharmaceutica and Research Foundation, Inc., and Janssen Phamaceutica International in Collaboration with Organon International.

The series was first published by Animula (Budapest, Hungary), and the four volumes were released in 1998, 2000, 2002 and 2004 at CINP congresses in Glasgow, Brussels, Montreal and Paris. In 2010, with the support of Robert H. Belmaker (President, CINP 2008-2010) and the help of Gregers Wegener (Webmaster, CINP), the Biographic Sketches and Cumulative Indexes were separated from Volume IV into a Volume V (Appendix) and the series was reprinted as a CINP publication, distributed by AMAZON. Currently each volume is available for purchase from AMAZON separately. Since the five volumes represent an entity, the publisher has been requested to make them available as a series.

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Paul H. Wender +
Elora Weringer +
Wolfgang Wesemann +
David Wheatley + +
Richard P. White +

Peter C. Whybrow +
Brigitte Woggon +
Jong Inn Woo +

Itaru Yamashita + +
Tomoyi Yanagita +
Jose Yaryura-Tobias +
Moussa B. H Youdim +
Arthur Yuwiler +

Mioslav Zapletalek +

* One or more of the contributions co-authored

Thomas A. Ban
May 23, 2013

Thomas A. Ban, editor: **An Oral History of Neuropsychopharmacology**
The First Fifty Years
Peer Interviews
(10 Volumes)
Brentwood: American College of Neuopsychopharmacology; 2011

Volumes

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

Content

By the mid-1990s, the pioneer generation of psychopharmacologists was fading away. To preserve their memory and contributions, Oakley Ray, ACNP's secretary, raised funds from Solway Pharmaceuticals to found the ACNP-Solway Archives of Neuropsychopharmacology. He also arranged for videotaping peer interviews with the pioneers at annual meetings of the ACNP to be stored in the archives. The project, known as the "oral history project," was gradually extended to include newer members of the College, and later non-members, who made outstanding contributions to the field.

In 2005, Thomas Ban, in collaboration with Jonathan Cole and George Gardos, began editing the transcripts of the interviews, and in 2006, with ACNP's Fiftieth Anniversary approaching (in December 2011), he proposed to prepare a collection of edited interviews for the Anniversary. With the approval of Ronnie Wilkins, ACNP's Executive Director, he was helped by ACNP staff members, first by Kay White, then byNicole Greer, and ultimately, by Laura Bersacola Hill, to get the videotapes transcribed, and then after dividing the material into ten volumes, he was joined by ten distinguished colleagues to become his co-editors. Eight were responsible for editing a single volume (Edward Shorter, Max Fink, Fridolin Sulser, Jerome Levine, Samuel Gershon, Herbert Kleber, Carl Salzman and Martin Katz) and a ninth editor was responsible for two volumes (Barry Blackwell). From the ten volumes, the first deals with the state of the art of psychiatry and pharmacology, at the time of the emergence of neuropsychopharmacology; five (Two to Six), cover the story of a single area of research, clinical activity and education; two (Seven and Eight), cover more than one area; Volume Nine is focused on the changes over the years and Volume 10 examines the role of ACNP during the fifty year span.

Altogether, the 10 volumes record the first fifty years in the history of neuropsychopharmacology, told by 213 clinicians and basic scientists, in 235 videotaped interviews, conducted by 66 colleagues, between 1994 and 2008. Each volume includes an introduction to its themes and a biography of each contributor's career by the volume editor. The volumes are connected by prefaces, written by the series editor, in which the research contributions are placed in their historical context. The entire series has an Overview at the beginning and a Postscript at the end, supplemented with a chronological list of key publications and selected quotations from each interview.

The series was published by the ACNP, with Laura Bersacola Hill preparing the material to be released at the Fiftieth Anniversary of the College. Each volume is available separately from Amazon and, since the ten volumes represent an entity, the publisher has been requested to make them available as a series.

Interviewees:
Alphabetical list of interviewees with the volume identified (by Arabic numeral in parenthesis) in which their edited transcripts are included:

Manfred Ackenheil (8)
Martin M. Adler (6)
George K. Aghajanian (2)
Bernard W. Agranoff (3)
Huda Akil (3)
Hagop S. Akiskal (7)
George S. Alexopoulos (7)
Nancy C. Andreasen (2)
Burton Angrist (5)
Victoria Arango (7)
Joseph Autry (4)
Julius Axelrod (3)
Frank J. Ayd, Jr. (1, 9 & 10)

Ross J. Baldessarini (5)
Thomas A. Ban (4 & 9)
Jack D. Barchas (3)
Samuel H. Barondes (3)
Herbert Barry III (6)
Charles M. Beasley, Jr. (8)
Robert H. Belmaker (5 & 10)
Frank M. Berger (3 & 9)
Barry Blackwell (4)
Jack Blaine (6)
Dan G. Blazer II (7)
Floyd Bloom (2)
Charles L. Bowden (4)
Philip B. Bradley (2)
Joseph V. Brady (1)
Walter A. Brown (5)
William E. Bunney, Jr. (5)

Enoch Callaway III (2)
Arvid Carlsson (3 & 10)
William T. Carpenter, Jr. (5)
Charles Jelleff Carr (1)
Bernard J. Carroll (5)
Kanellos D. Charalampous (6)
Dennis S. Charney (8)
Thomas N. Chase (7)
Guy Chouinard (5)
Eva Ceskova (8)
Paula J. Clayton (7)
Robert A. Cohen (1)
Jonathan O. Cole (4, 9 & 10)
C. Keith Conners (7)
Leonard Cook (1)
Thomas B. Cooper (7)
Erminio Costa (7)
Joseph T. Coyle (8)

Svein G. Dahl (7)
Annica Dahlström (3)
John M. Davis (5)
Kenneth L. Davis (8)
José M. Delgado (2)
Thomas Detre (1 & 10)
Peter B. Dews (1)
James W. Dingell (3)
Edward F. Domino (1)
David L. Dunner (7)

Michael H. Ebert (8)
Burr S. Eichelman (7)
Joel Elkes (1 & 10)
Jean Endicott (7)
Salvatore Enna (3)

Jan A. Fawcett (5)
Irwin Feinberg (2)
Hans Christian Fibiger (3)
Max Fink (2 & 9)
Barbara Fish (8)
Ellen Frank (8)
Alan Frazer (3)
Alfred M. Freedman (1)
Arnold J. Friedhoff (5)
Kjell Fuxe (3)

Donald M. Gallant (4)
Silvio Garattini (3)
George Gardos (4)
Peter Gaszner (8)
Mark S.George (7)
Samuel Gershon (1)
J. Christian Gillin (2)

Alexander H. Glassman (7)
Ira D. Glick (8)
Burton J. Goldstein (4)
Frederick K Goodwin (5)
Louis A. Gottschalk (1 & 9)
John F. Greden (5)
Paul Greengard (3)

Angelos E. Halaris (5)
Uriel M. Halbreich (7)
Katherine A. Halmi (7)
Ernest Hartmann (2)
George R. Heninger (8)
Fritz A. Henn (8)
Hans F. Hippius (1)
Gerard E. Hogarty (4)
Leo E. Hollister (1 & 9)
Philip S. Holzman (2)

Turan M. Itil (2 & 9)
Leslie L. Iversen (3)

Jerome H. Jaffe (6)
David S. Janowsky (5 & 9)
Murray E. Jarvik (3)
Donald R. Jasinski (6)
Dilip V. Jeste (7)
Lewis L. Judd (8)

Samuel C. Kaim (2)
Daniel P. van Kammen (5)
Eric R. Kandel (3)
John M. Kane (4)
Shitij Kapur (5)
Alexander G. Karczmar (3)
Martin M. Katz (4, 9 & 10)
Seymour Kaufman (7)
Robert M. Kessler (2)
Seymour S. Kety (2)
Eva K. Killam (2)
Keith F. Killam (2)
Herbert D. Kleber (6)
Gerald D. Klee (6)
Donald F. Klein (4 & 9)
Rachel D. Klein (7 & 9)
Joel E. Kleinman (8)
James C. Klett (4)
Joseph Knoll (3)
James H. Kocsis (4)

Irwin J. Kopin (3)
Conan Kornetsky (6 & 9)
Stephen H. Koslow (8)
Mary Jeanne Kreek (6)
David J. Kupfer (7)
Albert A. Kurland (1)

Harbans Lal (3)
Salomon Z. Langer (3 & 10)
Louis C. Lasagna (1)
Paul Leber (8)
Yves Lecrubier (4)
Heinz E. Lehmann (1)
Jerome Levine (4 & 9)
Alfred J. Lewy (5)
Jeffrey A. Lieberman (4)
Sarah Hollingsworth Lisanby (7)
Vincenzo G. Longo (2)

Roger Maickel (8)
Arnold J. Mandell (8)
Aleksander A. Mathé (8)
William T. McKinney (7)
Douglas M. McNair (4)
Herbert Y. Meltzer (5 & 9)
Roger E. Meyer (6)
Claude de Montigny (5)

Charles B. Nemeroff (8)
Ernest P. Noble (6)

Charles P. O'Brien (6)
John E. Overall (4)
Gregory F. Oxenkrug (5)

Steven Marc Paul (3)
Eugene S. Paykel (4)
Candice B. Pert (3)
Roy Pickens (6)
Alfred Pletscher (3 & 9)
Robert M. Post (5)
William Z. Potter (5)
Herman M. van Praag (5 & 9)
Arthur J. Prange (5)
Beny J. Primm (6)

Frederic Quitkin (4)

Judith L. Rapoport (7)
Allen Raskin (4)
Barry Reisberg (7)
Elliott Richelson (5)
Karl Rickels (4)
Trevor R. Robbins (10)
Donald S. Robinson (5)

Carl Salzman (8)
Paul Ronald Sanberg (3)
Elaine Sanders-Bush (3)
Merton Sandler (3)
Gerald J. Sarwer-Foner (1 & 9)
Alan F. Schatzberg (4)
Joseph J. Schildkraut (5)
Joseph C. Schoolar (6)
Nina R. Schooler (4)
Marc A. Schuckit (6)
Charles R. Schuster (6)
Richard E. Shader (8)
Eric M. Shooter (7)
Baron Shopsin (5)
George M. Simpson (4 & 9)
Solomon H. Snyder (3)
Louis Sokoloff (2)
Sydney Spector (3)
Stephen M. Stahl (8)
Larry Stein (1)
A. Arthur Sugerman (2)
Fridolin Sulser (3)
Stephen Szára (1)

Gary D. Tollefson (8)
William J. Turner (1)

Eberhard E. Uhlenhuth (4)

Oldrich Vinar (4)
Nora D. Volkow (6)

Leong E. Way (6)
Matthew J. Wayner (6)
Daniel R. Weinberger (2)
Myrna M. Weissman (7)
Paul H. Wender (7)
David Wheatley (4)
Peter C. Whybrow (5)
Andrew Winokur (4)

James H. Woods (6) Richard J. Wurtman (3) Joseph Zohar (10)
Joseph Wortis (1)

Reviews

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Thomas A. Ban
May 23, 2013

HISTORICAL DICTIONARY IN NEUROPSYCHOPHARMACOLOGY

Introduction by Carlos R. Hojaij

I have the honor to coordinate Project One of INHN: "Historical Dictionary of Neuropsychopharmacology".

The main purpose of a dictionary is the orderly presentation of words/concepts related to a particular area of knowledge. Clarity of these concepts is of utmost importance, since it is through these words/ concepts that we construct and interpret our reality.

Preparation of a Historical Dictionary of Neuropsychopharmacology will provide us with an opportunity to examine and clarify the meaning of words/concepts used in neuropsychopharmacology and ascertain that they communicate them clearly.

While preparing this Introduction I found that several terms, like, psycho, pharmaco, neuro, etc. appear in several different combinations. For example: neuropharmacology, psychopharmacology, neuropsycopharmacology, pharmacopsychology, pharmacopsychopathology, pharmacopsychiatry, behavioral pharmacology, pediatric pharmacology, geriatric pharmacology, pharmacogenetics, etc. The picture looks quite chaotic, but on closer examination, it seems to reflect a constant increase in the number of perspectives or even disciplines involved in studies of the mind via the brain.

Another initial observation I had was that at a certain point in time, the term "neuropsychopharmacology" replaced "psychopharmacology". It probably reflects the early expectations from neuroscience to provide the basic underpinning for the clinical aspects of the field. .

While preparing this dictionary, we should keep in mind the words of Lothar Kalinowsky and Hanns Hippius in their book, "Somatic Treatments in Psychiatry", written in 1971, forty-two years ago: "The great advances achieved during the last decades in the effective treatment of mental diseases are due to the fact that psychiatrists utilized their clinical observations for their therapeutic experiments".

In his Foreword of The Dictionary of Modern Medicine, its editor, George Lundberg wrote: "When I use a word, I may mean it to say exactly what I mean it to mean. Okay. But how will anyone else know what I mean? That is the reason for dictionaries". In preparing our Dictionary we should keep in mind Lundberg's words as well.

With so many partially overlapping terms, and with changes in their meaning over time, it will be necessary to define each of them from the time they emerged to the present. It will be necessary to have an open dictionary in which the last inserted concept of today will not be the oldest tomorrow. It is extremely important to keep the Dictionary open, also to accommodate divergence and confrontation as truth and reality come via confrontation; compromise suppresses authenticity.

We should try to create a Historical Dictionary that will be passed from generation to generation. I would appreciate any suggestion you may have that could improve our project.

Please see our first "vignette" posted. You are warmly invited to send me via e-mail (crhojaij@biologicalpsychiatry.com.au) comments on this vignette, as well as new vignettes for consideration for posting on our website for comments from members of INHN.

Let's craft a great opus together!

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December 12, 2013

HISTORICAL DRUG INVENTORY OF PSYCHOTROPIC DRUGS

Introduction by Eric Konofal

I am writing to introduce myself as the person responsible for the project "Historical Drug Inventory on Psychotropic Drugs" (Project 2). I will be working on this project with Tom Ban, Barry Blackwell, Sam Gershon and Peter Martin in preparing vignettes on psychotropic drugs for inclusion in our Inventory and editing vignettes prepared by others.

We hope you will be interested in participating in this project by preparing vignettes for our Inventory and commenting on vignettes already included in it.

I am posting with this Introduction a vignette on "Methylphenidate" I prepared.
I am looking forward to working with you on this project.

June 27, 2013

Bromides by Thomas A. Ban

Potassium bromide was the first widely used sedative in medicine. It is the potassium salt of bromine, the element that was named for its "stench" ("bromos").

Bromine was first isolated in 1826 from the ashes of seaweed by A.J Balard, an apothecary in Montpelier, France. He found bromine in its natural form too corrosive for ingestion and prepared for clinical use the potassium and sodium salts of the substance (Shorter, 1997).

Bromine was introduced into medical practice by François Magendie in Bordeaux (France) and subsequently, in the 1830s and '40s, bromide was extensively used as a substitute for iodine in a variety of disorders (Garrison, 1960). It was only in the mid-1850s that Charles Lockock, a London internist, discovered the anticonvulsant property and sedative action of the drug. It was one of the many quaint examples of serendipity in which a false theory led to correct empirical results. Lockock, like many physicians in his time, believed that convulsions and epilepsy were caused by masturbation and since bromides were known to curb sex drive, he administered potassium bromide with the rationale that by reducing the frequency of masturbation he will be able to control epileptic seizures (convulsions) in his patient (Lehmann and Ban, 1970). The treatment was a success insofar as control of convulsions was concerned. It also focused attention on the sedating properties of the drug (Ban, 2006).

During the second half of the 19th century, potassium bromide was widely used for sedation and for the control of anxiety and convulsions (Balme, 1976). In 1900, Neil Macleod, a Scottish physician, reported on "bromide sleep" in the treatment of acute mania. Yet, the bromides were difficult drugs to use. Since they act by replacing chlorides, their activity depends not only on the amount of bromide given, but also on the chloride intake, fluid consumption and renal function of the patient. The problem is compounded by its slow excretion and rapid accumulation in the blood. The earliest manifestations of bromide intoxication are sleepiness and fatigue; and as blood-concentrations increase appetite is lost, weight decreases and a characteristic mental dullness appears. A toxic delirium is triggered when bromide levels pass a critical threshold (Ban, 1969).

In one particular aspect the bromides differ from all other sedatives: they don't induce drowsiness and sleep when given in a large single dose. Nevertheless, because of their relatively low efficacy coupled with high toxicity the use of bromides were virtually restricted for controlling seizures in pediatrics by the late 1960s (Ban, 2006).

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October 24, 2013

Methylphenidate by Eric Konofal

The story of methylphenidate begins with the recognition that piperazine derivatives, used as diuretics in the late 19th century possessed significant stimulating properties.

Chemische Industrie Basel (CIBA) is a Swiss pharmaceutical company where Max Hartmann, a chemist, in the early 20th century synthesized a piperidine, allyl-phenyl-cinchoninate, a powerful treatment for "uric acid diathesis". Hartmann continued his research with piperidines, and in 1924, he synthesized N-diethyl-3-pyridine carboxamide, a strong analeptic that was to be called nikethamide or picolinamide. With Werner Boshard, Hartmann published, in 1941, an article on pyridine-3-acetic acid. Three years later, subsequent transformations and reductions of some pyridil acetic acids, led to the isolation of phenyl-α-pyridil-2-acetic acid. Leandro Panizzon (1944), a medicinal chemist at CIBA, lead the synthesis of methyl-α-phenyl-piperidine-2-acetate (methylphenidate).

In 1950, Panizzon and Hartmann developed an improved synthesis for methylphenidate and obtained a US patent for its preparation. However, it was only, in 1954, that Meier, Gross and Tripod revealed that this substance has stimulating properties. In the same year, methylphenidate, with the brand name, Ritalin was patented by CIBA in the US for treating psychological disorders. By 1955, Ritalin passed the safety requirements of the US Food and Drug Administration in effect at the time, and in 1956, it was introduced for clinical use. In 1957, it was marketed in Europe to treat fatigue, psychasthenia or depression.

The substance was first used intravenously for the treatment of barbiturate intoxication (Rosenberg, Rape and Rumble, 1959), but by the end of the 1950s, it found its place in the treatment of narcolepsy (Yoss and Daly, 1959) and in "some abnormal psychical conditions", primarily, in a disorder that was first described by English physician George Frederic Still, in 1902, and was to be first referred to as "minimal brain dysfunction", and subsequently "attention deficit hyperactivity disorder" (Lytton and Knobel, 1959).

The overall clinical profile of methylphenidate resembles that of amphetamine, with the exception that its anorexic effects and actions on the peripheral circulation are less marked. It acts by inhibiting dopamine reuptake and with much less effect on norepinephrine reuptake (Findling, 2008).

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June 27, 2013

Thyrotropin releasing hormone (TRH) by Andrew Winokur

Thyrotropin releasing hormone (TRH) was isolated and characterized, in 1969, as a tripeptide pyroglutamyl-histidyl-proline amide (Boler et al. 1969; Burgus et al. 1969). TRH was the first of the hypothalamic releasing hormones to be isolated and characterized. This event represented one of the landmark scientific accomplishments of the 20th Century, and the two investigators who are most credited with carrying out this groundbreaking work, Roger Guillemin and Andrew Schally, shared the Nobel Prize in 1977 for this achievement. Work leading to the identification of the hypothalamic releasing hormones was carried out over a 20 year research effort marked by intense competition between Guillemin's and Schally's groups. The foundation for this remarkable effort was developed by the contributions of investigators during the previous half century, but it required the paradigm-shifting innovations of Guillemin's group and Schally's group to bring this massive research effort to the point of ultimate success. At that time, many prominent scientists were highly skeptical of the existence of the hypothalamic releasing hormones, and the National Institutes of Health (NIH), after years of heavily funding the work in both investigators' laboratories actually convened a special meeting, in 1966, to consider whether funding for this project should be halted in light of questions about the likelihood of success. A three part series in SCIENCE in 1978 thoroughly describes the background and circumstances related to the discovery of TRH and other hypothalamic releasing hormones, as well as describing the unique relationship between the two lead investigators (Wade 1978).

As noted above, the discovery of TRH as the first identified hypothalamic releasing hormone was a truly transformative development for the field of Endocrinology. This discovery provided explicit demonstration of the manner in which the brain plays an intimate, pivotal role in the regulation of peripheral endocrine function through regulation of the synthesis and section of hormones released from the anterior pituitary gland (Jackson 1982). It was now established that hormones were secreted directly from the brain, in contrast to the previously identified circumstance in which the hormones oxytocin and vasopressin were synthesized in the hypothalamus but then transported down neural pathways to the posterior pituitary gland, to be stored until being secreted from that site in the periphery into the general circulation. In the case of TRH, it is synthesized in hypothalamic neurons, transported to the presynaptic terminal region in the median eminence, where it is stored in synaptic vesicles. With firing of an action potential, the TRH neurons in this region release their vesicle contents in the portal circulation, from whence it diffuses directly to the anterior pituitary gland and is bound to TRH receptors on thyrotroph cells, leading to increased synthesis and secretion of thyrotropin (TSH) into the general circulation. In turn, TSH acts on the thyroid gland to stimulate synthesis and secretion of the thyroid hormones, in particular T4, which is then mainly enzymatically converted extrathyroidally to the more active form, T3. In turn, feedback inhibitory loops were demonstrated that involved effects of the thyroid hormones on both the anterior pituitary gland and back in the brain at the level of the hypothalamus. Thus, with TRH and the hypothalamic-pituitary-thyroid axis serving as the originally identified example of a neuroendocrine axis, the bidirectional relationship between brain and endocrine function was firmly established.

TRH has clearly been established to be the primary regulatory factor in the normal function of the thyroid axis. Hypothalamic hypothyroidism was identified as a condition in which patients developed hypothyroidism secondary to inadequate secretion of TRH from the hypothalamus. By 1972, parameters for the "TRH stimulation test" had been published, and this procedure became a standard, widely utilized diagnostic procedure to evaluate the appropriateness of the TSH response and to aid in the diagnosis of selected thyroid disorders (Snyder & Utiger 1972). In the TRH stimulation test, an indwelling cannula is placed in a vein, and plasma samples are obtained to determine the baseline TSH concentration. TRH, usually at a dose of 400-500 micrograms to obtain a maximal TSH response, is then injected intravenously, typically as a bolus injection or infused over 30 seconds. Blood samples are obtained at 10-15 minute intervals up to 60 minutes or longer following administration of TRH, and the increase in TSH concentration over the baseline value is determined. The peak TSH value after TRH administration is typically seen 30 minutes after TRH administration, and TSH levels typically return to baseline values by 60 minutes. Normative values for the TSH response to TRH have been established, and results from patients with suspected thyroid disorder can be described as blunted, normal or exaggerated. By the mid-1990's, the availability of ultra-sensitive radioimmunoassay procedures for TSH made the TRH stimulation test an unnecessary diagnostic procedure in the view of many endocrinologists, and the use of the TRH stimulation test for diagnostic purposes in the U.S. markedly waned. As noted in an editorial in THYROID, TRH has not been available in the U.S. since 2002, as Ferring Pharmaceuticals, the only supplier of TRH in the U.S., was required to remove their TRH product (Thyrel) from the market due to questions on the part of the FDA regarding their production processes (Rapaport et al. 2010). The editorial noted above was entitled "Time for Thyrotropin Releasing Hormone to Return to the United States of America". The authors of this editorial argued that there are still instances in which the use of the TRH stimulation test is important to diagnosis certain forms of thyroid disease states. Nonetheless, clinical grade TRH remains commercially unavailable in the U.S.

How did TRH attract the interest of some psychiatric investigators? Suggestions regarding a relationship between thyroid axis function and mood disorders had been expressed many years before the discovery of TRH. Notably, Prange et al. (1969) reported that administration of small doses of triiodothyronine (T3) to depressed patients, in conjunction with standard treatment with a tricyclic antidepressant drug, resulted in a more rapid onset of antidepressant activity. Additionally, Schildkraut et al. (1970) reported that addition of a low dose of thyroid hormone to a 10 day tricyclic antidepressant drug regimen produced an acceleration of norepinephrine turnover in rat brain. With the availability of TRH for experimentation purposes, it is not surprising that investigators rapidly examined the effects of TRH in various animal behavioral paradigms. In 1972, only three years after its discovery, TRH was reported to be active in the DOPA potentiation test of Everett, a putative animal model screen for drugs with antidepressant effects (Plotnikoff et al. 1972). The investigators examined the effects of TRH administered to groups of rats with partial or complete ablation of the peripheral thyroid axis (i.e., rats who had been hypophysectomized, thyroidectomized or both hypophysectomized and thyroidectomized prior to administration of TRH) (Plotnikoff et al. 1974). In the surgically ablated rats,

administration of TRH demonstrated full behavioral activity in the DOPA potentiation test. The results of these studies suggested that: 1) TRH administration would be associated with antidepressant activity, and 2) effects of TRH in the DOPA potentiation test were independent of the effects of TRH on the thyroid axis and likely represented direct CNS effects.

Prange et al. (1972) and Kastin et al. (1972) administered TRH or saline intravenously (i.v.) to depressed patients, and both groups reported significant improvement in symptoms of depression following administration of TRH. A notable feature reported in both studies was the finding that improvement in symptoms of depression occurred literally within hours of administration of TRH, a striking contrast to the well-established finding that the standard antidepressant drugs of the time, the tricyclic antidepressant compounds and the monoamine oxidase inhibitor antidepressants, typically took several weeks to achieve therapeutic effect. At the present time, there is a high degree of interest in the observation that administration of i.v. ketamine produces rapid improvement in depressive symptoms, a finding that may lead to significant advances in the pharmacotherapy of some forms of depression. In this context, it is interesting to note that rapid improvement following i.v. administration of TRH was first reported some four decades ago. A study of the effects of TRH administration to depressed patients by Itil et al. (1975) included both clinical assessments and evaluation by means of computed EEG analysis. Not only were depressed patients noted to demonstrate symptomatic improvement in this study, but EEG evaluation 24 hours after infusion of a single dose of TRH was reported to produce an activation of the computed EEG profile that was comparable to effects produced by stimulant compounds such as dextroamphetamine, as well as by the monoamine oxidase inhibitor tranylcypramine. Overall, with respect to the efficacy of i.v. TRH in controlled studies involving depressed patients, only about 42% of studies demonstrated efficacy associated with TRH administration as compared to placebo or to treatment with a tricyclic antidepressant compound (Prange et al. 1979). Variation in experimental design and in the characteristics of patients enrolled may account for some of the inconsistency in results reported in studies with TRH. Clearly, further studies are needed to more critically evaluate the therapeutic potential for TRH or a TRH analog in the treatment of depression.

The reports of Prange et al. (1972) and Kastin et al. (1972) included the additional observation that a subset of depressed patients demonstrated an inadequate or "blunted" TSH response to TRH administration. Over the years, dozens of studies have replicated the finding of a blunted TSH response to TRH in subsets of depressed patients (typically on the order of 25% of patients examined) (Loosen & Prange 1982). Suggestions about the significance of this blunted TSH response have included potential utility in diagnosing depression, prediction of treatment response or providing an indication of the risk for relapse after treatment has been terminated and the possibility that this finding may provide insight to pathophysiological mechanisms of relevance to depression (Loosen 1985; Kirkegaard et al. 1975; Banki et al. 1988). As noted above, TRH has not been available for clinical use in the U.S. since 2002, and as a consequence, the TRH stimulation test can no longer be employed for clinical studies in the U.S. In light of these circumstances, it does not seem likely that further studies investigating the relevance of the TRH stimulation test for patients with depression will be carried out in the U.S.

Studies examining the role of TRH in the central nervous system (CNS) have been pursued over the past 4 decades, and advances in this area offer the promise of enabling new approaches to clinical translational studies involving TRH or TRH analogs. Utilizing, at the time, a recently developed radioimmunoassay technique for TRH, Winokur and Utiger (1974) and Jackson and Reichlin (1974) reported on the widespread distribution of this "hypothalamic releasing hormone" throughout the rat brain. The hypothalamus was found to contain only one-third of the TRH content in the rat brain. The widespread distribution of TRH in the CNS, combined with previously reported behavioral effects associated with TRH administration provided a solid rationale to undertake further studies to elucidate the role of this tripeptide in the CNS, in addition to its established hypothalamic hypophysiotropic function. Specifically, studies were undertaken to examine the possibility that TRH plays a role as a neurotransmitter in the CNS. Findings that support a neurotransmitter role for TRH include: 1) the identification of the pre-pro-TRH gene and the pre-pro-TRH peptide in neurons throughout the CNS (Nillni & Sevarino 1999); 2) the presence of TRH in synaptic vesicles in the presynaptic neuron in both hypothalamic and extra-hypothalamic brain tissue (Winokur et al. 1977); 3) the presence of TRH receptors in high concentration in specific locations throughout the neuroaxis in lower species and in man (Manaker et al. 1985; Manaker et al. 1986); 4) the presence in the CNS of mechanisms to terminate the effects of released TRH by peptidases located in various brain regions, including a deamidating enzyme and two species of pyroglutamyl-amino-peptidases, (Torres et al. 1986; Hersh & McKelvy 1979); 5) demonstration of the ability of TRH to produce alterations in neuronal membrane conductance by means of intracellular recording techniques, as well as studies employing unit recording of actively firing neurons both in the hypothalamus and in other brain regions that demonstrated alteration in neuronal firing rate following administration of TRH by microiontophoresis (Winokur & Beckman 1978); and 6) demonstration of an array of physiological and behavioral effects associated with administration of TRH and TRH analogs in preclinical animal studies and in studies involving human subjects, as will be discussed in more detail below.

Animals pretreated with a variety of CNS depressant compounds, including ethanol, barbiturates, other anesthetic agents, or antipsychotic drugs that are then administered TRH demonstrate a significant shortening of sleeping time and a reversal of hypothermia induced by pharmacological treatment with a CNS depressant agent (Breese et al. 1975). This remarkable and unique analeptic action of TRH appears to represent a distinctive property of the tripeptide. Stanton et al. (1980) examined effects of TRH in a natural state of CNS depression, i.e., hibernation in the California golden-mantled ground squirrel. Administration of TRH to the hibernating ground squirrel produced a pronounced increase in brain temperature and metabolic rate, and within one to two hours following administration of TRH, ground squirrels demonstrated full behavioral arousal from hibernation. Arousal from hibernation was seen when TRH was administered into the CA1 region of the dorsal hippocampus of the hibernating ground squirrel, a region subsequently demonstrated to contain a high concentration of TRH receptors in this species. TRH is highly potent in producing this effect, as doses as low as 100 picograms resulted in full behavioral arousal from hibernation. However, the response was strictly dependent on providing the precise molecular structure of TRH, as administration of the deamidated free-

acid form of TRH (TRH-OH) in much higher concentration was completely devoid of physiological effects.

Stanton et al. (1981) extended studies of effects of TRH by microinjecting TRH into the same location (i.e., dorsal hippocampus) in ground squirrels that were euthermic and in the state of slow wave sleep. In this instance, administration of TRH produced effects that were similar in direction, but smaller in magnitude than the effects observed in the hibernating ground squirrel. Thus, administration of TRH to grounds squirrels during slow wave sleep resulted in a modest increase in brain temperature and metabolic rate, and a slight activation of EEG pattern and increase in EMG activity, although the animals did not exhibit full behavioral arousal. In contrast, when TRH was administered in the same paradigm to ground squirrels that were euthermic and awake, the effects observed were OPPOSITE in direction to the effects seen in the hibernating and in the euthermic sleeping ground squirrels, including a decrease in brain temperature and metabolic rate, a slowing of the EEG pattern and a decrease in EMG activity. When TRH was administered to ground squirrels that were behaviorally active, a readily evident reduction in motor activity was observed. The results obtained in this series of studies prompted the investigators to speculate that TRH plays a key role in the bimodal regulation of arousal.

Additional studies have examined the relationship between TRH and CNS activity states. Determination of TRH and TRH receptor concentrations in brain regions of ground squirrels sacrificed during different seasons demonstrated significant variations in both the tripeptide and its receptor in selected brain regions as a function of season (Stanton et al. 1982). The concentration of TRH in the hypothalamus of hibernating ground squirrels was significantly lower than that in euthermic ground squirrels sacrificed in the winter. Studies were conducted in another animal species that undergoes a state of profound CNS torpor, namely the South African lungfish, which enters a state of estivation during the summer dry season in its natural habitat (Kreider et al. 1990). Estivating lungfish studied in the laboratory demonstrated a significant reduction in TRH content in the diencephalic region (a region containing the hypothalamus) as compared to awake control lungfish, a finding comparable to the reduced hypothalamic TRH content previously reported in hibernating ground squirrels.

The primary approach to examining the relationship between TRH and CNS hyperarousal has been by means of experimental seizure induction. Studies utilizing a variety of seizure-induction paradigms, including electroconvulsive shock, kainic acid-induced seizures and amygdala-kindled seizures have all reported pronounced increases in TRH content in limbic regions, including amygdala, entorhinal cortex and hippocampus (Kubek et al. 1989; Kreider et al. 1990; Post & Weiss 1992). It has been speculated that the increase of TRH content provoked by experimental seizure-induction procedures unmasks an endogenous compensatory response to modulate excessive seizure activity, with TRH being a prime candidate to mediate the compensatory response to oppose seizure activity (Post and Weiss 1992). When TRH or TRH analogs have been administered in a variety of seizure-induction paradigms, a reduction in seizure activity has consistently been reported. Moreover, limited studies in humans with various forms of intractable seizures

have reported that administration of TRH or TRH analogs is associated with anticonvulsant effects.

Based on the types of observations summarized above, the TRH Hypothesis of Homeostatic Regulation was proposed, suggesting that TRH neuronal systems in the CNS play a key role in maintaining activity within a regulated range (Gary et al. 2003). Moreover, administration of TRH during states of CNS hypoarousal (e.g., hibernation in the ground squirrel) would lead to an increase in CNS activity, whereas administration of TRH during a state of hyperarousal (e.g., seizure activity) would lead to a reduction towards normal of the hyperarousal state. Based on this theoretical construct, a number of therapeutic applications for TRH and TRH analogs were proposed.

A few selected examples of translational research studies involving TRH will now be discussed. Nishino et al. (1997) administered TRH and the TRH analog CG-3703 (Grunenthal GmbH) in the canine narcolepsy model. Administration of both TRH and CG-3703 produced a statistically significant increase in wake time (i.e., a reduction in hypersomnolence) and a dose-dependent decrease in episodes of cataplexy in the narcoleptic dogs.

Szuba et al. (2005) administered TRH or saline in random order to bipolar patients who were studied during an episode of depression and examined behavioral responses during the next 48 hours. A substantial and statistically significant reduction in physician-evaluated depression scores was observed as soon as 9 hours after administration of TRH, with the improvement being sustained throughout the 48 hour observation period. This finding was consistent with the rapid improvement in symptoms of depression following administration of TRH that was originally reported by Prange et al. (1972). Data were also collected by means of the Profiles of Moods States (POMS) questionnaire. The use of the POMS provided access to several dimensions of physical and emotional symptom ratings by means of validated POMS subscales. Significant improvement was observed in bipolar patients who were randomized to receive an infusion of TRH on the depression, anxiety, mental confusion, fatigue and vigor subscales. Particular emphasis is drawn to the results on the fatigue subscale, which demonstrated that significant improvement in fatigue ratings was noted on the first day after TRH administration, but even greater improvement in fatigue ratings was observed on the second day after TRH administration. In bipolar patients, episodes of depression are particularly associated with symptoms of hypersomnolence, apathy, lethargy and fatigue. TRH or a TRH analog may present a novel treatment for bipolar depression, a condition for which a limited number of approved, effective treatments are available.

As noted above, the TRH Hypothesis of Homeostatic Regulation suggests that administration of TRH during a state of CNS hypoarousal would result in an increase in the arousal level to an optimal range of activity. The study of Szuba et al. (2005) identified pronounced improvement in ratings of Fatigue on the POMS subscale in patients with bipolar depression. Kamath et al. (2012) conducted a clinical study to examine the therapeutic value of TRH in patients with cancer who were suffering with prominent

fatigue symptoms. In an NIH "State of the Science Symposium" report, fatigue was cited as the most prevalent and most disabling symptom afflicting cancer survivors (National Institute of Health State of the Science Panel, 2003). In the study of Kamath et al. (2012), cancer patients were studied in a crossover design in which each subject received two infusions of TRH and two infusions of saline placebo a week apart in each case. Administration of TRH resulted in a pronounced and statistically significant increase in ratings of energy on a visual analog scale, with improvement in energy initially reported 8 hours after infusion of TRH and significant, persistent improvement in energy ratings being evident for 72 hours after a single TRH infusion. The estimated effect size (Cohen's d) for improvement in energy ranged from moderate to large. Numerous significant therapeutic effects of TRH administration were observed on several secondary outcome measures monitored in this study. These promising initial findings using i.v. TRH administration in patients with cancer related fatigue are being further explored with orally active TRH formulations.

In terms of practical applications of TRH pharmacotherapy, to date, only a single TRH product has been approved by a regulatory agency and is marketed for clinical use anywhere in the world. The TRH analog Taltirelin, which is marketed under the brand name Ceredist by Mitsubishi-Tanabe Pharma, was approved by the Japanese regulatory agency in 2000 and has been marketed in Japan, since 2000, for the indication of spinocerebellar degeneration (Gary et al. 2003). There is a lack of reports in English language journals detailing the evidence in support of the efficacy of taltirelin in patients with spinocerebellar degeneration. Nevertheless, the safety data reviewed by the Japanese regulatory agency were sufficiently benign to allow approval of taltirelin for this indication, and the compound has been marketed in Japan, since 2000, with a progressive increase in reported sales. The positive reception of this TRH product over the 13 year period of availability in Japan provides some support for the proposal that a TRH product can be used with acceptable safety and tolerability in human subjects. With regard to clinical translational opportunities related to TRH, it is pertinent to note that Kubek et al. (2009) have developed a microsphere nasal spray formulation of TRH and have demonstrated the utility of this formulation in an animal model of seizure induction. Kubek and colleagues have recently received funding from the Department of Defense to examine the utility of this TRH nasal spray formulation in the treatment of suicidality.

In summary, TRH was the first of the hypothalamic releasing hormones to be isolated and characterized, a landmark discovery that revolutionized the field of neuroendocrinology. TRH has been firmly established to play a key role in the CNS regulation of thyroid axis function, and studies of the physiology of TRH have been essential for elucidating mechanisms involved in the regulation of thyroid function. Soon after the discovery of TRH, studies were conducted in both animal models and in patients with depression that suggested that this tripeptide demonstrated behavioral activity and had the potential to bring about rapid improvement in symptoms of depression. While some more recent studies have supported the potential efficacy of TRH in improving symptoms of depression, other studies have failed to demonstrate beneficial effects, and additional work is clearly needed to evaluate the clinical utility of a TRH-based intervention in the treatment of depression. Considerable basic science data supports the proposal that TRH

plays a significant role in the CNS, including the possibility that it functions as a CNS neurotransmitter in addition to its classically identified role as a hypothalamic hypophysiotropic agent. The TRH Hypothesis of Homeostatic Regulation suggests that in states of CNS hypoarousal, administration of TRH results in an increase to normal levels of CNS activity, whereas, in states of CNS hyperarousal, administration of TRH serves to modulate the excessive CNS activity towards normal. Numerous therapeutic applications can be identified based on this TRH Hypothesis of Homeostatic Regulation. A few limited examples of translational studies with TRH or TRH analogs were discussed. Clearly, more evidence is needed to confirm and extend data supporting the clinical potential for TRH pharmacotherapy. It must be noted that, to date, only a single TRH compound, the analog taltirelin, has been approved by a regulatory agency and is marketed for clinical use. Thus, the promise of TRH to contribute to the treatment of patients with a broad range of disorders has not yet been realized, but a strong scientific base of knowledge has been developed to inform further research efforts to validate the therapeutic potential of this approach.

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December 19, 2013

PROFILES OF DISTINGUISHED NEUROPSYCHOPHARMACOLOGISTS

Introduction by Edith Serfaty

I am writing to introduce myself as the person responsible for one of the projects listed - "Profiles of distinguished neuropsychopharmacologists" (Project 4). I will be working on this project with Tom Ban, Barry Blackwell and Sam Gershon in identifying neuropsychopharmacologists who qualify for this distinction and edit their vignettes before they are posted on website.

The objective of this project is to create a 200 to 300 word vignette on those who made substantial contribution(s) to the development of the field with their contributions clearly identified and to post those vignettes as they are created on our website on this page

We hope you will be interested in participating in this project by recommending individuals for the distinction, preparing vignettes and suggesting amendments of already posted vignettes if needed.

I am posting vignettes on Nathan S. Kline, Roland Kuhn and Leo H. Sternbach with this announcement.

I am looking forward to working with you on this project.

June 13, 2013

Frank J. Ayd, Jr. by Barry Blackwell

Frank Ayd was born in Baltimore, in 1920, where he spent his entire life in private practice. Among the pioneer psychopharmacologists, he was a founding member of the American College of Neuropsyhopharmacology (ACNP) and like his peers in State Mental Institutions and the Veterans' Administration, he was a consummate clinician who witnessed first-hand and documented the earliest effects of chlorpromazine (Ayd 1955), reserpine, amitriptyline (Ayd 1960) and mephenesin (precursor to meprobamate). In addition to his own observations, he co-edited "Discoveries in Biological Psychiatry" (Ayd and Blackwell, 1970), the proceedings of a symposium at which each of the original clinicians and scientists described their role in the discovery of reserpine, chlorpromazine, iproniazid, imipramine, haloperidol, meprobamate, the benzodiazepines and lithium.

Ayd was energetic in communicating his knowledge to a wide professional and lay readership. He published probably the first psychopharmacology best seller, "Recognizing the Depressed Patient" (Healy 1997) and later in life, the massive 'Lexicon of Psychiatry, Neurology and the Neurosciences" (Ayd 2000). Until his retirement in 2003, he edited and published the "International Drug Therapy Newsletter," detailing advances and controversies in psychopharmacology to his peers in the field.

Frank Ayd died in 2008, at age 88; a devout Catholic, father of 12 children and a former consultant to the Vatican on medicine and ethics.

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August 1, 2013

Frank M. Berger by Thomas A. Ban

Frank Berger was born, in 1913, in Pilsen, Moravia, now part of the Czech Republic and received his M.D., in 1937, from Charles University in Prague. He began his professional career as a bacteriologist in his native country, but left Czechoslovakia, in 1939.

In 1943, Berger developed a method for the purification of penicillin, and while working in the laboratories of the British Drug Houses in London, searching for a substance that would inhibit the growth of Gram-negative microorganisms that cause the enzymatic destruction of penicillin, he examined several structurally related to α-substituted ethers of glycerol. It was in the course of this research that he noted that administration of small quantities of structurally-related α-substituted ethers of glycerol, and especially of mephenesin, to mice, rats and guinea pigs caused tranquilization, muscle relaxation and a sleep-like condition from which the animal could easily be roused. He recognized the potential of the substance for the treatment of anxiety and to overcome the shortcomings of mephenesin, e.g., short duration of action. He initiated at Wallace Laboratories of Carter Products, in the USA, a program that yielded, in 1950, the synthesis of meprobamate, a 2-methyl-2-n-propyl-1,3-propanediol dicarbamate. The new substance had tranquilizing action in animals like mephenesin, but its duration of action was almost eight times longer. In contrast to mephenesin, it depressed multi-neuronal reflexes without significantly affecting monosynaptic spinal reflexes.

The therapeutic effect of meprobamate in anxiety and tension states was first reported, in the spring of 1955, and the substance was introduced into clinical use in the United States in the summer of the same year. By the late 1950s, it was the most widely used prescription drug and it retained its lead until the late 1960s.

Subsequent to meprobamate, in the 1950s and ‘60s, Berger was instrumental in developing structurally related substances to meprobamate, such as carisoprodol, an analgesic and tybamate, another tranquilizer. He was also instrumental in developing Deprol, a meprobamate and benactyzine combination for use in depression.

In 1972, Berger resigned from Carter Wallace and retired from active research. He died, in 2008. in New York, at age 94.

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August 1, 2013

Charles Bradley by Walter A. Brown

Charles Bradley was born in Pittsburgh, Pennsylvania, in 1902. He graduated from Cornell University and Harvard Medical School, served his internship at Pennsylvania Hospital and his residency at Babies Hospital in New York.

In the mid-1930s, Charles Bradley gave 30 children with psychological problems one week of treatment with the stimulant drug amphetamine sulphate (Benzedrine). Most of the children received a single morning dose of 20 mg, eight got 10 mg because they couldn't tolerate 20 mg, and one received 30 mg. He carefully observed their behavior before, during and afterward. In 1937, he described the results of his study in a paper published in the American Journal of Psychiatry. Fourteen of these children, he wrote, underwent a "spectacular change in behavior . . . remarkably improved school performance." He also noted that some of the children became subdued and their behavior more socially acceptable and others experienced a sense of well-being. Bradley's subsequent research (1941) and that of others confirmed the effects of psychostimulants on school performance and behavior. Bradley and his colleagues (1948) also identified a behavioral syndrome with a presumably "organic" basis, characterized by impulsivity, hypermotility and short "attention span". This syndrome later became known as "minimal brain dysfunction," "hyperkinetic impulse disorder," "hyperkinetic reaction of childhood," and finally "attention deficit hyperactivity disorder" (ADHD). Twenty years after Bradley's initial observations (1957), colleagues at Bradley Hospital showed the specific benefit of psychostimulants in the treatment of ADHD. Bradley's observation (1937) now stands among the most important psychiatric treatment discoveries.

Charles Bradley made this discovery while serving as Medical Director of the Emma Pendleton Bradley Home—now Bradley Hospital—in East Providence, Rhode Island. The Bradley Home—founded by George Bradley, Charles's great-uncle, and named for George Bradley's neurologically impaired daughter, Emma—opened in 1931 to treat children with nervous disorders. A year later, Charles Bradley, fresh out of his training in child psychiatry, joined its staff.

The Benzedrine discovery was a byproduct of the thorough neurological evaluations carried out under Bradley's direction, which included pneumoencephalography. Bradley began treating children who suffered postpneumoencephalography headaches, presumably due to spinal fluid loss, with Benzedrine, speculating that because Benzedrine is a stimulant it would stimulate the choroid plexus to produce spinal fluid.

The Benzedrine did not do much for the headaches, but teachers noticed that some of the children taking Benzedrine experienced a striking improvement in their schoolwork. The children themselves noticed the improvement, particularly in math, and dubbed the medicine "arithmetic pills." Bradley pursued this observation in the controlled trial that confirmed Benzedrine's effect on school performance.

Like many other important medical discoveries, Bradley's was accidental. He used a drug

for the wrong reason in the wrong condition and got a totally unexpected result. His genius was in recognizing the importance of the unexpected result and pursuing it.

Bradley died, in 1979, in Tigard, Oregon.

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October 10, 2013

Bernard B. Brodie by Fridolin Sulser

Bernard B. Brodie was born August 7, 1907 in Liverpool, England. In 1911, his family moved to Ottawa, Canada.

Bernard B. Brodie received his PhD in Organic Chemistry, in 1935, from New York University, New York, NY. After a few years at the Goldwater Research Service of New York University (NYU) where Brodie was involved with imaginative research on anti-malarial drugs, in 1949, he joined (together with Julius Axelrod, Sidney Udenfriend and Bob Berliner) James Shannon, who became Scientific Director of the National Heart Institute of the National Institutes of Health (NIH). Thus began Brodie's illustrious career culminating in two stellar achievements: The creation of the Laboratory of Chemical Pharmacology (LCP) that became the Mecca of Biochemical Pharmacology and Neuropsychopharmacology and the "Brodie School" with its worldwide influence.

Brodie stressed the importance of asking scientifically relevant questions and then developing one's own methodology to get answers to these questions. The overriding research philosophy of the LCP was that Methodology drives Science. In Brodie's LCP, Bowman and Udenfriend developed the spectrophotofluorimeter that made it possible to measure quantitatively small amounts of drugs and their metabolites, and for the first time allowed to study drug-induced changes of biogenic amines in the central nervous system. The demonstration (1955, 1956) by Alfred Pletscher, Park Shore and B.B. Brodie that reserpine's tranquilizing action is associated with a time-dependent depletion of brain serotonin opened up worldwide research on the role of biogenic amines in brain. The heuristic and novel idea of explaining drug actions via their effects on neurotransmitter function (serotonin, norepinephrine and dopamine) was pursued at the LCP with such drugs as monoamine oxidase (MAO) inhibitors, other antidepressants, and hypotensive drugs. Altogether, these studies established important concepts of neurochemical pharmacology that included the action of psychotropic drugs on storage, uptake, release and metabolism of monoamines. They catalyzed research on psychotropic drugs worldwide and contributed to the evolution of Biological Psychiatry.

Brodie was also aware of the crucial role played by the postsynaptic transduction of the synaptic signal. Studies conducted at the LCP during the late 1960s and early 1970s have paved the way for elucidating the role of receptor – second messenger mediated activation of protein kinases, leading to phosphorylation of transcription factors (e.g., CREB), followed by changes in programs of gene transcription.

Besides studying the action of drugs on body function, the LCP pursued also studies on the

action of the body on drugs. Importantly, Axelrod and Brodie discovered the drug metabolizing enzymes (P450) and, consequently, the metabolic disposition of drugs and their metabolites could be followed in animals and man. Examples of the biotransformation of drugs and the potential of drug metabolites include the transformation of phenylbutazone to the pharmacologically active oxyphenylbutazone, and the formation of the active metabolite of imipramine, desmethylimipramine (DMI), which, as a selective norepinephrine (NE) reuptake inhibitor, became an important pharmacological tool. Collectively, the scientific achievements, catalyzed by the unique atmosphere of the LCP have shaped neuropsychopharmacological research worldwide.

Equally important to Brodie's scientific leadership was his mentorship of younger colleagues who all became leaders in their own respective fields and/or chairmen of major departments at American universities and at scientific institutions throughout the world. Brodie's LCP was nurturing ground of what is called the "Brodie School" with pupils sharing his love and enthusiasm for science all over the world. The first and second generation pupils took with them the inspiration, excitement and voracious appetite for novel experiments that characterized the spirit of the LCP. Robert Kanigel writes (1986) in "Apprentice to Genius": "For years scientists from all over the world had flocked his lab just to work beside him, sample his frighteningly original mind, and absorb the raw electric energy of the place". A count, of guest scientists, who trained at the LCP from 1950-1970 yielded 79 names from 29 different countries. Julius Axelrod, Arvid Carlsson and Paul Greengard (second generation pupil of Sidney Udenfriend) have received Nobel Prizes for their scientific accomplishments while many others of the Brodie School are equally worthy, chief among them Bernard B. Brodie.

Dr. Brodie received many honors, among them, in 1967, the Albert Lasker Award for Basic Medical Research, the Distinguished Service Award of the Department of Health, Education and Welfare, the Sollman Award in Pharmacology, the National Medal of Science and the Golden Plate Award from the American Academy of Achievement. In 1966, Dr. Brodie was elected as a member of the National Academy of Sciences.

Bernard B. Brodie, the creator of the "Mecca" of Biochemical Neuropharmacology and the Father of the "Brodie School," passed away, in 1989, age 82, in Charlottesville, Virginia, where he spent his last retirement years.

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October 24, 2013

John Cade by Samuel Gershon

John Cade was born, in 1912, in Murtora, Australia and received his M.D., in 1933, from the University of Melbourne. He worked as House Officer at St. Vincent's Hospital and trained in psychiatry before joining the Australian Armed Medical Corps, where he rose to major, in 1941. After spending two years as prisoner of war, Cade retuned home and joined Bundoora Repatriation Hospital in Melbourne.

Influenced by Rolv Gjessing's reports that altered metabolism with the production of mescaline-like substances was possibly responsible for a form of catatonia, and Albert Hofmann's discovery that lysergic acid diethylamide, an ergot alkaloid, has psychomimetic effect in minute amounts, Cade began his research in the mid-1940s at Bundoora. He assumed that manic-depressive illness is analogous to thyrotoxicosis and myxedema, and hypothesized that mania is a state of intoxication by a normal product of the body in excess, and melancholia is a state of deficiency of the same substance. To test this hypothesis, he compared the effects of intra-peritoneally injected manic urine with urine from normal subjects in guinea pigs and found the former more toxic in killing the animals than the latter. Cade identified urea as the culprit that killed the animals; but when he administered lithium urate to establish uric acid's toxicity enhancing effect on manic urine, he found that instead of enhancing toxicity, it protected the animals from urea's toxic effects. He attributed the protective effect of the substance to lithium and when trying to determine whether lithium salts alone have any discernable effect, he found that after injecting them in large doses of aqueous solution into guinea pigs, the animals became lethargic and unresponsive. Since Cade's investigations had commenced in an attempt to demonstrate the presence of a toxic substance excreted in the urine of manic patients, he compared the effect of lithium in 10 manic, 6 schizophrenic and 5 depressed patients, after taking the substance himself for about two-weeks to ascertain its safety, in the dose at which it was used before in gout, epilepsy, etc. He found that lithium was effective in controlling psychotic excitement, especially in manic patients. The publication of his findings, in 1949, in the Medical Journal of Australia, signals the rediscovery of lithium treatment in psychiatry.

Cade recognized that lithium exhibited remarkable specificity for mania, that it was not sedating to patients and that the treatment could be continued with a possible prophylactic benefit. Yet, concerned about its toxicity, after the death of one of his patients included in his first experiment, he virtually stopped using lithium in his hospital and stopped experiments with the substance.

In 1953, Cade was appointed Medical Superintendent of Royal Park Hospital, in

Melbourne. In the years that followed, he had done no further research with lithium but carried out investigations with protective foods in psychiatry and with high doses of thiamin in the prevention and treatment of memory disturbances in alcoholism. About fifteen years after the publication of his historical paper on lithium, he reported high magnesium levels in schizophrenia and during the 1960s, he studied the effects of manganese in mongolism.

Cade retired from his position at Royal Park, in 1977, and died at age 68, in 1980.

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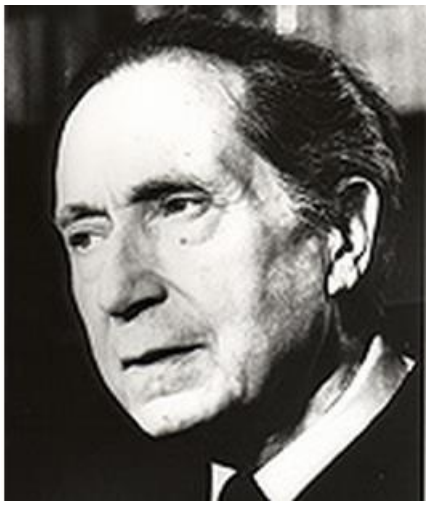
August 1, 2013

Jean Delay by Driss Moussaoui



Jean Delay was born in Bayonne, in the Basque country of France, in 1907. His father was a surgeon and wanted his only child to follow his professional path. He obtained his baccalaureate at the age of 14, and began his medical studies in Paris. Although he was a brilliant student, he chose to become a psychiatrist, which was hard for his classmates to understand, due to the poor reputation of psychiatry at that time. Meanwhile, he obtained a diploma in psychology, after completing his thesis on the "psychopathology of memory." Although still a student, he became involved in neurophysiological experiments.

Jean Delay became one of the youngest professors of medicine in France, and the main collaborator of Levy-Valensi. It was during this period that he introduced EEG in France and became interested in the biological treatments of psychoses, using electroconvulsive therapy, insulin therapy, and "pneumo-shock", which he invented himself. In 1947, at the age of 39, he became the chairman of the "Clinique des Maladies Mentales et de l'Encéphale." He started building up a prestigious team of specialists from every field of psychiatry and related sciences: neurophysiology, neuropathology, electrophysiology, psychology, psychoanalysis (Jacques Lacan gave lectures in his department for many years), psychopharmacology and psychosomatics.

Delay's international work started very early, in 1945, when he was nominated as an expert at the Nuremberg trial, during which he examined Rudolph Hess and Julius Streicher. In 1950, he organized, in collaboration with Henri Ey, the first World Congress of Psychiatry, in Paris. One of the aims of that congress which was attended by 2,200 participants from 52 different countries was to bring together psychiatrists from France and Germany, only 5 years after World War II ended. He became the first president of the Association for the Organization of World Congresses in Psychiatry, which was the parent association of the World Psychiatric Association (Moussaoui, 2003).

In 1950, Delay published a book on Biological Methods in Psychiatry in which he included a chapter on psychochemistry. From findings about the transient effects of barbiturates and amphetamines on the mental state of patients, "he was convinced" that someday, drugs would appear with a lasting influence on mental disorders (Pichot, 1992). In 1952, with Pierre Deniker, he published the first articles on chlorpromazine in the treatment of psychoses in the Annales médico-psychologiques, when used alone. The introduction of this first neuroleptic opened up the era of modern psychopharmacology. He was also the very first to conduct a clinical trial (1952) to assess the antidepressant effect of isoniazide; and was among the first (1954) to study the therapeutic effect of reserpine, a Rauwolfia alkaloid, in psychiatry. In his monograph, Chemotherapeutic Methods in Psychiatry (1961), which he published with Pierre Deniker, there is an overview of the research in

psychopharmacology that he had encouraged and directed. His interest and achievements in psychopharmacology led him to become president of the Collegium Internationale Neuro-Psychoharmacologicum, in 1966, after having been one of its founding fathers.

In 1959, Delay became a member of the Académie Française, which thus recognized his many talents—as a scientist, a psychologist and also, as a man of letters, as he wrote a number of successful novels.

Jean Delay had a difficult time with the May 1968 events in Paris, when students were questioning every symbol of authority in society. He decided to retire, in 1970, at the age of 63.

Brilliantly intelligent, Jean Delay was an exceptionally hard-working man. He made decisive contributions to the growth of the fields of psychiatry and mental health, in France and in the world at large, by the creation of the World Psychiatric Association (WPA), and by the recognition of the importance and the promotion of a systematic multidisciplinary approach in psychiatry. In recognition of this, the highest award of the WPA is named after him.

Jean Delay died in Paris, in 1987, but his legacy remains strong.

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September 26, 2013

Edmundo Fischer by Edith Serfaty

Edmundo Fischer was born in Budapest, Hungary, in 1904, and received his M.D., in 1929, from the University of Pecs. He began his professional career as a neurologist and psychiatrist in his native country, but left Hungary, in 1938, via Mexico and Chile to settle in Argentina, in 1950.

With the introduction of the first therapeutically effective psychotropic drugs in the treatment of mental illness, Fischer's interest turned to psychopharmacology, and in 1960, he became founding director of the Laboratory of Experimental Psychiatry at Borda Hospital, in Buenos Aires. Three years later, in 1963, he was instrumental in founding the Argentine Society of Psychopharmacology; and in 1965, he published "Psicofarmacologia", co-authored by G. Poch and Ronaldo Ucha Udabe, one of the first textbooks in the field.

Stimulated by Fabing's observations in the mid-1950s on bufotenin's psychomimetic effects, Fischer became involved in measuring tryptamine metabolites in urine and reported on significantly higher urinary concentration of bufotenin-like substances in schizophrenia than in normal subjects. His findings fueled the ongoing controversy in the 1960s and early 1970s on the role of dimethylated psychotoxic tryptamine metabolites in the pathogenesis of schizophrenia.

Pursuing research with the employment of biochemical measures in different diagnostic groups of psychiatric patients, Fischer found decreased urinary elimination of phenylethylamine (PEA) in "endogenous depression." Subsequently, after demonstrating that PEA antagonized reserpine effects in pretreated rats, Fischer was among the first, in the early 1970s, to explore the possible use of phenylalanine, the precursor of PEA, in the treatment of depression.

In 1974, Fischer played a role in the founding the World Federation of Societies in Biological Psychiatry. He died in Buenos Aires one year later, in 1975, at age 71.

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August 1, 2013

W. Horsley Gantt by Thomas A. Ban

Horsley Gantt was born, in 1893, in Wingina, Virginia, USA, and received his M.D., in 1920, from the University of Virginia, at Charlottesville. Gantt began with his professional career at the University of Maryland, in Baltimore, studying "liver pathology," but his interest shifted after serving for a year, from 1922 to 1923, as Medical Chief of the Petrograd (now Saint Petersburg) Unit of the American Relief Administration in Russia, at the time, in the Union of Soviet Socialists Republics.

In 1924, Gantt joined Ivan Petrovich Pavlov and for five years he was conducting research in conditioning at his Institute of Experimental Medicine. After returning to the United States, he continued his research in conditioning from 1930 to 1958, as Director of the Pavlovian Laboratory, The Johns Hopkins University School of Medicine, and subsequently, from 1959 to 1980, as Senior Scientist in the Pavlovian Research Laboratory of the Veterans Administration Hospital, at Perry Point, Maryland. He conducted his research primarily in animals, but also in man, including patients with mental pathology. He held appointments during the corresponding periods in the departments of psychiatry at Johns Hopkins and at the University of Baltimore.

Gantt began his research in psychopharmacology in the mid-1930s. Over a period of forty years, he was involved, first in studying "drug effects on conditional and unconditional reflexes", in general, then in studying the differential effects of drugs on "autonomic and somatic conditioned reflexes," and ultimately, in the study of "conditioning of drug effects." His findings with alcohol, acetylcholine, adrenaline, amphetamine, caffeine, chlorpromazine and reserpine, in the first set of studies, were supportive of Pavlov and his associates' reports that drug effects were dependent on the "temperamental type" of animals. In the course of these studies, he showed that acetylcholine improved conditional reflexes more in "neurotic" than in "normal" dogs, whereas adrenaline was less disruptive in "normal," than in "neurotic" animals. In the second set of studies, Gantt and his associates revealed that some drugs, for example chlorpromazine, reserpine and 5-hydroxytryptophan, influenced motor and cardiac conditional reflexes to the same degree, whereas others, for example mescaline, meprobamate and metrazol, affected autonomic conditional reflexes preferentially, and others again, for example, morphine, had a preferential effect on motor conditional reflexes. Finally, in the third set of studies, Gantt and his associates demonstrated that there was conditioning only to the central effect, but not to the peripheral effect of drugs. Thus, cardiac conditional reflexes could be formed to the central effect of bulbocapnin, but not to the peripheral effect of acetylcholine.

Gantt's studies stimulated interest in "Pavlovian" research, leading to the founding of the Pavlovian Society of North America, in 1955, and to the Collegium Internationale Activitatis Nervosae Superioris, about ten years later. Gantt was founding President in both

of these societies.

Horsley Gantt died, in 1980, at age 83.

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August 1, 2013

Nathan S. Kline by Barry Blackwell

Nathan Kline was born, in 1916, and died tragically at the age of 66, in 1983, following open heart surgery. A graduate of Swarthmore College and New York University College of Medicine, Kline was a practicing psychiatrist. He was among the very first pioneers to use and study drugs for the treatment of mental illness, beginning in 1952, when at age 36, he started a research unit at Rockland State Hospital in New York (named the Nathan Kline Research Institute after his death).

He was a founding member of the American College of Neuropsychopharmacology (1961) and its sixth President (1967). Kline was the only two time recipient of the Albert Lasker Clinical Medical Research Award; in 1957, for work on Rauwolfia Serpentina in the early treatment of neuropsychiatric disorders, and in 1964, for introducing the first MAO inhibitor (iproniazid) as an "energizer" in the treatment of mood disorders. Within a decade, Rockland Research Institute had established a worldwide reputation and a staff of over 300, attracting students and colleagues from around the world, who Kline insisted live in close proximity to their patients.

He was also a major proponent of lithium in bipolar disorder and also recognized its potential usefulness in alcoholism. In 1968, he installed one of the early computers at Rockland State to facilitate research. The early treatment successes helped initiate the process of de-institutionalization, leading nationwide to the closure of asylums. Kline did much to publicize and de-stigmatize mental illness with over 500 publications directed to both the medical profession and general public. His book, "From Sad to Glad", became a best seller. Kline was founder and Director of The International Committee Against Mental Illness, consulted with the World Health Organization and devoted much time and effort to promoting treatment of mental illness in developing countries.

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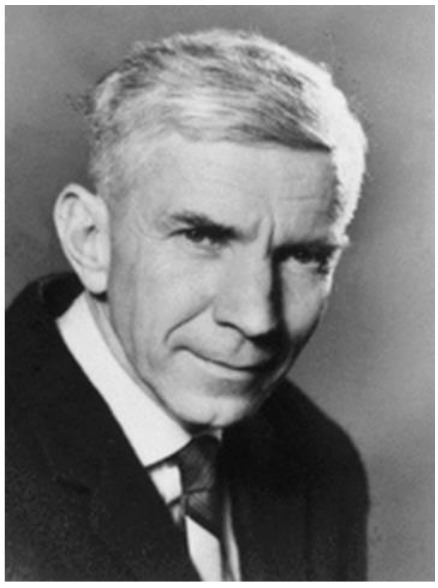
June 13, 2013

Roland Kuhn by Thomas A. Ban

Roland Kuhn was born in Biel, Switzerland, in 1912. He was trained in psychiatry at the University of Bern and in 1939, he was appointed senior physician at the Cantonal mental hospital in Műnsterlingen.



Kuhn became involved in the clinical testing of new drugs for Geigy, one of the major drug companies in the mid-1950s. He suggested the testing of one of the antihistamines, G22,355, a tricyclic dibenzazepine, because it showed the closest structural resemblance to chlorpromazine, a substance that was widely used in the treatment of schizophrenia. Contrary to his expectations, G22,355 had no therapeutic effect in schizophrenia. Instead, he observed that it was effective in some depressed patients, and especially in those with endogenous depression, in whom vital disturbance was in the foreground. Kuhn published his observations with G22,355 in 40 depressed patients in the 31 August issue of the Swiss Medical Journal, in 1957, and the substance was released in the same year for clinical use in Switzerland for the treatment of depression, with the generic name of imipramine, and the brand name of Tofranil. There was a strong opposition by mainstream psychiatry against pharmacological treatment of depression, but Kuhn prevailed and the introduction of imipramine was instrumental in encouraging the development of other drugs for the treatment of depression. Kuhn died in 2005.

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June 13, 2013

Dionisio Nieto Gómez by Antonio Torres-Ruiz

Dionísio Nieto Gómez was born in Madrid, Spain on March 13, 1908. In 1929, he received his M.D. 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 first to explore the psychopathology induced by strofariacubensis, 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 poisoning with thallium, arsenic, lithium, etc. (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 up 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

Alfred Pletscher by Fridolin Sulser

Alfred Pletscher was born, in 1917, in Altstaetten/SG, Switzerland. He received both his M.D. degree, in 1942, and his Ph.D. in chemistry, in 1948, from the University of Zurich, Switzerland. After a year as Visiting Scientist with Bernard B. Brodie at the National Heart Institute of the National Institutes of Health (NIH), he returned, in 1955, to Switzerland to assume the position of Director of Corporate Research at Hoffmann-La Roche, Basel. "My time in Brodie's laboratory was one of the highlights of my scientific career," he said. In an interview with Tom Ban, Pletscher reflected on his position in industry: "My primary motivation in industry was not profit, but helping people." This statement is an expression of Pletscher's humanistic philosophy. In 1978, he left industry and became Chairman of the Department of Research at the University of Basel.

Alfred Pletscher's scientific contributions had an enormous impact on the development of Biochemical Neuropsychopharmacology, worldwide. In 1955, together with Parkhurst Shore and Bernard B. Brodie, Alfred Pletscher demonstrated, using spectrofluorimetric methodology, that reserpine's tranquilizing action is associated with a dose-dependent depletion of brain serotonin (5HT). This finding opened up world-wide research on the neurobiology of monoamines (Pletscher 2005). Pletscher was first to demonstrate that pretreatment with iproniazid, a monoamine oxidase (MAO) inhibitor, not only attenuated the reserpine-induced decrease of brain 5HT, but was associated with behavioral stimulation by reserpine instead of tranquilization. Since the reserpine-like syndrome was viewed as a "model depression," the discovery provided the scientific rationale for the introduction of MAO inhibitors for the treatment of depression (Pletcher 1957). It also stimulated research for mechanisms of action of tricyclic antidepressants which, like iproniazid, also antagonized the "reserpine-like syndrome," but without blocking MAO, culminating in the discovery by Axelrod and Herting of the reuptake mechanism for the non-enzymatic termination of the action of biogenic amines.

When Pletscher returned to Switzerland, he developed the synthetic benzoquinolizines--tetrabenazine and Ro-41284—which displayed a short-lived reserpine-like syndrome associated with a short-lived depletion of brain 5HT, and were widely used as tools to discover "antidepressant" activity in laboratory animals (Pletscher 1957).

Pletscher was also instrumental in introducing the benzodiazepines, discovered by Leo Sternbach at Roche, in Nutley, USA—chlordiazepoxide (Librium), first, followed by diazepam (Valium)—for the treatment of anxiety disorders.

Another pivotal contribution to the monoamine field was the development of decarboxylase inhibitors and their combination with levodopa for the treatment of Parkinson disease (Pletscher et al. 1965). Pletscher's rationale for the combination was based on the discovery that these decarboxylase inhibitors enhanced the levodopa-induced rise in brain dopamine, while they decreased the concentration of peripheral dopamine. This combination of levodopa with a peripheral decarboxylase inhibitor is still a standard treatment of Parkinson's disease.

In meticulously designed studies, Alfred Pletscher utilized blood platelets as models for brain neurons to study uptake, storage, release and metabolism of biogenic amines and receptors for monoamines and peptides.

Collectively, Alfred Pletscher's scientific contributions have provided the conceptual framework for much of what we are doing today, e.g., studies on amine transporters, amine receptor-mediated second messenger formation and activation of protein kinases. His pioneering research endeavors and his scientific astuteness did not go unnoticed by the political authorities in Switzerland. Thus, in 1981, he was elected President of the research council of the Swiss National Science Foundation, and in 1988, President of the Swiss Academy of Medical Sciences. Alfred Pletscher catalyzed the creation of the Biocenter of the University of Basel, the Roche Institute of Molecular Biology, in Nutley, USA and the prestigious Basel Institute of Immunology.

Alfred Pletscher received many honors, among them four Honorary Doctor degrees from the Universities of` Paris (France), Genève, Lausanne, and Fribourg (Switzerland); the prestigious Marcel Benoist Prize, the Science Prize of the city of Basel and the CINP Pioneer in Psychopharmacology Award.

Alfred Pletscher, a true Pioneer of Psychopharmacology, passed away, age 90, on December 12, 2006.

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November 28, 2013

Leo H. Sternbach by Thomas A. Ban

Leo Sternbach was born in Abbazia, Croatia, in 1907. He studied pharmacy and organic chemistry at Jagellonian University in Cracow, Poland, and as a postgraduate student, synthesized several heptoxdiazine compounds. After a short academic career, Sternbach joined Hoffmann-La Roche, one of the major Swiss pharmaceutical companies, in Basel, moved, in 1941, from Switzerland to the United States, and some years later, became Director of Medicinal Chemistry at Roche's research facility in Nutley, New Jersey.

In 1954, while searching for drugs with psychotropic properties, he returned to his early interest as a postgraduate student, and synthesized a series of heptoxdiazines, which at the time, he recognized were quinazoline-3-oxides, and treated one of them with methylamine. From the reaction, resulted 2-methylamino-7-chloro-5-phenyl-3H-1,4-benzodiazepine-4-oxide, a substituted 1,4 benzodiazepine that was given the generic name, methaminodiazepoxide first, and chlordiazepoxide subsequently, in 1957. Pharmacologic screening revealed that the substance had similar pharmacologic profile to meprobamate, a widely used drug for relieving anxiety and tension, at the time. In 1960, chlordiazepoxide, the first benzodiazepine compound, was introduced into clinical use as an anxiolytic with the brand name of Librium. From the several other "benzodiazepines" Sternbach synthesized, diazepam was introduced, also primarily, for treatment of anxiety; flurazepam, nitrazepam, and flunitrazepam, for insomnia; and clonazepam, for epilepsy. During the 1960s, chlordiazepoxide, and especially, diazepam became widely used substances around the world; from 1969 to 1982, diazepam was the most prescribed drugs in the United States. They were instrumental in opening up research in the neuropsychopharmacology of anxiety. Sternbach died, in 2005, at age 98.

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June 13, 2013

Edward Trautner by Samuel Gershon

Edward Trautner was born, in 1886, in Germany and received his medical degree in his native country. He left Germany, in the 1930s, and after a short stay in Spain and England, he arrived in the 1940s, as a refugee to Australia, where he was invited by Professor Douglas Wright, head of the joint Department of Physiology and Pharmacology at the University of Melbourne, to join his faculty.

In 1949, John Cade published his report in the Medical Journal of Australia on "Lithium salts in maniacal excitement" that lead to the re-introduction of lithium therapy in psychiatry. Yet, the clinical use of the new treatment entailed difficulties because of lithium's toxicity that was to the extent that Cade himself prohibited the use of the substance in his own hospital. Recognizing the importance of rendering lithium feasible for clinical use, Trautner with his junior associates that included Charles Noack, Douglas Coats and Samuel Gershon, conducted a series of four studies, during the 1950s, that set the foundation for lithium therapy.

In the first of these reports, published in 1951, it was established that lithium, if administered in a dose, in which plasma lithium levels are kept within 0.6 mEq/l to 1.2 mEq/l, is a safe and effective treatment in manic depressive patients. Plasma level determinations in the study were carried out with the flame photometer, an instrument constructed by Victor Wynn at the University, just a year before. From the other three reports, one published in 1955, showed increase of lithium retention in mania and of lithium excretion, when mania is resolved; another, published in 1956, revealed possible use of lithium in maintaining manic depressive patients in remission; and the third, published in 1957, dealt with the treatment of lithium toxicity. Without Trautner's contributions, implementation of lithium treatment would have been considerably delayed. Treutner died in Queensland, in 1979, at age 93.

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August 1, 2013

CONTROVERSIES IN THE HISTORY OF NEUROPSYCHOPHARMACOLOGY

Introduction by Barry Blackwell

Now that the INHN website is functional, I am writing to introduce myself as the person responsible for one of the twelve tentative projects listed under About INHN - “Controversies in the History of Neuropsychopharmacology" (Project 5 – Controversies). I will be working with Tom Ban and Peter Martin to review and edit contributions.

We currently have several tentative offers for topics and we welcome any additional ideas based on your own involvement in, or thoughts about past or present controversies in the field. We envisage up to one thousand words that describe the issue, either from a protagonist point of view or as a commentary, on all the pros and cons. We request submissions in English in a narrative (essay) format with optional references. After an essay is posted the general membership will be invited to respond within four weeks by e-mail (inhn@inhn.org) and the editors will select and post the responses shortly thereafter.

We hope that the scope and quality of the contributions will justify future publication in book form.

I will be posting the first topic with this announcement on "A distinguished but controversial career - Jose Manual Rodriguez Delgado".

Stay tuned!

May 30, 2013

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

The term, "conflict of interest" is defined in the Webster dictionary as "a conflict between private interests and official responsibilities of a person in a position of trust" (Merriam-Webster 1985). It is used in reference to situations in which fiduciary interest, founded on trust or obligation, is compromised by another interest (Black 1978). If people act contrary to their fiduciary interest they act in "conflict of interest".

Prior to the 1980s, little attention was paid to "conflict of interest" in science and medicine. At present, authors in most medical journals and speakers at most medical conferences are required to disclose their financial involvement with the pharmaceutical industry (Krimsky 2006; Lemmens 2008). While receiving funds from industry is a financial motivation, it may or may not lead to an act in conflict of interest.

Neuropsychopharmacology studies the mode of action of psychotropic drugs for obtaining information on the biochemical underpinning of mental pathology in order to develop rational pharmacological treatments (Hollister 1996; Wikler 1957). Psychotropic drugs are the means and the end products of neuropsychopharmacological research. Developed by drug companies and registered by regulatory authorities, the prescription of psychotropic drugs is dependent on interaction between (academic) education and (industrial) marketing. The objectives of marketing (industry) and education (academy) are in conflict. The objective of marketing is to get a product prescribed in the widest possible population, whereas the objective of education is to guide the judicious and discriminate use of available drugs. Both successful education about the clinical use of psychotropic drugs and neuropsychopharmacological research, are dependent on established therapeutic effects of a drug in a well-defined population, whereas successful marketing is dependent on demonstrated therapeutic efficacy, as defined by regulation, in the widest possible population, in which the substance may have an effect in some patients.

Introduction of psychotropic drugs, during the 1950s, focused attention on the pharmacological heterogeneity within psychiatric diagnoses (Ban 1969, 1987). To meet educational and research objectives, there was a need to resolve this heterogeneity by identifying the treatment responsive sub-populations within the diagnostic groups (Ban 1969, 1987, 2007; Freyhan 1959; Klein 1973, 2008). This did not happen (Ban 2008; Klein 2008). Instead, in keeping with marketing interests, the randomized clinical trial was adopted for the demonstration of efficacy in a diagnostically defined, but pharmacologically heterogeneous population. Efficacy is a statistical concept relevant to the population rather than to the individual patient. Statistically significant efficacy of a drug indicates that the study population as a whole responds differently to a particular substance than to an inactive placebo with an arbitrarily defined statistical probability to qualify for a significant difference (Ban 1964, 2006; Hamilton 1961). It implies that there is a treatment responsive sub-population in the diagnostic group, but it does not identify the treatment responsive subpopulation (Ban 2006).

Introduction of the first neuroleptics, in the mid-1950s, coincided with the publication of

Karl Leonhard's monograph on the Classification of Endogenous Psychoses (Ban 2006; Leonhard 1957). In Leonhard's classification, schizophrenia was split into two major classes of disease, referred to as "systematic schizophrenia" and "unsystematic schizophrenia", with several forms and sub-forms in which moderate to marked responsiveness to neuroleptics varied from less than 1 in 4 patients in the "systematic hebephrenias", to more than 4 in 5 patients in "affect-laden paraphrenia", one of the three forms of "unsystematic schizophrenia" (Astrup 1859; Fish 1964). The differences in responsiveness were not restricted to therapeutic effects but were present also in susceptibility to adverse effects (Ban 1990). Findings of an international survey carried out, in the 1980s, showed that the prevalence of tardive dyskinesia was over 20% in the treatment refractory subpopulation in Leonhard's classification, and below 5% in the treatment responsive one (Guy, Ban and Wilson 1985, 1986). Adoption of Leonhard's classification of "schizophrenias" would have been in-keeping with educational needs by providing at least orientation points for prescribing neuroleptics more discriminately in patients with schizophrenia. It would have also provided through neuropsychopharmacological research, a pharmacologically sufficiently homogeneous population, to study the mode of action of neuroleptics in order to get information about the biochemical underpinning of "affect-laden paraphrenia". Again, this did not happen. Instead, a dopamine hypothesis of "schizophrenia," and not of "affect-laden paraphrenia," was formulated; and a series of new "haloperidol type" of potent dopamine receptor blocker neuroleptics gradually replaced generic "chlorpromazine-type of neuroleptics" in the entire schizophrenic population, including the subpopulation in which in Fish's study, they had virtually no beneficial effect (Carlsson and Lindqvist 1963; Snyder 1975; Van Rossum 1966). Since "haloperidol–type of neuroleptics" have stronger affinity to dopamine than to serotonin receptors, whereas "chlorpromazine type of neuroleptics" have stronger affinity to serotonin than to dopamine receptors, it led to severe extrapyramidal signs in many patients, with a high prevalence of tardive dyskinesia (Gyermek 1955; Gyermek, Lázár and Csák 1956; Lambert et al. 1959). Then, to undo the harm, prescription practices were reversed, and again, in keeping with marketing interests, a series of new "clozapine-type of neuroleptics", which similar to chlorpromazine-type of neuroleptics have stronger affinity to serotonin than to dopamine receptors, gradually replaced generic haloperidol-type of neuroleptics in the entire schizophrenic population, including the subpopulation in which more than 4 in 5 patients responded to them (Ban 2004; Ban and Ucha Udabe 2006; Meltzer, Matsubara and Lee 1989). The net result was a shift from neurological to metabolic side effects. Both shifts, the shift from "chlorpromazine-type of neuroleptics" to "haloperidol-type of neuroleptics", and from "haloperidol-type of neuroleptics" to "clozapine-type of neuroleptics", were led by academics. A full circle was closed, half a century passed without a single clinically more effective or selective neuroleptic than chlorpromazine for the treatment of schizophrenia.

The story of antidepressants in the treatment of depression is similar to the story of neuroleptics in the treatment of schizophrenia (Ban 1974, 2001, 2004).

At the time of its introduction, imipramine was found to be powerfully effective in 1 of 3 patients with endogenous depression, an umbrella diagnosis that no longer exists (Ban 1974; Klerman and Cole 1965). Endogenous depression included syndromes, which arose,

assumedly from a primary pathology of mood, which, in typical cases, shared common characteristics of sudden onset, episodic course and full remission between episodes (Ban 2000, 2002; Kraepelin 1896; Leonhard 1957; Schneider 1920). Patients diagnosed with one or another form of endogenous depression were clearly distinguishable from each other and from the general population (Ban 1987). Today, these "prototype-based diagnoses" are history; they are swallowed up by broad "consensus-based diagnoses", like "major depression" in the classification of the American Psychiatric Association, and "depressive episode", in the classification of the World Health Organization, in which incomplete remission occurs in around one-third of all cases (American Psychiatric Association 1994; Keller et al. 1995; Kessler et al. 1994; Michalak and Lam 2002; World Health Organization 1992). Consensus-based diagnoses cover up prototype-based diagnoses to the extent that even if a severely ill patient displays all the symptoms of "major depression" or "depressive episode," one still would not know whether the patient qualifies for "vital depression," the form of depression that Kuhn maintained, allowed him to discover imipramine's "antidepressant" effect (Ban 2000; Kuhn 1957, 1986).

The problem is further compounded by the drastic increase of the depressive population in epidemiological surveys in the first 20 years after the introduction of imipramine and other antidepressant drugs. These studies indicate that even the lowest prevalence figures of depression are seven to ten times higher in the "antidepressant era", i.e., after the introduction of the first antidepressants with demonstrated therapeutic efficacy, than before (Hoenig 1980; Silverman 1968). Prescribing antidepressants to this large population, in which even with an optimal 1 to 3 response rate to the pharmacological action of antidepressants, implies that more patients are exposed to potential side effects than one could expect to benefit from these drugs (Ban 2001, 2006, 2008; Szendi 2004). The shift from "prototype-based diagnoses" of depression to "consensus-based" unitary concepts of "depression", such as "major depression" in the DSM-III and "depressive episode" in the ICD-10, has perpetuated this state of affairs. It has also precluded the possibility for using old prototype based diagnoses for the identification of the treatment responsive subpopulation within "major depression" or "depressive episode". Yet, the shift was led by academics.

Clinical development of psychotropic drugs entered a new phase, during the 1980s, with the replacement of single-center isolated clinical studies by multi-center, centrally coordinated clinical investigations, designed with power statistics to prevent Type II error, i.e., missing of a statistically significant difference because of insufficient sample size. These studies are conducted in order to meet regulatory requirements for introducing a compound into clinical use. Yet, the findings of this research provide the evidence base for both marketing and education, thereby confounding, by the dawn of the 21st century, education in pharmacotherapy with the marketing of psychotropic drugs (Ban 2006).

Today, most "evidence-based" information in education about the use of psychotropic drugs is generated in such multi-center studies. Treatment guidelines prepared by opinion leaders and reports reviewing evidence-based information by task forces are no exceptions. By disqualifying papers from the first thirty years of pharmacotherapy on grounds of

methodological shortcomings, one relatively current such report on "Antidepressant medications and other treatments of depressive disorders" justified, on the basis of "a review of evidence," the preferential prescription of the newest and most expensive antidepressants over the old ones (Baghai, Grunze and Sartorius 2007; Ban 2008).

In the current state of confusion the contrary objective of education to marketing no longer provides the necessary balance for the optimal use of psychotropic drugs. The blurring of education with marketing has created a situation, in which educators in pharmacotherapy may inadvertently pursue activities in conflict with their fiduciary interests. Addressing monetary incentive alone in this confound, an ethical-legal issue, however important it is, distracts attention from the heart of the problem: that until the pharmacological heterogeneity within the diagnostic groups is not resolved, pharmacotherapy with psychotropic drugs will inevitably be dominated by marketing interests (Ban 2007).

Insofar as pharmacotherapy with psychotropic drugs is concerned, the pharmacologically heterogeneous diagnoses have restricted the relevance of pharmacodynamic information generated by neuropharmacological research, to the side effect profile of psychotropic drugs. And, insofar as neuropsychopharmacology is concerned, the lack of pharmacologically valid psychiatric diagnoses has deprived neuropharmacological research from clinical feedback to the extent that no clinically more selective or effective pharmacological treatment has developed since the introduction of the first set of therapeutically effective psychotropic drugs in the 1950s.

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December 26, 2013

Barry Blackwell: A distinguished but controversial career:
Manuel Rodriguez Delgado

Sometimes the personality of a scientist, his chosen field of enquiry and a changing social or scientific zeitgeist can collude to create unanticipated and career changing controversy. There may be no better example of this than what befell Jose Delgado during the half century of a distinguished career. I first learned of this while writing his obituary for Neuropsychopharmacology (Blackwell, 2012 a) but became so intrigued that my research eventually produced a brief 10,000 word biography, published in my memoir titled, "Science, Hubris, Nemesis and Redemption" (Blackwell, 2012 b).

Jose Delgado was born in Ronda Spain, in 1915, a founding member of the ACNP and lifelong Fellow, he died at age 96, three months before our organization celebrated its fiftieth anniversary.

Jose intended to emulate his father, an ophthalmologist, but fell under the spell of Santiago Ramon y Cajal, often considered the "Father of Neuroscience", Nobel Laureate in 1906.

Jose enrolled in Madrid Medical School, in 1933, to study both medicine and physiology. In 1936, the Spanish civil war erupted, his mentor Juan Negri fled the country and Jose joined the Republican side as a medical corpsman. After the fascist victory, he spent five months in a concentration camp before obtaining his M.D. and Doctorate of Science, both cum laude.

From 1942 to 1950, he began research in neurophysiology on selective brain ablation and electrical stimulation in animals, published 14 articles and won several prizes. In 2005, at age 90, he was interviewed for the ACNP's Oral History of Neuropsychopharmacology, where he tells how he went to Africa to buy primates for research, bonded with a gorilla and, unable to operate on his "new friend", donated the animal to a zoo.

In 1950, Delgado won a scholarship to Yale University in the Department of Physiology under the direction of John Fulton, whose pioneer work on pre-frontal lobotomy in chimpanzees encouraged the Portuguese psychiatrist Egas Moniz to perform the operation in schizophrenic patients, for which he received the Noble Prize, in 1949.

Delgado flourished at Yale; rising to Professor of both Physiology and Psychiatry, he eventually succeeded Fulton as Director of Research. Described as "a technological wizard," he invented the "stimoceiver"; implanted electrodes which established two way communications with the brain in mobile animals, allowing Jose to stimulate different regions, producing changes in affect and behavior. Encouraged by these results, and Moniz' example, Delgado extended his research to patients with chronic refractory epilepsy and schizophrenia.

This ground breaking research was published, in 1952. anticipating similar work by Bob

Heath at Tulane University. The year 1952 was a watershed year in neuroscience, when chlorpromazine was being given to patients with schizophrenia, spawning the neuropsychopharmacology revolution.

Delgado positioned himself between growing disapproval of mutilating brain surgery and his own belief that electrical stimulation of specific brain areas was scientifically superior to oral administration of drugs, whose effects were mitigated by liver metabolism, the blood brain barrier and uncertain distribution.

Events proved Jose wrong; the effects of electrical stimulation were imprecise, poorly replicated and yielded no useful therapeutic outcomes. Conversely neuropsychopharmacology thrived. Drugs were developed for every type of psychiatric disorder, deinstitutionalization occurred and, in 1970, the Nobel Prize went to Julius Axelrod and colleagues for discoveries about humoral transmitters at nerve endings that led to the catecholamine hypothesis of depression.

Nevertheless, in two decades (1950-1970), Delgado authored 134 scientific publications on electrical stimulation in cats, monkeys and patients, psychotic and non-psychotic. In 1963, he performed an experiment that attracted worldwide attention, including a front page article in the New York Times. After implanting his stimoceiver in the caudate nucleus of a fighting bull, Jose stood facing the bull, waving a red cape before stopping the animal in its tracks by activating the electrodes.

Soon after this, Delgado was invited to contribute a volume to a series on "World Perspectives." Its editorial board comprised twelve of the world's most distinguished leaders in ethics, sociology, economics, spirituality and science, including three Nobel Laureates. The series editor was a renowned philosopher, whose life was devoted to inviting leading scientists and thinkers to speculate on the societal and philosophical implications of their narrow fields; to "extrapolate an idea in relation to life".

Jose chose a provocative title for his volume, "Physical Control of the Mind: Towards a Psychocivilized Society". The text and tone were equally challenging. While Jose's discussion of his scientific findings was modest and objective, the philosophical speculations were grandiose and went beyond the data. None the less, his intent was benevolent; to encourage the development of "a future psychocivilized human being; a less cruel, happier and better man". In essence, he was proposing that science might accomplish what two millennia of religion failed to do!

Unfortunately, this rhetoric and hyperbole clashed with a changing scientific, political and social Zeitgeist, engulfing Delgado in controversy that would end his career in America. Without distinguishing between science and philosophy, Jose's research and ideas were attacked and denigrated on two fronts.

In 1972, Congress held hearings in response to efforts to end funding for this type of brain surgery. Testimony was given by a libertarian psychiatrist, a scientologist, at the time, who

disparaged drugs, ECT and biological psychiatry. This included a collage of selective, out of context, quotations from Delgado and other neuropsychiatrists.

Coincidentally, public and political outrage surfaced over covert CIA "mind control" experiments, designed to combat communism, initiated in the McCarthy era and extending into the mid 1960's (MK-ULTRA).

These twin forces manifested a plethora of websites fed by conspiracy theorists and alleged victims of psychosurgery that disseminated innuendo and largely unsubstantiated accusations for four decades. Delgado's name and book figure prominently, along with other well-known psychiatrists from among 43 Universities and Colleges, alleged to have been involved.

Mired in controversy, Delgado accepted an offer to become Chair of Physiological Science at a new medical School in Madrid and moved there, in 1974.

For the next quarter century, Jose continued to publish his research and philosophical ideas, achieving a lifetime total of over 500 articles and six books. His final book, in 1989, was titled "Happiness" and went through 14 editions.

In the last years of his life, Jose and his wife returned to America and lived in San Diego, where he died unheralded. Unjustly treated and harshly judged by segments of the public and his profession, Jose Delgado's ground breaking research, benevolent philosophy and memory deserved better. His career trajectory may provide budding scientists with a cautionary note about the pitfalls of mingling science with philosophy and the perils inherent in a changing social, political and scientific landscape.

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May 30, 2013

Paul Devenyi: Addictions are not treatable diseases

In 1960, Dr. E. M. Jellinek (not a physician) wrote a landmark book: "The Disease Concept of Alcoholism". He did away with the commonly held concept that alcoholics are weak, morally bankrupt individuals and even offered a scientific classification for different forms of alcoholism (Jellinek, 1960). Many people jumped on the "disease concept" bandwagon and it was extended from alcoholism to other drug addictions. Political correctness demanded that addicts are to be regarded as unfortunate sick people who need treatment and not jail or other harsh methods. We have lived under the "disease concept" for half a century. But not everybody bought into this concept (Heyman, 2009). Nonetheless, the addiction treatment industry mushroomed, ranging from dingy clinics to posh luxury resorts. The net result was that there was no progress in 50 years; addictions are just as untreatable today as they were half a century ago.

Addictions are not diseases, but the results of foolish human behavior, nourished by individual or social-cultural facilitating circumstances. They are not diseases per se, but in the process they may reach disease proportions.

Treatment consists of counseling, ("stop drinking", "quit drugs") and occasional pharmacotherapy (e.g., disulfiram to create an unpleasant reaction to alcohol, naltrexone to block the brain opioid receptors thus render the drug useless). The pharmacological approaches failed, because the patients have to be motivated to take the drugs indefinitely or at least for long periods and they don't. The treatment centers (so-called: "Rehab") are largely useless. Currently the US congress is planning to conduct an audit of them.

After nearly 50 years practicing as an addiction internist (mainly concentrating on physical complications), I drew the above conclusions and I am offering the following points for debate:

1. Addictions are not diseases but disorders of choice.

2. Some addictions become diseases by virtue of their complications.

3. There has been no progress in "treatment" in the last 50 years.

4. There is spontaneous recovery in a minority of addicts, but that is independent of the intensity of "treatment".

5. To solve the problem of addictions is not a matter of individual therapy, but social engineering, such as law enforcement and education.

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August 22, 2013

Comments by Peter R. Martin

Paul Devenyi succinctly explains why he believes that "addictions are not treatable diseases", simultaneously calling into question whether addictive disorders are in the medical domain and also whether they are treatable disorders. He claims that addictions are instead "the results of foolish human behavior, nourished by individual or social-cultural facilitating circumstances" that only as a result of their complications "may reach disease proportions". Of course, many illnesses physicians face in developed countries can be conceptualized in much the same way as Devenyi understands addictions. Most chronic diseases, the major challenge or modern medicine, require thoughtful management over a lifetime of exacerbations and remissions. "Cures" as can be obtained with antibiotic treatment of acute infections or surgical removal of pathologic tissue are simply not the goal for chronic diseases. A classic example of another disorder that closely resembles Devenyi's description of addiction is over-eating. While over-eating can progress to type 2 diabetes mellitus and diverse end-organ damage eventually, what then is the primary problem, the over-eating that causes obesity or the resulting insulin resistance? According to Devenyi, insulin resistance and its complications are the disease and over-eating is beyond the scope of medicine. Fortunately, this viewpoint is starting to change in modern medicine.

Devenyi clearly enumerates in his essay, five supporting points upon which his contentions are based and I will address each in turn:

First, "Addictions are not diseases but disorders of choice." This simply implies that "choice" is a black box, the interior of which is a mystery and hence immutable. In fact, loss of control of choice, not the complications of repeated alcohol/drug use, is the primary symptom of addiction. Many addicts seeking help are incapable of stopping their self-destructive behaviors and are highly sensitive to relapse-triggers within the environment. In fact, the neurobiological underpinnings of the choices people make are currently the focus of active investigation. Elucidation of the neural pathways that mediate reward and decision making, as well as the molecular biology of learning and memory have led to better appreciation of the pathophysiology of addiction and should result in therapeutic advances. Hence, the out-of-control behaviors that are self-destructive (addiction) may be

modified throughout a patient's life using pharmacological, as well as social and behavioral, strategies. In fact, most of psychiatry deals with emotions, sensory phenomena, cognitions, and other aspects of behavior that are not characterized by laboratory abnormalities, are not readily observed via radiologic studies, nor easily examined under the microscope. Neither can most psychiatric disorders be removed like an inflamed appendix. They, nevertheless, can be reliably diagnosed and managed by appropriate (non-curative) clinical interventions, a characteristic they share with a plethora of chronic medical diseases.

Second, "Some addictions become diseases by virtue of their complications." In fact, the more we understand brain reward mechanisms, the more apparent it has become that these neural pathways are highly sensitive to repetitive out-of-control drug use. Thus, in addition to the clinically apparent complications of various organ systems resulting from drug use, to which Devenyi refers, the reward pathways that actually initiate and perpetuate drug use are allostatically modified during the life-course of addiction and thus may profoundly influence the "choices" the addicted individual ultimately makes. Moreover, much current research deals with personality and cognitive styles that predispose young people to impaired decision-making and subsequent drug use disorders prior to their first use of alcohol/drugs and such premorbid characteristics might rightfully be viewed as predisposition to, rather than consequences of addiction. Research findings are also accumulating concerning genetic factors that contribute to development of addiction, as well as environmental factors such as exposure to drugs in utero or early life events that occur prior to emergence of addictions. Choice is not a "black box", but rather a difficult to unravel phenomenon with its own neurobiological underpinnings that should not be discounted. Some choices may ultimately lead to overt pathologies, but such choices can, nevertheless, be considered as pathologic even before the consequences are visible in tissue damage. Much as in cancer, early identification may lead to better outcomes using appropriate interventions. It is just the fact that wrapping one's mind around choice is so very difficult that makes some believe that the complications of addictions are the only part of this process that merit the term "disease."

Third, "There has been no progress in 'treatment' in the last 50 years." There have certainly been no addiction "cures" in the past 50 years, and frankly, I doubt whether there will ever be. In fact, the greatest advance in addiction treatment has been to stop viewing the addiction treatment process in inappropriate surgical or infectious disease terms, but rather as a chronic disease such as hypertension, diabetes, etc. If treatment of hypertension or diabetes is successfully managed with lifestyle changes and medications administered throughout the patient's lifetime, it reduces the probability of complications. Ultimately, management of addiction is also minimizing the emergence of the complications which Devenyi views as the only "real disease" component of addictions. There are, however, significant advances in cognitive behavioral and motivational approaches, as well as pharmacological strategies derived from our understanding of neurobiology, that alter the natural course of addiction. In fact, approaches to addiction treatment have served to shed light on a significant component of all medical diseases, namely health behaviors, so-called choices the patient alone can make, that are beyond the control of the physician, but nonetheless, can enhance response to treatments offered by the medical profession.

Consider recovery post-myocardial infarction (not to mention prevention of heart disease per se) or control of blood glucose in diabetes (if not prevention of the type 2 diabetes, in the first place), among many other examples.

Fourth, "There is spontaneous recovery in a minority of addicts, but that is independent of the intensity of "treatment"." A wise pediatrician told me while I was in medical training that most acute otitis media resolves without antimicrobial treatment; this does not negate the value of antibiotics, nor indicate that antibiotics might not help some cases of otitis media. Addiction likewise can resolve without treatment. That says little about the value of the treatment, but rather suggests that not all individuals who are diagnosed as having addiction are identical. Nor would we expect them to be the same, as we really do not fully understand the etiopathogenesis of any psychiatric disorder, not just drug use disorders.

Finally, "To solve the problem of addictions is not a matter of individual therapy, but social engineering, such as law enforcement and education." These environmental interventions can certainly influence the prevalence of alcohol/drug use disorders, but if an alcoholic is placed on an island where there is no alcohol, will he/she be cured, or will other behaviors emerge that replace the alcohol?" I ask this question to be thought provoking rather than because I know the answer. However, the more we investigate drug use disorders, the more we recognize that the problem(s) do(es) not only lie in the availability of the agent of abuse, but rather in individual differences in experiencing the world and coping with its challenges, and many of these pathological differences pre-date actual initiation of alcohol/drug use. Many of the psychoactive substances that people use in an out-of-control manner do not cause, but rather, they contribute to the suffering experienced by the addicted individual. Fortunately, in the last half century significant improvements have occurred in how we view and approach our patients afflicted with these disorders without deluding ourselves that we can cure their disease (Martin, Weinberg and. Bealer 2007).

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September 12, 2013

Reply to Peter R. Martin's Comments by Paul Devenyi

Peter Martin was a very talented research fellow in the institution I used to work. I am pleased to see that he developed into a very talented and highly respected psychiatrist. His response is eloquent, making many good points. I don't believe he is violently opposed to

what I said, but he certainly has a more optimistic view about the future of addictions and their treatments, than I have. I highly respect that.

The comparison between alcoholism and type 2-diabetes is often made. Yes, insulin resistance is the underlying disease along with several other factors (genetic, immunological). If, as in Martin's example, we compare the control of diabetes as a chronic disease with that of alcoholism, the latter is so far behind that similar outcomes in diabetes would give our health care system the shivers.

I agree with Peter that "loss of control" defines addictions more than for example cirrhosis defines alcoholism; when addiction reaches the "loss of control" stage, we can really talk about a disease. I am glad Peter is optimistic that "addiction may be modified throughout a patient life using pharmacological and behavioral strategies". I think pharmacological approaches have failed so far, but perhaps, behavioral ones might produce some success.

As to "pre-morbid characteristics" being predisposing factors, I never came to terms with "addictive personality". I still think addiction will be largely determined by the family a patient comes from, by cultural determinants and values of his social milieu and the peer group he associates with. Genetic factors underlying addictions have been proposed, but the evidence so far has been weak.

I still believe that "social engineering" represented by educators, the media, police, judges, social agencies, etc. could have more impact on the prevalence and perhaps the outcome of addictions than the medical profession.

As to Peter's alcoholic who is "placed on an island where there is no alcohol, will he/she be cured or will other behaviors emerge that replace the alcohol?" As Peter, I don't know the answer either. My guess is that even after many years if escaping from the island, he/she will drink in an uncontrolled fashion again. In the meantime, if the island has a medical school, he/she may become a psychiatrist.

Peter, thanks again for your reply and I am heartened by your overall optimistic approach that an old cynic, as I, doesn't have.

October 3, 2013

Reply to Paul Devenyi's Reply by Peter R. Martin

Paul Devenyi is hardly an old cynic! Rather Dr. Devenyi has a tremendous amount of clinical experience as an internist dealing with patients who have medical complications of

drug use disorders. He voices opinions which many would endorse and he expresses them well, indeed. His perspective is clearly guided by the patients he has seen, those who are fairly late in their addiction, when the physical consequences of drug/alcohol abuse begin to overwhelm the clinical presentation. This may well explain our different perspectives. All the same, friends can differ without acrimony and can both be correct, to some extent.

We are not doing as well with type-2 diabetes as Dr. Devenyi suggests, or stated otherwise, the outcomes are not much worse in addiction than in other common medical conditions (McLellan et al. 2000). Accordingly, the health care system is definitely shivering (paraphrasing Devenyi) and some of the principles employed in addiction treatment might actually benefit those with obesity and type-2 diabetes—if only internist/endocrinologists would recognize that the problem in these type-2 diabetes patients is substantially affected by their behavior (overeating) and the insulin resistance may emerge as a consequence—if you feed a rat excessive amounts of a high fat diet, it will develop insulin resistance, as do humans, probably (Pendergast et al. 2013).

Second, loss of control typically occurs in the very early stages of addictive disorders (Koob and Le Moal, 2005), not just in the later stages, as Dr. Devenyi implies. Devenyi's perspective makes some sense, because as an internist, he predominantly saw patients at a stage when various end-organs were affected by behaviors that had been ongoing for sometimes a decade, or more. It is the longitudinal study of those with family histories of addiction that has allowed us to state that neuropsychological deficits may precede the development of addictive disorders (Tarter et al 2003). Plenty of research suggests that such subtle abnormalities of brain wiring may be strongly influenced by genetic factors, a series of investigations that has its origins in Begleiter's seminal findings (1984) in boys at risk for alcohol dependence published three decades ago.

I do not dispute Dr. Devenyi's notion that "social engineering" represented by "educators, the media, police, judges, social agencies, etc. could have [an] impact on the prevalence and perhaps the outcome of addictions". However, I do not believe the medical profession can wash its hands of these self-destructive out-of-control behaviors which are squarely in the realm of psychiatry. In fact, it is just such issues that now are permeating the rest of medicine, and hence, expertise in management of these behaviors is increasingly of interest to physicians outside of my specialty.

Finally, let me close with mention of that poor alcoholic soul on a desert island without alcohol—let us hope he will have access to a medical school rather than alcohol. But who is to say he will become a psychiatrist? In my opinion, he may equally well turn to internal medicine or surgery….

Paul, it is quite enjoyable having this intellectual joust with you, and I sense that you have enjoyed it as well. Perhaps at this stage, we might have input from other colleagues in our community.

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October, 31, 2013

Paul Devenyi: Pharmacotherapy of addiction: not a success story

As an internist, I somehow strayed to this website and got myself embroiled in some controversies about my view that addictions are not treatable diseases, perhaps not diseases at all, but self-induced irresponsible behaviors of choice. This point of view is not popular, of course, and not politically correct. Unless psychiatrists and behavioral scientists come up with some useful behavioral strategies, the future does not look promising. I came to this conclusion after 50 years of a (wasted?) career in addiction medicine, where I was involved more in the management of medical problems and complications than in addiction per se. Since programs ranging from 12 steps to individual and group counseling did not produce overwhelming success, there was an increasing demand from public and professional circles that we come up with some viable pharmacotherapies, whereby the addicts go home with a prescription, take it and presto, he is no longer an addict. I thought it would be appropriate to this website to briefly review the available pharmacotherapies, which so far have not been a success story.

The oldest drug therapy for alcoholism has been Disulfiram (Antabuse), with more than 60 years history and still going. The drug arrests alcohol metabolism at the intermediate acetaldehyde level and the accumulating acetaldehyde causes a variably unpleasant reaction. The idea is that the alcoholic voluntarily takes the drug and if he drinks on it, gets punished; therefore, he would be too scared to drink. Attempts were even made with involuntary administration such as by a concerned spouse or an employee health nurse; these attempts usually fail, because alcoholics are clever to cheat and wiggle out of the forced administration. Voluntary use of the drug, which is the standard today, is unsuccessful because the minority of alcoholics who accept it at all, don't take it long enough for it to be useful. I just mention, in parenthesis, that depot injection of disulfiram was abandoned because the drug does not absorb reliably from depot sites.

For opioid addiction, a feasible treatment appeared to be naltrexone, an opioid antagonist which - by blocking the receptors - would render the opioid ineffective, thus wasteful. It was assumed that the narcotic addict would voluntarily protect himself from the pleasures of his drug, thus won't use it. Like with disulfiram, the trouble is that most addict won't take it and certainly not long enough to extinguish the dependency. A few years ago, reports appeared that naltrexone, in a non-specific way somehow decreases alcohol craving, thus people would find it easier to abstain or would drink less. To my knowledge, this did not catch on and I did not find a single alcoholic in my practice, to which it did anything. Similar anti-craving effect has been claimed for acamprosate (Campral), long popular in Europe and relatively new in North America, which supposedly controls the alcohol craving of the already detoxified alcoholic, thus he won't drink again.

In the 1980s, Doug Teller and I ran a study on bromocriptine, for cocaine addicts, a dopamine antagonist which supposedly diminished cocaine craving by decreasing the pleasure-causing effect of dopamine (cocaine increases dopamine in the brain). We could not distinguish the effect from placebo.

Methadone, a long acting opioid is an old and more or less accepted drug substitute treatment for heroin and sometimes other opioid addiction. In my view, true and long lasting successes are not unheard of, but rare. Buprenorphine, a partial opioid agonist with a long half-life, has been used in the last few years for opioid dependence and withdrawal, preferred by some over methadone. I don't know of any overwhelming success; personally, I did not use it.

Several drugs are used in addiction medicine for detoxification or drug withdrawal. "Cold turkey" withdrawal is inhumane and at times dangerous.

Depressant drugs are withdrawn gradually to avoid unpleasant and sometimes dangerous withdrawal symptoms. As such, it is a successful treatment. As to maintain a drug free lifestyle, withdrawal tapering seldom has a lasting impact. In principle, you taper the same drug what the patient was using or a long acting equivalent, such as methadone for opioids and diazepam for benzodiazepines. Alcohol is an exception; you don't use alcohol for its withdrawal, the commonly used drugs are benzodiazepines, thiamine to treat or prevent Wernicke encephalopathy and peripheral neuropathy, haloperidol for delirium tremens.

Non-depressant drugs, such as cocaine, cannabis, etc. do not require tapering.

A newer and intriguing approach to addictions - still in experimental phase - is immunization. At Cornell, they experimented with cocaine vaccine: cocaine, a small molecule that is complexed with a large protein (common cold virus), producing a cocaine antibody response when exposed to the drug and prevents cocaine to reach the brain and produce euphoria. The Chileans are working on an alcohol vaccine. This is an entirely new avenue to treat addictions and some animal experiments have been promising. One still has to doubt that this will be the panacea. It is not just the question whether it will work, but whom, at what age, under what circumstances to vaccinate? The medical ethicists would have a field day.

Finally, a word about cigarette addiction. I am not a believer that the various pharmaceutical agents are that effective (Nicotine substitution, Zyban, Chantix). A lot of people quit spontaneously and the major factor is social pressure: education, propaganda, legal restrictions - the very factors that are mentioned in my first essay in controversies that can have more of an impact on addictions than drugs or individual treatment techniques.

December 5, 2013

Edward Shorter: The Q-T interval and the Mellaril story: a cautionary tale

Is a lengthening of the Q–T interval in the ECG benign or pathological in drug action? This produced a small controversy in the 1960s that had a major impact on patient care. In 2000, the Novartis Company cautioned physicians about further use of the antipsychotic drug Mellaril (thioridazine). The company announced that the drug can entail dangerous cardiac complications. This information was already known in the mid-1960s, and not only did Sandoz (one of the predecessor companies of Novartis) ignore it, they attempted to discount it at scientific meetings and disregarded the warnings of several clinical scientists. Moreover, in various ad campaigns, Sandoz showed elderly "patients" in the artwork, emphasizing that the drug was suitable for geriatric cases, precisely the population most at risk of such complications. The story is a textbook case of ignoring scientific warnings in favor of corporate interests.

It was known early on that Sandoz's new antipsychotic agent thioridazine (Mellaril), launched in the United States in 1959, lengthened the Q–T interval. But was this good or bad?

There was the benign repolarization school. In 1964, M.H. Wendkos, a cardiologist at the Veterans Administration Hospital in Coatsville, Pennsylvania, published a paper on pharmacologic studies in a hitherto unreported "benign repolarization disturbance among schizophrenics" (Wendkos 1964). Wendkos re-stated this position in his presentation at a psychopharmacology meeting in Quebec (see below), arguing that the recorded ECG changes "represent a benign repolarization disturbance rather than an adverse cardiac effect" (Wendkos 1965).

But events were in the saddle, and galloped in a very different direction. Some background: It happens quite frequently that drugs are withdrawn or new warnings of their side-effects are circulated. Yet the story of Sandoz's antipsychotic medication Mellaril (thioridazine) represents an almost textbook case of a company marching into trouble by ignoring warnings.

On July 31, 2000, Novartis Pharmaceuticals sent a letter to all physicians and pharmacists in Canada, warning that the use of the drug Mellaril should be significantly curtailed. The preparation should henceforth be restricted only to those schizophrenic patients "who fail to show an acceptable response . . . to other antipsychotic drugs." The reason? "Mellaril has been shown to prolong the QTc interval in a dose related manner, and drugs with this potential, including Mellaril, have been associated with torsade de pointes-type arrhythmias and sudden death" (Novartis Pharmaceuticals Canada, 2000).

Simultaneously, the August 18 issue of the Psychiatric News cautioned its readers that thioridazine "will include a new boxed warning regarding potentially fatal cardiovascular effects and will be restricted to second-line use." The reason again was that "TdP (torsades de pointes) develops spontaneously, usually without warning, and requires immediate emergency intervention." The note stated that the risk of sudden death was "high"

(Psychiatric News 2000).

These warnings came more than thirty years too late. Here is how the controversy unfolded:

In 1963, H.G. Kelly and coworkers in the Faculty of Medicine of Queen's University in Kingston, Ontario, reported 28 electrocardiograms that depicted a quinidine-like effect of thioridazine on ventricular repolarization (prolongation of the QT interval) in doses as low as 200 mg. a day. T-waves were flattened and sometimes inverted, occasionally S–T segments became convex and new waves appeared. In that study, two fatal cases of arrhythmia occurred (Kelly et al., 1963).

By this time, the Sandoz company, of course, knew of the Queen's University deaths, and their medical advisor, Roy Stewart, a Montreal cardiologist, brought this to the attention of Thomas Ban, chief of the clinical research service at Verdun Protestant Hospital, a psychiatric inpatient facility in the outskirts of Montreal. It was at Stewart's request that Ban designed a clinical study, conducted in collaboration with André St. Jean, Scientific Director at Hôpital des Laurentides in L'Annonciation, Quebec, comparing the effects of thioridazine, chlorpromazine, and trifluoperazine on the ECG. In 1964 the investigators reported that thioridazine "modifies the terminal portion (S–T segment, T and U waves) of the human ECG." They found that, whereas similar changes took place in only 1 of the 6 subjects taking trifluoperazine, and in 3 of 6 taking chlorpromazine, such changes were noted in all 6 of the 6 patients on thioridazine by the 8th day of drug administration, i.e., with 200 to 400 mg of thioridazine per day (Ban and St. Jean, 1964).

The study had been completed in 1963, but before it was published, the following incident occurred at Hôpital des Laurentides: A patient who had been receiving high (1500 mg per day) doses of thioridazine over a period of ten weeks, suddenly became unconscious and passed into a state of shock. It happened that there were two physicians in the room, one of them a cardiologist. An ECG demonstrated ventricular tachycardia. It was noted that a prior ECG of the patient, six weeks after the initiation of thioridazine therapy, had shown bradycardia and prolongation of the QT (Desautels et al., 1964).

These findings led Ban and co-workers to conduct a survey to determine the incidence of cardiac conductance changes with thioridazine. It was clear that such complications existed, but what was the size of the problem? Ban presented the results later, in 1964, at the fourth congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) in Birmingham, England. Of the 92 patients receiving drugs other than thioridazine, 12, or 13 percent, displayed an abnormal ECG. Seventeen, or 77.3 percent of all patients receiving thioridazine, manifested abnormal ECG's (Ban et al., 1965).

In 1964 or 1965, Ban travelled to Basel to report these findings to Sandoz and met with the president and head of pharmacology of the firm (Ban TA, personal communication to E Shorter, 11 Mar 2013).

On June 4, 1965, the Quebec Psychopharmacological Research Association organized a

special symposium at the Hôpital des Laurentides on ECG changes with psychoactive drugs. Ban and coworkers reviewed the aforementioned studies as well as some findings based on a further series of four studies, which indicated that "the lowest dose (of thioridazine) which brought about changes was 150 mg per day" (St Jean et al., 1965). At the same meeting, Edward Kingstone, in his review of the literature on "neuroleptic drugs and the ECG," pointed out that in 1964, Graupner and Murphree also described ECG changes associated with the use of thioridazine (Kingstone, 1965). Of the 55 patients they studied, 44 percent developed abnormal electrocardiograms. Most of the changes were concerned with the T-wave. They appeared at all dose levels, from 150 to 900 mg per day (Graupner and Murphree, 1964).

In organizing the symposium, Ban wanted to ensure that a fair picture of Mellaril was offered. He had mentioned the meeting to Sandoz, and the company paid the travel cost for Wendkos to attend (Ban, 2011).

Here is where events took over. Other investigators began learning of the cardiac dangers of thioridazine. In the mid-1960s, Louis Gottschalk, then at the Cincinnati General Hospital, warned Sandoz privately that Mellaril was dangerously increasing the QT interval. Gottschalk later said in an interview, "We got the idea to find out whether there are any differences in the psychoactive drug metabolites in people that get these cardiac irregularities. And lo and behold, we did discover that a metabolite that is not psychoactive, sulforidazine, does have an adverse cardiovascular effect . . . and [we] tried to get the drug companies to provide further financial support so we could study the biochemical basis. . . . But they were doing so well marketing their drugs, that they would not fund it" (Gottschalk, 2011a). Gottschalk, who in the meantime had moved to the Irvine campus of the University of California, reported with co-workers the existence of this previously unknown metabolite of mesoridazine and thioridazine in 1974 (Dinovo et al., 1974); details of a GLC analysis followed in 1976 (Dinovo et al., 1976).

Did Sandoz then become interested? Not really. Gottschalk later said, "Everybody told me that the metabolite was not pharmacologically active. I asked the head of the organic chemistry department at UCI whether she could manufacture it for me because I wanted to test the effects of the metabolite on cardiovascular function in dog experiments. She could do it for a certain amount of money, but I never was able to obtain the necessary funds. In general, pharmaceutical companies are not very interested in trying to discover what triggers the adverse side effects of drugs" (Gottschalk, 2011b).

Gottschalk was not the only researcher to be brushed off by Sandoz. In 1974, Donald Gallant and co-workers at Tulane University reported a double-blind ECG comparison of thioridazine and thiothixene (Dillenkoffer et al, 1974). "Only one of the 13 thiothixene patients had prolongation of the Q–T," said Gallant later in an interview, "but 13 out of 13 patients on 800 milligrams a day of thioridazine, and 7 of 13 on 400 milligrams a day had prolongation of the Q–T interval. We published that. In fact, my cardiology fellow that read the EKGs could identify thioridazine, blind. . . . After we published, somebody from Sandoz called and started yelling on the phone at me, criticizing me, saying I was unethical

for publishing the data. This was 1972 [1974], and I was shocked that someone from a pharmaceutical firm would start telling me I'm unethical for publishing these findings. . . . It was solid, solid data and Sandoz Company never made any mention about it" (Gallant, 2011).

These early warnings did not prevent Sandoz from further marketing the preparation. Indeed, to go by the visual content of the company's advertisements for Mellaril, the drug was pitched to physicians as especially suitable for geriatric use, a population at risk of cardiac complications. And in 1978, George Simpson and co-workers at Rockland State Hospital found that it was precisely in the elderly that thioridazine prolonged QT intervals (Branchey et al, 1978). "I stopped using thioridazine at that time," Simpson later said in an interview (Simpson, 2011).

An analysis of images depicted in Mellaril advertisements in Diseases of the Nervous System (after 1989 the Journal of Clinical Psychiatry) showed that Sandoz launched four major ad campaigns featuring elderly "patients." For example, in three ads, which appeared between May and July 1983, a clearly elderly woman was shown and the text stated that Mellaril "helps keep the disturbed geriatric at home" (Dis Nerv Syst, 1983). An ad featuring an older male golfer ("effective control of psychotic symptoms") ran 14 times (Dis Nerv Syst, 1979–80). Ban in his Psychopharmacology for the Aged, published in 1980, noted that "thioridazine has become one of the most extensively employed psychotropic drugs in the aged" (Ban, 1980).

While the Ban studies showed that cardiac conductance changes appeared at daily dosages above 150 mg., the above-mentioned ads indicated that dosages below 300 mg were relatively safe. ("Daily doses in excess of 300 mg should be used only in severe neuro-psychiatric conditions.") (Dis Nerv Syst, 1979–80).

For Sandoz – and its successor organization Novartis – it was irresponsible, not to say reckless, to have ignored such warnings for more than thirty years, putting the lives of many patients at risk. The entire story of shortsightedly placing corporate interests ahead of science could be found in an MBA curriculum on how not to market a pharmaceutical preparation.

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July 18, 2013

Comments by Peter R. Martin

Edward Shorter's recent submission to the INHN Controversies series, entitled "The Q-T interval and the Mellaril story - a cautionary tale," raises the quite topical issue of our preoccupations with "torsades de pointes" resulting from second generation antipsychotics such as ziprasidone and several other psychotropic medications. For example, in September

2011 (and updated in March 2012), the FDA issued a warning concerning increased incidence of QT elongation with doses of the antidepressant citalopram above 40 mg per day, which is considered the maximum allowable dosage, increasing the risk of "torsades." However, a recent study (Zvin et al., 2013) reported no increased risk of abnormal arrhythmias thus questioning the merit of FDA warning. Are we over-reacting to minimal risk, having been sensitized to or even "traumatized" by thioridazine-induced QT prolongation during a previous era? I believe we have learned to better understand this often unpredictable complication associated with use of a large range of psychotropic medications. The electrophysiologic pathogenesis of long QT syndrome as a channelopathy with genetic underpinnings and the dose-dependence of acquired QT prolongation (Raj et al., 2009) suggest that despite some medications' association with prolonged QT, they do so to differing degrees among individuals and can be managed if appropriately monitored. Concern about QT prolongation may appear exaggerated at present, whereas it was perhaps underappreciated or ignored in the past. Most importantly, potentially useful psychotropic medications should not be discarded, but rather be used carefully. We might learn from the "cautionary tale" of thioridazine, but not be overwhelmed by it.

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August 8, 2013

TEXTBOOK ON THE HISTORY OF NEUROPSYCHOPHARMACOLOGY

Introduction by Peter R. Martin

I am writing to introduce myself as the person responsible for one of the twelve projects of INHN, listed on our website. I will be working with Tom Ban and Sam Gershon to accomplish this project.

The table of contents of this project we are posting today was developed several months ago and we will be in contact with those who tentatively already accepted to contribute a chapter to the text. Please let us know if you would be interested in contributing any of the chapters listed in the table of contents, or a chapter that you think would be suitable for a textbook on the history of the field.

The length of your chapter could be from 2000 to 8000 words. We have no limit on number of references, but request your submissions in English.

We intend to post chapters on our website, as they arrive, and they will be open for discussion and comments.
We hope that the scope and quality of the contributions will justify future publication in book form.

We have posted today one chapter (Chapter 2) of the book: "The Birth of Neuropsychopharmacology" by Thomas A. Ban.

I am excited about this undertaking and looking forward to working with you on this project.

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June 6, 2013

Thomas A. Ban: The birth of neuropsychopharmacology

Introduction

Neuropsychopharmacology studies the relationship between neuronal and mental events with the employment of centrally acting drugs. Developments that lead to the birth of neuropsychopharmacology began in the early 1950s with the introduction of therapeutically effective psychotropic drugs. It continued with the identification of monoamine neurotransmitters in the brain, and the construction of the first spectrophotofluorimeter, an instrument with a resolution power to detect and measure changes in the concentration of monoamine neurotransmitters (Ban and Ucha Udabe, 2006).

One of the essential prerequisites of successful neuropsychopharmacological research is a continuous exchange of information between basic scientists and clinicians. It was, in 1957 that communication between the various disciplines involved in neuropsychopharmacological research began. Three major events heralded the beginning of the psychopharmacological era: (1) the organization of the First International Symposium on Psychotropic Drugs in Milan; (2) the inclusion of a Psychopharmacology Symposium at a World Psychiatric Association Congress, and (3) the founding of the Collegium Internationale Neuro-Psychopharmacologicum, an international organization that provided a platform for interaction for the disciplines involved in neuropsychopharmacological research (Ban and Ray, 1996).

Lithium

Arguably, developments that lead to the birth of neuropsychopharmacology began, in 1949, with the rediscovery of the therapeutic effect of lithium in mania by John Cade, an Australian psychiatrist. The original discovery dates back to 1896, when Carl Georg Lange, a Danish psychiatrist, reported on the therapeutic effect of lithium in periodic mood disorders (Ban, 2006 a).

Cade's rediscovery of lithium was followed by the publication of several papers on the therapeutic and adverse effects of the substance. Trautner and his associates, between 1951 and 1956, established the therapeutic window for lithium in the plasma and demonstrated lithium's effectiveness in maintaining manic patients in remission after successful treatment with electroconvulsive therapy (Gershon and Trautner EM, 1956; Noack and Trautner, 1951; Trautner et al., 1955). And Schou and his associates, in 1954, verified lithium's therapeutic effects in mania. Still, the acceptance of lithium by the psychiatric establishment, and especially the British psychiatric establishment, was slow. It was a series of articles by Mogens Schou, in the late 1950s that helped to break the barriers and set the stage for the introduction of lithium in the treatment of manic-depressive illness around the world (Schou, 1957, 1959).

Chlorpromazine

The rediscovery of the therapeutic effect of lithium in mania was followed, in 1952, by the discovery of the therapeutic effect of chlorpromazine (CPZ) in psychoses. Developments

that lead to the synthesis of CPZ began, in the 1930s, with the synthesis of the first antihistaminic drugs. CPZ, an antihistaminic phenothiazine, was synthesized, on December 11, 1951 by Paul Charpentier, in the laboratories of Rhône-Poulenc, a French pharmaceutical company, and the potential use of CPZ in psychiatry was first recognized by Henri Laborit, a surgeon and physiologist in the French army, in the course of his research with artificial hibernation in the prevention of surgical shock (Caldwell, 1970; Laborit and Huguenard, 1952). Clinical investigations with CPZ at Saint-Anne's hospital in Paris, began on March 24, 1952, and the six historical publications of Delay and Deniker, during the six months that followed, set the stage of the introduction of CPZ in psychiatry (Delay and Deniker, 1952a, b, c; Delay, Deniker and Harl a, b, c).

CPZ became available on prescription in France in November 1952, under the proprietary name of Largactil. Subsequently, within a short period of three years, from 1953 to 1955, CPZ treatment in psychiatry spread around the world. The first international colloquium on the therapeutic uses of CPZ in psychiatry was held at Saint-Anne's Hospital, in Paris, in October 1955. And two years later, in 1957, the importance of CPZ was recognized by the scientific community with the presentation of the American Public Health Association's prestigious Albert Lasker Award to the three key players in the clinical development of the drug: Henri Laborit, for using CPZ as a therapeutic agent first and recognizing its potential for psychiatry; Pierre Deniker, for his leading role in introducing CPZ into psychiatry and demonstrating its influence on the clinical course of psychosis; and Heinz Lehmann, a German born Canadian psychiatrist, for bringing the full practical significance of CPZ to the attention of the medical community (Lehmann and Hanrahan, 1954). In the same year, Daniel Bovet, a Swiss born Italian pharmacologist was awarded the Nobel Prize in Medicine for the identification of curare alkaloids and the synthesis of antihistaminic drugs, which, through Feldberg's recognition of the sedating effect of these compounds, led to the development of chlorpromazine (Ban, 1996).

Reserpine

In 1952, the same year as the therapeutic effect of chlorpromazine in psychosis was discovered, Muller, Schlittler and Bein, in the laboratories of CIBA, one of the major Swiss pharmaceutical companies at the time, isolated reserpine, the substance that accounted for about 50% of the antihypertensive and psychotropic effect of the Rauwolfia serpentina root (Bein, 1970).

Rauwolfia serpentina (snakeroot plant) had been in use for hundreds of years in various preparations by the Ayurwedic practitioners of India. Yet, it was only in 1949 that Rustom Vakil brought to the attention of Western medicine the potential use of these preparations in hypertension, and mental illness, and it was only in 1953 that R.A. Hakim focused attention on the potential use of Rauwolfia preparations in schizophrenia (Ban, 1996).

Hakim's paper triggered clinical research in psychiatry with Rauwolfia serpentina first, and reserpine, subsequently. The findings of this research were published, in 1954, in four papers written by Delay and his associates, Klin, Noce et al, and Weber (Kurland, 1996). Three years later, in 1957, in recognition of the importance of these compounds in

psychiatric therapy, three of the key players in the clinical development of reserpine were honored with the Lasker Award: Rustom Vakil "for producing a document which brought Rauwolfia alkaloids finally and decisively into Western medicine"; Nathan Kline "for his outstanding work since early in 1953 bringing to the attention of American and European psychiatrists the value of Rauwolfia alkaloids and especially of reserpine in the treatment of mental and nervous disorders"; and Robert Noce for recognizing "the potentialities of reserpine not only as a treatment for the mentally ill" but also "in mentally defectives in state schools" (Ban, 1996).

Imipramine

The serendipitous discovery of the therapeutic effect of imipramine in depression was the result of search for a CPZ-like substance for the treatment of schizophrenia by Geigy, at the time a major Swiss pharmaceutical company. The discovery is linked to the name of Roland Kuhn, a Swiss psychiatrist, working at the Cantonal mental hospital of Münsterlingen (Ban, 2006).

The story of imipramine begins in the mid-1950s, when Kuhn suggested the testing of G 22,355, the dibenzazepine compound of Geigy that showed the closest structural resemblance to CPZ, with the hope that it would have similar effects in schizophrenia. His expectations were not fulfilled. Yet, in January 1956, when he administered the substance to one of his female-patients with severe endogenous depression, he recognized that G 22,355 might have therapeutic effects in depression. Encouraged by his findings, Kuhn administered G 22,355 to 2 more female patients with severe endogenous depression. In both patients, the drug had favorable effects. Furthermore, in all 3 patients, discontinuation of treatment resulted in relapse that was reversed by resumption of the medication. Subsequently, Kuhn treated 40 depressed patients with G 22,355 at the clinic, and it was on the basis of his observations of these patients that he concluded that the drug is effective in endogenous depression, in which vital disturbance was in the foreground (Kuhn, 1970, 1996).

Kuhn's first paper on the treatment of depressive states with an iminobenzylderivative G 22,355, was published in 1957, in the August 31st issue of the Swiss Medical Journal. Two days later, on the 2nd of September, he also presented his findings at the 2nd World Congress of Psychiatry in Zurich. G 22,355, the first tricyclic antidepressant, was released for clinical use in Switzerland by the end of 1957, with the generic name of imipramine, and the brand name of Tofranil.

Iproniazid

In 1957, the same year that imipramine was released for clinical use in Switzerland, Loomers, Saunders and Kline presented their findings on the therapeutic effect of iproniazid, a monoamine oxidase inhibitor, in depression, at a regional meeting of the American Psychiatric Association, in Syracuse, New York (Kline, 1970).

Iproniazid, an isonicotinic acid hydrazide, was synthesized, in 1951, by Herbert Fox at Roche laboratories, in Nutley, New Jersey (USA) for the chemotherapy of tuberculosis

(Fox and Gibas, 1953). In 1952, using iproniazid in tubercular patients, Selikoff, Robitzek and Orenstein noted that the drug produced euphoria and overactive behavior in some patients. In the same year (1952), Zeller and his associates revealed the potent monoamine oxidase inhibiting properties of the drug. It took five years from the time of these early findings before the therapeutic effect of iproniazid were reported in the United States (Ban, 2001).

Early Neuropharmacological Advances

Monoamine oxidase (MAO) is the enzyme responsible for the oxidative deamination of neurotransmitter monoamines, such as serotonin and norepinephrine. The presence of these substances in the brain was first shown, in 1953 and 1954, respectively; and the first spectrophotofluorimeter, with a resolution power to measure the concentration of these monoamines and their metabolites in the brain, was constructed, in 1955 (Bowman, Caulfield and Udenfriend, 1955; Twarog and Page, 1953; Vogt, 1954). One year later, in 1956, Pletscher reported a decrease in brain serotonin levels after the administration of the Rauwolfia alkaloid, reserpine, a substance that produced depression in some patients, when used in the treatment of hypertension, and an increase in brain serotonin levels after the administration of the monoamine oxidase inhibitor, iproniazid, a substance, as noted above that produced euphoria in some patients, when used in the treatment of tuberculosis. Also in the same year (1956), Holzbauer and Vogt published their findings that reserpine depleted not only serotonin but also norepinephrine in the brain; and Brodie, Pletscher and Shore demonstrated that among the available Rauwolfia alkaloids, only those with a sedative action cause depletion of 5-HT. Then, in 1957, at the First International Symposium on Psychotropic Drugs, Carlsson and his associates had conclusively demonstrated that reserpine depleted the catecholamines, dopamine and norepinephrine. They had also shown that pretreatment with iproniazid prevented the disappearance of catecholamines after reserpine injection (Pletscher, 2006).

Concluding Remarks

In 1957, Abraham Wikler published his classic text on "The Relation of Psychiatry to Pharmacology," in which the words "psychiatry" and "pharmacology" were linked for the first time. Wikler raised the possibility that from studying the mode of action of psychotropic drugs with known clinical effects, one might be able to deduce the biochemical basis of mental disorders. In reviewing Wikler's book, Leo Hollister, one of the pioneering neuropsychopharmacologists, noted that "This bootstrap operation is at the heart of neuropsychopharmacology and has dominated the dialogue between psychiatry and pharmacology since" (Hollister, 1996).

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June 6, 2013

Edward Shorter: Endocrine psychiatry in a historical perspective

Introduction

Psychiatry's encounter with endocrinology gives a new dimension to the "tortures of Tantalus," for whom the grapes were always so close but never quite within reach. Over the last hundred years, psychiatry has continually grasped for endocrinological riches, and failed, and given up in despair. Today, to the extent that "psychiatric endocrinology" exists, it is placed well on the back burner of the field (Fink and Shorter, 2010).

The "Powdered Organ Extract" Era

The story of psychiatric endocrinology begins with flagging male sexual ardor, "male hypoactive sexual desire disorder," in the clunky terms of DSM-5. In 1889, Parisian physician Charles-Edouard Brown-Séquard, who decades earlier had performed the first experimental adrenalectomies, treated patients with extracts of ground-up testis. Then seventy-one years old, Séquard also treated himself with the extract, and reported, "I should add that intellectual tasks became easier for me than for some years and that I regained everything that I lost. I must say as well," he deadpanned, "that other forces that were not lost but quite diminished, have considerably improved as well" (Brown-Séquard (1889). Brown-Séquard's experiments aroused as much laughter as imitation. Yet, it was the commencement of endocrine investigations in the field of psychiatry.

Around the turn of the century, a young Parisian physician, Maxime Laignel Lavastine, now entirely forgotten, became the true founder of scientific neuroendocrinology. Around 1908-09, he studied the range of endocrine organs, linking their hyper- or hyopoactivity to psychiatric illnesses. (Of course, various non-psychiatrists had preceded him: with the discovery of hyperthyroidism, "Grave's disease," in 1835; adrenal hypofunction ("Addison's disease") in 1849; and hypothyroidism ("myxedema"), in 1873. Yet, none of the English internists who made these discoveries had primarily psychiatric interests.) Trained in internal medicine and psychiatry, Laignel-Lavastine surveyed a range of "psycho-glandular relationships," finding that disorders of function in thyroid, pituitary, adrenals, and ovaries affected character in different ways. He treated endocrine hypofunctions with ground-up extracts, finding for example, that neurasthenia responded (or was thought to respond) to thyroid extracts (Laignel-Lavastine, 1908a). Presciently, Laignel-Lavastine associated melancholia with the endocrine organs. "It is quite evident that the melancholic syndrome is indeed mental, but simultaneously physical and psychic. It seems to me that melancholics are particularly indicated for coming research on endocrine disorders" (Laignel-Lavastine, 1908b). Laignel then drifted away from endocrine psychiatry, and the French dominance in the field gave way to the German.

Melancholia was in the center of the German radar. In 1921, Karl Kleist, originator of the concept of "bipolar disorder," who taught psychiatry at the University of Frankfurt, speculated that the "autochthonous degeneration-psychoses" (meaning the chronic non-deteriorating psychoses, unlike those described by Emil Kraepelin as "dementia praecox") had a large endocrine component (Kleist, 1921). A whole raft of German research along these lines was launched. In 1922, Josef Westermann, a student of Kurt Schneider's at the

University of Cologne (of "Schneiderian criteria" fame), concluded of Schneider's "vital depression," "It is conceivable that the basic biological disorder of vital depression, which is certainly to be conceived as endocrine, is similar to the corresponding biological mechanisms that trigger schizophrenia" (Westermann, 1922). Vital depression" was close to melancholia, and the thought that it had much in common with schizophrenia would be reprised many decades later (National Institutes of Health, 2009).

Similarly, the German-speaking Europe led the pack around the First World War in marketing commercial endocrine preparations, such as Roche's "Pituglandol," to the (largely unsuspecting) public (Roche-Austria, 1913). This was big business.

Yet, there was genuine science in the powdered extract organ era. In 1932, U.S. neurosurgeon Harvey Cushing laid out the rudiments of what would later be called the "hypothalamic-pituitary-adrenal" (HPA) axis. As yet, the role of the hypothalamus was unknown, but Cushing associated a tumor-linked overdrive of this axis with "striking constitutional transformations," including depression and psychosis (Cushing, 1932).

But clouds were forming. The absence of solid links between endocrines and psychiatry was a source of growing dubiety, and the budding field was especially dragged down by associating presumed ovarian malfunctions with mental illness. When James Collip, who led biochemistry at McGill University (and under whose aegis ACTH had been isolated in the anterior pituitary gland, in 1933), gave Heinz Lehmann, chief of Montreal's Douglas Hospital, a supply of pituitary extract to try in schizophrenia, Lehmann believed the patient was better, mainly because the extract had a high alcohol content (Lehmann, 1993).

Cortisol and Dexamethasone

The discovery of the steroid hormones of the adrenal cortex transformed endocrine psychiatry. It was Swiss chemist, Tadeus Reichstein, and Edward Kendall, a biochemist at the Mayo Clinic in Minnesota, who in the mid-1930s, identified the corticosteroid hormones, especially cortisone and its activated version cortisol, which Reichstein isolated, in 1937 (Shorter and Fink, 2010). Cortisol, also known as hydrocortisone, plays an important role in the endocrine psychiatry story because in melancholia, the adrenal gland hypersecretes it.

These early successes gave a new push to endocrine psychiatry. In Bristol, England, Robert Hemphill and Max Reiss explored endocrine treatments for schizophrenia and melancholia (Hemphill, 1944). Harvard physiologist, Walter Cannon put the endocrine glands and the autonomic nervous system on the behavioral map, in 1914, with the "flight or fight syndrome" (Cannon, 1914). And in Montreal, Hans Selye, who had little time for Cannon or Reichstein, but was mainly interested in his own research, publicized a supposedly endocrine-based "general adaptation syndrome" (that today has disappeared from endocrinology) (Selye, 1950).

It was, however, a new test for detecting various adrenal cortex hormones in the urine, introduced by Wilhelm Zimmerman, in 1935, that led to the direct association of cortisol

with psychiatric illness (Zimmerman, 1835). Cortisol itself became available for clinical use, in 1950, when two scientists at Merck developed its synthesis, and in 1956, psychiatrist Eugene Bliss at Utah, together with endocrinologist colleagues, reported that stress and emotional upset increased blood levels of cortisol in psychiatric patients (Bliss et al., 1956).

In 1956, Francis Board and David Hamburg at the Michael Reese Hospital in Chicago, shone the searchlight directly on cortisol and depression, finding that serum cortisol was significantly higher in "neurotic depressions" than in controls, and that it was very much higher in psychotic depressives than in controls: There was thus a range of cortisol elevations corresponding to the type of depression, with the highest corresponding to the most severe. This is one of the most significant findings in post-World-War-II psychiatry (Board, Persky and Hamburg, 1956).

Now the scene shifts from Chicago to London. In 1962, James Gibbons, a senior lecturer at the Maudsley Hospital, and Paul McHugh, a visiting fellow on a National Institutes of Health fellowship, collaborated on a study of the biochemistry of depression. They found a smooth correlation between the severity of depression and the level of plasma cortisol. Moreover, as the patients improved, their cortisol levels dropped. Their data were so striking as to make depression look like a disease of cortisol (Gibbons and McHugh, 1962)!

With this huge new interest in corticosteroids and psychiatric illness in the background, in 1968, Bernard Carroll, a psychiatrist-endocrinologist in Melbourne, together with colleagues, discovered the first biological test in psychiatry: that patients with melancholic depression fail to suppress the secretion of cortisol, when administered the artificial steroid hormone dexamethasone (Carroll, 1968). Dexamethasone nonsuppression was, in other words, a biological marker of melancholia. The test was not exclusive to melancholia, because patients with other illnesses, such as dementia and anorexia nervosa, also exhibited nonsuppression in the Dexamethasone Suppression Test (DST). Yet psychiatrists usually could figure out clinically, whether their depressed patients were also demented, or anorexic, and the specificity and sensitivity of the DST were just about on par with those of the interictal EEG (Shorter and Fink, 2010).

Radioimmune assay (RIA) became available, in the 1960s, for the study of peptide hormones that mediate endocrine signaling. In the early 1970s, researchers led by Edward Sachar, first at Montefiore Hospital in the Bronx and then at Columbia University, where Sachar became head of psychiatry, in 1976, pursued the new RIA technology with studies of prolactin and growth hormone in schizophrenia and depression. From the late 1960s to the mid-1970s, Sachar and his group also documented elevated cortisol production and especially abnormal nocturnal cortisol secretion in depression (Sachar et al., 1973). This last discovery, led Sachar to abandon his early formulation of cortisol hypersecretion in depression, as resulting from a breakdown of ego defenses against anxiety. Sachar's larger role in the history of psychoneuroendocrinology, however, was the recruitment of a talented next generation of researchers. His life was sadly ended by suicide in a post-stroke depression, in 1984, before his concept of a neuroendocrine "window on the brain" could come to fruition.

The 1970s, were really the heyday of endocrine psychiatry. A broad picture of the underlying neurochemical differences between depressive illness and schizophrenia began to emerge. As Carroll pointed out in 1976, depressive patients have high cortisol levels in serum, urine, and cerebrospinal fluid (CSF), as well as abnormal DST results, whereas schizophrenic patients with similar rated levels of depressive symptoms and ego defense breakdown have normal HPA function (Carroll, 1976). At the time, psychiatry was still struggling to strike itself free of psychoanalysis: Diseases were not just constructs "mediated by a nonspecific breakdown of psychological defense mechanisms," as Carroll put it tongue in cheek, but were actually real phenomena.

Downhill

I wish I could report that from these triumphs the endocrine approach went on to become dominant in psychiatry, surpassing the study of the neurotransmitters and pointing the way to future advances. Unfortunately, the opposite happened: endocrine approaches went downhill, essentially vanishing from psychiatry, by the 1990s. The germinative event was an assault from the towering heights of psychiatry upon Carroll's dexamethasone suppression test. Early in its trajectory, the DST had become touted, somewhat unwisely (and not by Carroll), as a "screening test for depression." Just emerging from the swamp of psychoanalysis, many psychiatrists felt uneasy around brain biology, and clung to the DST as a biological measure that could tell them what they seemed incapable of learning clinically: whether their patients were "depressed." It was unhelpful that DSM-III, in 1980, elided the difference between melancholic illness, for which the DST is a reliable guide, and non-melancholic illness, for which it is not. Instead, DSM-III created "major depression," embodying a highly heterogeneous clinical population that a biological test, such as the DST, would individuate poorly.

In July 1982, the National Institute of Mental Health held a workshop ostensibly on "neuroendocrine tests," but in fact it was really on the DST. Few attendees had much clinical experience with the DST. And the report about the specificity of the DST that emerged from the meeting was unremittingly negative (Hirschfeld, Koslow and Kupfer, 1983). (This illustrates one of the great problems in the "consensus approach" in U.S. psychiatry: the consensus may be ill informed.)

Worse was to come. In 1983, the American Psychiatric Association asked a similar task force to assess the DST, and the APA report, in 1985, emitted after much infighting and acrimony, was even harsher. "The task force found no incontrovertible role for the DST in current clinical practice" (APA Task Force, 1987).

In retrospect, the entire DST affair was a tragedy for psychiatry. The field had permitted its attention to be diverted to the issue of screening tests, whereas the importance of the DST lay in identifying an underlying biochemical abnormality in serious depression. Not all depressive patients had this abnormality. How did those who did have it differ clinically? What was their distinctive biochemistry? Their molecular genetics? These questions were never asked, as the fledgling biological psychiatrists, fresh from the

wreckage of psychoanalysis, were too inexperienced with the physicality of the body to discern where future study should go. Instead, bewitched by pharmaceutical largesse, they leapt into neurotransmitters.

Thyroid Psychiatry

Psychiatry has long known that thyroid disturbances play a big role in mood disorders. As English physician Helen Boyle pointed out, in 1930, ". . . . There is too high a percentage of manic-depressives who show evidence of thyroid disturbance for the connection to be due to coincidence . . . Out of 100 consecutive cases at the Lady Chichester Hospital, six were cyclothymics, and in four of these the patients had large thyroids. Of the ninety-four others only eight had large thyroids" (Boyle, 1930).

Yet, it was only modern techniques in the study of neurochemistry that permitted the systematic investigation of the hypothalamic-pituitary-thyroid axis. A team at the University of North Carolina led by Arthur Prange made thyroid their particular mission. And in 1969, Prange and colleagues reported an interesting finding: administration of L-triiodothyronine (T3) augments the benefits of imipramine in depression (Prange et al., 1969). As research on the peptide hormones began to rage, in 1972, the Prange group reported another important biological finding: that the TSH response to TRH is blunted in depression. Depression was, in other words, marked by "hypothalamic underactivity" (Prange et al., 1972). Prange later called this surmise (which may actually not be true) an "endocrine scar" (Prange, 1998).

This research led to much international interest in thyroid metabolism and in TRH, as factors in depression, or milestones on the pathway of pharmaceutical intervention. In 1990, Prange's student Peter Whybrow and Mark Bauer reported on the benefits of augmenting lithium treatment of bipolar disorder with thyroid hormones (Bauer an Whybrow, 1990). Yet on the whole, psychiatry's interest in thyroid proved readily exhaustible.

Sprigs of Hope

In the absence of pharmaceutical treatments for endocrine abnormalities, psychiatry lost interest in the hormones. As Paul McHugh, who had become chair of psychiatry at Johns Hopkins University, said in 2007, "You can't persuade people to do DSTs. I do them but I can't get anyone else to do them" (McHugh, 2007). Attention now shifted to genetics and neurotransmitters. Endocrine psychiatry seemed dead.

Yet not quite. On the therapeutic side, the postmodern trail to endocrine psychiatry commenced, in 1984, when Charles Nemeroff, at Duke University, identified a possible pharmacological target: high CRF concentrations in the CSF of depressed patients, who were studied in Sweden by Eric Widerlov; Nemeroff postulated that "CRF hypersecretion is, at least in part, responsible for the hyperactivity of the hypothalamo-pituitary-adrenal axis characteristic of major depression" (Nemeroff et al., 1984).

This appealing suggestion, that would have opened new therapeutic avenues in the

treatment of depression, has not been confirmed. Several studies have converged on the finding that M Wong and associates reported, in 2000: despite their hypercortisolism, "depressed patients had normal levels of plasma ACTH and CSF CRH" (Wong et al., 2000).

Research at the National Institute of Mental Health has nuanced slightly these negative findings. As Philip Gold and George Chrousos concluded, in 2003: "There is evidence of abnormal CRH secretion in the hyperactive HPA axis function of melancholics." Yet, "...There is hyperactivity of the CRH system without there necessarily being hypersecretion of CRH per se" (Gold and Chrousos, 2013).

Despite high hopes, it is now apparent that CRH receptor antagonists are not the magic bullet for depressive disorders (or anxiety, for that matter). One example: a trial of a selective CRHR1 antagonist "failed to demonstrate efficacy in the treatment of major depression," as Brendon Binneman et al. at Pfizer reported, in 2008 (Binneman et al., 2008). High hopes had been placed also in the glucocorticoid receptor antagonist RU486 (mifepristone) that Alan Schatzberg's group at Stanford—where, in the words of Kenneth Davis the "neuroendocrine window was just exploded in" (Davis, 2011)—had hoped to develop. In trials for psychotic depression that were somewhat puzzling (because of a high placebo response in that illness), RU486 failed to demonstrate efficacy in the treatment of depression, although the results for psychosis were slightly more encouraging (DeBattista et al., 2004). Bernard Carroll and Robert Rubin were discouraging about the entire enterprise of treating psychotic depression with RU486 (Rubin and Carroll, 2006). On the whole, as the first decade of the new millennium closed, the prospects of pharmacological interventions in the HPA axis were yet remote. As two investigators at Organon Laboratories concluded, in 2008, ". . . Drug treatments based on manipulation of the HPA axis have not yet entered clinical practice" (Thomson a Craighead, 2008).

A second intriguing avenue leads from the secretion of the peptide hormone oxytocin in the posterior hypothalamus to autism. In 1998, Charlotte Modahl and associates, at the Boston University School of Medicine, found lower levels of plasma oxytocin in autistic children than in normal controls (Modahl, et al., 1998). In 2003, Eric Hollander and associates at the Mount Sinai School of Medicine reported that oxytocin infusions reduced the stereotypies characteristic of autism and intellectual disability (Hollander et al., 2003). (The stereotypies constitute a form of catatonia, and in fact respond readily to anticatatonic remedies) (Wachtel et al., 2008). These findings have produced a great deal of speculation – notably from Thomas Insel, director of the National Institute of Mental Health – that the "dark matter" of social neuroscience might lead to endocrine breakthroughs in autism (Insel, 2010). Whether these dizzying theoretical perspectives will be realized remains open.

On the diagnostic side, endocrine perspectives have shown more promise. The DST emerges as a possible predictor of suicide, as William Coryell and colleagues at the University of Iowa found, in 2001. Of 78 patients with major depression or psychotic depression ("schizoaffective disorder") entered in a long-term follow-up study between

1978 and 1981, 32 had abnormal DST results. Of these patients, the suicide risk was 26.8 percent, compared to only 2.9 percent among patients with normal DSTs (Coryell and Schlesser, 2001). Studies in the VA Greater Los Angeles Healthcare System (Yerevenian, et al., 2004), and the Karolinska Institute (Yokinen, et al., 2008) confirmed these results.

What will become of Tantalus? Will these diagnostic and therapeutic perspectives encourage psychiatry to cool its love affair with neurotransmitters and reexamine the beguilements of the endocrine approach?

Stay tuned.

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July 25, 2013

Comments by Andrew Winokur

Dr. Shorter has provided a fascinating historical journey through the origins of work in the field of "endocrine psychiatry", as well as providing some candid observations on the current lack of stature that the field holds in contemporary psychiatric research. As an individual who entered the field, in the mid-1970's, and became substantively engaged in research in the area of psychoneuroendocrinology, this commentator was strongly influenced and inspired by many investigators who had already provided substantial contributions to the field. Names that come readily to mind as leading psychoneuroendocrine researchers of that era include Carroll, Mason, McEwen, Rose, Rubin, Sachar, Stokes, Weitzman and Wurtman, among many others. While I had thought that I had a decent knowledge of the background to work in this field, Dr. Shorter's historical overview provided me with an introduction to the contributions of true pioneers, such as Maxime Laignel Lavastine, who he describes as the true founder of scientific neuroendocrinology, and many others Thus, Dr. Shorter's exceptional scholarship with regard to the history of this area provided a wonderful education for this reader.

Dr. Shorter shares some opinions about the fall in stature of the field of endocrine psychiatry. To cite two examples from his piece: "Today, to the extent that 'psychiatric

endocrinology' exists, it is placed well on the back burner of the field", and "Unfortunately, the opposite happened: endocrine approaches went downhill, essentially vanishing from psychiatry by the 1990's". There are valid reasons to emphasize disappointment in how the field has evolved, and the apparent lack of tangible payoffs in terms of new diagnostic applications or therapeutic interventions based on developments in endocrine psychiatric research. It should also be noted that Dr. Shorter does conclude his essay with a section entitled "Sprigs of Hope". Nevertheless, to this commentator, there are more reasons to emphasize the positive contributions of the field of psychoneuroendocrinology over the past 50 plus years, as well as to see a basis for anticipating further contributions to basic science and to improved care of psychiatric patients in the years to come, growing out of further research developments in this area.

The aspect of endocrine psychiatry or psychoneuroendocrinology that I would like to highlight relates to advances in understanding of interrelationships between endocrine function and CNS activity that have implications for behavior, for providing insights to the pathophysiological mechanisms of psychiatric disorders and for the development of novel therapeutic interventions. In the early part of the 20th Century, the anterior pituitary gland was viewed as the "Master Gland" that orchestrated and coordinated the functioning of the entire endocrine system (Krieger, 1980). Gradually, evidence became available indicating that the hypothalamus played an important role in the regulation of endocrine function, but it took an intensive 25 year research effort on the part of Guillemin's group in Houston and Schally's group in New Orleans to accomplish the initial isolation and characterization of a group of peptide compounds referred to as the hypothalamic releasing hormones, monumental work that led to these two investigators being awarded the Nobel Prize, in 1977 (Guilimen, 1980). This paradigm shifting work established the existence of compounds that were synthesized in typical CNS neurons, but were released into a vascular system (the portal vessel) to pass, in the manner of other hormones, to distant sites where they acted on receptors on anterior pituitary cells to stimulate, or in some cases, inhibit the release of anterior pituitary hormones. Distinctions between what was a hormone and what was a neurotransmitter/neuromodulator started to become obscure. Many additional examples of the extraordinary degree of integration across neurotransmitter and hormonal function were rapidly identified. In work by Pfaff, McEwen and others, peripheral hormones such as gonadal steroids and glucocorticoids were demonstrated to have receptors located in the CNS, including in the hypothalamus and in other brain regions such as the hippocampus. Thus, the brain was identified as a site of action for peripheral hormones, and effects of various hormones on CNS neurotransmitter activity were identified (McEwen, 1980). Peptides initially identified as hypothalamic releasing hormones were soon demonstrated to be present in many regions of brain and spinal cord, as well as in peripheral structures in some cases (Krieger et al., 1983). "Dale's Principle" of one neuron-one neurotransmitter had to be revised with the demonstration of the co-localization of monoamine and neuropeptide substances (Burnstock, 2004). Moreover, studies demonstrated that a monoamine neurotransmitter might be released at a lower level of neuronal activity in some cases, while a co-localized peptide compound might be released from the same neuron at a more rapid rate of neuronal firing (Bradley et al., 2002). The hypothalamic releasing hormones were demonstrated to be under regulatory control by various monoamine neurotransmitters, providing some of the rationale for the use of

"the hypothalamus as a window into the brain," as an approach to gain inferential evidence in support of the monoamine theories of mood disorders (Sachar et al/. 1976). The explosion of work on peptides in the CNS extended far beyond the hypothalamic releasing hormones to also include dozens of other peptide compounds that were shown to be present in brain tissue and to be associated with a wide array of neurophysiological and behavioral effects. Included among these neuropeptide compounds were the endogenous opiates, the "gut and brain" peptides and the recently identified orexins, which were originally identified just over a decade ago, and have already been demonstrated to be implicated in the pathophysiology of narcolepsy as well as to represent a promising target for therapeutic intervention (Reisine, 1993, Sakurai, 2007). Finally, significant advances in the field of psychoneuroimmunology include a direct linkage to neuroendocrine mechanisms, and work in this area has been proposed to be of potential relevance to the pathophysiology and treatment of mood disorders (Miller et al., 2009).

The list provided in this brief commentary represents only a partial accounting of scientific advances that have emerged from research spanning at least 5 decades that provides new insights to the interrelationships between the endocrine system, brain function, behavior and psychiatric disorders. I believe that this impressive foundation of basic science knowledge offers significant potential to contribute to important new insights about pathophysiological alterations related to a variety of psychiatric disorders, as well as to open new avenues for novel therapeutic interventions.

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Aug. 29, 2013

Comments by Walter Brown

Although one expects a paper about "endocrine psychiatry" to offer information on the relationships among hormones, the brain and behavior, one does not expect such a paper to provide much in the way of entertainment. But Ned Shorter's piece is as enjoyable as it is erudite. His wit makes complex ideas and data far more digestible than they would be otherwise; he's the only person I know who makes this topic amusing. And I always learn something from Ned. Like Andrew Winokur, I thought I knew of the main players in this field, but Ned introduced me to Lavastine and his seminal work.

My only quibble with Ned is the term "endocrine psychiatry" itself. That term seems to imply that the relationship between hormones and psychiatry is a separate branch or division of psychiatry. There are bidirectional influences between psychiatric symptoms and other systems as well, the immune system and the cardiovascular system, to name just two. But I think it's problematic to treat these various influences as separate categories or disciplines of psychiatry. I can imagine a plethora of psychiatric subspecialties—endocrine psychiatry, immunopsychiatry, cardiovascular psychiatry and so on—with uncertain and artificial boundaries. And the term "endocrine psychiatry" is not entirely accurate. However one looks at the relationship between hormones and psychiatry, much more than hormones and psychiatric symptoms come into play; neurotransmitters, brain circuits and somatic symptoms are drawn in.

Ned depicts several of endocrine psychiatry's lost opportunities. Probably foremost among them is the unfortunate tale of the DST. Clinical and basic researchers stopped looking at the pituitary adrenal axis in depressive illness after the DST failed to satisfy hopes—understandable but unrealistic—that the DST would be psychiatry's first laboratory diagnostic test. As Ned points out, although the DST and other measures of pituitary adrenal function are not useful as screening or diagnostic tests, they have the potential to provide information about the pathophysiology of depression. They could provide a

rational way to subtype this extraordinarily heterogeneous illness. A second look is clearly in order.

Another lost opportunity, or perhaps more accurately an unexploited opportunity, provided to psychiatry by the endocrine system is the potential of the psychological symptoms induced by both endocrinopathies and the administration of hormones to point to the pathophysiology of these symptoms. The well-known influence of testosterone on libido, cognition and other psychological events comes to mind. Many of the brain processes and intermediate steps that mediate the relationship between testosterone and behavior have been elucidated. And a good bit is now known about how premenstrual shifts in gonadal steroids bring on the irritability of severe PMS. Over the past two decades, studies using an array of research designs and techniques have identified brain serotonin and its enhanced sensitivity to gonadal steroids as a key element of PMS pathophysiology.

But other potentially informative endocrine effects have not been explored. The ability of corticosteroids to induce hypomanic and manic states is a case in point. The hypomania and mania induced by corticosteroids and ACTH mimic in every detail the hypomania and mania characteristic of bipolar disorder, including their prevention by lithium. Elucidation of the brain changes that mediate the effects of corticosteroids on the mood and behavior characteristic of mania might uniquely inform our understanding of the pathophysiology of bipolar disorder. The technology is available to take a look at this matter but it remains to be fully explored.

December 26, 2013

BOOKS IN NEUROPSYCHOPHARMACOLOGY: CLASSIC AND CURRENT

Introduction by Samuel Gershon

I am writing to introduce myself as the person responsible for the projects "Books relevant to the history of neuropsychopharmacology: information and discussion" (Project 8). I will be working on this project with Tom Ban and Peter Martin. Our objective is to list suitable books on our website and to ascertain that each book listed is accompanied by information on its "contents" and a statement about the book by the author if alive or by the person who submitted the book for inclusion on our list.

We hope you will be interested in participating in this project by submitting suitable books with the required information for inclusion on our list. We also hope that you will be contributing to the discussion with your comments on the books posted (inhn@inhn.org).

I am posting with this Introduction, information on Per Bech's "Clinical Psychometrics" (Wiley and Blackwell, Oxford 2012), and Thomas A. Ban's "Psychopharmacology" (The Williams & Wilkins Company, Baltimore 1969).

I am looking forward to working with you on this project.

July 11, 2013

Thomas A. Ban: Psychopharmacology (1969)
The Williams & Wilkins Company, Baltimore (485 pages)
Reviewed by Thomas A. Ban

INFORMATION ON CONTENTS: "Psychopharmacology" is divided into three parts. In Part One, "General Psychopharmacology," the development of a psychotropic drug from "synthesis" to "clinical applications" are described in six chapters: (1) "general principles," (2) "animal pharmacology," (3) "human pharmacology," (4) "clinical pharmacology," (5) "clinical investigations" and (6) "recent progress," i.e., progress in the methodology of drug evaluation in these different areas of research from the late 1950s to the late 1960s. In Part Two, "Systematic Psychopharmacology," the information collected in Part One, on structurally and pharmacologically different groups of psychotropic drugs in different stages of their development are reviewed in 12 chapters from which one covers drugs with behavioral effects without and with psychotropic action; ten deal with different groups of psychotropic drugs used in the 1950s and '60s, such as the "barbiturates," "amphetamines," "phenothiazines," "Rauwolfias," "butyrophenones," "thioxanthenes," "tricyclic antidepressants," "monoamine oxidase inhibitors," "propanediols" and "benzodiazepines"; and one, is dedicated to "psychotherapeutic" and "psychotopathic" drugs which do not fit any of the eight groups. In Part Three, "Applied Psychopharmacology," the clinical use of psychotropic drugs in psychiatry, in the late 1960s, with consideration of the information presented in Parts One and Two, is discussed in three chapters from which one deals with new "concepts" and "definitions" related to the new treatments, another with "general therapeutic principles" and the third, with treatment of different psychiatric disorders. The Volume includes a Vademecum Psychopharmacorum with the chemical names, therapeutic uses and reported adverse effects of psychotropic drugs available at the time, and is supplemented with an Index.

AUTHOR'S STATEMENT: "Psychopharmacology" was based on my over ten years of experience in clinical investigations with psychotropic drugs at the time (1969) as the Co-Principal Investigator with Dr. Heinz E. Lehmann on a grant from the U.S. Public Health Service to support an Early Clinical Drug Evaluation Unit at the Verdun Protestant (now Douglas) Hospital, a psychiatric inpatient facility in the outskirts of Montreal. (See, "Lehmann and Ban's ECDEU Progress Report, 1961-1963," in the "Archives" of the INHN Website).

With the steadily accumulating preclinical and clinical information on psychotropic drugs, I became increasingly aware of the heterogeneity of the information provided in pre-clinical brochures and of the inconsistency in the language used in describing drug-induced changes in clinical reports. The problem was compounded by the lack of integration of information from preclinical and clinical research. My objective was to bring together and organize the available information on psychotropic drugs generated by researchers working in different disciplines and operating in different frames of references in a manner that would help to translate findings from one level of functioning to the next, e.g., from biochemical to neurophysiological, and from one setting to another, e.g., from laboratory to clinical.

The writing of the text was greatly facilitated by an invitation to conduct a workshop on "What preclinical information does the clinician expect to be given prior to conducting a clinical trial with a new drug" at the 1966 annual meeting of the American College of Neuropsychopharmacology (Abstract, ACNP Bulletin, Volume 4, 1966). I also benefitted from the request to write a series of reviews on the different groups of psychotropic drugs for Applied Therapeutics (Applied Therapeutics, Vol. 8, 1966: 145-75, 423-7, 530-5, 779-85; Vol. 9, 1967: 66-75, 366-71, 677-80). There was also my increasing involvement in teaching psychopharmacology to psychiatric residents in the Department of Psychiatry at McGill University. The material presented at the ACNP Workshop provided the basis of the first part of the book, "General Psychopharmacology"; the papers published in Applied Therapeutics for the second part, "Systematic Psychopharmacology": and the "handouts" used in teaching, for the third part, "Applied Psychopharmacology." In my concluding remarks, I pointed out that pharmacotherapy with psychotropic drugs focused attention on the pharmacological (biological) heterogeneity within the traditional nosological categories of mental illness, in terms of therapeutic responsiveness to psychotropic drugs, and postulated that progress in pharmacotherapy in psychiatry will depend on how fast this heterogeneity is resolved. "Psychopharmacology" was published by Williams and Wilkins, in 1969. It was the first comprehensive text in the field. It shared, in 1970, the Clarke Institute Annual Research Award with Harvey Stancer's contributions to the role of catecholamines in affective disorders.

July 11, 2013

Thomas A. Ban: Depression and the Tricyclic Antidepressants (1974)
Ronalds Federated Graphics Limited. Montreal. (74 pages)
Reviewed by Thomas A. Ban

INFORMATION ON CONTENTS: In the seventeen years following the introduction of imipramine (1957), a large number of tricylic antidepressants (TCAs) were synthesized. By 1973, at least 38 TCAs had been clinically investigated, and almost one quarter of those which had been studied, were introduced into clinical use. Yet, TCAs could control psychopathology only in one-third (or two-third including placebo responder) of depressed patients and the behavioral rating scales used in clinical investigations did not collect the necessary information to predict which patient will respond and which patient will remain refractory to these drugs. In the mid-1960s, the possibility was raised that biochemical measures related to the pharmacological action of TCAs might provide pharmacologically more homogeneous sub-populations within depression, in terms of responsiveness to treatment, than psychopathology-based clinical diagnoses. The search for biological markers of depression or subpopulations of depression continued in the late 1960s and was still on the ascending part of an inverted U in the mid-1970s, at the time "Depression and the Tricyclic Antidepressants" was written. The monograph is divided into five chapters, including "Introduction" and "Concluding Remarks" with three chapters, one on "Drugs," another on depressed "Patients," and the third, on "Depression" in between. In the "Introduction," the story of the iminodibenzyl nucleus, the basic constituent of imipramine, is outlined from the time of its synthesis, in 1899, to the time of its introduction in the form of imipramine in the treatment of depression. In the chapter on "Drugs," that follows, the pharmacological properties of TCAs with special reference to "structure-activity relationships" and their "metabolism" in humans, is discussed. In the chapter on "Patients," questions related to efficacy, differential effects and maintenance therapy are addressed, as well as preliminary findings relevant to identification of subpopulations within depression, and prediction of treatment response to TCAs, with the employment of the Verdun Conditioning Procedure (see "Lehman and Ban's ECDEU Progress Report 1961-1963," in INHN "Archives"), and the Tartu Conditioning Test Battery, are presented. In the chapter on "Depression," the role of central cholinergic mechanisms are examined in depression; findings relevant to the catecholamine (norepinephrine) and indoleamine (serotonin) hypotheses of depression are reviewed; biochemical measures for dividing depression are entertained; and the possibility is raised for using the amplitude of the autonomic "startle response" for the identification of depression in which assumedly serotonergic mechanisms are primarily involved. Finally, in the "Concluding Remarks," the status of pharmacotherapy of depression with TCAs, in the mid-1970s, is presented and augmentation strategies of therapeutic effects are discussed. Although seventeen years of research did not yield any definitive biological marker of depression or of any subpopulation of depression, expectations to find such markers were high in the mid-1970s, and the monograph concludes (in the paragraph before the last): "It is quite conceivable that in the not too distant future, clinical diagnosis will be supplemented with psychophysiological, neurophysiological and biochemical correlates of the clinical state. In the same manner, it is quite conceivable that in the not too distant future, in the proper selection of pharmacological treatment, behavioral, neurophysiological and biochemical laboratory data will be utilized, and dosage (of TCAs) will be based on the individual's

ability to metabolize and distribute the compound using kinetic principles."

AUTHOR'S STATEMENT: "Depression and the Tricyclic Antidepressants" is an expansion of my lectures to psychiatric residents at McGill University, during 1973. The information covered in the monograph was also discussed in seminars with Fellows of the World Health Organization Training Program in Biological Psychiatry at McGill, in the mid-1970s. The monograph was printed, in 1974, with the U.S. Library of Congress Catalog Card Number 74-76737 by Ronalds Federated Graphics Limited, Montreal, Quebec, Canada.

August 8, 2013.

Per Bech: Clinical Psychometrics (2012)
Wiley-Blackwell: A John Wiley & Sons Ltd. Publication, Oxford. (202 pages)
Reviewed by Per Bech

The Danish original of this monograph was published by Munksgaard, Copenhagen, Denmark, in 2011 with the title: Klinisk psykometri.

INFORMATION ON CONTENTS: "Clinical Psychometrics" is divided into ten parts, including the "Introduction," "Summary and perspectives" (part 9), and the last part (part 10) with the title "Who is carrying Einstein's baton?" Part 1, deals with "classical psychometrics" (Kraepelin, Spearman, Hotelling, Eysenck); part 2 with "modern psychiatry - DSMIV/ICD-10"; part 3 with "modern dimensional psychometrics" (Fischer, Rasch, Siegel, Mokken); and part 4 with "modern psychometrics – item categories" (Likert, Overall, Cohen). From the remaining four parts in three, "the clinical consequences of IRT (item response theory) analysis" is discussed, and in one (part 8), the possibility of using "questionnaires" as "blood tests" is addressed. From the three parts which deal with the "clinical consequences of IRT analysis," one (part 5) is dedicated to the "pharmacopsychometric triangle," another (part 6), to "health related quality of life," and the third, to the "concept of stress." The volume is complemented by a "glossary," "appendices," "references" and an "index."

AUTHOR'S STATEMENT: The central concept of this book is the "Pharmacopsychometric Triangle" in which (A) covers the desired clinical effect of a drug, (B) the unwanted, or side effects produced by the drug, and (C) the patient-reported quality of life as a balance between (A) and (B), covering the "mental dimension of health."

The measurement-based care, as evaluated by the "Pharmacopsychometric Triangle," is in this book discussed within the frame of reference to brief clinically and psychometrically valid scales, where the total scores are "sufficient statistics." "Effect-size" (response) and "number needed to treat" (remission) are two other important statistics.

From a pure psychometric point of view it is the "item response theory model," and not "factor analysis" that is recommended for showing that the summed total score of a brief scale is a "sufficient statistic." The item response theory model provides descriptions of the difficulty to rank order each individual item in a scale to secure by addition a total score.

This is the first book that identifies by the "item response theory model" the valid scales for measuring the effects of "antipsychotic," "antimanic," "antidepressant" and "antianxiety" activity of drugs within the "Pharmacopsychometric Triangle." The author was first, in the late 1970s, to introduce the "item response theory model" in clinical psychiatry.

In the Appendix of this book, Max Hamilton's lecture from 1977 on the clinical validity of

depression scales is presented. It was one of Hamilton's most important presentations that have never been published internationally. The Appendix also includes illustrations of both, the "item response theory model" and "principal component analysis."

July 11, 2013

Comments by Martin M. Katz

There are several somewhat unusual aspects to Per Bech's book on Clinical Psychometrics. First, despite the great need for a historical treatment of how the relatively new science, neuropsychopharmacology, developed quantified methods for psychopathology and the capacity to measure treatment-induced change, no one has come forth to do this important job. Bech not only provides the historical perspective but he manages by surveying recent research to sort out the various rating and other psychological methods that have been developed over several decades, highlighting the continuing controversies that exist in regard to measurement strategy and technical details that underlie method development. We expect a psychologist to write this type of book. It is unusual, of course, that Bech, as a psychiatrist, has fortunately most of the skills to carry off this very complicated task.

This is not a book, however, that psychiatrists will rush to buy. They are not generally comfortable with quantifying their clinical judgments and have rather little exposure to any training in this area. Contrary to the general belief that psychologists have paved the way for the construction and acceptance of rating methods in clinical research, Bech presents another view. He identifies Kraepelin and Hamilton, two of the most prominent psychiatrists on the world scene as the leaders here. By making a case for that conclusion, he might inadvertently enlist a great many psychiatrists in the further development of this field. Bech actually balanced this view in the text, by also describing the prominence of Galton, Spearman, Eysenck, the contributions of Maurice Lorr and John Overall, and several other psychologists. To fully appreciate what is covered, e.g., which scales are currently available and what they are capable of measuring, we note the clarity with which he presents this information and his particular perspective on the right kind of strategy and associated technologies for constructing these instruments.

Bech classifies test development into two periods, the "classical" and "modern". In describing factor analysis he contrasts supporters of the two factors versus those who rely on rotations and thereby, uncover a multi-factorial structure of psychopathology. Beyond that he cites limitations of factor analysis, generally, pointing out that it cannot be used to validate phenomena, and more importantly, is not designed to develop methods, but only to provide classification of variables. He appears to be convinced that the age of factor analysis is over, and that the field should move on to the use of the "item response" model. He sees the latter method as better suited to solving the problems in this field. I am not sure here, however, that his glossary definitions of "validity," which stress clinical

significance and unidimensionality, correspond to the commonly accepted psychometric definition; i.e., the simpler notion that validity is the extent to which a method measures what it purports to measure. I, therefore, think I understand his stance on the number of factors, but take issue with his conclusion. He, like Max Hamilton and Pierre Pichot, appears committed to brief scales and the two factor approach. Those on the other side of the issue conceive of each of the disorders as multifaceted and utilize factor analysis to uncover their dimensional structures.

Thus, the factor analysts view it as a data reduction method aimed at uncovering the two or more components that can most parsimoniously explain what the method is actually measuring. Further, when the disorder is conceived to be multidimensional, it is then necessary to identify each of the components, and from the factor analysis results, create ways of quantifying them. Currently, that is done through principle components analysis and rotation. Bech presents thoughtful views on these matters but does not do justice to the multifactor approach. A historical example of the contrasting lines of thinking here is where he focuses on the Hamilton Depression Scale (Ham-D) and the Brief Psychiatric Rating Scale (BPRS), but provides limited information on their predecessors, the Wittenborn Psychiatric Scales and Lorr's Inpatient Multidimensional Psychiatric Scales (IMPS), both multifactorial scales. In these two cases, the authors' targets were the facets of psychopathology and the importance of developing a set of items for each of these facets. The basic psychometric principle followed was that more reliable and valid measures of the components, e.g., "anxiety", can be achieved by having the judges rate a set of observed behaviors that reflect that component, than by having an observer rate a more complex, global concept such as "anxiety". It was Lorr, as Bech points out, who wrote and compiled the 63 items and determined the factor structure of psychopathology. Overall and Gorham used Lorr's factors to craft global definitions based on interpretation of his factor items, in order to create their 16 "global" items for the original BPRS. We are aware of how well the BPRS used in hundreds of studies, worked these many years, particularly in the evaluation of change in overall severity of the disorder in drug trials. But when it comes to reliably and validly measuring the dimensions of psychopathology, equally important in the science, the IMPS is a more effective instrument and applicable to a wider range of problems in clinical research.

This was perhaps the only shortcoming I could find in this otherwise balanced and clear-headed judgment of the major issues in our field. For psychiatry, Bech highlights in reviewing the history of the rating scales, that Kraepelin constructed his own rating method, to be followed by scales developed and modified by Max Hamilton and Pierre Pichot, all three attempting to create a functioning science for psychiatry. Their focus on the importance of scales will no doubt surprise psychiatrists and may prove a positive influence on their approach to them in clinical practice. The history Bech presents is inspiring. Not only does he elevate rating scales in the minds of researchers and clinicians, but he also, following philosophers Jaspers and Wittgenstein, in restoring respect for the phenomenologic approach to characterizing the nature of psychopathology.

I heartily recommend this book as a text for Clinical Methods courses for psychologists

and psychiatrists. I view Per Bech's effort as filling a significant gap in the practice of current clinical research and an important contribution to the science of psychopathology.

August 1, 2013

Reply to Martin M. Katz by Per Bech

In the scientific game, the dialogue between the author of a submitted manuscript and the journal's referees is quite essential.

Traditionally, however, the dialogue between the author of a book and an invited reviewer of this book is considered outside the scope of this game, and quite inappropriate. The progressive aspect of the INHN is to break down this tradition, so as to increase the interest in scientific games in the name of research.

Martin Katz' review of my Clinical Psychometrics has exactly captured my reason for publishing this book, namely by its reference to Kraepelin, Hamilton and Pichot to awaken the minds of clinical psychiatrists to the uses of rating scales. Generally psychiatrists are, as pointed out by Martin Katz, uncomfortable with the quantifying of their clinical judgments and they often have rather little exposure to any training with these scales. A shortcoming of my book, as stated by Martin Katz, is the treatment of factor analysis. With reference to Ockham's razor, i.e., the principle of simplicity (the law of parsimony), I have preferred to focus on the first two components when interpreting the results from a principal component analysis. My book is essentially concerned with the psychometric validation procedure which demonstrates whether items in a rating scale can objectively measure dimensions of clinical severity (e.g. degrees of schizophrenicity, degrees of depressiveness, or degrees of neuroticism). In this connection, item response models are the psychometric validation of measurement to be used when demonstrating these dimensions of severity, i.e., that the total score of a rating scale is a sufficient statistic.

The importance of factor analysis or principal component analysis does not lie with the measurement issue but, as stated by Martin Katz, in identifying the multi-facets of, for example, depression. In patients with treatment-resistant depression, I have actually used principal component analysis and identified a principal component which encompass concentration problems, fatigability, lassitude, and sleep problems. Furthermore, I employed item response theory models to measure the severity of this neuropsychiatric or neuropsychological syndrome. The importance of factor analysis is its ability to explore for new dimensions, but the clinical relevance is outside the explorative nature of factor analysis.

Martin Katz has for many years, as a psychologist, worked very close together with psychiatrists in the field of psychopharmacology, especially in depression. I appreciate his very balanced review of my book. It has really been my goal to: "fill a significant gap in

the practice of current clinical research."

August 29, 2013

Comments by Donald F. Klein

Per Bech's remarkable book has been outlined by its author, commented on by Martin Katz and replied to by Bech, who emphasizes the value of continuing critical dialog. These remarks continue this thread.

"Clinical Psychometrics", floods this reviewer with many contextual memories. When, in the 1950s, the paradigm destroying antipsychotic effects of chlorpromazine were first noted, they incited a storm of disbelief. There were many independent replications of anti-psychotic benefit, however to scientifically verify that these observations were not clinical fabrications, the quite recent technology of the randomized, double blind, clinical trial was employed.

However, massive criticism, mostly by objectivity averse psychoanalysts, argued for objective diagnostic and clinical change measures, probably in the dim hope that objectivity was impossible. At that time, discerning objective manifestations of psychiatric disease was impossible. In current psychiatry, objective measures are still ambivalently regarded as shown by their absence in DSM 5, despite NIMH's fevered search for biomarkers.

However, if independent raters agreed with each other, then there had to be something observable out there, that allowed more than chance agreement. Rater agreement (reliability) then served as a surrogate for objective description. However, ill-defined accusations of lack of validity without specification of the multiplicity of validity criteria, served to derogate systematic observation.

Bech, using pithy summaries, explains the foundational observational and analytical work of Wundt, Kraepelin, Spearman, Galton, Pearson, Fisher, Eysenck, Hamilton and Pichot, among others.

Strikingly, Bech argues that the ubiquitous factor analysis does not provide appropriate measures of change or a foundation for diagnosis. This critically challenges much current work, as well as the NIMH sponsored Research Domain Criteria (RDoC) manifesto for dimensional primacy via multivariate analysis.

The more "modern" (since the 1970s!!) psychometric developments sparked by Rasch, Guttman and others, is generally labeled Item Response Theory (IRT). Bech holds these produce the only appropriate severity measures.

Guttman defined a hierarchy aimed at producing a unidimensional severity scale, based on the proportion of subjects endorsing each item. Since items endorsed by most subjects are easy (less pathological), whereas rarely endorsed items are difficult (very pathological), if an item of specified severity is endorsed, then all easier items should also be endorsed. Each potentially useful item is mathematically evaluated to see if it consistently takes its place in such a hierarchy. Items that are endorsed by the few, but not by the many, just don't fit, although they may be useful for other purposes. Change is determined by differences in Guttman defined severity. This exposition seems quite clear, even if the mathematics is well beyond me.

This fundamental Rasch analysis is unique in that its item pool is initially selected by expert psychiatrists, as reflective of a particular syndrome. Rasch analysis produces a severity scale, not a diagnostic scale. Bech holds that such a scale sufficiently describes an individual's degree of severity by its total. This is not the case for familiar, but multi-dimensional, indices such as the Hamilton 17 item scale.

Factor analyses depend upon the rule of thumb selection of the number of factors, that then are rotated (by various methods) to differing definitions of simple structure. Bech holds that these procedures do not flow from a logical basis that allows firm deductions or sampling inferences. This defect is affirmed by the lack of factor replication across various samples.

Bech also argues that the use of factor analysis differs between American and British traditions. The mathematics of factor and principal component analyses yields a principal factor, marked by consistently positive loadings, and a second orthogonal factor with both positive and negative loadings. The British tradition uses only the contrast evident in the second factor. ["In contrast, an American approach rapidly emerged in which factor analysis was used to identify as many factors as possible".] Bech argues that these factors, even if "rotated to simplicity", cannot be represented by a simple total, since they contain heterogeneous items with regard to both severity and group discrimination. This impairs their use both as change and diagnostic measures.

In a clinical trial, some of the items loading a supposedly simple factor may significantly contrast drug with placebo, whereas other items from the same scale do not come close. Therefore, a factorial scale score that sums its items attenuates the distinction between drug and placebo. This had been noted in a widely unnoticed 1963 paper (Klein DF & Fink M. Multiple item factors as change measures in psychopharmacology. Psychopharmacologia 1963; 4: 43-52.)

Katz has reasonably suggested a "multi-vantaged" approach to patient evaluation. In particular, evaluations are amplified by video recordings that can be "blindly" assessed, by multiple experts, without knowledge of treatment or time of observation. In addition to the methodological gains, such recordings allow a more fine grained evaluation of the patient's physical appearance, verbal flow, affective manifestations, change over time, etc.

Where Katz seems to part company with Bech is his reliance on scales produced by multiple factor analysis as well as depending on multiple statistical analyses, without correction for multiplicity. Katz argues (and I agree) that specific tests of antecedently supported and hypothesized effects do not require a "family wise" significance level correction. However, such specifically stated antecedent hypotheses are not apparent (to me) for many of the claimed findings.

At one time, long past, NIMH supported methodological advances in psychopharmacology that often benefited from designs using concurrent placebo control groups. Such clinical trials sufficed, both for demonstrating that specific drug activity existed and gaining FDA approval for marketing. However, this group average outcome difference does not determine which patients actually require medication for a positive response exceeding their counterfactual response while on placebo. This parallel group design obscures understanding of this critical issue.

Both Bech and Katz have addressed this problem. It was recently suggested that the inclusive clinical trials design promulgated by Chassan may be necessary to solve this problem [Klein DF (2011): Causal Thinking for Objective Psychiatric Diagnostic Criteria. In: Shrout PE, Keyes K, Ornstein K (Eds.) Causality and Psychopathology, New York City: Oxford University Press, pp 321-337].

A discussion of this specific issue, in the dynamic framework for controversy provided by INHN, would be most worthwhile.

October 31, 2013

Reply to Donald F. Klein by Martin M. Katz

Don Klein's comments on Per Bech's book are helpful in advancing understanding of the author's main points, and in focusing on some important issues regarding measurement and the manner in which we currently approach the evaluation of new drugs for the mental disorders. He raised at least three issues that currently obstruct long-term solutions to problems in clinical psychopharmacology, specifically in the conduct of clinical trials. He also alluded to points in which in my review of Bech's book I differed with the author. I believe he agreed with my position that the multiple factor solution is the more effective use of factor analysis in extracting information about drug actions. At the same time, he is uncomfortable with the actual content of the factor measures, alluding to both Bech's reservations about factor analysis, generally, his own prior work, and to the procedures applied in my "multivantaged" approach. To further clarify my position, I respond to the issues raised as follows:

1. It is important in all method development to be clear about what, specifically, is to be

measured. I believed the critical problem in current trials research is its almost exclusive focus on evaluation of change in the severity of the overall disorder, to the exclusion of evaluating drug effects on the major components of the disorder. When I proposed the multiple factor solution, it was because we first sought measures of the facets of psychopathology, measures that were essential to not only assess severity of the overall disorder, but the intensity of each of the major components of that multidimensional disorder. In that method work then, the target was valid measures of these facets, not of "change" due to a specific drug or drug class. The componential approach applied, affected how the rating scales were developed, but also highlighted the need to go beyond rating scales to achieve more "objective" measures. Klein refers, e.g., to the new DSM 5, to illustrate how "ambivalently" the concept of objectivity continues to be treated by the profession. We, therefore, expanded the measurement approach through use of other psychological methods, e.g., self-report inventories, measures of expression (through video), and psychomotor performance, in order to achieve more valid measures of the components.

2. Klein points to the use of factor measures in drug trials in which the items in a given factor are differentially sensitive to change. He see this rightfully, as obscuring the drug-placebo differences; implying that the factor should only include items that are change sensitive. If the intention in creating the factor is to develop a "change" method specific to the measurement of the effects of that drug or like drugs, then one might want to confine the factor items only to those that have been demonstrated to be change-sensitive. The method developed is then targeted to be more sensitive than existing methods, to the actions of that drug or like drugs. If, however, a new drug is tested that has different effects than the established ones, this particular method will be of limited use in detecting those effects. The prime intention when working in this sphere has, therefore, been to create measures of the facets of psychopathology of a given disorder or set of disorders, e.g., "anxiety", that can be applied in the measurement of any type of treatment intervention. The position is that the "multivantaged" approach is what is most needed now in clinical trials of new agents and in clinical studies in psychopharmacology, generally. I believe that with colleagues, Alan Frazer and Charles Bowden, we have clearly demonstrated the advantages of that approach, its capacity, e.g., to provide information on the nature, timing, and sequence of actions of diverse antidepressants, in a series of studies. The results of these studies are summarized in my recent, "Depression and Drugs" book (Springer, NY, 2013).

3. On the third issue, Klein cites the limitation of drug-placebo comparisons by calling attention to the fact that finding a drug effect in a class of disorders, does not help with the prediction for any given patient. Separating the placebo from the drug effect in a patient is an important problem, particularly for clinicians trying to treat treatment-resistant patients. Klein raises this to initiate discussion of more precise methods for accomplishing that aim. The prediction literature on that problem for the depressive disorders indicates that for the most part, we do not have at treatment outset, any reliable specific symptom predictors of drug response. The work of Szegedi et al (Early improvement in the first two weeks. J Clin Psychiatry 2009; 70: 344-353), Stassen et al (Delayed onset of action of antidepressant drugs? Eur Psychiatry 1997; 12: 166-176), and Katz et al. (The componential approach. J Clin Psychopharmacology 2011; 31: 253-254) show that no

improvement in the patient within the first two weeks of drug treatment in severity of the overall disorder or in levels of anxiety or hostility results in >90% of patients failing to respond positively at outcome, whereas 70% of those having a positive treatment outcome will have shown significant improvement (>20%) by the end of the 2nd week of treatment. These relatively new findings do not solve the problem Don Klein raises, but in utilizing "early response" to treatment as a predictor, it is an approach that can help reopen the issue.

December 12, 2013

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

INFORMATION ON CONTENT: The discovery, in the early 1950's, of the role of the central neurotransmitters and that of the new drug treatments for the mental disorders sparked a wave of research in the new science of neuropsychopharmacology. In the first two chapters, the book describes the impact of the new drugs on theory and research on the major depressive disorders, focusing on the interactions between neurochemistry and behavior and the role of diagnosis in clinical research. The author sets the stage for later detailing the misplaced reliance on diagnosis and introduces dimensional analysis to replace it in framing both basic and clinical research. In Chapter 3, "depression is a storm, not a lowering of spirit", he describes the psychological factors that have been seriously neglected in the burgeoning of recent neurochemical studies. He reports results of empirical studies of the clinical phenomena and the need to turn to literary artists who have been afflicted, to characterize the personal experience. Combining these approaches led to a new strategy of measurement. In Chapters 4 and 5, he describes the "Rashomon" approach to measuring the state, the "multivantaged method", and the resultant dimensions of anxiety-agitation-somatization, depressed mood-retardation, hostility-interpersonal sensitivity that represent the major part of the variance underlying its structure. Chapter 6, "False Assumptions," critiques the basis of most current drug research. Much of that work is guided by earlier misconceptions of the disorder and of the nature and timing of drug actions. New evidence contradicts these assumptions and cites a new path to research in this area. Chapter 7, "New Hypotheses", reports results from a follow up study that compared differently targeted antidepressants. It was designed to test hypotheses about drug actions derived from the earlier NIMH's Collaborative Depressive Study and to extend knowledge on how neurochemical and behavioral changes interact to resolve the disorder. Chapter 8, in describing a "more effective model for the clinical trial of new drugs," demonstrates the advantages of applying the dimensional conception of depression and the "componential" model, in place of the now 50 year old established "diagnostic" model. Finally, in Chapter 9, the author presents conclusions and describes a new theory about the nature of the depressive state, "the conflictual neurobehavioral state" hypothesis, a concept that views it as one of turmoil, not as unidimensional, but as one of conflicting central nervous system states, a "down, depressed retarded state" concurrent in the experience with an opposed "aroused, negatively excited, anxious" state.

AUTHOR'S STATEMENT: The book is a product of the author's experience in two major Collaborative studies of the Psychobiology of Depression that extended over a period of several decades. The themes covered, ranged from results of basic studies which detail the specific relationships between central neurotransmitter systems, serotonergic and noradrenergic, and the elements of behavior, to a rethinking of the neurobehavioral concept of the disorder itself. Noting the neglect of behavior in more recent drug research, it views depression, not as a singular disorder, but as comprised of multiple dimensions. It further recommends replacing the dominant role that diagnosis plays in framing most all clinical

research with the dimensional profile. To achieve that goal, a new conception of the disorder is presented and a new strategy of measurement, the multivantaged method, as the framework for future research. The empirical results of two collaborative studies characterize the behavioral phenomena. The components of depression are then combined with the descriptions by literary artists of the actual experience of the disorder. These results lead to a re-conceptualization of how the drugs act to resolve the disorder, and a new theory as to the experience of the depressed state, based on the interaction of opposed neurobehavioral states. In introducing the new methodology, the author seeks to change the approach to clinical trials. The established model, developed more than 50 years ago, is out dated and does not do justice to the many drug actions and forms in which the disorder is manifested. There is a Postscript. In the appendices, detailed descriptions are presented of the brief form of the Multivantaged Assessment Method and the newly developed Video Interview Behavior Evaluation Scales (VIBES).

August 8, 2013

Comments by Samuel Gershon

Dr. Katz's career was completely contemporaneous with the introduction of imipramine into psychiatry and was actively involved with most aspects of studies in the area of depression and its treatment and evaluation. He was a primary player in the United States National Institute of Mental Health (NIMH) Collaborative Psychobiology of Depression Program, launched in 1970, which ran for 10 years. He was involved in very many of the NIMH and United States Veterans Administration (VA) collaborative studies in these areas. This background, together with his own research on the clinical assessment concerns about the methods and the approaches used for the evaluation of change caused him considerable concern. He then undertook methods to develop new approaches that might present an evaluation of different facets of the clinical state. From his position, he was perfectly situated to look at the data from all points of the compass. His conclusions offer the reader a very sobering picture of our current status of knowledge and he concludes we need to reevaluate our many positions and beliefs. He quotes a Collegium Internationale Neuro-Psychopharmacologicum (CINP) task force report "we still have found no biological 'markers' of the disorder nor are we completely clear as to mechanisms underlying their efficacy in depression" or their mode of action. He goes on to note the vast disparity in accumulated knowledge in genetics and neurosciences with the fact that no new compounds have been developed in the last 30 odd years. He feels that part of the problem may be in the central clinical problems in this area, as well as the design and assessment aspects of the study. He has spent many years of his own research in trying to address these questions. In conclusion, the volume forces us to look at these discrepancies with these new approaches in mind,

August 15, 2013

Reply to Samuel Gershon by Martin M. Katz

Sam Gershon is one of the pioneers of psychopharmacology. I am pleased that he is in agreement with my current perspective on the state of research in the field and that he praises the contents of the book.

He and I are disturbed as are many researchers in clinical psychopharmacology, with the failure during the past three decades, to develop new classes of antidepressants. Through the kind of analyses and recommendations outlined in my book and the contributions of others in the field, we hope to encourage young investigators to rethink the nature and definition of the multi-dimensional depressive condition, and to be more innovative in uncovering the specific actions of established and new treatments.

A change in mind set on the disorders by psychiatry and the introduction of more efficient and less expensive methodology for clinical trials can stimulate the pharmaceutical companies to restart full operations in the development of new psychotropic agents.

September 12, 20013

Comments by Per Bech

We all have to listen carefully when a psychologist has released a book on the treatment of depression with drugs. Even more so, when the psychologist is Martin Katz, who was executive secretary of the first advisory committee to Jonathan Cole's Psychopharmacology Service Centre in the USA in the late 1950s, and was director of the Laboratory of Experimental Psychology in Herman van Praag's Department of Psychiatry at Albert Einstein University in New York, in the early 1990s.

The neurobehavioral approach to depression is described in this small and well-written book in which Martin Katz links the functioning of the serotonergic and noradrenergic neurotransmitter systems in the brain to different clinical components of depressive states. Katz's story is in a certain sense the opposite story to Arvid Carlsson's when identifying the functioning of these neurotransmitter systems. Carlsson was inspired by the work of the experienced psychiatrist, Paul Kielholz, who found clomipramine to be the most potent mood activating tricyclic antidepressant and desipramine to be the most motor activating tricyclic antidepressant. Building on Kielholz's clinical findings, Carlsson showed that the dual actions of these antidepressant drugs entailed an initial effect on serotonin reuptake inhibition and thereafter an effect on noradrenaline reuptake inhibition. Had Carlsson accepted the claims in many reviews that all antidepressants have the same therapeutic profile, he would not have been able to discover what he did. In the same way, had Martin Katz followed meta-analytic findings, he would not have discovered that the profile of clinical depression is a psychological storm, a state of psychological turmoil, a term he borrowed from William Styron's description of his own depressive illness, in his book,

"Darkness Visible."

Using principal component analysis in clinical trials with both the Hamilton Depression Scale and the self-reported Symptom Checklist (SCL-90), Katz and his co-authors identified three components explaining 75% of the variance. The three components are: depressed mood, anxiety-arousal symptoms, including sleep, and hostility – interpersonal sensitivity.

Using these three components, Katz compared the serotonin reuptake inhibitor paroxetine and the noradrenaline (norepinephrine) reuptake inhibitor desipramine in a placebo-controlled study. In patients who had a good clinical response, it was possible to show within the first two weeks of therapy that drugs acting on serotonin reuptake have an effect on anxiety as well as on hostility some days before their action on noradrenaline and depression.

On the basis of his findings, Katz's recommendation to the industry is that clinical trials with new potential antidepressant need not last more than two weeks, and that the classical practice of relying only on the total score on the Hamilton Depression Scale might result in the throwing out of many good babies, good drugs, with the bathwater.

In 1994, Martin Katz asked in a paper whether we are doing the right thing when we are using the traditional meta-analytic studies with the total Hamilton score as outcome measure in clinical trials with antidepressants. Over the last two decades, Katz has confirmed that using the total Hamilton score is wrong. His small book tells us how to perform clinical trials with antidepressants. All those who are searching to find new antidepressants with a more rapid mode of action than the ones in clinical use need to read his book - listen to the words of the wise.

September 19, 2013

Reply to Per Bech by Martin M. Katz

It is difficult in a brief commentary to capture the main themes of a book in which the author attempts to rethink the nature of a major mental disorder and evaluate the impact of diverse new drug classes in its treatment. I have Per Bech to thank for grasping my intentions as well as the technical recommendations for changing the direction of research on the mechanisms of action of antidepressants. In linking the results of our experiments to the early ideas of the astute Paul Keilholz on how the drugs work clinically, and to the sequence of neurochemical actions uncovered by Carlsson, he provides a meaningful context for the observation that we are currently approaching research problems in this area in the wrong manner. Depression, as Bech notes from our results, is multidimensional and he agrees that we must cease relying so heavily on diagnosis in the structure of research in psychopharmacology. If we adopt the dimensional approach, it will have major effects on

how we design clinical trials of new agents. It will also, hopefully, stimulate experimentation on agents with novel mechanisms, research that will restart development in an area that has uncovered no "new" classes of antidepressant drugs for several decades. Bech, with his depth in the field of methodology places our work in the proper context for psychopharmacology and reinforces the need to move ahead in drug discovery with a new concept of depression and a broader range of approaches to behavioral measurement.

November 14, 2013

Donald F. Klein and John M. Davis: Diagnosis and Drug Treatment of Psychiatric Disorders (1969)
Williams & Wilkins, Baltimore. (480 pages)
Reviewed by Donald F. Klein

INFORMATION ON CONTENTS: Foreword: Jonothan O Cole; Introduction: Brief historical summary of somatic psychiatric care; I. Diagnosis and the diagnostic process; II. Psychotropic drug management; III. Diagnosis of schizophrenia; IV. Review of antipsychotic drug literature; V. Treatment of Schizophrenia; VI. Diagnosis of affective disorders; VII. Review of mood-stabilizing drug literature; VII. Treatment of affective disorders; VIII. Diagnosis of neuroses and personality disorders; IX. Review of minor tranquilizer literature; X. Treatment of neuroses and personality disorders; XI. Critique of treatment studies; XII. Theoretical inferences on clinical groupings of psychotropic drugs; Author Index; Subject Index; 36 tables detailing the treatment reviews; 10 figures.

About 1964, John Davis suggested this book to me as a collaboration of clinical trials expertise with a depth of literature review and theoretical concerns.

The initial material included an unusually detailed discussion of the theory of diagnosis and the importance of syndromes. The belief that psychiatric diagnosis could arise from the multivariate study of scales was criticized.

There was a general chapter on psychotropic drug management, followed by a series of three layer cakes regarding schizophrenia, affective disorders, neuroses and personality disorders. Each first section was a critical statement about the development of this diagnosis and its substantiation. A critical review of the drug literature followed, documenting each trial. Such reviews have been effectively superseded by meta-analyses. However, a detailed comparison of trial designs, analyses and outcome measures is a necessary precursor for fleshing out anonymous effect sizes. An attempt to integrate clinical trials data, clinical experience and practical matters follows, providing detailed treatment guidance.

Following these data rich chapters, was a critique of the design of treatment studies. A scheme for large clinical research facilities to facilitate psychopharmacological development was outlined. Unfortunately, this proved Utopian. The last chapter emphasized the utility of psychopharmacological dissection. It emphasized the existence of syndromes and the fact of remission was critical to nosology. This material shrinks the current over emphasis on endophenotypes and dimensions. That current psychopathological theory emphasizes either an excess or deficiency of some neurotransmitter—in rheostat fashion—was also criticized as incompatible with known clinical data. A theory of cybernetic deficiencies of control feedback mechanisms was suggested that is still largely unremarked.

AUTHOR'S STATEMENT: Published in 1969, this was the first clinical textbook of psychopharmacology. The title of the book was unique in that it emphasized drug

treatment. It was upsetting when we were told by the eminent publisher that due to some incomprehensible technical difficulty that the word "Drug" had been omitted from the book's cover. They hoped that I would agree that this was of little consequence. However, my reaction led to a re-embossed cover. A corrected stick-on was provided for the spine, which promptly peeled off.

The book sold well as academic texts go. We were frequently told by residents that it served as an indispensable solitary, resource.

Over the next decade, the exponential psychopharmacologic development warranted a second edition. In particular, the entire field of childhood psychopharmacology had blossomed.

November 28, 2013

Joseph Knoll: How Selegiline [(-) – Deprenyl] Slows Brain Aging (2012)
Bentham e Books. (142 pages)
Reviewed by Joseph Knoll

INFORMATION ON CONTENTS: (-)-Deprenyl/Selegiline (D), a phenylethylamine, is a levomethamphetamine derivative with a propargyl group attached to the nitrogen atom. The substance is registered in 63 countries and marketed world-wide under more than 100 trade-names to treat Parkinson's disease (PD), Alzheimer's disease (AD) and major depressive disorder (MDD). D was developed in the early 1960s, in the midst of the golden era when, within less than 20 years, the development of new families of pharmacological agents led to the science of neuropsychopharmacology, which changed the principles of behavioral studies in a revolutionary manner and radically altered human attitudes toward derangements in psychic function. This book looks back to the theoretical foundation of the development of D (Introduction). Chapter 1 briefly summarizes the "First Research Period (1960-1978)," when the drug achieved its place in research and therapy as the first selective inhibitor of B-type monoamine oxidase (MAO). Chapter 2 describes the discovery of the catecholaminergic activity enhancer (CAE) effect of D and the development of R-(-)-1-(benzofuran-2-yl)-2-propylaminopentane (BPAP), currently the most potent selective enhancer substance which exerts this effect in femto-picomolar concentrations. Chapter 3 demonstrates that from weaning until sexual maturity increasing enhancer regulation operates in the catecholaminergic and serotonergic neurons. This mechanism is responsible for the exuberant physical strength and mental vigor in the uphill period of life in mammals. Sex hormones bring back the enhancer regulation to the pre-weaning level. This mechanism terminates developmental longevity and constitutes the foundation of the transition from adolescence to adulthood. Chapter 4 analyzes the antioxidant and neuroprotective effect of D and their relation to the enhancer effect. Chapter 5 analyzes the aging-related decline of dopaminergic activity and the reason why low dose of D slows brain aging and prolongs life. After analyzing the benefits of D in PD (Chapter 6), AD (Chapter 7) and MDD (Chapter 8), the unique quality of the enhancer substances compatible with lifelong preventive medication to slow brain aging is discussed (Chapter 9). Finally an Appendix summarizes the milestones in D research, extracting the most significant papers of the several thousand published on D.

AUTHOR'S STATEMENT: The age-related decay in the supply of the brain with β-phenethylamine (PEA), due to the progressive increase of MAO-B activity in the aging brain, and dopamine, due to the better than average decline of the dopaminergic neuronal activity during the post-developmental phase of life, are biochemical lesions of aging. The speed of deterioration of behavioral performances with the passing of time and longevity depends significantly on the pace of these lesions. D increases the supply of PEA and dopamine in the brain, and thereby, counteracts the aging process. Our first longevity study has proven that male rats maintained on lifelong D preserved their learning ability longer, lost their ability to ejaculate later, and lived longer than their placebo-treated peers. Due to their CAE effect, D and BPAP, maintain the activity of the catecholaminergic neuronal system on a higher activity level. None of the types of drugs used today to increase catecholaminergic and/or serotonergic neuronal activity in the brain share with D or BPAP

the enhancer effect. PEA-derived D and tryptamine-derived BPAP are synthetic analogues of physiological enhancer substances and act accordingly. The enhancer substances do not change the environmental milieu of the enhancer-sensitive neurons, when administered in the specific enhancer dose-range. They just change the lower excitability catecholaminergic neuron to one with better performance characteristics. In our second longevity study, we selected out of a population of 1,600 male rats, the 94 sexually lowest performing (LP) males and the 99 highest performing (HP) rats. We treated 44 LP rats with saline and 50 HP rats with D. The saline-treated LP rats lived 134.58 (2.29) weeks, their D-treated peers lived 152.54 (1.36) weeks, as long as the selected saline-treated HP rats (151.24) (1.36 weeks). Thus, maintenance on D transformed the low performing rats to high performing ones. Experimental and clinical studies with D strongly support the proposal that preventive administration of a synthetic enhancer substance during post-developmental life could significantly slow the unavoidable decay of behavioral performances with the passing of time, prolong life, and prevent or delay the onset of aging-related neurodegenerative diseases, such as PD and AD. Since D is, at present, the only worldwide registered CAE substance in humans, implementation of a properly designed clinical trial on healthy volunteers to measure its anti-aging effect by maintaining subjects on the substance from sexual maturity may be warranted.

September 5, 2013

Comments by Ildiko Miklya

In this book which Thomas Ban described in his Foreword as "the most impressive work, a tour de force, by one of the pioneers of neuropsychopharmacology," Joseph Knoll, the developer of (-)-deprenyl (D) (Selegiline) summarizes the development of his drug from the early 1960s up to the present. At the beginning, D became known world-wide as the first selective inhibitor of B-type monoamine oxidase (MAO) and was used in hundreds of laboratories as an important experimental tool in MAO research. D, described in thousands of papers, registered in 63 countries, and marketed under more than hundred trade names, is used to treat Parkinson's disease (PD), Alzheimer's disease (AD), and major depressive disorder (MDD). D is today the only available drug which, as a specific β-phenylethylamine (PEA)-derived catecholaminergic activity enhancer (CAE) substance via a previously unknown mechanism, facilitates dopaminergic and trace-aminergic activity in the brain. From this monograph, the reader will understand that PEA, a natural brain constituent is primarily a CAE substance. Because in a higher dose range, PEA is a strong releaser of catecholamines from their intra-neuronal pools, this effect concealed its physiological CAE effect, and this property remained undetected. Amphetamine and methamphetamine, the PEA derivatives with a long-lasting effect, act like their parent compound. In low concentrations, they are also CAE substances. The development of D, the only PEA-derivative which preserved its CAE effect but completely lost its catecholamine-releasing property, enabled the discovery of the enhancer regulation in catecholaminergic and serotonergic neurons. In a chapter of this book, the author clarifies how his finding that tryptamine is like PEA, a natural enhancer of the catecholaminergic

and serotonergic neurons, inspired him to develop between 1995 and 1999 R-(-)-1-(benzofuran-2yl)-2-propylaminopentane [(-)-BPAP], a tryptamine-derived selective enhancer substance which exerts this effect in femto-picomolar concentrations. In the last chapter, experimental evidence is presented for the importance of (-)-BPAP in the operation of enhancer regulation. Nevertheless, it seems to me that the main aim of the author with this book was to convince clinicians that time is ripe for a proper trial to test the anti-aging effect of preventive D treatment. Let me quote this message of the author with his own words: "It is the main aim of this book to piece facts and arguments together which all goes to show that selegiline, due to its CAE effect, slows the aging-related decay of the catecholaminergic brain engine, and this is why the maintenance on a low daily dose of selegiline helps to maintain physical and mental vigor in the latter decades of life, and is also a chance to significantly decrease the prevalence of PD and AD. To motivate clinicians to think the matter over inspired this work."

October 17, 2013

Reply to Ildiko Miklya by Joseph Knoll

I am thankful to Dr. Miklya that instead of going into the details that selegiline [(-)-deprenyl] became known world-wide and is still generally viewed and recorded as the first selective inhibitor of B-type monoamine oxidase (MAO), she pointed to the importance of the catecholaminergic activity enhancer (CAE) effect of (-)-deprenyl for future research. Her comment brings together how (-)-deprenyl, a b-phenylethylamine (PEA)-derivative, a selective CAE substance, allowed discovery that PEA is primarily a natural CAE substance, and how discovery of enhancer regulation led to the development of R-(-) – 1 – (benzofuran – 2 –yl) – 2 - propylaminopentane [(-)-BPAP], currently known to be the most potent and selective enhancer of catecholaminergic and serotonergic neurons. Since experimental and clinical studies strongly support the expectation that preventive (-) - deprenyl medication improves the quality and prolongs the duration of life and could prevent or delay the onset of aging-related neurodegenerative diseases, like Parkinson's and Alzheimer's, it is unfortunate that the implementation of a proper trial on healthy volunteers to measure the anti-aging effect of Selegiline has still not been undertaken. I am pleased that Dr. Miklya took notice of my statement that to motivate clinicians to consider this matter, inspired my work.

November 7, 2013

Comments by William M. Petrie

Dr. Joseph Knoll's new publication, "How Selegiline(-)-Deprenyl Slows Brain Aging," is

an interesting personal account of the development of (-)-deprenyl, from its theoretical background prior to 1950 to its emergence in the 1960s as an MAO inhibitor, and in Dr. Knoll's view, its most important effect as a catecholamine enhancer. His book pieces together the facts and arguments to describe this catecholamine enhancing effect of (-)-deprenyl, which is unrelated to its MAO-B inhibition.

Dr. Knoll describes a neuroprotective effect of (-)-deprenyl in a variety of paradigms, which he relates to the drug's effect on extending longevity in Wistar-Logan rats. These effects are seen in a low, non-MAOI dose, which prompts Dr. Knoll to suggest a role in slowing aging. (-)-Deprenyl accomplishes this through increasing the supply of phenylethylamine and dopamine in the brain. Male rats maintained on the agent for life enjoyed improved learning, later sexual activity and longer life. For those of us interested in treatment options in geriatric health and disease, the drug deserves serious reevaluation.

November 21, 2013

Reply to William M. Petrie by Joseph Knoll

I am thankful to Dr. Petrie that he focused on the unique catecholaminergic activity enhancer (CAE) effect of (-)-deprenyl, which is unrelated to MAO-B inhibition and explains why an enhancer substance, like (-)-deprenyl, improves cognition, attention, memory and reaction times, and brings about subjective feeling of increased vitality and energy.

Since, to motivate clinicians to consider this new line of (-)-deprenyl research was my main aim when writing this book, I am especially pleased with Dr. Petrie's view: "For those of us interested in treatment options in geriatric health and disease, the drug deserves serious reevaluation."

December 26, 2013

BIOGRAPHIES, AUTOBIOGRAPHIES AND SELECTED WRITINGS OF NEUROPSYCHOPHARMACOLOGISTS

Introduction by Barry Blackwell

I am writing to introduce myself as the person responsible for the project "Biographies" (Project 9) on our website.

Instructions for submitting new material are given below with my e-mail address and phone number. Comments you wish to post on existing material should be submitted to inhn@inhn.org.

In "Biographies," we post information on Autobiographies, Memoirs, Biographies, Collected or Selected Writings about a particular scientist's contributions in the preceding sixty years during the development of neuropsychopharmacology. Submissions may be made either by the author or a member of INHN to the program coordinator (Barry Blackwell: blackwellbarry@hotmail.com). In addition to the author's own description of their work (see below) they are invited to include a copy of book or text to be available for review by a member of INHN selected by the coordinator or who may volunteer to write one.

The author's own review should be in two parts; a synopsis of the format and content of the submission as well as a commentary on the contents. An independent reviewer may follow this format or choose their own. There are no specifications about the length of a review which must be submitted as a Word document in Times New Roman, size 12 type, 1.5 spacing and adjusted on the right.

For questions or concerns please communicate with me by e-mail (above) or phone at 414-940-0844. I look forward to hearing from authors and members. Books may be forwarded to me at: 1800 North Prospect Avenue, Apt #15C, Milwaukee, Wisconsin 53202.

Please join me in making "Biographies" a success.

Nov. 21, 2013

Barry Blackwell: Bits and Pieces of a Psychiatrist's Life (2012)
XLibris Corporation. (606 pages)
Reviewed by Barry Blackwell

Format and Contents:
This is a memoir modeled after Mark Twain's belief it is best to hit the highlights and omit the tedious interludes of everyday life, an idea he never fulfilled. As such it has an unusual, perhaps unique, format comprised of 31 major themes or PIECES, divided into Preparation, Professional and Personal Life. The 31 PIECES consist of 260 bits of varying length made up of short stories, essays, poems, medical articles and editorials, some previously published in professional or lay journals and books. They include 100 poems that mingle sonnets, haiku, limericks, classical rhyme and meter with contemporary free forms that occasionally mimic the subject – a crumbling Egyptian pyramid; Midwest Flight 105 crashing on the page. The book's format invites the reader to nibble and not gobble its contents while its 608 pages seek to satisfy the readers head, heart, soul and funny bone.

Subject Matter:
PART ONE: PREPARATION
Piece 1. Literary Considerations. The book begins by explaining the format, describing the author's muse and its midlife evolution from scientific to creative writing.

Piece 2. The Blackwell Name. Next comes a genealogy, a toponymic name first mentioned as a village in William the Conqueror's Doomsday Book (1066). The name is traced from that origin through colorful ancestors from different lineages in Britain and America, dating back to before the Mayflower and leading to a 19th century migrant dynasty that includes the first woman physician in the world, Elizabeth Blackwell, and the first woman pastor in America, Nettie Brown Blackwell who authored a book challenging Darwin's assertion that the male was superior to the female of the species. These two women's spouses and siblings were deeply involved in the emancipation movements for slaves and women.

Piece 3. India. The author's life story begins in detail at age four, in India, during World War II until the Japanese conquered Burma and bombed Calcutta leading to the repatriation of women and children by convoy to England, dodging U-boats only to be greeted by German rockets.

Piece 4. Boarding School. Amebic dysentery in India before antibiotics and the blitz in Britain meant that from age 5 to 18 was spent in Indian and British boarding schools, a safe distance from germs and bombs. The rewards and rigors of this life shaped the author's personality.

Piece 5. In Time of War. Graduation from high school led to drafting into the Royal Army Medical Corps during the Korean War. Trained as a sanitary inspector and equipped with a motorcycle, the author was posted to Salisbury Plain, close by Stonehenge. Subsequently, an officer in a reserve field ambulance, he served in every rank in the British

Army from private to major. This Piece also records the family's service and sacrifice in two World Wars with reflections on the draft, the 'right to bear arms' and a serio-comic reflection on the relative success of Brits and Yanks at disposing of Presidents and Royalty.

Piece 6. Cambridge University. From blue collar origins, the first family member to go to university began in profligate style by playing rugby, rowing and carousing before graduating with a mediocre degree. A decade later, the prodigal returned, among the first in his class to obtain a doctoral degree (in pharmacology).

Piece 7. Guy's Hospital. Medical student and captain of the oldest rugby club in the world. Becoming serious about patient care, deciding on psychiatry (paying a price) and publishing a first article (Why Patient's Come to the Emergency Room) in the Lancet as a first year intern. Reflections of the synchronicity between the author's career trajectory and the evolving field of psychopharmacology.

Piece 8. The Maudsley Hospital. Six months neurology training was followed by psychiatry at the Maudsley Hospital where, as a first year resident, aged 28, the author discovered and described the life threatening interaction of cheese and the MAO Inhibitors, published in the Lancet. This led to a two year fellowship in animal (rats and cats) and human pharmacology, explaining the mechanism of action and variables involved. Residency included multiple publications on a variety of topics including a pioneer effectiveness study on the use of MAOIs and a critical controversial review and study of lithium prophylaxis. Anonymous annotations and leading articles on contemporary psychiatric topics were commissioned by the Lancet.

PART TWO: PROFESSIONAL

Piece 9. Family Practice. Too clumsy to be an animal pharmacologist, more interested in people and reluctant to relinquish the breadth of medicine, the author became the junior partner in a suburban London family practice. He continued in research by collaborating with David Goldberg (a contemporary at the Maudsley) on the epidemiology of mental illness in primary care. They used and standardized David's General Health Questionnaire (GHQ), the first instrument to identify mental illness in primary care, publishing the findings in the British Medical Journal. Together with the time constraints of this type of work, came a revived preference for the depth and research opportunities of psychiatry, which always co-habits with plenty of medicine.

Piece 10. America. Recruited to be the Director of Psychotropic Drug Research for a pharmaceutical company in Cincinnati, Ohio, in 1968, at age 34, the author, his wife and three children migrated to America. This important Piece summarizes the sweeping cultural, political, economic and scientific changes that took place in the next 44 years (1968-2012) that profoundly influenced professional life, including the pharmaceutical industry, psychopharmacology, the practice of psychiatry, health care, academic medicine and medical education. The Bits in this Piece describe a long delayed transition from immigrant to citizen, issues with assimilation, the ubiquitous influence of growing

economic greed and income disparity on the practice of medicine, as well as political gridlock and the constitutional flaws that enable it. All of these have shaped the career success and failures related in ensuing Pieces.

Piece 11. The Pharmaceutical Industry. A two year stint in the research department of a pharmaceutical company provided exposure to the burgeoning industry, the opportunity to meet leading investigators in the field and to teach medical students and residents one day a week in the strongly psychoanalytic University of Cincinnati Department of Psychiatry. Better still, it allowed time to pursue research interests and mentoring with Frank Ayd, a consultant, resulting in co-editing "Discoveries in Biological Psychiatry," documenting first person accounts of all the major drug discoveries by the pioneers who made them and leading to induction into the ACNP (1970).

Piece 12. Psychopharmacology: Then and Now. This important Piece includes Bits that cover a fluctuating forty year involvement in drug research, the education of students and residents, the evolution of the ACNP and Big Pharma, including innovations and disappointments. These are illustrated with in-depth essays on key events and selected scientists, concluding with working under Tom Ban as a volume editor in the Oral History of Neuropsychopharmacolgy (OHP) in time for the fiftieth anniversary of the ACNP (2011).

Piece 13. Psychosomatic Medicine. Abiding interest in the interface of medicine and psychiatry was consummated with a return to academic medicine at the University of Cincinnati including appointments in Psychiatry and Pharmacology, as well as Director of the Psychosomatic Unit. With the collaboration of talented nurses and creative psychologists, we developed a novel approach to "illness behavior" that challenged the psychoanalytic model and had implications for the evolving field of Behavioral Medicine and Chronic Pain Management.

Piece 14. Medical Education. This Piece covers a twenty year time span (1974-1994) as Chair of Psychiatry at two medical schools with adjunctive appointments in Pharmacology, Medicine and Behavioral Medicine. Wright State University in Dayton, Ohio, (1974-1980) was a brand new medical school, one of over 30 new schools in a nation-wide attempt to train "humanistic" primary care physicians willing to work in underserved areas. Bits in this Piece record the multidisciplinary attempts at innovative curriculum as well as the ultimate failure of the project for reasons not widely recognized in the contemporary attempt to achieve similar goals. The University of Wisconsin Milwaukee Clinical Campus (1980-1994) was an equally ambitious attempt to found an urban campus to train students and residents for the parent program in Madison with the outcome described in Piece 16.

Piece 15. Compliance. This short piece of only three Bits reflects a career long interest in why people often fail to follow medical advice and how to deal with the problem by defining its dynamics and building a therapeutic alliance.

Piece 16. Milwaukee. This covers the time from helping to found the Milwaukee Campus

(1980) until retirement (1998). It documents a period of profound change in health care, during which five out of six inner city hospitals went bankrupt, sometimes merged and all eventually closed. The Bits include state-wide research on medical residents' struggles to adopt the physician role, homelessness and mental illness (including a sabbatical at NIMH on a National Task Force), the evolution of the AIDS epidemic, the birth and death of managed care, community activities and the eventual demise of the academic program in psychiatry, later with the entire urban campus, contributed to by the economic management policies of a "not for profit" corporation. ("No Margin, No Mission").

Piece 17. The Bread and Butter of Psychiatry. This is a collection of five short stories and six poems portraying the nuances of a psychiatrist's role in combining talk therapy with medication, at a time when the profession feels under siege from federal failure to implement guidelines for parity of medical and mental health care, allowing insurance companies to deny and erode treatment of this kind.

Piece 18. Spiritual Pilgrimage. This tells of a four year post retirement involvement in a Catholic Seminary, studying religion and philosophy in a Master's program along with male seminarians and middle aged women, pursuing the hope of second careers in parishes facing the priest shortage. It employs poetry and a term paper on the "Virgin Birth" to portray the counterpoint between religious faith and scientific skepticism, leading to the author's conclusion he is "spiritually handicapped".

Piece 19. Good Deeds. In the time before and after dropping out of the seminary (which soon closed due to impending bankruptcy brought on by the pedophile crisis), the author rescinded the decision to retire from his profession and embarked on four projects that employed a psychiatric background. These were a return to work as the sole psychiatrist staffing four mental health clinics run by Catholic Charities; founding "Faith in Recovery", a not for profit organization to develop educational and support groups for people and families, dealing with mental illness in faith communities; as a mentor for fifteen years to two men suffering from bipolar disorder with recurrent psychotic episodes and finally as the only psychiatrist in a women's prison looking after the half of that population with a mental illness (2008-2012). Generous remuneration provided help to pay for his son's education as a future family physician.

PART THREE: PERSONAL

Pieces 20 – 31. These final 12 Pieces are devoted to aspects of personal life with bits that include poems, essays and amusing anecdotes. They cover marriage, parenting, divorce, sex, domesticity, hobbies, pets, travel, beauty, ageing and finally life in a retirement community. Some reflect on the interplay of professional and personal life, others are ubiquitous to the human condition, viewed through a psychiatrist's eyes.

EPILOGUE

Apart from the gratification of examining one's own life, a critical question for the author of a memoir is "for whom is it intended"? Other than friends and family, perhaps medical students contemplating psychiatry, residents uncertain of what may lie ahead, neuroscience graduates anxious about the future of the field, fellow mental health professionals facing

similar challenges, patients who sit on the other side of the desk or lie on the couch and finally, anyone whose career has been molded by the unpredictable, unanticipated ups and downs of life.

For myself, I hope two things are clear to the reader; my career has been devoted to helping those most in need and it was driven by an intense curiosity about the human condition. My entire body of research and writing (over 200 publications and 4 books) was undertaken to understand and explain to others what I was doing at the time. My salary and the fun of doing it was all it took. None of this was funded by Big Pharma, Foundations or the Federal Government. Almost all of the research was collaborative with medical students, medical and psychiatric residents, nurses, psychologists, patients, pharmacists, graduate students, pharmacologists, statisticians, internists, an anthropologist, ethicist, sociologist, meditation guru and two drug company detail men (whose careers were not enhanced!). Best of all, much of it was published in leading European and American journals, now buried in long forgotten archives.

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