Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Collated 26

Profiles of clinicians and researchers who were instrumental for the birth and/or contributed to the development of neuropsychopharmacology

Julius Axelrod, Frank Ayd, Frank Berger, Hans Berger and Hermann Blaschko

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Julius Axelrod by Irwin J. Kopin

Julius Axelrod (30 May 1912 – 29 December 2004) shared the 1970 Nobel Prize with Ulf von Euler and Bernard Katz for his discoveries related to catecholamine metabolism and termination of the actions of norepinephrine by reuptake into the nerve terminals from which it was released. In his Nobel lecture (Axelrod 1972), Julie cited over 50 of his papers that elucidated the regulation of norepinephrine biosynthesis, storage, release, metabolism, and inactivation in brain, as well as at peripheral sympathetic nerve terminals. Equally important, he showed that drugs, such as amphetamine, cocaine and antidepressants affect norepinephrine reuptake. This means of

terminating actions of neurotransmitters has been verified for other neurotransmitters: serotonin, dopamine, glutamate and gamma-aminobutyric acid (GABA), providing an important target for drug development, particularly “serotonin-selective reuptake inhibitors” (SSRIs), e.g. fluoxetine (Prozac).

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

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November 6, 2014

Frank J. Ayd, Jr. by Barry Blackwell

Frank Ayd was born in Baltimore, in 1920, where he spent spent his entire life in private practice. Among the pioneer psychopharmacologists, he was a founding member of the American College of Neuropsychopharmacology (ACNP) and like his peers in in 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-coedited "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 now part of the Czech Republic and received his M.D., in in 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 of 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

Hans Berger by Antonio E. Nardi

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

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

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

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June 26, 2014

Hermann Blaschko by Joseph Knoll

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

In 1933, Blaschko moved from Germany to England and on the encouragement of Professor Joseph Barcroft, began with his studies on adrenaline metabolism at the Institute of Physiology in Cambridge. This led to his discovery that it was the same enzyme, he referred to as amine oxidase, and not substrate specific enzymes, as many believed at the time, which

metabolized tyramine, dopamine, noradrenaline, adrenaline and aliphatic amines, in general (Blaschko, Richter and Schlossman 1937a; Hare 1928). They also demonstrated the presence of the enzyme in the liver (Blaschko, Richter and Schlossman 1937b). In 1938, after Zeller's separation of diamine oxidase from amine oxidase, the name of Blaschko's enzyme was changed to monoamine oxidase to indicate that its function is restricted to the oxidative deamination of monoamines. Extending his research from the metabolism of adrenaline to the synthesis of catecholamines, in 1939, Blaschko described l-DOPA decarboxylase and discovered that it is the enzyme involved in the decarboxylation of levodopa to dopamine. Furthermore, by the mid-1940s, Blaschko recognized that tyrosine converts into levodopa, levodopa into dopamine, dopamine into noradrenaline and noradrenaline into adrenaline (Blaschko 1952).

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

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

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July 17, 2014

April 9, 2020