Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Collated 27

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

Charles Bradley, Philip B. Bradley, Bernard B. Brodie, John Cade and John Delay

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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 post-pneumoencephalography 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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Philip B. Bradley by Marina Dyskant Mochovitch

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

In 1951, while still a postgraduate student, Bradley joined Joel Elkes's newly founded Department of Experimental Psychiatry at the University, and in the early 1950s he developed a technique for studying electrical activity in the brain in conscious animals (Bradley 1952; Bradley and Elkes 1953a). With the employment of the new technique, he studied the effects of several centrally acting drugs on the electrical activity of conscious cat (Bradley and Elkes 1954). His findings with atropine and physostigmine provided further substantiation of Abraham Wikler's (1952) finding of a dissociation between the effect of anticholinergic drugs, such as atropine, on

behavior and on the electroencephalogram (EEG) in dog (Bradley and Elkes 1953b). This "lack of correlation" was not present with the other drugs they studied, such as amphetamine, lysergic acid diethylamide (LSD) and chlorpromazine (Bradley 2000; Bradley and Elkes 1953b).

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

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

By the 1980s, Bradley research shifted to the study of receptors and his findings with the employment of microiontophoresis, reported in 1984 and 1986, contributed to the classification of opioid and serotonin receptors, respectively (Bradley and Brooks 1984; Bradley et al 1986; Dhawan et al 1996). One year later, in 1987, Bradley published his *Introduction to Neuropharmacology*.

Philip Bradley died in 2009.

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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 spectrophotofluorometer 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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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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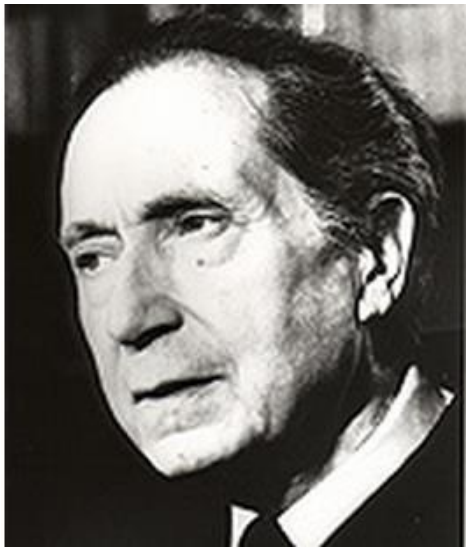
Jean Delay by Driss Moussaoui



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 five 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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