

## **Barry Blackwell: Pioneers and Controversies in Psychopharmacology**

### **Chapter 8: Nathan (“Nate”) Kline and the Monoamine Oxidase Inhibitors**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### **A Personal Reflection**

I first met Nate as his co-host with Frank Ayd at the Baltimore Conference in 1970 where he received the Taylor Manor Award for his discovery of the first anti-depressant. I was puzzled by the title chosen for his talk and looked up the meaning of *Picaresque* in my dictionary. According to OED it is “An episodic style of fiction dealing with the adventures of a rough and dishonest but appealing hero.” From the French *picaro* for rogue.

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

*“Research Scientists are wide-eyed manipulators. When an observant brat discovers for the first time that he can push buttons, turn faucets, open doors, dial phone numbers and exploit his parents, he is astonished and delighted at his ability to uncover and control the physical and social environment. Some of us never recover.*

*“Until fairly recent times, the researcher was paid substantially less than those earning an honest living. In many cases this was because he felt guilty taking any money at all for doing something he so much enjoyed. This position is not as ridiculous as it sounds since the Royal Society in England was formed by wealthy gentlemen for the sheer pleasure of carrying out experiments. We are not only granted these extra-ordinary prerogatives, but equipment and supplies are provided plus a salary to boot.*

*“Few joys equal the realization of fantasies in which a successful researcher indulges, few joys equal the fantasies themselves. Imagine being able to spend a whole lifetime poking around to see what will happen. The fact that the questioning and answering is sophisticated and according to certain rules doesn't change the basic activity. For those of a mechanical bent it is possible not only to keep on purchasing the most intriguing Erector Sets but even to have one built to specifications.*

*“If you like to sleep late and work in the evening, no one really objects and, if the work gets a bit dull, it’s always justified to visit a laboratory (located in some seasonal climate) that is doing the same sort of activity. If you climb high enough up the hierarchy, you can then direct others to carry out all sorts of interesting things you don’t have time to do yourself. One of the sweetest smells in the world, that of fresh galley proofs, is an added attraction; the absolute power to, subtract from, and alter an article that is to become part of the world’s ‘permanent’ literature guarantees permanent immortality.*

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

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

Use of the collective pronoun in the final paragraph suggests Nate might have believed he was speaking on behalf of the 19 other pioneers being honored. I do not recall any comments made by them nor did I, as a very junior participant, speak up. But a few months later I did have an opportunity to challenge Nate when he published a review paper in the Journal of the American Psychiatric Association about lithium, calling it “The 20-year Cinderella of Psychopharmacology.” In a letter to the editor I chided Nate, suggesting that the title was appropriate for a topic which had begun to resemble a Fairy Tale. This sparked an entertaining correspondence in which no egos were badly damaged. I was 36-years-old at the time.

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

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