

Pioneers in Psychopharmacology

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Introduction

In pursuing the history of any field, even one in which many of the main exponents are still alive, it can be very difficult to establish facts and priorities. Detailed scrutiny of the events leading to the recognition of the antidepressant effects of iproniazid, in which Nathan Kline was involved, may fail to establish the exact sequence of events or the sources of inspiration for a discovery (Healy, 1997). Quite apart from the 'facts' behind the antidepressant story, Kline's role in the story beautifully illustrates one of the sayings of Francis Galton, to the effect that in history the driving force may not lie with the first discoverer of a new scientific fact, but rather with the individual who was the first to persuade the world of the importance of a particular discovery. This maxim applies with some force to the three individuals who have been honoured by the CINP in 1998 for their pioneering roles in psychopharmacology – Pierre Deniker, Joel Elkes and Heinz Lehmann* whose contributions to the field have included original research and also key initiatives to capture the central ground of academic and public opinion for the new science. They have been science makers rather than just scientists.

Pierre Deniker

One of the striking things about the field of neuropsychopharmacology is that no Nobel Prizes have ever been awarded for some of the major clinical breakthroughs; in the case of prefrontal leucotomy, indeed it almost seems as though the prize was awarded for what retrospectively has appeared to be psychiatry's greatest failure. The foundational discovery in neuropsychopharmacology was clearly the establishment of the clinical utility of chlorpromazine. There is little question that Pierre Deniker and Jean Delay were responsible for this

discovery (Delay et al., 1952). They were responsible for much more than this, however. While the credit for the discovery of the antipsychotic effects of reserpine is given to Kline, Deniker and colleagues were in print with equally convincing findings on the effects of reserpine within a month, so that it must have been a close call as to who made the initial discovery (Delay et al., 1954). Based on a comparability between the psychotropic effects of chlorpromazine and reserpine, Deniker and Delay went on to delineate the concept of a neuroleptic and their conceptual formulations in this area have dominated the field for 40 years (Deniker, 1970, 1983).

As important as these discoveries and conceptual developments were, the efforts of Delay and Deniker to convene a series of meetings, starting with one which brought investigators from around the world to Paris in 1955, to share experiences with chlorpromazine and debate the significance of the development, were at least as important. The Paris Colloquium was the first international psychopharmacology meeting and, in convening it, Deniker and Delay did much to create the momentum that gave rise to the field that we now call neuropsychopharmacology.

Pierre Deniker has been honoured with many awards, including a Lasker award in 1957. That he did not receive a Nobel Prize is probably due to the complexities of discovery that the rich history of chlorpromazine exemplifies. Henri Laborit appears to have been the first to recognize that there were distinctive psychotropic effects to the phenothiazine antihistamines, emerging from the laboratories of Rhône-Poulenc in the late 1940s, and perhaps the first to recognize that, among these agents, chlorpromazine in particular had significant properties (Swazey, 1974). However, recognizing such effects is somewhat different from establishing their clinical utility and, in particular, persuading the world of the importance of the effects. Hearing of the anaesthetic effects of chlorpromazine from his brother-in-law, Deniker obtained from Rhône-Poulenc supplies of the drug, which he and Delay went on to evaluate for its clinical usefulness. In so doing, they established the distinctive effects in clinical settings of chlorpromazine that have been the basis for the use of neuroleptics ever since.

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* Editor's Note: Pierre Deniker, Joel Elkes and Heinz Lehmann were jointly awarded the Pioneers in Psychopharmacology Award at the XX1st CINP Congress in Glasgow in July 1998.

Prior to convening the Paris Colloquium along with Jean Delay in 1955, Deniker had travelled several times to the United States to persuade clinicians there of the importance of the findings, thereby laying the basis for the introduction of psychopharmacology to the USA. He subsequently played a distinguished role in the CINP, becoming its president in 1972. He has written a series of key articles, chapters and books, outlining the history of neuroleptics, the discovery of the extrapyramidal side effects of these agents, the conceptual underpinning for their clinical use and the shape of modern psychiatric practice that the neuroleptics introduced (Deniker, 1970, 1983).

Deniker, in addition, was also a sensitive and astute clinician. Early in the evolution of chlorpromazine, he grasped that, while the drug produced a neuroleptic effect which was visible at higher doses, the behavioural toxicity that could be caused by these higher doses was something to be avoided. This meant that while others around the world were moving to ever higher and later to megadose, regimes of neuroleptics, clinicians in Paris, under the influence of Deniker, were much less likely to do so. When Steck came to Paris at the end of 1954, after chlorpromazine had already been in use for 3 years, he reported on novel extrapyramidal side-effects of both chlorpromazine and reserpine and on drug-induced akathisia, only to find that these effects were all but unknown to Paris clinicians. Owing to the sensitivity of their treatment approaches, Parisian psychiatrists had managed to avoid many of the problems that were to tarnish the reputation of neuroleptic treatments in later years.

To honour Pierre Deniker is also to recognize the contributions of Jean Delay, Jean Thuillier, Pierre Pichot, Thérèse Lempérière and a host of others, who made Paris one of the first centres of international neuropsychopharmacology.

Joel Elkes

Joel Elkes came to the United Kingdom in 1931 from Lithuania. He trained in medicine in St. Mary's Hospital London and showed an early interest in research on the nervous system. He moved to the University of Birmingham after qualification. His early research work on the structure of myelin parallels that of Francis Schmitt. In the early 1950s, Joel Elkes became a leading exponent of the view that neurochemical transmission was important in the central nervous system, a view that he and Phillip Bradley developed into a distinctively modern vision of neurotransmitters and receptors before the end of the 1950s (Bradley and Elkes, 1958). At a series of meetings Elkes, in the face of scepticism and disbelief from some of the most eminent neuroscientists of his day, outlined this

new view of brain functioning. The ideas, involving regional neurochemistry, are central to modern neuropsychopharmacology, but were so different from anything that had gone before as to be almost incomprehensible to many senior scientists of the day.

Joel Elkes became head of the Department of Experimental Psychiatry in Birmingham, the first such department of its kind in the world. He was a professor of psychiatry, when there were only three other chairs of psychiatry in the United Kingdom. He was the only non-psychiatrist to hold a chair in psychiatry in the United Kingdom then or since, and his has been the only chair of experimental psychiatry in Britain. He established a department whose range of research interests extended across clinical trials, neuroanatomy, neurophysiology, neurochemistry and animal behaviour. It was in this department that the first blind controlled trial of chlorpromazine was carried out in 1953–54 (Elkes and Elkes, 1954). The only comparable department in the Western world at that time was Jean Delay's department in Paris. The links between the two departments were close. Elkes drew together a cohort of researchers, including Philip Bradley, Brian Key, Michael Chance, Charmian Elkes and Willy Mayer-Gross, whose contributions were seminal to the establishment of modern neuropsychopharmacology (Elkes 1970, 1998a, b).

Elkes' achievements were recognized in the United States by Seymour Kety and others, who lured him across the Atlantic to the NIMH Institute at St. Elizabeth's Hospital in Washington. He was subsequently appointed to the Chairmanship in Psychiatry at Johns Hopkins University. In both of these settings, Elkes again established centres of multi-disciplinary psychopharmacology, embracing all the avenues of research in the field, from clinical studies to detailed neurophysiological and neurochemical technologies. The names of those who worked or trained with him read like a *Who's Who* of modern American neuropsychopharmacology, including Floyd Bloom, Solomon Snyder, Steve Szara, Ross Baldessarini, Joe Brady, Lino Covi, Joe Coyle, Len Derogatis, Daniel van Kammen, Uhli Uhlenluth, Herbert Weingartner and many others. In honouring Joel Elkes, therefore, the CINP is also honouring the contributions of many others, including Philip Bradley, Charmian Elkes, Willy Mayer-Gross from the early years, as well as Floyd Bloom, Solomon Snyder and others from later years.

As with Pierre Deniker, Joel Elkes' contributions lay not only in the field of scientific achievement but also in the broader area of persuading the world of the importance of the new discoveries. He was involved in the foundation of the International Symposia for Neurochemistry, the International Brain Research Organization and the American College of Neuropsychopharmacology, of

which he was elected the first president in 1961. He played a part in founding the first journal dedicated to psychopharmacology ('Psychopharmacologia') and he convened the first World Health Organization Study Group on Psychoactive Drugs in 1958. In the early years of psychopharmacology, he was one of the most eloquent advocates of the importance of the new discipline. Even in his eighties, as a speaker at international meetings, he has retained a unique capacity to still a noisy and restless auditorium and make people aware that their work involves more than the routine drudgery of science – that they were also working on issues of fundamental concern to humanity. He can deliver a unique message to that place in the listener's heart where Meaning and Hope meet.

Heinz Lehmann

Heinz Lehmann was one of many refugees from Germany who came to North America in the years immediately preceding World War II. He was one of the first to use chlorpromazine in North America and the first to publish on its efficacy, for which he won a Lasker award in 1957 (Lehmann and Hanrahan, 1954). He was one of the first to recognize that this agent was in some sense anti-psychotic rather than simply a tranquillizer, and one of the first to publish this recognition. He was the first in North America to use imipramine, recognizing, when few others did, the importance of the reports of its efficacy from Kuhn in Switzerland (Lehmann et al., 1958).

Lehmann worked closely with other pioneering clinical psychopharmacologists in North America, such as Nathan Kline, Tom Ban, Fritz Freyhan, Joel Elkes and others. He was one of an influential group of European psychiatrists who gave intellectual underpinning to the emerging discipline of clinical psychopharmacology in the United States during the mid- to late 1950s, when the centres of academic excellence were dominated by psychoanalysts. He participated in the establishment of the Psychopharmacology Service Center, the Early Clinical Drug Evaluation Unit and the American College of Neuropsychopharmacology. Along with Tom Ban and others, he helped establish the methodology for evaluating new psychotropic agents by means of a comprehensive battery of preclinical and clinical assessments. His group was the first to report on many new agents from trimipramine to trazodone, defining distinctive profiles of many of these.

At a time when biological therapeutics were viewed with considerable suspicion by the population at large and psychotherapy was viewed as all but the only ethical treatment for nervous disorders, Lehmann embodied humanity, wisdom and charm in a manner that disarmed opponents. At the height of the student unrest of the late

1960s, when several senior Professors of Psychiatry had been forced to resign, Lehmann engaged in public debate with Herbert Marcuse at McGill University on the question of whether psychiatry was an instrument of oppression. In the course of his presentation, he had cream sprayed over his face. Licking it away, he continued without a break, won that debate and in so doing helped turn the tide in a larger crisis. At much the same time, as President of the CINP, he took the organization's bi-annual meeting to a Prague occupied by Russian tanks, in a move that was of considerable importance to both the CINP and neuroscience within Eastern Europe.

Heinz Lehmann, however, was no simple biological psychiatrist. He was and remains a man committed to psychopharmacotherapy and to the possibilities for more effective therapy that were opened up by modern psychotropic drugs (Lehmann, 1996). He embraced and continues to endorse behavioural and analytic approaches to mental disturbances used, in conjunction with psychotropic interventions, in a manner that transcends parochialism and partisanship.

Coda

Neuropsychopharmacology is a discipline that reaches into the heart of human identity. It is a field of endeavour that should transcend political and commercial interests; a science to which humanity can look to with hope for relief from suffering in the first instance, but also with hope for a liberation of wider human possibilities. In honouring Pierre Deniker, Joel Elkes and Heinz Lehmann, the CINP has chosen figures who speak as much to the future of the discipline as to its past.

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