Pioneers in Psychopharmacology II

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Introduction

In 1998, the first Pioneers in Psychopharmacology Awards were presented at the XXIst CINP Meeting in Glasgow to Pierre Deniker, Joel Elkes and Heinz Lehmann. These three individuals had distinguished themselves and Psychopharmacology not only by the quality of their work but also by their ability to persuade others of the importance of the new field that was opening up (Healy, 1998). At the XXIInd CINP Meeting in Brussels in July 2000, Paul Janssen, Mogens Schou and Alec Coppen became the second group to receive such awards for distinguished achievement.

Paul Janssen

Paul Janssen came from a background in both pharmaceuticals and medicine. His father had a pharmaceutical company, although this was not a research-based enterprise. After training in medicine and a spell in national service, Janssen returned to the family company and established a laboratory there. The aim was to produce patentable compounds, which would be sold under licence to other companies. The company quickly developed a presence in a range of treatment areas from analgesics and psychotropics to anti-diarrhoeals and anti-fungal agents. Altogether, during the subsequent 45 years, over 100 compounds were patented; at one point five of these compounds were in the World Health Organization’s list of essential drugs.

In 1958, research on opioids led to the discovery of the butyrophenones, of which haloperidol was the first to become well known. Janssen had the new compound tested by some of the most eminent clinical investigators in Europe, each blind to the involvement of the others (Janssen, 1998). He convened a meeting of the investigating teams in Beerse in 1959 to give an account of their experiences (Beerse Symposium, 1960). The papers from this meeting clearly map out almost everything of importance regarding haloperidol, from its actions on Tourette Syndrome to its effect on delirious and psychotic states, especially those involving hallucinations. Haloperidol went on to become the best-selling neuroleptic worldwide.

The discovery of haloperidol marked a decisive event in the history of the neuroleptics. Senior figures in the field were still struggling to define what it was about this new group of drugs that produced benefits. The emergence of an agent that managed psychoses without inducing sedation and which provoked extra-pyramidal effects at very low doses decisively favoured the concept of a neuroleptic first outlined several years previously by Delay and Deniker (see Deniker, 1975, 1998).

The development of haloperidol also mandated the use of amphetamine models as a screening test for the development of neuroleptics. Not content with this, however, Janssen moved on to seek compounds that would dually block the effects of both amphetamine and tryptamine. In 1961 this gave rise to dipiperone (pipamperone), arguably the first rationally designed serotonergic–dopaminergic antagonist (SDA). Clinical trials conducted in the mid-1960s demonstrated the benefits of the new compound but the clinical world was not ready for this kind of development (Janssen, 1998).

Later interest in serotonin receptors led the Janssen company to be at the forefront of the development of ligands for and exploration of this group of receptors. These efforts resulted in compounds such as ritanserin and ketanserin and an elucidation of the serotonergic component to neuroendocrine secretion, sleep architecture, blood pressure and a range of other functions. Similar development work in recent years has given rise to a range of agents with effects on G-proteins that permit us to establish the functional role of these proteins in the cellular economy (Leysen and Janssen, 1987).
The development of ligands for receptors such as the 5-HT₂ receptor, also permitted the development of more potent SDA agents of which the best known, risperidone, was first developed in 1984. Along with the resurrection of clozapine, the emergence of risperidone created what is now known as a group of atypical antipsychotics.

These achievements in the antipsychotic field put Paul Janssen in a select group of medicinal chemists who have had more than one genuinely novel compound reach clinical practice. Janssen’s compounds not only made it to clinical practice but also became market leaders. However, in addition to trail-blazing in psychopharmacology, Janssen’s genius lies in the fact that psychopharmacology was only one string to his bow. A series of azoles, anti-diarrhoeals, analgesics, anaesthetic agents and other compounds have emerged from his laboratory, many achieving first-choice status in their respective fields. This range of discoveries makes Janssen a true giant in modern medicinal chemistry as well as a pioneer in psychopharmacology.

Mogens Schou

Mogens Schou’s involvement with the development of lithium is perhaps the most singular story in psychopharmacology. Lithium, an agent for which passable evidence of psychotropic benefits had been established as early as the nineteenth century, had fallen from grace in both psychiatry and medicine in 1949, when John Cade rediscovered its psychotropic properties (Johnson, 1984). It is doubtful, however, if Cade’s original work would have had much impact without Schou. A number of groups of French psychiatrists had been stimulated by Cade’s report into trying lithium only to drop it again. Cade himself moved on to other elements and never displayed the tenacity of purpose needed to bring lithium to the forefront of psychiatric therapeutics. This role fell to Schou.

In working on lithium, Schou conducted the first randomized placebo-controlled trial (RCT) in psychiatry that had a positive outcome. This study demonstrated lithium’s benefits conclusively (Schou et al., 1954). The lack of interest in both Schou’s approach to evaluating therapeutic efficacy and his interest in lithium was demonstrated when the editor of the *British Journal of Psychiatry*, Elliott Slater, suggested that Schou take his publication elsewhere. The delay caused by this compromised Schou’s claims for priority on the use of RCTs in psychiatry (Schou, 1998).

Schou subsequently became convinced that lithium had prophylactic effects to ward off further episodes of mania or depression (Baastrup and Schou, 1967, 1968). These claims, put forward with Paul Christian Baastrup, provoked a reaction from investigators at the Institute of Psychiatry, notably Michael Shepherd and Barry Blackwell which led to a protracted controversy. While this controversy appears to have been extremely distressing for all parties at the time, it clarified a number of significant methodological points that have since been incorporated in clinical trial designs and have coloured the general approach to the evaluation of psychotropic drugs (Angst et al., 1970; Baastrup et al., 1970).

From its first use in the 1950s up to the 1990s Schou spent his time clarifying aspects of the pharmacokinetics and toxicology of lithium, aiming to ensure its optimal and safest usage. Work on plasma lithium levels led to the establishment of dose ranges and to the successive refinements of recommendations for optimal dosing.

Work on the renal excretion of lithium and on its impact on the kidney as well as work on a range of other organ systems mean that as much if not more is known about lithium than about any other psychotropic drug.

This is an extraordinary achievement given that lithium is a non-patentable metal. Schou in the course of his career has achieved the equivalent impact in dissemination of trial results, as well as in the monitoring and overcoming of hazards of therapy, as might have been achieved by a pharmaceutical corporation. He has used research to ensure a market for the compound. He has maintained its profile in the face of efforts by pharmaceutical companies to develop a range of other more profitable mood-stabilizing agents to substitute for it. And he has maintained his efforts into his late eighties. Such steadfastness of purpose has been unequalled in psychopharmacology.

Alec Coppen

After training in the Institute of Psychiatry in London following the Second World War, Alec Coppen entered research in Biological Psychiatry at a time when there were few biological psychiatrists. His research from the start was on mood disorders, at a time when these were comparatively under-investigated with most researchers focussing their efforts on schizophrenia. This research involved a dual track approach throughout, with clinical studies on the one hand supplemented by studies of biological markers on the other.

Coppen’s early work with David Shaw and others involved a determination of electrolyte distribution in mood disorders, demonstrating striking differences during the course of mood disorders (Coppen and Shaw, 1963). His clinical studies at the same time involved studies of the supplementation of antidepressant therapies with tryptophan, leading to the first evidence that modulating the serotonergic system can produce dramatic responses...
in some cases (Coppen et al., 1963). This study contributed significantly to the development of the serotonergic hypotheses of affective disorders. Along with George Ashcroft in Edinburgh and Herman van Praag in Holland, Alec Coppen provided a counterpoint to the prevailing North American view that the catecholamines were the key neurotransmitters in affective disorders. His article in 1967 on the biochemistry of affective disorders (Coppen, 1967) is regularly cited as providing an alternative to Schildkraut’s catecholamine hypothesis.

Coppen’s subsequent work on mood disorders involved clinical trials with a number of novel agents, including some of the early tricyclics, mianserin and others. He demonstrated the possibilities of supplementing antidepressant effects with a range of agents including thyroid hormones, folate and vitamins of various sorts. He also helped initiate a movement towards longer-term treatment studies (Coppen, 1996).

Many of these studies were conducted at a time in the 1960s and early 1970s, when to be involved in biological research in psychiatry was to be involved in ‘the work of the devil’, in a way that is almost impossible to imagine now. Coppen had to cross picket lines to lecture at meetings set up by Van Praag, who at one point had police protection because of death threats (Coppen, 1996). Research of this kind, therefore, involved not only the skilful eye of a researcher to pick questions that were likely to yield answers but also the political skill to both disarm and engage opponents.

Alec Coppen’s career demonstrates that science is not just about inspired investigators battling on their own to establish points of view. It can also involve systematic experiments to stop therapeutic or diagnostic band-wagons in their tracks as well as the difficult exercises of multi-centred studies aimed at answering critical questions in the field.

When the controversies between Mogens Schou on the one hand and researchers from the Institute of Psychiatry, hostile to lithium, on the other came to a head in the late 1960s, Coppen was foremost among those who sought to resolve the issues by hammering out an agreed protocol for a study that would answer the questions of lithium’s benefits decisively one way or the other. His study published in 1971 helped resolve just these issues in favour of lithium (Coppen et al., 1971). Since then he has been an advocate for the benefits of lithium therapy, helping to raise the profile of its anti-suicide effects as well as its efficacy in prophylaxis.

Other achievements include mounting a coordinated multi-national effort to test the utility of the Dexamethasone Suppression Test (DST) for affective disorders. This large complicated study proved that the DST did not have the specificity for affective disorders that had previously been claimed for it (Coppen et al., 1986). A similar multi-centred study cast doubt on the idea of a therapeutic window for the tricyclic antidepressants, a hypothesis that Coppen had been one of the first to put forward.

Coda

Deniker, Elkes and Lehmann each provided a unique contribution to psychopharmacology but shared a common commitment to educating the wider field on the contours of the new discipline taking shape. The careers of Janssen, Schou and Coppen have another set of commonalities. They flourished at a time when individual effort and genius were what counted. Unlike, Deniker, Elkes or Lehmann, none came from centres of recognized excellence. Epsom, Risskov and Beerse had no traditions of producing pioneers in scientific fields. But in addition to flourishing without institutional or other supports, one has to wonder whether today’s conditions which are so dramatically different would not in fact have inhibited the development of careers like Janssen’s, Schou’s and Coppen’s. It is difficult to see how the field could now give rise to a figure, who might bring a non-patented drug to the forefront of pharmacotherapeutics. It is difficult to discern figures now who have the stature to articulate some of the leading hypotheses of the day but who then undertake the work that disproves their own hypothesis. Finally there do not appear to be emerging figures capable of blue-skies research with no thought of market returns who might end up with no less than five discoveries on the WHO’s list of essential drugs. If today’s conditions do not support careers like these, we can wonder whether we are heading in right direction. All three of these pioneers have some doubts on this score (Coppen, 1996; Janssen, 1998; Schou, 1998)

References


