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†*Reading about. . .*

Psychopharmacology

by Trevor Silverstone

When asked by the book review editor to write an article discussing some 'important, memorable, relevant, unusual or informative books (or articles)' in the field of psychopharmacology, I was uncertain quite what was wanted.

In the course of my ruminations on this topic it struck me that one of the most significant factors which has promoted recent progress in the field of psychopharmacology has been the continuing dialogue conducted between laboratory-based research workers probing into the ways psychotropic drugs interact with neurotransmitter systems in the brain, and clinical psychiatrists evaluating in patients the way these same drugs alter the symptoms and signs of mental illness. As direct access to the living human brain is denied to us, we have perforce to depend on animal studies to elucidate mechanisms of drug action; on the other hand as there are no reliable animal models of human psychopathology, evaluation of therapeutic applications of drugs must depend entirely on clinical assessment. Furthermore, in order to gain an understanding of the underlying neurochemical basis of such psychiatric illnesses as schizophrenia or the affective disorders, drug studies provide, in my opinion, one of the most potentially fruitful approaches currently available. The value of cross-disciplinary fertilization of psychopharmacological research, and of the use of drugs as tools for understanding the mechanisms of psychiatric illness, is nicely exemplified in those investigations undertaken over the last thirty years which have, by elucidating the relationships between drugs and central neurotransmitters in schizophrenia, greatly increased our understanding of this illness.

The story begins, as in most stories involving drugs, with the organic chemist. In her extremely lively and readable book *Chlorpromazine in Psychiatry* (1974) Swazey recounts how, in December 1950, chemists in the French pharmaceutical company Rhone-Poulenc, who were looking for an antihistamine with a central action, synthesized chlorpromazine. Pharmacological screening indicated that this drug had a marked CNS activity with relatively low toxicity and by April of the following year, that is within five months of the compound being synthesized, clinical studies in a wide range of psychiatric conditions were begun. Delay and Deniker soon observed the beneficial effects of the drug in states of psychotic excitement and their findings were instrumental in initiating further clinical studies in a number of centres in Europe and North America. Deniker has described these early clinical explorations in his chapter in that most enjoyable and revealing book called *Discoveries in Biological Psychiatry* edited by Ayd and Blackwell. The first placebo-controlled trial firmly establishing the place of chlorpromazine in psychiatry was undertaken in England (Elkes and Elkes, 1954). And a large multi-centre study conducted under the auspices of the U.S. National Institute of Mental Health (1964) convincingly confirmed the efficacy of phenothiazine compounds such as chlorpromazine in the management of acute schizophrenia. As a result of these reports chlorpromazine and other neuroleptic compounds emerged from the research laboratory into clinical use; the time scale of this process was remarkably quick by current standards.

Another relevant, but at the time seemingly unrelated, observation was the finding by Connell that patients who had self-administered high doses of amphetamine developed symptoms closely resembling those seen in paranoid schizophrenia; in most cases these symptoms remitted shortly after amphetamine was stopped. Connell's (1958) account of the way the first cases were discovered at times reads like a detective story. Thus, by the end of the 1950's, there were two important questions to be answered: (1) What were the neurochemical effects of chlorpromazine in the mammalian brain? (2) What changes in neurochemical transmission were brought about by amphetamine which might explain the paranoid delusions and auditory hallucinations provoked by the drug? It would of course be particularly encouraging if the same neurotransmitter system could be found to be involved in both effects.

† An occasional feature in the Book Section where contributors give their personal choice of important, memorable or informative literature.

For the answers it was obviously a case of going back to the laboratory. As it turned out preliminary answers to both questions came from one research group, that headed by Arvid Carlsson in Gothenburg, Sweden. Carlsson (1978), in a recent review, recounts how in 1963 he and Lindqvist discovered that chlorpromazine and haloperidol stimulated the accumulation of the metabolites of dopamine and noradrenaline in the CNS without affecting the overall levels of the neurotransmitters themselves. This finding suggested that the neuroleptic drugs might act by blocking neuronal receptors for dopamine and noradrenaline. It later became clear that dopamine, rather than noradrenaline was the neurotransmitter likely to be most involved in the clinical action of neuroleptic drugs. The other important discovery Carlsson made, namely that amphetamine releases dopamine and noradrenaline from central neurones, first appeared in a useful source book entitled *Amphetamines* edited by Costa and Garattini (1970). Thus within a decade of the two key questions being posed, the answers were to hand: the neuroleptics acted by blocking dopamine receptors, amphetamine caused release of dopamine (and noradrenaline) within the CNS. A further necessary ingredient in the story, that of the anatomical structures involved in dopaminergic transmission in the mammalian brain, a previously relatively unstudied neurotransmitter system, was provided by another Swedish investigator, Ungerstedt (1971), who used a histofluorescence technique to excellent effect.

The fact that amphetamine psychosis could be ameliorated by neuroleptic drugs strongly implied, as Angrist and Gershon (1974) pointed out, a relationship between central dopaminergic activity (they said hyperactivity) and some forms of psychosis. The clinical observation by these authors that pre-existing schizophrenic symptoms could be exacerbated by small doses of amphetamine, was consistent with their view that some form of heightened sensitivity of dopamine mechanism might be present in the central nervous system of patients suffering from this illness. Recent work has attempted to address itself directly to this point. However, schizophrenia only occurs in man as far as we know and dopamine receptors can only be directly examined in human brain from patients who have died. This limitation confining observations on human dopamine receptors to post-mortem material can obviously lead to considerable problems in interpretation. Furthermore the great majority of patients who come to post-mortem study have been treated with neuroleptic drugs, often for many years at a high dose; this could in itself markedly influence receptor sensitivity. In spite of these difficulties, exciting results are emerging which suggest that there may indeed be an abnormality in the dopamine receptors in the brains of patients suffering from schizophrenia (Owen *et al*, 1978).

There the story must rest for the present. Following its development will, I trust, increase the reader's understanding, not only of the particular problems raised by the specific issue of schizophrenia but, more generally, of the value to psychiatry of continuing communication between the scientist in his laboratory and the doctor in his clinic.

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