

EDITORIAL

Psychopharmacology tomorrow: 1984 or *The Little Prince*?¹

At the time of its publication George Orwell's *1984* seemed barely conceivable and, in any event, far in the future. Now that 1984 has arrived it is beyond our competence to argue whether Big Brother actually watches us and whether yesterday's friends have become today's enemies. We are, however, constrained to contemplate the position of so powerful an instrument as psychotropic medication, especially if we take into account the ways in which it has been abused. Aldous Huxley had predicted this possibility in his *Brave New World*, demonstrating once again that creative artists are often able to foresee events, especially those that are generated by psychological motivation.

By the same token, we may recall another fable – *The Little Prince* by Antoine de Saint-Exupéry, who died in 1944 on his last military mission, shortly after the appearance of his book. This masterpiece at once impressed readers all over the world by its poetic approach to a humanistic view of a planet which was still struggling with the horrors of the Second World War.

It is the purpose of this editorial to emphasize what the author regards as the current mainstreams in psychopharmacology that may eventually result in positive achievements. It remains to be seen, however, whether this powerful medical tool with its potential for the chemical control of the mind will inexorably follow the Orwellian predictions or will evolve more closely to the idyllic Saint-Exupérian view of the Little Prince who tamed the shrewd fox by making friends with it.

First, a brief word about early psychopharmacology. The term 'psychopharmacology' was coined by David Macht as recently as 1920. An elementary psychopharmacological tradition preceded its introduction but, in the light of developments over the past 60 years, it is already more appropriate to regard this as 'pre-historic'. Both the *Iliad* and the *Odyssey* recount many 'psychopharmacological' tales; stories from the Middle Ages are filled with magical, love or hate elixirs; and the Maya and the Aztec priests compelled those who were to be sacrificed to take special potions.

Two particular features of this 'pre-historical' psychopharmacology are characteristic: preparations were given to healthy people to modify their states of mind; this procedure was usually carried out against their wishes and/or without their knowledge.

Modern psychopharmacology dates from Laborit's work on chlorpromazine and its introduction into psychiatry in the early 1950s. Delay & Deniker treated schizophrenic patients with this drug in 1952–3, and a large number of compounds aiming at the central nervous system as a target-organ were then synthesized. Many of these drugs came to be called psychotropics or CNS-acting drugs. Table 1 (modified after Wilhelm, 1977) summarizes the chronological essentials of the process.

Significantly, the early discovery of new psychotropic groups was almost always due to 'serendipity', usually springing from a fortuitous clinical observation. Thus Laborit, an anaesthetologist, was originally studying chlorpromazine to reduce surgical shock; Kline noticed the potential antidepressant activity of rimifon because of the euphoria reported from tuberculosis sanatoria after its introduction; Kuhn was studying imipramine as a supposedly mild neuroleptic on the basis of early animal studies, but his acute clinical observations opened the chapter of tricyclic antidepressants.

Such examples emphasize the central role of competent physicians with the flair necessary to underpin Pasteur's comment of chance favouring the prepared mind. On the other hand, they also illustrate certain weak points in the extrapolation of animal data to man (Boissier *et al.* 1961). Psychopharmacology should obviously go beyond the mere imitation of established drugs. It should be based on a deeper knowledge of the physiopathology of mental disease.

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Table 1. Main psychotropic advances

Year	Innovation	Development*
1970–80	Piracetam Clobazam Zimelidine Deprenyl Clozapine	6 Nootropics 4 Benzodiazepines 1,5 5 Selective antidepressants 2 Non-catatonic antipsychotics 15 Benzodiazepines 1,4 3 Polycyclic antidepressants 9 Phenothiazines 4 Butyrophenones
1969	Sulpiride	9 Butyrophenones
1958	Haloperidol	15 Tricyclic antidepressants
1957	Imipramine Tranlycypamine	9 MAO-inhibitors 7 Benzodiazepines 1,4
1955	Chlordiazepoxide	33 Phenothiazines
1954	Meprobamate	
1952	Hydroxyzine Chlorpromazine Reserpine Iproniazid	
1949	Lithium	
1938	Diphenhydantoin	
1936	Amphetamine	
1935	Metrazol	
1933	Insulin	
1850	Opioids	
18th century	Belladonna	
15th century	Purgatives	
800 B.C.	Nepenthes	

After Wilhelm (1977).

* Drugs mentioned are marketed or patented.

Several general criticisms in this field are often encountered, including those directed at the term 'psychopharmacology', a word which is semantically ambiguous inasmuch as it recalls a Platonic or Cartesian dualism separating the soul (psyche) from the soma. We are, however, forced to admit that the meaning given to the term by most psychiatrists is essentially pragmatic, rooted in clinical realities. Psychotropic drugs, according to Delay & Deniker in their original classification, can induce only three types of effect: (a) a diminution of mental activity by *psycholeptics*; (b) an enhancement of mental activity by *psycho-analeptics*; and (c) a distortion of mental activity by *psychodysleptics*. Important subgroups were subsequently proposed. The psycholeptics, for example, were divided into those that facilitate hypnotic function, the *hypnotics*; those that control mainly productive symptoms, the *neuroleptics*; and those that reduce anxiety, the *tranquillizers*. Remarkably enough, and presumably because it was based on clinical realities, this rationale for classification (Shepherd, 1972) is still dominant a quarter of a century after its introduction.

SPECIFIC TRENDS IN PSYCHOPHARMACOLOGY

1. Antipsychotics

Until recently, the antipsychotic drugs were widely equated with neuroleptics. These compounds induce catatonia in animals, thereby reflecting an antagonism to dopaminergic (DA) receptors. Their administration is also associated with the risk of extra-pyramidal side-effects, including tardive dyskinesia. More than ten years ago this view was challenged by the introduction of clozapine, an efficient antipsychotic (Ackenhain & Hippus, 1977) which does not induce catatonia in the rat in high doses. This drug does, however, exhibit other side-effects, and its mode of action remains insufficiently understood.

Two recent approaches are also relevant in this context:

(a) The development of non-neuroleptic anti-psychotic drugs that do not block post-synaptic DA-receptors but stimulate DA-presynaptic autoreceptors. By virtue of a negative control action synaptic release is inhibited. Such a mechanism is triggered by low doses of apomorphine or by a new substance, '3-PPP' (3(3-hydroxyphenyl)-*N-n*-propylpiperidine) (Nilsson & Carlsson, 1982; Arnt *et al.* 1983). DA-autoreceptor stimulation reduces DA-neurotransmission in the manner of the classical antipsychotics, but more gradually and probably more selectively, i.e. it modulates the DA-mesolimbic system more than the nigro-striatal system. The possibility of producing new antipsychotic compounds free of parkinsonian side-effects is thereby increased.

(b) Still more remote from traditional psychopharmacology is the recent cholinergic approach to schizophrenia, particularly in childhood. Cantor *et al.* (1980) regard a pre-synaptic deficit as a basic element in the physiopathology of this disorder. A similar deficit has been incriminated in Down's syndrome, which therefore seems akin to senile dementias of the Alzheimer-type (SDAT) from the point of view of both physiopathology and cognitive symptomatology (Marott-Sinex & Merril, 1982).

2. Anxiolytics

For many years the benzodiazepines (BDZ) have figured prominently among the most widely used groups of drugs. They undoubtedly appear to meet a therapeutic need, linked to the inherent stress and conflicts of modern life. It remains to be established, however, whether these drugs counteract a biologically protective, and so essentially 'normal', form of anxiety or help to control pathological anxiety related to neurotic states with their psychosomatic syndromes, which paralyse the patient and impair adaptation. If this is the case, then the benzodiazepines are deficient in at least two respects: (1) they do not control the neurovegetative consequences of stress efficiently enough, their impact being essentially behavioural; (2) all the classical, 1,4-benzodiazepines induce memory deficits in humans as well as in a few experimental models (Soubrie *et al.* 1976; Jensen *et al.* 1979). It seems that the 1,5-benzodiazepine – like clobazam, which we have studied experimentally (Giurgea *et al.* 1982) – are devoid of this troublesome and frequent side-effect (Salkind *et al.* 1979).

The anxiolytics of the future should not affect memory adversely and might even facilitate cognitive functions, thereby enhancing the efficacy of cortico-subcortical control. They should also induce less sedation and facilitate appropriate neuro-vegetative post-stress recovery more efficiently.

3. Antidepressants

Metals

The therapeutic use of lithium (Schou, 1968) and, to a lesser extent, the recent implication of aluminium in Alzheimer's disease (De Boni & Crapper McLachlan, 1981) may direct new interest towards other ionic mood-modulators.

Selective antidepressants

Considerable efforts are currently under way to identify new antidepressants like zimelidine, a potent serotonin re-uptake inhibitor with very little action on the noradrenergic system. Several workers (Scuvee-Moreau & Dresse, 1982; Quinaux *et al.* 1982; Olpe *et al.* 1980; Olpe, 1981) have developed interesting experimental approaches to this problem by studying the differential effects of an antidepressant on the electrical activity of the locus coeruleus (for the noradrenergic system) and of the dorsal raphe (for the serotonergic system) in the rat. Selective 5-HT promoting antidepressants might well open the way to new compounds more active than their predecessors in the treatment of so-called 'masked depression' (Kielholz, 1973), in which there is a particularly high incidence of somatic complaints.

The puzzle of repetitive administration

All known antidepressants are clinically effective only after 10–15 daily administrations. Vague concepts like receptor 'impregnation' have been invoked speculatively to account for this long delay

of action. In animal experimentation one adequate dose of antidepressants is usually active after 30–60 minutes. It is therefore possible to describe a differential pharmacological pattern for antidepressants compared with other psychotropic drugs. Obviously, however, animal models cannot be regarded as reliable homologues of depression in the human subject.

Chiodo & Antelman (1980*a*) have introduced a novel element to this issue. Working with rats, they measured the DA-receptor sensitivity by using the apomorphine-induced inhibition of the spontaneous electrical activity of DA neurons as an indicator. Apomorphine stimulates presynaptic autoceptors and therefore reduces post-synaptic availability in catecholamines. In theory, an antidepressant should counteract this effect. This was indeed the case, but the authors have reported a number of unexpected temporal effects: (a) antidepressants given repetitively over 10 days markedly reduced the apomorphine effect; (b) no such effect was obtained after only one or two administrations; (c) after only one injection a maximal antidepressant effect was obtained after 7 days and without further drug administration. The effect resembles that which might be expected from continuous administration over a 10-day period. A similar response has been reported with convulsant electroshock (Chiodo & Antelman, 1980*b*). Were these findings, which have already provoked controversy (Welch *et al.* 1982), to be confirmed, they would have obvious practical as well as theoretical implications – for example, the possible reduction in the quantity of antidepressant medication required for treatment.

Psychotropic drugs and receptors

From the large area of drug-receptor interactions, two examples of psychopharmacological significance may be selected:

(a) Since the work of Ehrlich, receptor theory has been dominated by the notion of mechanistic relationships between the molecular configuration of an agonist or antagonist and its receptor. Other mechanisms of central origin may, however, considerably modulate those interactions, as suggested by Poulos & Hinson (1982). For example, tolerance to the capacity of haloperidol to induce catatonia is seen in the same rat in the same environment according to whether the animal does or does not anticipate receiving the drug. A Pavlovian conditional reflex to the experimental situation, a 'shortened conditional reflex' (Giurgea, 1981), might therefore critically modify habituation of the receptor. Accordingly, an animal will exhibit tolerance to a given drug in one environment, but not in another.

(b) The existence of several subtypes of receptor has become increasingly clear. Thus pirenzepine, a drug with gastric antacid properties, displays a preferential antagonism for the muscarinic receptors situated in the cerebral cortex and the hippocampus, i.e. for those that are particularly implicated in the cognitive functions of the central cholinergic system (Hammer *et al.* 1980; Caulfield *et al.* 1983).

4. The pharmacology of cognitive (noetic) activity

Two examples may be taken to illustrate this rapidly expanding field.

(a) The importance of the brain's own 'pharmaceutical industry' is now widely accepted. Endorphins and neuropeptides appear to play a central role in relational behaviour and cognitive life – for example, stress-induced analgesia (Wall, 1982; Jungkunz *et al.* 1983), the vasopressin positive effects on memory (Legros *et al.* 1978; Timsit-Berthier *et al.* 1980), and the possible endorphin involvement in psychoses (van Praag, 1977).

(b) Recent work suggests a central cholinergic deficit in Alzheimer's disease, namely a reduced activity of choline-acetyl-transferase (CAT), the main presynaptic cholinergic marker (see the review by Corkin *et al.* 1982). Bartus *et al.* (1981) have extended this concept, proposing an enhanced central cholinergic efficiency by means of the injection of choline together with a substance which might facilitate choline central activity because of its favourable influence on brain energy metabolism. They chose for the purpose piracetam, the prototype of nootropic drugs. These are selective activators of cognitive (noetic) activity, whose experimental and clinical pharmacology have been described in detail (Giurgea, 1972, 1981; Giurgea & Salama, 1977). Bartus *et al.* (1981) demonstrated

that the combination of choline and piracetam improves the important memory deficit seen in ageing rats in a passive avoidance one-trial learning situation. Other studies (Greindl & Preat, 1976) have shown that such a potentiating interaction between choline and piracetam, which facilitates retrieval of a weak, subliminal memory, can be demonstrated in normal, young adult rats (Giurgea *et al.* 1981). This work was based on three propositions: (a) choline is not only a natural cholinergic precursor, but is able to activate directly the post-synaptic cholinergic receptors (Krjnevich & Reinhardt, 1979); (b) piracetam facilitates cholinergic hippocampal neuronal activity (Wurtman *et al.* 1981; Olpe & Lynch, 1982); (c) central cholinergic modulations directly influence memory functions independently of age (Deutsch, 1973).

CONCLUSIONS

Lehmann (1977) has made a number of pragmatic suggestions about the possible directions to be taken by psychopharmacology in the future. To these may be added two general considerations.

First, psychopharmacology may contribute to the nosological refinement of mental illness in biological terms, which will improve the rational basis for pharmacotherapy. Secondly, further knowledge both of the modes of action of psychotropic drugs and of cerebral physiopathology will provide more secure foundations for an understanding of the somatic basis of mental dysfunction, leading in turn to the discovery of new compounds that are more efficient in the control of psychopathology and that may help with efforts to cope with stressful life events.

Though excess and misuse of psychotropic drugs will doubtless continue, an awareness of deontological factors and the vigilance of the medical profession stand safeguard against an Orwellian future. On the other hand, psychotropic drugs are unlikely to change either man's basic inner conflicts or his aggressiveness, and no Little Prince-drug will induce men to become brothers. Between these extremes, we may predict that modern psychopharmacology, little more than thirty years after its inception, is and will continue to feature prominently among the positive, humanistic endeavours of contemporary medicine.

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