PSYCHOTROPIC DRUGS — THEIR ACTION AND VALUE *

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The views expressed in this article reflect my personal impressions. That is to say, they are not based on a statistical survey and analysis. They serve me as a rough guide in my use of these drugs, but I concede that they provide little or no ground for arguing my viewpoint against an opposing one. It must also be remembered that the patients I generally see are not strictly comparable to those seen by the general practitioner. He is more likely to be seeing and treating milder cases, and his experience with these drugs may therefore differ from mine on this score.

I do not overlook the fact that the therapist's expectancy of results influences them. From time immemorial doctors have been searching and waiting for a drug that will smooth away needless anxiety, irrepressible thought, torturing fantasies, extreme mood swings and disordered thinking and behaving. And as each drug appears with the promise that it is the long-sought-for panacea, there must be few who do not turn to it with fresh hope that it will answer their needs. In that first embrace we get our best results. That at least, has been my experience, no matter what the drug. With the continued use of a drug one often enough becomes sobered by the diminishing returns. There is nothing novel in this experience. Others have drawn attention to this fact, over the generations. I mention it only to arouse wariness about published statistical results with the psychotropic drugs. The time factor exerts a profound, though unconscious, influence; the best results, I would say, are obtained when the drug is fresh on the market. When the drug is new the expectancy of therapeutic efficacy is high, and the longer it is in use the more realistic and case-linked are the expectations.

A dual and reciprocal factor operates to influence the results. When the doctor prescribes a drug, with the expressed or implied promise that it will help, the patient is likely to make a favourable, initial response to it. But with time, if the underlying causes of the patient's disturbance have not been removed, the drug's influence becomes more and more impervious to the doctor's expectancy, the doctor becomes more and more disenchanted, the patient's faith in the drug dissipates, and the initial efficacy of the drug begins to wane. A vicious circle of suggestion and counter-suggestion always influences results with any new drug, and I doubt whether the double-blind technique can entirely eliminate this influence. Some exaltation of hope must enter the mind of the recipient, whether he receives the inert or active substance, with resultant relief of the symptoms.

The present is a convenient time, in the history of psychotropic drugs, for a survey. As a group, they are no longer new to us. Commencing with chlorpromazine, which was introduced to the profession for use in psychiatric patients in 1952, we have been using these drugs for 10 years. This is a reasonably long acquaintanceship. Is our continued use of them justified? In what type of patient? What measures of help have they given our patients? What supplementary help is required? Where have they failed us? I hope to give my answers to these questions as I go on.

Classification

Psychotropic drugs may conveniently be classified as follows:

A. Those with muscle-relaxant, anti-convulsive and tranquillizing properties — mephenesin derivatives, e.g. meprobamate.
B. Those with sedative, hypotensive properties — rauwolfia alkaloids, e.g. 'serpasil'.
C. Those characterized by sympathetic inhibition — phenothiazine derivatives:
- **(*a*) Piperazine group, e.g. 'stelazine', 'trilafon'.**
- **(*b*) Chlorpromazine group, e.g. 'largactil', 'siquil'.**
- **(*c*) Piperidine group, e.g. 'melleril'.**

D. Thymoleptic (mood-regulating) or analeptic drugs:
1. **Psychomotor stimulants:**
   - **(*A*) Sympathomimetic drugs, e.g. amphetamine, and some phenothiazine derivatives, e.g. imipramine ('tofranil').**
   - **(*B*) Direct CNS stimulants, e.g. methylphenidate, pipradol, acetylcholine derivatives, e.g. 2 dimethylaminoethanol; and some phenothiazine derivatives, e.g. stelazine, siquil.**
   - **(*C*) Sympatholytic drugs, e.g. imipramine.**
2. **Psychic energizers:**
   - **(*A*) Monoamine oxidase inhibitors:**
     - **(*i*) Hydrazine derivatives, e.g. iproniazid ('marplan', 'marsilid'); nialimide ('niamid'); and phenelzine ('nardil').**
     - **(*ii*) Tranylcypromine ('parnate').**
   - **(*B*) Sundry:**
     - **(*i*) Amitriptyline hydrochloride ('tryptanol').**
     - **(*ii*) Chlorprothixene ('truxal').**

Despite the disparate clinical appearance of conditions such as anxiety state, obsessional state and schizophrenia, they have the common feature that they have no detectable associated pathological disturbance of the brain substance. The attempts to elucidate the nature of the disturbances underlying these conditions were much influenced by observations of the effects of certain drugs, like mescaline and lysergic-acid-diethylamide (1943), which produce disturbances of mental functioning without affecting consciousness. These drugs artificially produce transitory mental disturbances, which are an

* Contributed to a symposium on modern trends in psychiatry, held under the auspices of Southern Transvaal Branch (M.A.S.A.), on 1 November 1961 in Johannesburg.

exaggeration of the clinical conditions referred to above, and do so without inducing any permanent damage to cell structure.

It may seem surprising that a psychotic state, viz. schizophrenia, is grouped with neurotic conditions, but the fact that they stand at opposite poles clinically does not alter the fact that they both present the same challenge to the understanding of their intrinsic patho-physiology. The difference in clinical gravity and course no doubt relates to the fact that the genetic bias is more pronounced in the case of schizophrenia. This bias means that there is, in schizophrenia, a more deep-seated and permanent fault than in the other conditions, but the nature of the fault is probably the same in both conditions. This difference may also explain why the personality, sooner or later, becomes affected in schizophrenia.

LSD and Mescaline

LSD and mescaline are related to a number of substances that influence mental functioning, by the presence of an indole nucleus in them all. Among them are the amines, serotonin and nor-epinephrine, which are normally present in the brain, and reserpine. Reserpine tends to induce depression, while the inactivation of serotonin is thought to do the same.

LSD and mescaline are hallucogenic. *In vitro* LSD and related compounds inhibit serotonin, and it has been suggested that this action on serotonin may account for the psychotogenic effects of these drugs.[1] Other inhibitors of serotonin *in vitro*, such as 2-brom-d-lysergic acid diethylamide, do not however produce such effects.[2] Certain serotonin antagonists, like methysergid ('deseril') and chlorpromazine, which have little or no disturbing effect on the psyche, but which oppose serotonin peripherally, are being used with benefit in the treatment of symptoms in the carcinoid syndrome, migraine, bronchial asthma and rheumatoid arthritis.[25]

Mescaline is similar in structure to amphetamine and epinephrine. The former is well known for its stimulating effect on cerebration. Mescaline, and LSD in infinitely smaller quantities, provoke a schizophrenia-like reaction in humans, with vivid, brilliantly coloured hallucinations and illusions, feelings towards depersonalization and distortion of body image and frequently of the time sense, mood changes, delusions and fantasies, which, because consciousness is not clouded, are recordable and recallable by the subject. The effect lasts up to 24 hours and more, and can be inhibited by the exhibition of tranquillizers. It is more pronounced in schizophrenic subjects.[3]

Various theories have been put forward to explain the effects of LSD and mescaline: that they interfere with the metabolism of epinephrine, to produce a toxic by-product;[4] that they block the action of serotonin and that they inhibit synaptic transmission.[5] Their lasting value, in the treatment of psychiatric disorders, has yet to be established.

The discovery of serotonin and nor-epinephrine in the brain raised the possibility that they might play a part in mental functioning and dysfunction, in view of their chemical relationship to the psychotogenic drug, LSD.

Serotonin circulates in the blood platelets and derives, by enzymic action, from 5-hydroxytryptophane, which is found in the intestinal glands of Lieberkühn. In the blood, serotonin is broken down by the enzyme, monoamine oxidase, into 5-hydroxyindolacetic acid, which is excreted in the urine.[6] The serotonin that is stored inactive is presumably activated in the brain on the passage of a nerve impulse, and it exerts its influence on the brain at the synapses, by inhibiting transmission.[5] The serotonin in the blood is unable to do so, because it cannot get across the so-called brain-blood barrier, though its precursor, 5-hydroxytryptophane, is able to do so.[7] The amount of serotonin in the brain, with opinions favouring either excess or deficiency, may be related to the symptomatology of mental illness, for instance in schizophrenia. This tends to be borne out by the observation, on the one hand, that the antimetabolites of serotonin, such as LSD, are psychotogenic,[8] and on the other, that drugs releasing or increasing brain serotonin favourably affect mental symptoms.

Monoamine Oxidase (MAO) Inhibitors

The MAO inhibitors (their hydrazine radical) produce their effects by releasing serotonin in the brain, while the phenothiazines are thought to block the action of nor-epinephrine. Psychotropic drugs may thus be serotonergic, adrenergic (stimulating nor-epinephrine production), or may act by blocking either the sympathetic or parasympathetic centres in the central autonomic nervous system.[10] Reserpine lowers the brain concentration of nor-epinephrine and serotonin.

The monoamine oxidase enzyme presumably breaks down the activated or released serotonin in the brain, as it does in the blood. Whether this normal enzymic activity gets out of hand, or some other action interferes with it, and the reason why the one or the other event should occur, is not known, but on the basis that the monoamine oxidase is the source of the evil, inhibitors of the enzyme have been introduced to correct the mental symptoms of certain psychiatric conditions, especially depression. The relationship between the blood level of monoamine oxidase and mental symptoms has not been established, but the therapeutic results with the use of MAO inhibitors have been such as to support their use.

Nor-epinephrine, like serotonin, is activated by a nerve impulse and inactivated by MAO.[14] It is possible that it may act on the brain through its derivatives, adrenochrome and adrenolutin, which are known to be psychotomimetic.[15,16] The exhibition of MAO inhibitors effects an accumulation of catecholamines (epinephrine and nor-epinephrine) in the brain.

Apart from its effect in breaking down serotonin, freed at the synapses, it is possible that monoamine oxidase may be implicated in the blood-brain barrier.[12] The barrier function, it has been suggested, reflects the interplay of several enzyme systems,[13] of which the monoamine oxidase is one, so that the exhibition of MAO inhibitors presumably both prevents the breakdown of serotonin and alters the barrier permeability to it.

My own view, speaking of the MAO inhibitors as a class, is that the best that can be expected of them is that they sometimes relieve depression, especially of the endogenous type, when it is mild, but that they are no substitute for ECT. Exceptionally, they give surprisingly good results. The use of MAO inhibitors in combination with ECT has much to recommend it. It frequently reduces the number of ECTs required. It is possible that ECT increases the permeability of the brain-blood barrier, permitting readier access of the MAO inhibitors to the brain.[11]

Increase in brain serotonin in dogs has been found following electro-convulsions, and its increase in the human brain following ECT may possibly explain the efficacy of ECT in depressed patients.

Tranquillizers

The claim made for tranquillizers, that they provide sedation without hypnosis, is not well-founded. Not a few patients have discovered that they can use a so-called tranquillizer to put them to sleep at night. The differences in effect between tranquillizers and the older sedatives and narcotic drugs (differences which are not essentially dependent on relative dosages) suggest that they are based on different patterns of neurophysiological action.[18]

The phenothiazines differ in their effects according to their site of action in the brain, of which there are primarily three; the hypothalamus, the reticular system of the medulla, mid-brain and diencephalon; and the limbic system, particularly the amygdaloid and hippocampal segments.[17] The weaker phenothiazines depress mainly the hypothalamus and parts of the reticular system, as evidenced by the relatively higher incidence, in their use, of anti-emetic, sedative and autonomic-endocrine effects, while the more potent phenothiazines influence especially the limbic system, as is suggested by their tendency to produce extrapyramidal symptoms.[17] The selection of site is dependent on the type of halogen and the structure of the side chain associated with the phenothiazine ring. The chemical structure of the phenothiazine compound determines its potency and toxicity. A halogen joined to the nucleus increases the potency of the product, as does a piperazine ring in the side chain.

The weaker phenothiazine derivatives tend to induce autonomic-endocrine side-effects and allergic reactions (dermatitis, jaundice, agranulocytosis), whilst the more potent pheno-

thiazines tend to provoke seizures and extrapyramidal reactions.

It is thought that reserpine, phenothiazine and meprobamate depress the reticular system by depleting or inactivating the nor-adrenaline, which is present in relatively large concentration in the reticular system. The depletion of adrenaline stores raises the threshold and central responsiveness to noxious stimuli and lowers the level of circulating epinephrine.[19,20]

The phenothiazines and possibly meprobamate and other compounds containing the amide group ($0 = C - NH_2$) chelate sympathomimetic amines (adrenaline and nor-adrenaline), as shown by the frequency with which they cause hypotension.[20] Both the phenothiazines and reserpine accelerate the rate of oxidation of adrenaline and nor-adrenaline.[20] Amphetamine, which is an analogue of nor-adrenaline, probably exerts its antidepressant effect by stimulating the reticular system.[24]

The depletion of adrenaline stores probably decreases the formation of indoles, which have been imputed as a toxic factor in the causation of schizophrenia.[20] It may thus be that the exhibition of the phenothiazines in schizophrenia serves a dual purpose, viz. tranquillization and the elimination of a toxic factor causing the condition, by the one physio-chemical operation.

The production of extrapyramidal symptoms of the phenothiazines suggests support for the theory of the chemical genesis of schizophrenia, for this condition is frequently characterized by similar behavioural and expressional disturbances. The National Institute of Mental Health in the USA has reported the beneficial effects of giving large doses of certain amino-acids (l-methionine and l-tryptophan) to chronic schizophrenic patients.

Other chemical mechanisms for dealing with the indoles have also been formulated, viz. their binding by ceruloplasmin, an increase of which is induced by phenothiazines, and the pre-emption of binding sites on brain proteins by reserpine, phenohiazines and tofranil.[20] Tofranil is believed to sensitize receptors for nor-epinephrine.

It has been suggested that the phenothiazines, in addition to blocking nor-epinephrine, act by increasing the liberation of serotonin.[21]

The phenothiazines have been a special boon to the victims of the schizophrenic conditions and they have also been of some value in the psychoneuroses. In the case of schizophrenia, some of the phenothiazines, like largactil and stelazine, have almost replaced the insulin coma treatment. There are however patients who require insulin, and to persist with the phenothiazines when they prove unavailing, as is sometimes done, is, I feel, jettisoning a tried and proved treatment before there is an equally effective substitute. Stelazine is useful, I would say, in delaying schizophrenic deterioration and perhaps modifying the ultimate breakdown, but whereas insulin coma treatment, where it helped, gave the victim a remission from the corroding schizophrenic process, the phenothiazines help only as long as they are used.

Anxious and insecure patients often reject a tranquillizer because of the side-effects. This is however the least of the criticisms that can be levelled against the phenothiazines. The greatest danger, in a way, is their usefulness, for by easing anxiety they tend to reconcile the victim to his underlying condition. The price of chronicity is not immediately recognized and is therefore not considered. Even allowing for the fact that alternative treatments may not be able to offer any better prognosis, in some cases, at any rate, the danger nevertheless exists that the widespread use of tranquillizers may be removing from human experience the constructive, character-building value of anxiety. These drugs may be contributing to the de-individualization of the human being, already at the mercy of so many economic and socio-political forces working to that end.

Some measure of the influence of the tranquillizers on the prognosis of mental and emotional disturbances may be derived from the observation made by Benson and Schiele that the discharge rate of psychiatric patients has exceeded the admission rates since 1955, i.e. since these drugs were first employed.[22] Shepherd *et al.*, in their study, however, find that the psychotropic drugs have not substantially affected the contours or flow of the patient population. They note that fewer patients were admitted with a diagnosis of schizophrenia.[23]

I prefer, generally speaking, not to use meprobamate and phenothiazines in the treatment of psychoneuroses, but I would not deny a patient the relief they, or a sedative, can give in countering some transitory, distressful symptom, such as acute insomnia, agitation or restlessness.

Psychotropic Drugs

The use of psychotropic drugs is not without danger, so much so that some of them have been dropped from general use. Familiarity with their side-effects and toxic manifestations is necessary to obviate adverse and deleterious reactions to them.

The most frequently met with side-effects of parnate are insomnia, headache and dizziness. Less commonly a feeling of general weakness, drowsiness, dryness of mouth, anorexia, agitation, nausea and vomiting are encountered. A transitory hypertension, and rarely hypertension, with severe headaches, may be provoked. Renal disorder, liver pathology and blood dyscrasia have not been reported. Overdosage may result in central excitation with hyperpyrexia, or in vasomotor collapse. It is advisable not to combine parnate with tofranil or other antidepressant drugs.

Stelazine produces 3 groups of side-effects:

1. Akathisia-like symptoms: jitteriness, restlessness and agitation, insomnia.

2 Dystonia: spasms of limbs, convulsions, oculogyric crises, dysphagia, dysphasia.

3. Parkinsonism: masked facies, salivation, tremor, rigidity, ataxia, shuffling gait.

Other, less common, side-effects are nasal congestion, drowsiness, sweating. Transient jaundice and blood dyscrasia have been reported in a few cases. Hypotension may occur.

The combination of anti-Parkinsonism drugs with stelazine, especially in the first weeks of therapy, usually prevents side-effects. Stelazine should not be given to comatose or stuporose patients and with caution in combination with opiates and sedatives.

Vascular shock of severe degree has followed the application of ECT in patients receiving chlorpromazine hydrochloride.[2]

The psychotropic drugs have helped, both experimentally and clinically, to extend our insight into the mysteries of mental function and disorder. The success of the MAO inhibitors in depression, however partial it is, points to the operation of a neuro-humoral factor in mental functioning, while the differential action of the phenothiazines lends support to the role attributed by modern neurophysiology to the reticular system, viz. that it mediates integrative and adjustive behaviour. The new neurophysiology has oriented attention towards the reticular system and the neuro-humoral substances, such as serotonin, nor-epinephrine and acetylcholine, and the evidence is rapidly accumulating defining their link with mental function and disturbance.

SUMMARY

The mode of action of psychotropic drugs is reviewed. Two fresh concepts of cerebral functioning are outlined: one is the part played by a neuro-humoral substance, serotonin, at the synaptic level, and the other is the role of the reticular system in promoting homeostasis. The central influence of serotonin is suggested by the psychotogenic effects produced by its antimetabolites, LSD and mescaline. This would appear to be confirmed by the beneficial results obtained from the exhibition of inhibitors of the enzyme, monomine oxidase, which participates in the breakdown of serotonin.

The phenothiazines promote tranquillizations and homeostasis by a differential action on the reticular system, based on their chemical structure.

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