NEW HORIZONS IN THE CHEMOTHERAPY OF MENTAL DISEASE*

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It is not to the novelty of the new tranquillizing drugs that I must pay tribute for the great pleasure I am afforded in speaking before you, but to their popularity. In the United States the consumption of these medicines has soared at a fantastic and alarming rate since they first were hesitantly placed on the market in 1954. It is claimed that in total sales, tranquillizing drugs are exceeded only by antibiotics and vitamins. It has indeed become Big Business in the best American tradition. Even in Great Britain, concern has been expressed over a similar situation. I can speak only for the United States when I express the opinion that the medical

* A paper presented at the South African Medical Congress, Durban, September 1957.

profession has relinquished a considerable measure of its authority in the face of public demand. The word tranquillizer has achieved an honoured place in the several advertising and entertainment media—radio, TV, the ladies' magazines and of course on Wall Street. American psychiatry, sundered by ideological conflict, has failed to adopt a definitive position in this matter. In consequence, the bulk of physicians had little authority to resist the demands of their patients for the 'magic pills' on the one hand; and on the other the blandishments of skilful salesmen from the pharmaceutical houses. In fact, in the case of one or two of these drugs, illicit drug-store sales without prescription became commonplace. The psychiatrist has traditionally been a clinician, unsophisticated in the field of investigation. Necessary requirements by drug houses for clinical trials of their drugs overtaxed the few psychiatrists willing to try them, with the inevitable sequel of hurried, uncontrolled reporting, and sometimes unreasonable claims. On at least one occasion introduction of a new drug with mass advertising has preceded any report on its value in the literature. It has truly been a deplorable state of affairs.

Objective appraisal of the tranquillizers is hard to extract out of what is literally a public debate. I will give you my opinion for what it is worth. It is at least the critical opinion of one who has been associated with the development of these agents for therapeutic purposes since 1953. Given judiciously and systematically, the more powerful tranquillizers such as chlorpromazine are more effective in the treatment of schizophrenia and states of excitement than any other treatment, chemical or otherwise. In neurotic patients and normal individuals suffering from an excess of tension, all the tranquillizers may afford symptomatic relief. To what extent this is significantly greater than that afforded by other treatments is not clear. It is abundantly clear, however, that there is often no more justification for their prescription in this latter group of patients than there is for placebos or a sea voyage. It is to be hoped that the fad will soon pass, and with it the erroneous concept that personal inadequacies in the face of daily problems are susceptible to chemical solution. The path will then be clearer for the consolidation and enhancement of the notable gains these drugs have already made in the treatment of the seriously mentally ill.

The use of drugs to treat nervous and mental afflictions is as old as the hills. Aldous Huxley has commented that stimulating and depressant herbs were known to primitive man long before he had learned to till the soil. Even one of the brightest stars in the ataractic galaxy, reserpine, was employed by Indian physicians many centuries ago. The modern chemotherapeutic era in neuropsychiatry was ushered in by the discovery in France in 1952 of the unusual sedative properties of chlorpromazine. Shortly thereafter, the chemically dissimilar but pharmacologically related, reserpine was isolated from the old Indian snakeroot plant. Both these compounds enjoyed immediate success in clinical psychiatry and both produced sufficiently interesting effects upon the central nervous system to excite the interest of the laboratory workers. In consequence, many other similar substances have been synthesized and some marketed. And in addition, some notable advances in our understanding of central nervous system function may be expected in the near future.

What is a tranquillizing drug? No satisfactory definition of the term has ever been given. For my part, bromide and phenobarbital are good tranquillizers. If one were to except these on the grounds that they impair cortical function as they sedate, one would still have to include morphine as a tranquillizer. On this basis too, meprobamate (Equanil), perhaps the most popular of them all in America would be omitted, since in large doses it does cause mental confusion. To side-step controversy, one may say that there are two classes of tranquillizers. The phenothiazine series, of which chlorpromazine is the parent, and the reserpine derivatives comprise the powerful tranquillizers. Meprobamate, phenaglycodol (Acalo) and hydroxyzine (Atarax) represent the milder tranquillizers. While adequate criteria for their use are still not determined, the first group is in greatest demand for the psychotic patient and the mild group for the ubiquitous tension and anxiety states.

There are too, other drugs not classed as tranquillizers which must be considered. Many new non-barbiturate hypnotics have been developed in recent years (methylprylon) in the hope that they would lack the addictive properties of the barbiturates. It is doubtful whether this hope has, or can be, realized. Any drug which relieves anxiety, does not have unpleasant side-effects, and which in cumulative doses tends to euphoria, will be addictive in some individuals. It is well worth noting that the powerful tranquillizers like chlorpromazine have not offered convincing evidence of habituation, possibly because of unpleasant side-effects and lack of euphorizing qualities. Clear cases of meprobamate addiction, however, are to be found in the literature, complete with reports of withdrawal syndromes almost identical with those following deprival of barbiturates.

Benactyzine (Suavitil, Parasan) is an anti-cholinergic substance investigated by Jacobsen, the discoverer of Antabuse. In some patients it produces a state of well-being and is free of noxious side-effects. However, in many it evokes feelings of depersonalization and interruption of thought processes which are intolerable. It remains to be seen whether it will survive its clinical debut.

A number of other miscellaneous chemicals which includes lysergic acid diethylamide (LSD), ipronazid and various serotonin antagonists are in process of exploration both in laboratory and ward. They will be mentioned again later.

Lastly upon the chemotherapeutic horizon are to be seen the central stimulants, personified of course by amphetamine. Despite a number of recent introductions, e.g. ritalin, meratran, and a great deal of painstaking research, there are no major advances to report in the past 15 years.

The phenothiazine series of compounds is worthy of further consideration. Chemically rather simple, they are constructed upon the triple 6-carbon ring phenothiazine molecule in which two of the carbon atoms are replaced by a single nitrogen and sulphur atom. Attached to the nitrogen atom is a one to four membered carbon side-chain terminating in a substituted amino group. Later phenothiazines have a nitrogen-containing ring structure in place of the simple amino group (piperazine or piperidine). In some members of the series a halogen atom is added to the phenothiazine nucleus.

Small changes in chemical constitution appear to bring about considerable differences in pharmacology. For

example, drugs with the amino side-chain like chlorpromazine or trifluorpromazine (Vesprin) evoke many peripheral autonomic effects such as hypotension, dryness of mouth, etc. When this is replaced by a piperazine ring, autonomic effects are inconspicuous but extrapyramidal signs become commonplace. It is not possible to go further into the details of these correlations in this paper.

The therapeutic and toxic effects of chlorpromazine are well established and little needs to be said here. The author has always believed that intensive dosage with rapid increments of the drug to the limit of tolerance (which may run above 3,000 mg. daily) is the most successful and economical way of treating the acute or chronic schizophrenic patient. For manic and delirious cases where inhibition of motor activity is the primary concern, lower doses usually suffice. Despite clinical trials with over a dozen phenothiazines, none has proved therapeutically a great deal better than chlorpromazine. However, as is well known, this agent is handicapped by a multitude of side-effects, idiosyncratic responses such as jaundice and dermatitis. In very high doses it may cause confusion or convulsions. Substitution of fluorine for chlorine, as in Vesprin, appears to reduce, but not eliminate autonomic effects and also increases potency weight for weight. Exclusion of any halogen moiety as in promazine (Sparine) greatly reduces therapeutic potency except in so far as sedation is concerned. For this reason promazine is a good intravenous sedative and is used quite extensively for this purpose in alcoholic patients. In larger doses, it has had, in the author's hands, a convulsive incidence approaching 25% and cannot be recommended for the treatment of schizophrenic patients. Passing over a number of others in this group because of excessive toxicity or therapeutic mediocrity, we arrive at the piperazine phenothiazines. These have in common, a high potency—therapeutic doses averaging one tenth of that of chlorpromazine, a slower onset of action, progressively increasing sedation (the reverse tends to be true for chlorpromazine) and a powerful action on the extrapyramidal system. Prochlorperazine (Compazine), trifluorperazine (SKF 5019) and perphenazine (Trilafon) are in this class. While essentially similar, the latter two drugs appear to be more successful therapeutically than compazine. Since the literature at present contains only one or two references, it may be of interest to consider Trilafon in more detail.

TRILAFON

Thirty-seven psychotic patients were treated by a standard intensive method using Trilafon. With the exception of one case of Huntingdon's chorea, they were all schizophrenic. 17 suffered with acute illness (less than 6 months duration) and 19 had been ill for periods ranging from 9 months to 15 years. Females outnumbered males by two to one. Dosage of Trilafon ranged from a minimum of 4 mg. daily (in a child) to 208 mg. daily. Average length of intensive treatment, i.e. before discharge from hospital or cessation of treatment, was just over one month. About one half of the patients continued to receive a maintenance dose in the out-patient clinic. Where necessary, the drug was given in equivalent dosage intramuscularly until the patient was able to take it orally. No other treatment was administered during the period of study. Clinical results were classified as follows:

Recovered	5
Substantially improved (able to leave hospital)	13
Improved symptomatically	13
Unimproved or worse	7

Most of the patients in the last two categories were as might be expected those with chronic illness.

The following side-effects were encountered:

	%	
Persistent drowsiness	55	21
Gastric distress	8	3
Hypotension	8	3
Lactation	3	1
Dermatitis	3	1
Weakness	8	3
Parkinsonian syndrome	50	19
Dystonia (torsion spasm)	23	9

Lactation is a highly sporadic and interesting sequel to phenothiazine therapy. We have noted it with several of the phenothiazines. The secretion when analyzed proves to be true milk. While this was not so with the trilafon patient, lactation induced by other drugs has sometimes been accompanied by menstrual irregularities, not, of course, associated with the pregnant state.

Extrapyramidal syndromes are a most impressive aspect of phenothiazine treatment. It will be noted that the incidence with Trilafon is 50%. This is also true of Compazine and SKF 5019. With these drugs parkinsonism appears with doses of 30 mg. daily and up varying of course greatly in different individuals. It is always reversible upon reducing dosage or discontinuing the drug. The disorder is characterized by rigidity, some tremor, salivation, masking of the face and gait difficulties. The onset of this condition is frequently preceded by several days of restlessness and feelings of tension. Some investigators have considered this to be anxiety and have offered a psychodynamic theory in explanation. The author, however, regards it as acathisia—the motor restlessness described by Wilson. In addition, to parkinsonism, Trilafon produces two other neuromuscular abnormalities. Dystonic symptoms or torsion spasm may precede or develop independently of parkinsonism. One 12 year old schizophrenic girl developed spasm of the left neck muscles and shoulder girdle after a single dose of 4 mg. It sometimes has an explosive onset and may be almost epileptic in appearance. More usually, it persists for several days with periods of exacerbations sometimes involving the whole of one side of the body, but generally restricted to the neck and shoulders. A further side-effect is also likely an extrapyramidal manifestation. Complaints of dysphagia are made without parkinsonism or dystonia. On examination there is to be found localized rigidity of the tongue and pharyngeal muscles without actual incoordination of the swallowing mechanism.

While the aetiology of these fascinating effects is not clear, they are reproducible in monkeys, and in laboratories we have been attempting to find neuro-histological and bio-electric correlations of these disorders of function.

Benzotropine methanesulfonate (Cogentin) is highly effective in relieving these extrapyramidal symptoms when they become bothersome to the patients. Given parenterally, the effect is almost immediate. Cogentin also has a stimulant effect upon those who are lethargic from Trilafon—though not on normal individuals. Possibly there is a yet undiscovered neurophysiological relationship between sedation and

parkinsonism as induced by these drugs. It should be stressed that parkinsonism is rarely seen with doses of less than 30 mg. daily and is always reversible. Whether or not it is related to, or is necessary for a good therapeutic result is an open question. In the opinion of this author, it is not, and we do not deliberately attempt to produce the condition.

We have also used Trilafon to treat tension in small numbers of non-psychotic patients in doses of up to 24 mg. daily. With the exception of lethargy, there were no complaints of side-effects. Reduction of tension was variable, ranging from almost total relief to none at all.

Children appear to be especially sensitive to Trilafon, as Table I below indicates. This is somewhat unexpected in view of the fact that chlorpromazine is usually better tolerated by children than by adults.

TABLE I. EFFECTS OF TRILAFON ON EXTRAPYRAMIDAL SYSTEM

Sex	*Age*	*Diagnosis*	*Dose at onset*	*Day of Treatment*	*Disorder*
F	12	Schizophrenia	4 mg. (1st dose)	1	Dystonia Dyspagia
M	4	Schizophrenia	4 mg. daily	5	Parkinsonism
M	13	Neurodermatitis	4 mg. bid	3	Dystonia
F	12	Behaviour Disturbance	4 mg. tid	64	—
F	9	Behaviour Disturbance	4 mg. tid	6 months	—
M	16	Schizophrenia	5 mg. qid (IM)	4 days	Dystonia Parkinsonism

In summary, Trilafon is a highly potent drug which exerts beneficial effects upon acute and chronic schizophrenic patients which are as good as or better than with other phenothiazines. Side-effects of consequence comprise several variants of extrapyramidal dysfunction when the dosage is increased over 30 mg. daily (though they may appear with less). (See Table I).

It is necessary to exercise caution in giving it to children since the appearance of dystonia, while not dangerous, is certainly very alarming to the parents.

We are currently investigating two other phenothiazine drugs in the hope of finding one which has the high potency of Trilafon but without the extrapyramidal action. So far, however, almost all the really effective phenothiazines have caused this condition to some extent.

Reserpine and other alkaloids from Rauwolfia also produce parkinsonism as well as a multiplicity of effects, very much like chlorpromazine. We use reserpine seldom for the following reasons. It has a slow and somewhat unpredictable time of onset of effect. The ratio between parkinsonism and therapeutic level is small. It has a tendency to produce depressive reactions which may reach psychotic proportions. This property is shared to a much lesser degree with chlorpromazine. Depressive reactions have been notably frequent with the use of reserpine in treating hypertension. Despite the dissimilarity of chemical structure, the actions of reserpine and chlorpromazine are remarkably alike.

THE 'CENTRAL-RELAXANT' DRUGS

The term central-relaxant has been coined to describe a number of other drugs introduced in the past few years. They share muscle-relaxant properties which can be demonstrated experimentally, and sedative properties with little or no action upon the autonomic nervous system. In general, side-effects are few and they give none of the striking neurophysiological changes of the phenothiazines. In toxic doses, they produce confusion, coma, and ataxia, although the margin of safety is high. Meprobamate (Miltown or Equanil) is a derivative of the older drug mephenesin which itself had muscle-relaxant properties but was not found too effective clinically. Meprobamate has enjoyed enormous popularity in the United States and has been used indiscriminately by the public. In therapeutic doses of 400 mg. three or four times a day, it has a mild sedative action and a quieting effect upon the tense or agitated. Muscle spasm, especially when of psychogenic origin, is diminished. In somewhat larger doses, meprobamate may lead to mild euphoria, and in excessive dosage produces mild symptoms of intoxication very reminiscent of barbiturate or alcohol intoxication.

Meprobamate is even more limited in usefulness in the treatment of psychotic patients than are barbiturates. It is not a useful hypnotic in the presence of severe insomnia or agitation.

Despite its popularity, there is no clearly incontrovertible evidence to indicate that meprobamate is superior to barbiturates or bromide for the treatment of psychoneurotic and tension symptoms. Controlled studies are difficult to achieve and the therapeutic influence of other variables may well exceed that of the drug itself. In several attempts at controlled and double-blind studies to evaluate meprobamate, the author's group found it less effective than a placebo on one occasion, and more effective than phenobarbital on another.

The site and mode of action upon the nervous system is controversial. A specific change in thalamic electrical activity has been described without associated alteration in cortical leads. However, typical barbiturate-like fast EEG activity has been reported by others.

It seems that addiction to meprobamate does occur. Lemere in Seattle has reported several cases who developed severe withdrawal symptoms after discontinuance. The author has also seen two cases, both women, who were taking 4,800 mg. daily or more. Within 36 hours after withdrawal, they became irritable, confused and had grand mal seizures for several days.

As long as man reacts to stress with unresolved tensions, so long will he seek relief by one means or another. Meprobamate and to a lesser extent chlorpromazine and reserpine drugs are in fashion just now. The author fails to believe that these agents are specifics for anxiety. What advantage they enjoy over their predecessors lies chiefly in their lessened toxicity.

Phenaglycodol (Acalo) is a chemical cousin of meprobamate which has been recently introduced. Somewhat

more potent milligram for milligram it is essentially similar in action and side-effects. Clinical reports are too few to make an assessment at present.

Hydroxyzine (Atarax) is an antihistaminic drug which has sedative and muscle-relaxant properties with some mild autonomic effects. It is used in the same way as meprobamate.

Interest in the central stimulant drugs has increased of late because of their antagonism to the sedative and depressing properties of most of the tranquillizers. A number of stimulant-tranquillizer combinations are on the market. Their value is doubtful because there is so much individual variation in responsiveness to these drugs. In one patient, the stimulation is dominant, in another sedation is paramount. Meretran and Phenidylate are two recent non-amphetamine introductions. The author considers them less satisfactory than dextroamphetamine or desoxy-ephedrine, though they are perhaps better antagonists of reserpine-induced depression. A really good cerebral stimulant is still wanting.

HALLUCINOGENS

The subject matter of the remainder of this paper is more theoretical though no less controversial. The story of the Swiss chemist Hoffman's accidental discovery of lysergic acid diethylamide is well known by now. The substance, derived from ergot, belongs to the group of hallucinogenic agents. Very probably a majority of the drugs in the pharmacopoeia would cause hallucinations if the dose were sufficiently large. Atrophine, cortisone and mapharside are common examples. The term hallucinogen is best reserved for chemicals which in relatively small doses cause a temporary and reversible psychotic state as their main effect. LSD is unique in that doses of 20 millionths of a gram will do this. It is possible to secure measurable effects with as little as 4 millionths of a gram. The psychosis is undoubtedly a true exogenous toxic type of reaction with hallucinations, delusions, impairment of judgment, memory and orientation. However, it frequently bears a close resemblance to an acute schizophrenic reaction. On this account LSD is being used in experimental psychiatry as an experimental tool in schizophrenia research. Under the influence of the LSD psychosis patients may recall forgotten events, and release anxiety which has caused some to employ it adjunctively to psychotherapy. Good results are claimed. In passing, it may be said that schizophrenic patients, particularly chronic ones, are resistant to LSD and show minimal effects with even massive quantities.

LSD is also a powerful antagonist to serotonin. Serotonin or 5-hydroxy-tryptamine is thought to be an important neurohumor mediating inhibitory nerve impulses in the central system. Theories have been advanced that too much, or too little serotonin in the brain is responsible for mental disturbance, Irponiazid (marsalid) which will be mentioned again inhibits the enzyme mono-amine oxidase which normally destroys serotonin. In consequence, serotonin accumulates in the brain. Since iproniazid itself may produce a psychosis in large doses, the theory gains support. Reserpine administration on the other hand, appears to interfere with the power of the brain to bind serotonin, which is excreted in large quantities as its breakdown product, hydroxy-indoleacetic acid. Free circulating serotonin then, is responsible for the typical reserpine effects. It is supposed while these observations are highly attractive there are too many gaps and contradictions to justify great optimism. BromLSD for example, which is an even more potent inhibitor of serotonin than LSD does not produce psychoses. Further, chlorpromazine which is the most effective blocking agent of the LSD psychosis does not release serotonin.

Acting on the plausible assumption that an excess of serotonin has at least some connection with abnormalities of brain function, work is in progress to develop anti-serotonins—antimetabolites, of which a number of already known. Preliminary clinical trials have been disappointing.

Another substance which is coming into prominence as a hallucinogen is bufotenine found in toads, cohoba snuff and probably in some poisonous mushrooms. It is very closely related to serotonin, being dimethyl tryptamine. These, and other observations form the foundation of the 'Indole hypothesis' which postulates that a defect in the metabolism of indole-containing substances in the body leads to production of brain poisons in the body which in turn underlie mental illness.

This hypothesis has been linked with anoher hypothesis—the 'Adrenaline theory', since by a sort of tchemical legerdemain breakdown products of adrenaline can be viewed as indole derivatives. Catabolites of adrenaline have already been reported as causing artificial psychoses—notably adrenochrome and adrenoxin, which incidentally are formed in the course of time in vials of commercial adrenaline—giving so-called pink adrenaline. Further support is lent this hypothesis by the fact that mescaline, another well-known hallucinogen obtained from the North American cactus (Peyote) is chemically similar to adrenaline.

Unfortunately, these theories, attractive though they are, fail to recognize clearly that an artificial psychosis is in fact a delirium of special type—a disorder reflecting almost any disturbance of brain metabolism as, for example, anoxia or high fever. Unfounded though they may prove to be, it is highly encouraging to witness the almost daily strides being made in elucidating the process of brain metabolism. Consequential to this will be the synthesis of valuable clinical weapons. Iproniazid, one of a number of inhibitors of monoamine oxidase is such a one. Supposing there to be a deficiency of serotonin in the brain tissues in states of depression, the addition of iproniazid ought to help by reducing serotonin breakdown. Early clinical trials are said to be promising.

It would indeed be possible to continue longer in this vein but my time is up. Psychopharmacology or, if you prefer, neuropharmacology is growing up. Whether it is still in the neonatal period or whether it is nearing maturity is not yet clear. As a result of the research of the past five years, all the new tranquillizing drugs may fall by the wayside, but at least we have a road along which to travel.