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THE NATURE OF DRUGS WITH MENTAL ACTIONS AND THEIR RELATION TO CEREBRAL FUNCTION*

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If our descendants should ever look back at the present era in psychiatry, they would probably call it the age of psychopharmacology. Scientific interest in drugs with mental actions has been mounting rapidly in the last five to ten years. Meetings, conferences and symposia have multiplied in parallel. On the pharmacology of a single drug, chlorpromazine, at least 262 papers have appeared between 1954 and 1956. Although I am not running for election, I propose nevertheless to take the high road tonight. The material to be presented includes the author's clinical experience, research and the consensus of the literature. We shall consider some of the newer agents, specifically the tranquilizers and hallucinogens.

Practically every drug in the pharmacopeia may exert a mental action under certain conditions, in a broad and non-specific sense. Specific psychopharmacological agents are fewer in number. Specificity is defined clinically here to indicate that the qualitative action of the agent is characteristic and appears regularly at relatively low dosage in most

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subjects. The tranquilizers and hallucinogens are specific agents in this sense.

First of all, a few words about mescaline and LSD. These two agents belong to the group of hallucinogens or psychotomimetics. Single dosage of one of these drugs elicits symptoms in normal subjects which are clinically similar to symptoms in patients with a naturally occurring mental disorder. The reactions include autonomic effects, hallucinations and other perceptual disturbances, emotional aberrations, depersonalization, and disturbances of the thought processes. The effects of a single dose last six to twelve hours. They have been useful as research instruments in experimental psychiatry and are also claimed to produce therapeutic effect in some individuals.

Attempts have been made to explain their actions in terms of biologically occurring substances. Mescaline is a primary amine with some resemblance to epinephrine and norepinephrine. However, its pharmacological actions as a whole cannot be classified as typical of those of these sympathomimetic amines. For example, mescaline initiates reflexes by chemoreceptor stimulation in heart and lungs, stimulates autonomic ganglia and lowers arterial blood pressure on intravenous injection in cats and dogs. LSD is lysergic acid diethylamide. Structurally it is a member of the ergot alkaloid group, with a lysergic acid nucleus and a side-chain similar to that in the ergonovine series. As with mescaline, most of the pharmacological effects of LSD provide little information on its psychotomimetic action. Information is beginning to appear on the disturbances of central neurophysiology produced by both drugs but their relationship to the hallucinatory state is obscure.

The most challenging pharmacological action of LSD noted to date is its capacity to antagonize the effects of serotonin. Serotonin, or 5-hydroxytryptamine, occurs naturally in various tissues of a number of species. In the brain, it is present in highest concentrations in the brain stem, particularly the hypothalamus—the same areas in which norepinephrine is concentrated. Its physiological functions are not fully established as yet. With respect to brain, there is initial evidence that it may function as a neurohumoral transmitter. LSD exerts a specific and potent antagonism to various effects of serotonin. This has been mostly demonstrated in peripheral smooth muscle, such as the rat uterus, cat pulmonary vessels and other test objects. According to one concept, the mechanism of this antagonism between LSD and serotonin is a com-

petitive inhibition on an antimetabolite basis. LSD and some of the other known hallucinogens contain an indole nucleus in their structure, as does serotonin.

On account of these facts, speculations have arisen that the mental actions of LSD and some other indole-containing hallucinogens are mediated by antagonism to the action of serotonin normally present in brain. Stated in another way, this would mean that the serotonin in our brain may help keep us sane. If so, it would follow that certain naturally occurring mental disorders may be due to a metabolically induced serotonin disturbance.

There is evidence for and against this particular mode of origin of some experimental psychoses and the issue is far from resolved. Serotonin disturbance in naturally occurring mental disorders is a more far-reaching concept and consequently a much more tenuous speculation. However, these ideas have and are generating much research and may have made some penetration into normal brain mechanism. We shall pick up the thread again in the discussion of reserpine.

We turn now to the major tranquilizers. Tranquilization is an expression which has recently been introduced into pharmacology and clinical psychiatry. The tranquilizer group has also been designated by the names ataraxics, phrenotropics and others. Chlorpromazine and reserpine are the two best known and most effective; meprobamate (Miltown, Equanil) is just about as popular but is less effective therapeutically in highly disturbed states.

Tranquilization is a descriptive term. It is intended to indicate a general reduction of motor activity, emotional calming, reduced hostility, anxiety and general excitability to external stimuli, quietness and some drowsiness. It is implied that these effects occur without true hypnosis or anesthesia, since the subject is easily roused to alert contact with the environment. As Dr. Paul Hoch* may tell you, it is usually claimed that the tranquilizers are qualitatively superior to the barbiturates on the basis of producing less drowsiness, less mental clouding and impairment of mentation. This qualitative distinction may ultimately prove to be somewhat less clear than now seems apparent. Reserpine tranquilization, for example, is quite similar clinically to that produced by morphine and by small doses of the long-acting barbiturates. In addition, there is a need for more quantitative data to evaluate the amount of

* Hoch, Paul H. New drug therapy in psychiatry: Clinical uses and abuses in mental disorders. Presented at the 1956 Graduate Fortnight and to be published in a later number of the Bulletin.

therapeutic action per unit of hypnotic effect for the tranquilizers as compared with the sedatives.

In addition to being a descriptive term, tranquilization has implied fundamental differences in the mode of action of the newer drugs as compared with standard sedatives.

Chlorpromazine and reserpine have very dissimilar chemical structures. Chlorpromazine is a synthetic phenothiazine derivative with about 1000 or so congeners; its structure is similar to that of certain potent antihistaminic agents but chlorpromazine itself has only weak antihistaminic activity. Reserpine is a complex alkaloid of the Rauwolfia species; it also has a large number of congeners and is quite similar to yohimbine in structure and pharmacological actions. Both chlorpromazine and reserpine may be said to have no effects, merely side-effects. There may be some truth in this quip because their properties are so numerous and complex. In spite of their chemical dissimilarities, the two drugs have certain common properties in addition to the tranquilizing action. These may be summarized briefly as follows: depression of diencephalic activity; disturbance of the temperature regulation mechanism; hypotensive action; the production of parkinsonism-like syndromes; local anesthetic action; and various hormonal dysregulations.

Chlorpromazine has effects not exhibited by reserpine. These include: potentiation of the effects of analgesics, hypnotics and narcotics; weak adrenergic blocking and sympatholytic action; weak antihistaminic activity; liver toxicity; and a strong antiemetic action. The significant point is that tranquilizing action is not correlated with or easily explained by any of these properties so far.

The type of action on the autonomic system differs. Reserpine strongly reduces sympathetic outflow to the periphery by virtue of its diencephalic depressant activity. The resulting picture is therefore one of relative parasympathetic dominance. Many clinical effects of reserpine are explainable on this basis: the hypotensive action, bradycardia, facial flush, nasal stuffiness, miosis, and increased gastrointestinal activity with diarrhea. Chlorpromazine has significant autonomic actions but these are more diversified and do not produce a shift in general autonomic balance.

There is a considerable amount of information available on the autonomic actions, particularly with reference to Dr. Page's* territory, the

* Page, Irvine H. A clinical evaluation of antihypertensive drugs. Presented at the Post Graduate Forum. To be published in a later number of the Bulletin.

cardiovascular system. I shall remove myself from that territory with the simple statement that the autonomic effects of both drugs do not show a 1:1 correspondence with their tranquilizing action. This statement is true for practically all drugs which have autonomic and mental effects because of the complicated interrelationships between these two sets of actions. There is some interesting indirect evidence that the depression of central sympathetic centers by reserpine is a mechanism which is separate and discrete from its tranquilizing action.

This leads us to a possible explanation of the tranquilizing action on the basis of other known central mechanisms.

Neither drug produces the low voltage, fast activity in the EEG which is so characteristic of small doses of the barbiturates and other sedatives. With larger doses, chlorpromazine produces a normal sleep pattern in the EEG whereas the effects of reserpine are more varied. Both drugs have been reported to exert an action on the brain stem reticular activating system. There is an impressive amount of evidence that the activating system is related to level of consciousness. Stimulation of the system produces alert, aroused behavior in animals; lesions produce lowered consciousness and responsiveness. The corresponding electrocorticogram is characteristic for each state. Chlorpromazine in animals depresses the ascending portion of the reticular activating system. This property in itself would explain the somnolence but not necessarily the entire tranquilizing effect, since reticular system level of activity has not been shown yet to correlate with emotional states. One research group has also found that rather high doses of chlorpromazine stimulate the activating system.

Rather unexpectedly perhaps, reserpine has definite excitant actions on the central nervous system of animals. The drug stimulates the reticular activating system; it lowers the threshold for electrical stimulation of the limbic system and the seizures become more prolonged and powerful; it lowers the threshold for convulsions produced by transcranial electrical stimulation (electroshock); and increases monosynaptic spinal reflexes.

If reserpine does stimulate the reticular activating system in man, the expected effect would be in the direction of behavioral arousal. Its tranquilizing effect would then have to be explained by another concurrent action, probably depression of the hypothalamus. Bilateral hypothalamic lesions in cats and monkeys produce a somnolent state

similar to that produced by reserpine and chlorpromazine in man. It is classic to regard the hypothalamus as an autonomic and somatic motor coordinating center for the flight-fight reaction. Both drugs probably depress hypothalamic function. Some of the evidence is as follows: their suppression of sham rage in decorticate animals; disturbance of temperature regulation; and the various endocrine changes which may be initiated at the hypothalamic level. At usual dosages, reserpine is a weaker hypnotic than chlorpromazine, probably because of the combined reticular activating stimulation and hypothalamic depression by the former drug. There is also evidence that chlorpromazine depresses the activity of the limbic system in animals; this system is probably normally involved in emotional reaction to the environment.

Both drugs affect the cerebral cortex directly, although this action is difficult to disentangle from the interaction of cortical-subcortical circuits. Chlorpromazine suppresses certain conditioned reflexes in doses which do not affect responses to unconditioned stimuli. The drug also appears to increase the degree of inhibition exerted by the cortex on the hypothalamus.

Although both drugs produce parkinsonism-like syndromes in some subjects, conversely they may reduce tremor and other involuntary movements when administered in cases of extrapyramidal disorders. The theories for this apparently paradoxical set of actions involve the interrelationships between the reticular activating system and extrapyramidal nuclei, and are of course highly speculative.

The most challenging biochemical aspect of reserpine action is its relationship to brain serotonin. According to the research group at the National Institutes of Health, the central actions of reserpine are mediated through serotonin. Normally, serotonin is considered to exist in a bound state. After administration of a single dose of reserpine to animals, a profound drop occurs in the first 24 hours in the concentration of brain serotonin which then slowly returns to normal after a six to seven day period. The amount of decrease in brain serotonin depends on the amount of reserpine administered, but a drop is still measurable with dosages in the range of those used in human therapy. Along with the decrease in brain serotonin, there occurs an increase in the urinary excretion of 5-hydroxyindole acetic acid. This latter compound is a breakdown product of serotonin. It arises from action of the enzyme, amine oxidase, on the serotonin which has been released from the bound state.

Serotonin levels in the intestinal tract and blood platelets also fall after a single dose of reserpine. The drug would therefore appear to be a general releaser of serotonin from the bound state in the body depots.

Certain findings appear to indicate that the level of serotonin in the brain is correlated with behavior. When rabbits are given reserpine alone, they are sedated. The free form of brain serotonin is presumably at a low level. When reserpine plus amine oxidase inhibitor (Marsalid) are given together, the animals become hyperactive, have dilated pupils and other signs (which are also present after independent administration of LSD). Because destruction by amine oxidase is inhibited, it is deduced that free brain serotonin which has been released from the bound state by reserpine may be at a high level. In concordance, if large amounts of serotonin precursor (5-hydroxytryptophane) are administered alone, the animals show the same symptoms that follow administration of reserpine plus amine oxidase inhibitor.

According to the N.I.H. group, other therapeutic agents such as barbiturates and chlorpromazine do not have effects on brain serotonin. There is some preliminary evidence that reserpine in man causes increased urinary excretion of 5-hydroxyindole acetic acid.

The results of the N.I.H. group, therefore, show a provocative relationship between three substances, all of which contain the indole nucleus: LSD, serotonin, and reserpine. There are many issues, however, that need clarification. These include the possible relationship of the N.I.H. findings to the earlier theory of LSD action by competitive inhibition of serotonin on an antimetabolite basis. The jig-saw puzzle is disturbed by the findings of another group, namely: that very low doses of LSD (and mescaline) facilitate rather than antagonize serotonin contraction of rat uterus, whereas both reserpine and chlorpromazine antagonize this effect. It is also possible that the lowering of brain serotonin may be coincidental rather than causally related to the therapeutic effect of reserpine. And even if there should be a direct relationship, the actual role of brain serotonin in the etiology or pathogenesis of the mental disorders still remains an open question.

The central actions of meprobamate have received less study than those of reserpine or chlorpromazine. Meprobamate is a simple carbamate structure and is not correlated chemically with either chlorpromazine or reserpine. This fact makes any theory about competition of these three drugs for a single receptor site most unlikely. Meprobamate

also differs pharmacologically in many respects from chlorpromazine and reserpine. Its most specific neuropharmacological action is a depression of polysynaptic spinal reflexes. Parkinsonism-like symptoms have not been described on administration to man. It does not antagonize stress and anxiety reactions in monkeys or rats. It does produce significant changes in autonomic functions and has a rather pronounced protective effect on electroshock seizures in animals. Meprobamate potentiates barbiturate sleeping time in mice (as do reserpine and chlorpromazine). It has no effect on serotonin release from the central nervous system.

Some other tranquilizers introduced more recently are promazine and frenquel. Their clinical effectiveness is not fully established as yet. The neuropharmacology of frenquel is still in the developmental phase and the most recent clinical evaluations indicate that its therapeutic action is quite capricious.

It is apparent then that there are discrepancies between the tranquilizing capacity and pharmacodynamic effects of the drugs that have been discussed. This discrepancy is highlighted by the fact that both reserpine and chlorpromazine have a common, wide spectrum of clinical indications. Further obvious difficulties arise because chlorpromazine and reserpine may both intensify psychotic states in a fair number of patients.

What about the future? Chlorpromazine and reserpine can each be related to larger groups of known drugs, both in the chemical and pharmacodynamic sense. Further experimentation will probably be guided by this knowledge in clarifying mechanisms and selecting more effective compounds for trial. In particular, the refinement of the tranquilizing action and its separation from other discrete mechanisms is an immediate goal. This will depend in part on the increase in knowledge about the underlying neurophysiological and biochemical mechanisms of brain function. Work in behavioral laboratories should provide the necessary interactional psychology, without which the total effects of drug administration cannot be explained.

In a word, after science has moved on, our descendants will then be able to decide whether the age of psychopharmacology was worth it all!