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IN THE
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PREFACE

By the Editor, *British Medical Journal*

THE number of new drugs being marketed has increased over the last decade and goes on increasing. While many are minor variations on existing remedies, others have been original discoveries which have brought great benefit to the patient. In order to help the practising doctor to compare the newer drugs with each other and with those many old remedies that are still the best of their kind, the *British Medical Journal* published from 1958 to 1960 a series of authoritative articles under the general heading "Drug Treatment of Disease." They have been fully revised by their authors, and form the chapters of this book.

Here roughly grouped for convenience and supplemented by an Index, the papers will, we hope, be of help to the doctor in choosing the best drug for his patient. Their emphasis is deliberately on only one part of treatment—the medicinal. But modern remedies are apt to be both more potent and more toxic than their predecessors, so that a series of articles devoted to their properties and uses seemed timely.

HUGH CLEGG

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PHARMACOLOGY OF TRANQUILLIZING DRUGS

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BY definition "tranquillizers" cause sedation without, as a rule, clouding consciousness. Because these substances change the responsiveness to external stimuli and influence processes of emotion and thought, specialized neurological and psychological methods are required to assess their efficacy. In order to use the drugs judiciously, much more than is at present known should be found out about the nature of their action.

The tranquillizers can be classified into two main groups. The first comprises the drugs used mainly in psychoses (reserpine, chlorpromazine, and their congeners), while the second group consists of substances predominantly administered to patients suffering from neuroses or to normal people undergoing a severe emotional or physical ordeal.

I. DRUGS USED MAINLY IN PSYCHOSES

The members of the first group have in common the production of profound alterations in brain metabolism, but, in spite of great similarity in the indications for their use, in the therapeutic effects obtained, and in some of the side-effects encountered, the biochemical actions appear to be totally different.

Reserpine

The reserpine-like substances interfere with the retention in brain tissue of a number of amines, such as 5-hydroxytryptamine (5-HT) and the "catecholamines" (adrenaline, noradrenaline, and hydroxytyramine), of which noradrenaline is the main representative in nervous tissue (Pletscher *et al.*, 1956; Paasonen and Vogt, 1956; Holzbauer and Vogt, 1956). These substances are mainly concentrated in the hypothalamus and the tegmentum of the midbrain (Amin *et al.*, 1954; Vogt, 1954), and 5-HT also in parts of the limbic system (Paasonen *et al.*, 1957); they presumably play a role in the specialized function of these regions.

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The biochemical action of reserpine is not restricted to the brain: 5-HT also disappears from platelets and intestine, noradrenaline from peripheral sympathetic neurones (Muscholl and Vogt, 1958), and sometimes from the adrenal medulla. We do not know whether the depleting action in brain is restricted to the amines just listed: there may be others of even greater functional importance which are as yet unidentified and which are also lost.

The fundamental process which causes reserpine to lower the stores of amines in the tissues is not known for certain; yet Hughes *et al.* (1958) have obtained evidence that reserpine blocks an energy-requiring transport mechanism which allows uptake of these amines by the cell against a concentration gradient. The block takes place instantaneously when the reserpine reaches the tissue, but the amines leak out of the cells only slowly, and such signs of reserpine treatment as are related to the loss of amines follow this slow time course.

Though we cannot interpret the action of reserpine in terms of its interference with the binding of amines in brain because we do not understand the role played by these compounds in central function, the fact remains that reserpine has metabolic effects on hypothalamus, mesencephalon, and limbic system. In view of the role attributed to the limbic system in emotional processes (MacLean *et al.*, 1956), this finding may be significant. It is corroborated by electroencephalographic evidence of seizure-like waves in the limbic system of reserpinized animals (Gangloff and Monnier, 1955; Killam and Killam, 1957). MacLean *et al.* (1956) caused functional inactivation of the hippocampus (part of the limbic system) of cats by injecting solid carbaminoylcholine into the tissue and setting off permanent synchronized neuronal activity simulating an epileptiform seizure; they observed that such cats had behavioural changes and alterations of conditioned reflexes which greatly resembled those after reserpine; they also showed that reserpine slows down the turnover of sulphur in the hippocampus.

We do not know whether the interference with hippocampal function is related to the disappearance from those sites of the accumulated 5-HT. Altogether, the assessment of the relation between disturbance of function and state of the amines stored in special parts of the brain is at present entirely speculative. We do, however, know that in the peripheral nervous system, where conditions are less complex, the disappearance of noradrenaline from adrenergic neurones leads to failure of peripheral sympathetic activity. It is to be expected that, in prolonged treatment of psychiatric patients with large doses of reserpine, depletion must be such as to cause varying degrees of peripheral "functional sympathectomy." Analyses of urinary excretion of noradrenaline after ad-

ministration of reserpine have confirmed this expectation by demonstrating a fall in the excretion of noradrenaline (Gaddum *et al.*, 1958; Kuschke and Ditfurth, 1958).   Whether the disappearance of noradrenaline and other amines from the brain interferes with the activity of the sympathetic centres was tested in experiments in which this activity was monitored by recording the action potentials from the preganglionic fibres in the cervical sympathetic nerves of the cat (Iggo and Vogt, 1960).   After four days of treatment with large doses of reserpine, nervous discharge in the undisturbed animal was not impaired; furthermore, noise and asphyxia elicited increased electrical activity just as they do in the normal cat.   Needless to say, all this activity had no peripheral effects, since the postganglionic adrenergic fibres had lost so much of their transmitter substance noradrenaline as to be unable to activate peripheral tissues.   Central sympathetic activity, however, does not appear to depend on the presence of appreciable stores of amines in the cerebral tissues.

Chlorpromazine

Chlorpromazine is known to be a potent inhibitor of many enzymatic processes, and its depressing action on the brain is likely to be related to this property.   The turnover of phospholipids, so important in cerebral function, is among the processes affected; and the respiration of electrically stimulated slices of guinea-pig brain is inhibited by very low concentrations of chlorpromazine (Ansell and Dohmen, 1956; McIlwain and Greengard, 1957).   In view of the general action of chlorpromazine on enzymes it is not surprising to find that its pharmacological actions are unusually numerous (Courvoisier *et al.*, 1953).   Many of these are undesirable sideeffects from the point of view of the clinician; such are the depression of the bone marrow, the autonomic actions, the galactorrhoea, and the production of Parkinsonism, an effect chlorpromazine shares with reserpine.

The electroencephalographic findings after chlorpromazine are different from those after reserpine.   The site most consistently affected appears to be the region of the reticular formation responsible for wakefulness and arousal: the threshold to stimuli such as pain, electric currents, and injections of adrenaline is raised and the responses are shortened or even abolished (Hiebel *et al.*, 1954; Himwich, 1955; Bradley, 1957; Bovet *et al.*, 1957).   However, the magnitude of this effect varies with the experimental conditions, and the importance attributed to it therefore with the individual experimenter.   Some consider the therapeutic effects to be more closely linked with electroencephalographic changes in the limbic system,

where high doses cause bursts of spikes which originate in the amygdala and can lead to generalized seizures (Preston, 1956). The attractiveness of this view lies in the fact that it provides a common basis for the action of reserpine and of chlorpromazine.

A third site of action of chlorpromazine is shown by the ingenious technique of "self-stimulation" (Olds *et al.*, 1957). Olds discovered that animals carrying electrodes implanted in certain parts of their brain appear to derive satisfaction from electrical stimulation of these parts. When the animals have found out that treading on a lever will deliver a shock, they begin to operate the lever at frequent intervals. Rats given chlorpromazine no longer administer the shocks to their brain when the stimulating electrodes are implanted in the posterior hypothalamus, but continue self-stimulation when the electrodes lie in the anterior hypothalamus. The drug must therefore produce some important change in the posterior hypothalamus.

The use of these pharmacological observations for the explanation of the therapeutic action is limited by our lack of knowledge of cerebral function. If one assumes the therapeutic effect in psychoses to be due to an inhibition of overwhelming drives and irrepressible stimuli which are kept up by pathological processes in the brain, one can visualize these drugs as acting by inhibition of the metabolism in the offending regions of the brain. It is impossible to tell whether the limbic system is one of these offending regions and the spikes observed correspond to certain inhibitory phenomena occurring there, or whether the limbic system is stimulated by the drugs and such stimulation leads to useful inhibitions of other parts of the brain.

CHANGES IN PERSONALITY

There is no doubt that chlorpromazine and reserpine produce profound changes in personality. Some assessment of the changes can be made by psychological experiments on normal people and animals. For obvious reasons, tests on man can only be carried out in a very limited way; in such an investigation on the effect of a single dose of the chlorpromazine analogue mepazine ("pacatal"; N(1-methylpiperid-3-yl)phenothiazine HCl), highly skilled work had to be performed by the subject on the so-called triple tester. The result (Steinberg, 1957) was impaired performance, reduction in the tachycardia which normally accompanies effort, and lowering of the "level of aspiration," which means the improvement the subject expects to make on a repetition of the test.

More striking still are the effects observed in animals, to which the drugs can be given more freely: previously aggressive animals become tame and easy to handle; they develop an indifference to

unpleasant stimuli shown in the loss of conditioned avoidance responses. Rats and monkeys, for example, were trained to avoid an electric shock by leaving a particular area of their cage when an acoustic or visual signal heralded the coming of the shock. After an injection of chlorpromazine or reserpine they failed to heed the conditioning signal, though they were perfectly capable of performing the motor effort required to avoid the shock (Smith *et al.*, 1957). Their behaviour had become inappropriate, and normal contact between animal and environment had been lost.

The results of these psychological tests suggest that a patient, though benefited while under treatment with one of these potent drugs, cannot be considered equivalent to a perfectly normal human being. The same conclusion is reached if we remember the general inhibitory effects produced on cerebral metabolism by these substances: it is inconceivable that inhibition should be entirely restricted to the unwanted cerebral activities.

II. DRUGS USED MAINLY IN NEUROTIC AND NORMAL PEOPLE

The drugs of this group lack the profound effects on brain metabolism seen in the first group; in fact, nothing is known about the biochemical side of their mode of action. Four substances, completely unrelated in chemical structure and in their pattern of pharmacological actions, will be discussed.

Methylpentynol

The first, methylpentynol ("oblivon"), is a higher alcohol and entered therapeutics as a hypnotic. Trotter (1953) introduced it into dentistry to reduce apprehension, and its success was proved by controlled double-blind trials. It then became important to ascertain by psychological tests whether it was safe to allow such patients to go home unescorted or to drive a car. It was found that the subjects, though unmistakably less inhibited in their behaviour after a dose of 0.5 g. than before, performed well in tests which mimicked driving activities (Trotter, 1954). On the highly exacting triple tester, however, the performance, level of aspiration, and tachycardia of effort were reduced (Dicker and Steinberg, 1957).

Benactyzine

Benactyzine ("suavitil," benzilic acid diethylamine ethyl ester HCl) is a substance with an atropine-like action. Its effect on

behaviour was discovered on animals (Jacobsen and Skaarup, 1955): a cat, used to obtaining food by pressing a lever and given benactyzine, went on pressing for food in spite of being greeted by a blast of air when operating the lever; when untreated, the cat refused to touch, and even hissed at, the lever. The drug also inhibits conditioned avoidance responses and thus has in common with reserpine and chlorpromazine the production of indifference towards disturbing stimuli. The results of tests on anxious people have been contradictory, and proof of efficiency in a controlled trial is still lacking (Davies, 1956; Coady and Jewesbury, 1956; Alexander, 1957; Raymond *et al.*, 1957). The dose is about 1–4 mg. three times a day.

Hydroxyzine

Recently, promising reports have been published about the tranquillizing effects of a new antihistamine drug, hydroxyzine ("atarax"). In a clinical trial on students suffering from psychological disorders (Becattini and Gallini, 1957), the drug, given in a daily dose of about 0.1 g., scored higher than benactyzine. Hydroxyzine is a chlorobenzhydrol derivative, and chemically related to the anti-hallucinatory drug azacyclonol ("frenquel"). It appears to relieve anxiety without impairing critical faculties; it is also useful in conditions of agitated coma; such patients may require up to 1 g. per day in divided doses (Ayd, 1957). It has fewer side-effects than benactyzine, but increases any tendency to seizures. It has in common with the tranquillizers hitherto discussed an inhibitory effect on conditioned avoidance reflexes (Levis *et al.*, 1957). It raises the arousal threshold to sensory stimuli (Bradley, 1957), probably by an action on the reticular formation.

Meprobamate

The fourth drug, meprobamate ("equanil," "miltown"), is chemically and pharmacologically related to the central relaxant of skeletal muscle, mephenesin. Its tranquillizing action, however, is exerted by doses (0.4–0.8 g. several times a day) which are too small to affect muscular tone. Its mode of action differs from that of all other tranquillizers. Monkeys and rats become manageable and fearless, but the loss of fear does not lead to loss of conditioned avoidance reflexes. Thus—and this is in contrast to the behavioural effects of reserpine, chlorpromazine, benactyzine, and hydroxyzine —appropriate avoidance of noxious stimuli is not impaired (Berger, 1957), though inhibition ("freezing" of rats, for instance) by

imminent danger is greatly reduced (Hunt, 1957).   Specific effects on emotional behaviour were also shown in ducklings, which lost their fear of strange objects and the capacity of "imprinting"—that is, becoming attached to a parent duck or a decoy (Hess, 1957).

In man, double-blind clinical trials on meprobamate (Hollister *et al.*, 1957) have shown improvement of anxiety neuroses and even of certain psychoses.   In contrast to the other tranquillizers, it did not impair performance or level of aspiration in psychological experiments on the triple tester (Steinberg, 1957).   These observations, and the findings with conditioned reflexes, show that the drug is capable of checking emotional responses while not interfering with skill, rational behaviour, and adequate responses to environmental stimuli. These would seem to be advantages for the ambulatory patient.   It would be of the greatest interest to know the precise site and mode of action of meprobamate.   When low doses are administered to monkeys, electroencephalographic changes (of a type associated with decreased activity) are found only in a number of thalamic nuclei (Hendley *et al.*, 1957).   This is no proof that the thalamus is the only or even the fundamental structure through which meprobamate exerts its clinical action, but it shows that the pattern of activity of this drug is different from, and less diffuse than, that of other tranquillizers, and that the thalamus plays some important part in its effects.

It will be obvious from the above that many problems remain to be solved.   Thus it should be emphasized that, within a group of chemically related substances, important differences may occur in the pattern of effects produced.   This gives hope that minor modifications in the structure of existing drugs will lead to the discovery of more useful remedies.   Too few data exist on the comparison of the actions of the new drugs with similar actions of old, well-established remedies. And, most important of all, the dangers of blunting emotional responses by giving tranquillizers to normal people are not fully understood but very real indeed.   In patients in whom an emotional disturbance may have a paralysing effect and render life unbearable, a tranquillizing drug may restore normal behaviour and increase efficiency.   In normal people, however, the counterpart to blunting emotional responses appears to be reduced performance, and only in very exceptional conditions will this not be too high a price to pay for the subjective feeling of well-being produced.

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