if it is searched for. A typical dilemma may be illustrated by the nocturnal panic attacks of the woman torn by resentment for some reason and anxious to punish her husband by refusing him intercourse; while at the same time anxious about the integrity of her marriage if she pursues her desires. It would be ingenuous not to accord such a situation the importance it deserves. It may be found, and indeed it frequently is, that she adopts the course of alternately accepting and rejecting one of the two possible courses of action, and a self-perpetuating cycle is thus established. The habit of switching from one solution to the other may be broken once it is realized how anxiety is being caused, and the psychiatrist may be called on to give a clear lead if he legitimately can.

With an intelligent patient it is worth spending a little time showing how morbid anxiety is established, and how in its turn it produces somatic dysfunction. This is necessary if he is to collaborate with any enthusiasm in the future treatment of his case. He must be able to see where he is going and what the purpose of his efforts is to be. It must not be forgotten that, although only a minority of psychiatrists in this country are analytically orientated, the same does not apply to the general public, who are Freudian to a man. A good deal of time may have to be spent explaining why infantile experience is being ignored. Indeed, it is said that there is now a cult which concentrates on intrauterine experience, and a young woman recently asked that we should discover what her parents talked about when she was a foetus.

We accept it as axiomatic that attitudes and sentiments can be taught to a child, and forget that a similar technique may be taught to an adult. This re-educational or habit-forming psychotherapy requires certain conditions. First, the patient should understand in concrete rather than abstract terms what is being aimed at, and this objective should be framed in positive rather than negative terms. Keeping calm instead of getting panicky is too abstract, and not rushing about the place has the disadvantage of being negative. Secondly, he must consider very carefully whether he objects to the habit, for if he does he will never acquire it. Thus it would be pointless to suggest gentleness to a professional boxer, and dangerous to invite more extroverted aggression from a nursemaid. Thirdly, the desirability of the habit must be sold to him so that he will really want it. The conditions that govern all human endeavour have then been set up.

The usefulness of relaxation therapy in the treatment of anxiety states is becoming increasingly known (Garmany, 1952). The technique involves the teaching of a precise motor habit and is not to be confused with the relaxation of the analyst's couch, which is quite a different matter. The teaching is based on the fact that tense muscles in anxious patients show continuous action potentials, and that these may be dispelled concurrently with the symptoms. The ordinary patient is quite incapable of relaxing to order, and must be taught in the same methodical way that would be shown by a golf professional who hoped to implant a swing. At Westminster Hospital it has been found convenient and effective to entrust this work to physiotherapists who have been specially instructed in what is required, and small classes of six are taken twice a week. There is a separate class for each sex, and a separate class for beginners. The patients who benefit most are those who are bright, obsessional enough to have the drive to master the technique, and middle-aged. In theory patients benefit from both relaxation and from re-educative psychotherapy. In practice it has been found that younger patients stand immobilization less well than those over 40. Conversely, they learn new mental habits more easily, as might be expected. Patients with recently developed panic attacks, when these do not herald a depressive illness, do very well with relaxation.

It will be noted that there is no mention of prefrontal leucotomy in the treatment of anxiety states. This quite truly indicates a belief that the indications for this operation in tension states are very few and far between. There are,

however, occasions on which the operation has been recommended and carried out, but such a case did not occur during this series.

Summary

A study has been made of 158 patients with the diagnosis of anxiety state, which represented about 25% of a consecutive series of patients seen in the out-patient department of a teaching hospital. All cases showing tension were included, whether hysterical features were prominent or not, following the Geneva International List.

The incidence of constitutional predisposition was found to be very high even when restrictive criteria were applied in assessment. The operative stress factors were far more commonly to be found in the personality itself than in external factors, such as housing or domestic difficulties. The incidence of tension states is highest in the fourth decade, and relatively low in adolescence and old age.

The use of drugs in treatment is discussed together with a consideration of the forms of psychotherapy found most useful in this condition.

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"MERATRAN"

A NEW STIMULANT DRUG*

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There have been a number of reports in the medical press of the United States on the properties of α -(2-piperidyl) benzhydrol hydrochloride ("meratran") and its value in the treatment of depression and fatigue states. Brown and Werner (1954) found that in the larger animals, such as dogs, meratran produced a marked increase in purposeful activity which, although it was more intense than that produced by amphetamine, was not accompanied by the irritability and anorexia produced by the latter. Furthermore, there were no changes in the blood pressure, heart rate, or respiratory function which could be attributed to the drug. There was no depressive phase following stimulation, and the margin of safety was wide. Himwich and Rinaldi (1955) thought that the site of action of the substance was probably on the reticular substance of tegmentum, while Heath (1954) found that meratran, unlike any other known drug, produced rapid high-voltage spikes in the region of the septum of monkeys.

In view of its stimulant powers and its ability to awaken rabbits from barbiturate-induced sleep, Fabing (1954) decided to try the effects of meratran upon cases of narcolepsy. He found it to be highly effective for this condition, and subsequently decided to try it on cases of mild depression (Fabing *et al.*, 1955). They

*This work was done with a grant from the Endowment Funds of St. Thomas's Hospital.

found an initially favourable response in a high proportion of cases of reactive depression and around half of the cases of endogenous depression. Many of these cases were drawn from their "office" practice and so probably included many milder cases such as would also be treated by general practitioners in this country. For such symptoms as easy fatigue, lack of energy, afternoon "let down," and a variety of vague physical symptoms such as headache or dizziness, this drug is said to be useful, as also in cases of tic and blepharospasm. Fabing (1954) has found it helpful in certain cases of spasmodic torticollis; Schut and Himwich (1955) report that it was useful in relieving the apathy of chronic schizophrenia, while Pomeranze (1954) reported favourably upon its place in geriatric practice. Antos (1954) reports that it is helpful in combating the lethargy which is associated with convalescence, reserpine, and other drugs.

However, Fabing (1955) also specially warned us that this drug is not without its dangers and is definitely contraindicated in all cases showing anxiety and agitation. "If the nervous system is 'set' in a pattern of pathologic activity, the drug will enhance the existing pathologic behaviour. Thus a manic patient becomes more excited, a deluded patient becomes more actively paranoid, an obsessional patient becomes more obsessive, an anxious patient becomes more anxious, and an agitated patient becomes more agitated."

Present Investigation

We were fortunate in this department in being allowed ample supplies from the U.S.A. of the new drug for clinical trials before it became generally available elsewhere in this country. In all, it has now been given to well over 200 psychiatric patients of various types and to over 20 "normals." We found it even more important than with amphetamine that cases be carefully picked before using this drug because of certain complications we have found arising from its use. This article therefore dwells not only on the use of meratran therapy but also on some of its real dangers.

The majority of our patients were suffering from depression of one sort or another. Of over 100 patients treated by one of us (A. A. R.) a high proportion had already been referred previously to an out-patient E.C.T. clinic, while other cases were drawn from among the more chronic neurotic patients attending the psychiatric out-patient department of St. Thomas's. This now has nearly 16,000 attendances a year for diagnosis or treatment of various kinds, so that ample material is available for testing such drugs. They were a different sample from that treated by Fabing (1955) by reason of their severity and chronicity, and also different from the second group treated by one of us (W. G. A. B.). In this second group of patients the depressions were generally of a much milder type and were mostly specifically referred for meratran therapy when the indications for this had become clearer from the results obtained in the earlier more severely depressed and anxious group of patients.

Action in the "Normal"

Twenty-four persons were given up to 3 mg. during the day by mouth for varying periods of time up to a week. Two of these reported no change as a result of the drug, but the remainder bore out Fabing's statement about the effects of the drug upon his mildly depressed patients. "Normals" would report an insidious elevation of mood, with heightened confidence, greater ability to concentrate, and an increased work output. The elevation of mood was not of sufficient degree to be characterized as euphoria. It reached a subjectively detectable level some 30 to 40 minutes after taking the drug and persisted for up to 12-14 hours afterwards. Only two reported the occurrence of undesirable after-effects, and

it was noticeable that the "let down" or "hangover" effects following other stimulant drugs is not one of the obvious after-effects of meratran. Some subjects, however, did report some interference with their sleep, although the dose given did not exceed 3 mg. and it was not given after 4 p.m.

Reactive Depression

In reactive depressions, of which many cases are included in the second series (W. G. A. B.), it was found that up to a maximum of 7.5 mg. a day, given in three doses of 2.5 mg., generally proves adequate. Larger morning doses (5 mg.) may be given, followed by a smaller afternoon or evening dose (2.5 mg.), depending on whether any diurnal swing of mood is present. Generally it is wise to start with a much smaller dose of only 1 mg. three times a day and then gradually increase it if there are no bad effects. Many depressed patients normally exhibit sleep disturbance, and, in our experience, meratran should generally be combined with the giving of hypnotics at night. Thus many patients with reactive depression were given barbiturates at night in addition to meratran, and were helped by this combination.

Those reactive depressions which are uncomplicated by anxiety, hysterical, or obsessional traits seem to respond best to meratran. When obsessional features are present, meratran can aggravate rather than relieve the condition. Tension tends to be increased in such patients, and there is an additional aggravation of the tendency to ruminate obsessively, so that the depression may become apparently more severe and often agitation supervenes as well. Our findings in patients with reactive depression also showed that anxiety is frequently increased by this drug, and this is what tends to limit its usefulness and create one of its possible dangers. It is, however, important to note that the drug generally seems to increase states of existing anxiety rather than create it where it was not present before. The drug had nothing like the same deleterious effect on sleep as amphetamine has in our patients, but some people's sleep was affected by it to a lesser degree. It was difficult to decide always whether this was due to a change in the course of the depression or to the specific effect of the drug itself. Sleep disturbance was, however, also occasionally reported by some controls.

Of a group of 68 patients whose depression seemed more reactive than endogenous, and were treated by one of us (W. G. A. B.), 25 out of 29 of the purer type of reactive depression were helped by meratran; while in reactive depression with obvious hysterical features only 11 out of 22 improved. Of eight further patients with organic disease and depression, six were improved. Where anxiety or obsessional features were present only three out of nine patients were helped. In the reactive depressions with hysterical features it will be seen that only 50% were helped. It seemed characteristic of this last subgroup that the majority of those so helped did not complain of any disturbance of sleep with their depressive symptoms. Patients with these reactive depressions had trials of the drug, lasting from a few days to three months in some cases, without apparently harmful physical effects. Tolerance has not so far developed in these patients. Longer-term studies are, however, needed on this point.

Endogenous Depressions

As a whole, this group was certainly not helped as much by meratran as were the reactive depressives. In another series of 65 patients treated by one of us (A. A. R.), most of whom were suffering from severer depressions, many of them of an endogenous and involuntal type and attending an E.C.T. clinic, only 14 patients obtained any lasting benefit; and in view of the self-limiting cyclical course of some depressions the correct figures of improvement may well have been even lower. A further seven cases in this series showed transitory elevation of mood, an elevation which is much more common in endogenous than in reactive depressions; this transitory effect in endogenous depressions is also produced by amphetamine in similar circumstances. Many of these patients also become worse during treatment.

Sometimes a depressed patient not previously showing obvious anxiety can become acutely anxious, agitated, deeply depressed, and possibly suicidal in the course of a day or two. Although it is possible that this was part of the natural course of an endogenous or involutional depressive illness and due to the withholding of E.C.T., nevertheless it is our clinical impression that some of this worsening in such depressions may be directly due to the effects of meratran.

Fabing (1955) warns us against using this drug where E.C.T. is the correct treatment, and we have confirmed his finding on this point. For instance, in one case of involutional depression with obsessional doubts, the doubts took on temporarily the quality of delusions, and the patient suddenly remarked that "it all fitted in." The picture then began to show schizophrenic features, as he was quite unable to say what did actually fit into what. Another patient, who had steeped himself in the works of Blake and Jung, described a large amount of archaic material in the form of vivid images which he was able to call to his mind at will. It is perhaps of interest to quote here very briefly four other cases to illustrate the sort of effects that may follow the use of meratran on unsuitable cases.

Case 1.—A prison officer aged 44 complained of listlessness, tiredness, and moroseness. His personality showed certain obsessional traits and he was found to be depressed, tense, and anxious. He was given 2 mg. of meratran twice daily, but returned to hospital two days later acutely depressed, self-reproachful, with extreme agitation, tension, and pressure of talk. He was with difficulty restrained from resigning his job on the spot.

Case 2.—A nursing sister aged 36, undergoing treatment as an in-patient for endogenous depression with depersonalization, was given meratran up to 4 mg. daily. She had an exacting, tidy, conscientious, and somewhat withdrawn personality. On a dosage of 2 mg. twice daily she became, in the course of three days, more deeply depressed, very agitated, and full of suicidal ideas. She recovered after receiving E.C.T.

Case 3.—A married woman aged 31, complaining of fear of contaminations, especially by insects, accompanied by compulsive washing and the destruction of "contaminated" articles, together with feelings of depression, received gradually increasing doses of meratran without any apparent change until a dosage of 2.5 mg. three times a day was reached. She then became very depressed, agitated, and suicidal. Her compulsions, which had died down while she was in hospital, returned with all their old force.

Case 4.—After the administration of 3 mg. of meratran daily for 14 days a man aged 43 with a cyclothymic illness developed a hallucinatory paranoid state, which necessitated admission to an observation ward. The condition subsided spontaneously within two days, and he subsequently recovered from his depressive phase after two E.C.T.s.

Inquiry about Case 4 showed that this was not an exacerbation of a misdiagnosed schizophrenic psychosis. It was seen in the setting of a recurrent depressive episode in a long-standing manic-depressive illness. It must, we think, be attributed, at any rate in part, to the effects of the drug itself. It resulted from the administration of minimal doses of 1 mg. thrice daily over a period of 14 days. Other cases have flared up with small doses given over shorter periods of time. It seems that, in the present state of our knowledge, it is not always possible to predict when this type of response to meratran will occur. It can be most alarming when it does.

Spasmodic Torticollis

Five cases of this distressing condition were treated by one of us (W. G. A. B.), four of which showed varying degrees of improvement, but only one was completely relieved, thus confirming Fabing's (1954) observations in this disease. The five cases had lasted from one to three years and had not been helped by other treatments. One case did not improve at all despite the administration of up to 35 mg. of the drug daily; with this dose the patient showed an increase of tension symptoms. As a whole, patients with this disease appear to tolerate much larger doses of the drug than do the ordinary run of neurotic and psychotic patients. For instance, the best improvement occurred in a man of 42 who had been ill for a year and had received 20 mg. daily

over a period of three months. As in the depressions, any improvement occurring as a result of the drug generally begins to appear within the first few days of starting treatment.

Post-leucotomy States

Many patients in the initial period following operations are lethargic, and some continue to have a degree of lethargy months or even years after modified operations. Five such patients were treated by one of us (W. G. A. B.) with meratran. All improved on doses ranging from 3 to 14 mg. daily, and we were very impressed with its possibilities in this group. One patient who had previously had amphetamine, found meratran much more helpful. Although, of course, such a result is encouraging, further work is needed to confirm this particular finding.

Complications

Undoubtedly the most serious side-effect of meratran is the tendency of the drug to exacerbate pre-existing anxiety, and to produce on occasions, and unexpectedly, very marked aggravation and flare-up of the mental state. Recent experience has shown, fortunately, that the tendency to flare up anxiety symptoms can be combated by the suitable combination of meratran with other drugs. Thus, combinations of meratran with chlorpromazine hydrochloride or amylobarbitone sodium during the day have given encouraging results in preventing too great an increase of tension when this is present: our practice has been to combine each dose of meratran (2.5 mg.) with chlorpromazine hydrochloride, 50 mg., or amylobarbitone sodium, 1½ gr. (100 mg.). In the U.S.A. reserpine is also being used.

Insomnia as a distressing side-effect of meratran is rarely complained of and generally means a flare-up of anxiety features; it certainly does not occur as often as with amphetamine. Also we have confirmed Fabing's (1954) observation that meratran does not destroy appetite even in quite large doses as the amphetamines do. Some patients do, however, complain of nausea, and we have seen one macular rash fading within 24 hours of stopping the drug. No other serious complications have been met with apart from the psychotic episodes already discussed. Unfortunately we have not always been able to predict their occurrence, and this means that meratran must be used with the greatest care. The introduction of amphetamine saw similar exacerbations of psychotic symptoms in some unsuitable types of patient, but it is our impression that meratran may be found more powerful in this respect, and, because of its absence of side-effects and generally smoother action, it is prone to produce these complications more swiftly, unexpectedly, and sometimes more severely than happens with amphetamine.

Discussion and Conclusions

Although much work remains to be done with this drug in the clinical research field, particularly in the treatment of fatigue states, and also in other conditions where amphetamine or its derivatives in small doses have proved useful, we have found that meratran is contraindicated in conditions where there is any severe tension, agitation, or anxiety. Obsessional symptoms may be greatly worsened, especially with larger doses. Outside hospital it should not be given to the schizophrenic or severely depressed patient. In the treatment of the severely ill hospital patient, meratran, like amphetamine, will also probably have little part to play in treatment.

Eventually the drug may be of value in general practice and in out-patient clinics where milder cases of depression, particularly reactive depressions, are common. For instance, it is our impression that the drug is capable of greatly improving energy output and lessening fatigue so long as tension is absent. However, in view of the severity of abnormal mental symptoms which may occasionally be induced by quite small doses in unsuitable cases, it is essential that caution should be used in prescribing it. Certainly too widespread and uncontrolled a distribution and use of

meratran at the present time could result in distressing medical and social sequelae. For while we have found the means of combating a flare-up of anxiety by the addition of barbiturates or chlorpromazine, it remains to find out how the occasional severe psychotic episode resulting from its use can be predicted and so prevented. Further clinical research may indicate more clearly the type of patient in which this is likely to happen.

Summary

An extensive clinical trial of the new stimulant drug "meratran" is described and its value in the treatment of reactive depression confirmed.

Unlike the amphetamine group of drugs, meratran generally causes little disturbance of appetite or sleep, and in this respect would seem to be superior to any stimulant drug at present available.

Promising results were obtained with it in the treatment of spasmodic torticollis and post-leucotomy anergia. This requires further investigation.

The value of the drug reported by American workers in endogenous depressions is not confirmed. It is our experience that such patients are often made worse by meratran.

The chief drawback to this drug's therapeutic usefulness is its tendency to exacerbate pre-existing anxiety; this necessitates exact diagnosis before administering it. Fortunately, combination with other drugs (chlorpromazine hydrochloride or amylobarbitone sodium) will often prevent this.

Psychotic episodes which can only be attributed to the action of meratran itself are reported in this series. Owing to the poverty of bodily side-effects, no warning of their imminence is given, and they can occur on minimal doses of the drug. At present there is no way of anticipating these disturbances.

We wish to record our thanks to Dr. William Sargent for helpful advice and criticism, and to the Wm. S. Merrell Co., of Cincinnati, U.S.A., for the generous supplies of meratran.

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A second edition of the historical record of the King Edward VII's Hospital for Officers (Sister Agnes's) has now been published; the price is 2s. 6d. a copy and the proceeds will go to the hospital, which is independent of the Health Service. The new edition brings the history of the hospital up to date, since it reopened in Beaumont Street, London, W.1, in 1948 after the bombing of 17, Grosvenor Crescent in 1941. This "postscript" shows that the tradition of royal interest in the hospital, which began when King Edward VII insisted that the work of the Sisters Fanny and Agnes Keyser for the wounded officers of the Boer War should be continued in peacetime, has continued strongly. In 1950 Princess Margaret paid the hospital an informal visit, and shortly before his death King George VI came to invest a patient with the G.C.V.O. Her Majesty the Queen is the fifth sovereign to become its patron. Last year 761 patients were admitted, and a gift from the British War Relief Society, Inc., of America has made the planning of a new nurses' home possible. This should be ready in 1957.

GROUP BEHAVIOUR IN CHRONIC SCHIZOPHRENICS TREATED WITH "MERATRAN"

BY

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A new drug, α -(2-piperidyl) benzhydrol hydrochloride ("meratran") with the following formula

has been described in the U.S.A. as being an anti-depressant similar to the amphetamines in its central action but without their peripheral sympathomimetic effect. In clinical trials conducted by Fabing *et al.* (1955) a group of 25 chronic patients, of whom 19 were schizophrenics, were given meratran, the experiment being controlled by placebo tablets. They showed improved co-operativeness and ward adjustment, but the results were not analysed statistically. Delusions and anxiety were said to be contraindications (Schut and Himwich, 1955). Similar claims were made in cases of depression, narcolepsy, and long-term schizophrenia with deterioration and psychomotor retardation—active delusions, anxiety, and agitation being regarded as contraindications (Fabing, 1954, 1955)—with average doses of 2 mg. three times a day orally (Andren, 1955) and with resultant increase in activity unaccompanied by euphoria (Forster *et al.*, 1955).

It was thought opportune to study the action of a new drug such as meratran on group behaviour in chronic deteriorated schizophrenics, and to determine what effects were produced and, if any improvement resulted, whether it was reasonable to conclude that any of this was due to the drug or whether it could be shown to be due to some other factor.

For this project a group of 20 chronic male schizophrenics, the most deteriorated and withdrawn patients in a hospital of 900 patients, were selected. They were all more or less retarded, and were lacking in any sense of self-consciousness or group feeling, though they were in the same ward. Their ages ranged from 31 to 72 (average 46.3 years) and their duration of stay in hospital ranged from 3 to 38 years, with an average of 16.6 years.

These 20 patients formed part of a big rehabilitation and occupational research project, in which they in particular spent most of the day in some activity on the farm or in the ward, but on an average eight patients were quite unemployable in any fashion. They were also subject to habit-training which had freed them from nocturnal incontinence, and their night sedation had been cut down to nil.

Design of the Experiment

The 20 patients were divided at random into two groups of 10. Their behaviour was studied, being tabulated under the headings of feeding, letter writing, reading, conversation,