PRESENTED FOR

THE DEGREE OF DOCTOR OF MEDICINE

OF THE UNIVERSITY OF GLASGOW

There have been a number of reports recently, in the Medical Press of the United States, on the properties of Meratran (Pipradrol) and of its value in the treatment of Depression and Fatigue States. The trial by clinicians in that country began early in 1953; its selection resulted from the experimental work of Brown and Werner who found the drug to be of extremely low toxicity in both acute and chronic toxicologic experiments, and who noted that doses which were quite small in relation to the lethal dose, induced prolonged periods of purposeful hyperactivity in experimental animals. Dogs remained friendly and ate readily, on doses which produced hyperactivity. Unlike some analeptic drugs, convulsions did not occur until lethal doses were given intravenously. No secondary depression of the Central Nervous System followed withdrawal of the stimulating drug. Furthermore, doses of the compound which caused hyperactivity in the experimental animal, had little or no effect on blood pressure, pulse or respiratory rate.

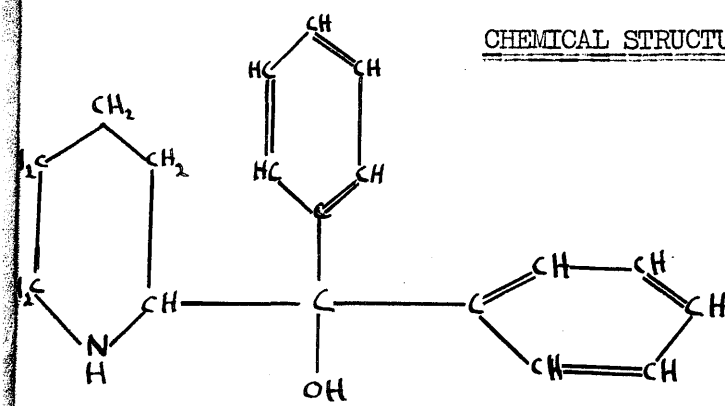
Himwich and Rinaldi were of the opinion that the drug acted primarily on the Reticular Substance of the Tegmentum, while Heath observed that Meratran, unlike any other known drug, produced rapid high-voltage spikes in the region of the Septum of Monkeys.

In view of its stimulating powers, as exhibited for example in its ability to awaken rabbits from Barbiturate-induced sleep, Fabing decided to try the effects of Meratran upon cases of Narcolepsy, because it is believed to be a disorder characterized by an abnormal inhibitory state in the Central Nervous System, and therefore responsive to stimulant drugs. He found Meratran highly effective in this condition, and was of the opinion that therapeutically it was superior to the Amphetamines. Subsequently, with Hawkins and Moulton, reasoning by analogy, that drugs of the Amphetamine series, which are effective in the treatment of Narcolepsy, are also effective in the treatment of milder depressions, especially Reactive Depressions; Patients with this type of mood disorder were studied next; they found an initially-favourable response in a high proportion of cases of Reactive Depression, and around half the cases of Endogenous Depression. Many of the cases were drawn from their "office" practice and so almost certainly included many milder cases such as would 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 complaints such as atypical headache or vertigo, this drug is said to be useful, also in cases of Tic and Blepharospasm. Fabing has found it helpful in certain cases of Spasmodic Torticollis.

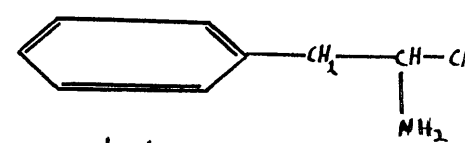
Shute and Himwich report that it is useful in relieving the apathy of chronic schizophrenia, while Pomeranze reported favourably upon its placein Geriatric Practice. Antos reports that it is useful in combating the lethargy induced by Reserpine and other drugs. However, Fabing warns that the drug is not without its dangers and is definitely contra-indicated in all cases showing anxiety and agitation. He states "If the Nervous System is set in a pattern of pathological activity the drug will enhance the existing pathological 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".

In view of the considerable interest aroused by this drug, and its apparant usefulness in various conditions, I was asked by the Director of the Department of Psychological Medicine in one of the large Teaching Hospitals in the South where, until recently, I was engaged in full-time research work, to undertake a clinical investigation of its value in view of the encouraging reports which we had received from workers in America. This investigation forms the basis of this work.

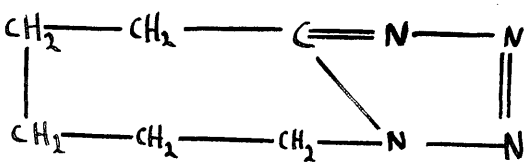
CHEMICAL STRUCTURE.



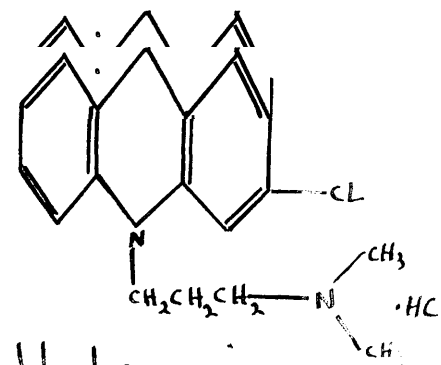
MERATRAN (Ipsapirodol)



amphetamine



pentamethylenetetrazol
(cardiazol)



chlorpromazine
(LARGACTIL)

Chemically this substance is not related to the Ephedrine or Amphetamine compounds and, likewise, it has differences in its action. It is named (alpha)-(2-piperidyl) benzhydrol and has the above structural Formula. The Hydrochloride salt is a white, odourless powder witha slightly bitter taste. One part dissolves in sixty parts of hot water. At present it is dispensed in Tablets of 1; 2.5; and 5 mgms.

Action in the Normal.

Twenty normal individuals were given 3 mgms. of Meratran per day in divided doses of 1 mgm. at 8 a.m., then again at 11 a.m. and finally at 2 p.m. This group, who had repeatedly been used in drug trials of this sort (actually they were students) did not know the nature of the preparation, and who did not enquire, were, I think, relatively immune to extraneous suggestive influences. They received the drug for a period of three weeks.

Two of these persons did not experience any noticable effect from the drug; the remaining eighteen reported an insidious elevation of mood which reached subjectively-detectable levels some 30-40 minutes after the ingestion of the initial morning dose, and which persisted until retirement and sleep that evening. No appreciable alteration of the induced mood elevation resulting from the first daily dose of Meratran was noticed following ingestion of the second and third doses. All agreed that the initial morning dose seemed the most effective despite the lack of any hang-over effect the next morning. I conclude that the duration of action of the drug is for a period of around twenty-four hours, certainly not less then sixteen. There would seem to be a threshold effect. The elevation of mood was accompanied by an increased ability to concentrate, increased work output, and heightened confidence. It was not of sufficient degree to be characterized as euphoric, and was not associated with any marked increase of speech output. Not one of the Trial Group mentioned Anorexia, Palpitation, or restlessness as a result of taking this drug. Two, however, complained of slight initial insomnia; enquiry revealed slight irritability in the cases of these two patients; it was not specifically mentioned as an effect and conceded only after reflection. One of this group experienced nausea in the three days immediately after commencement; it was not at all severe and, as I have mentioned, was only a transient feature.

Repeated checks of the various physical systems of these volunteers (although, of course, it was out of the question to institute total surveillance and, on this account, the results are open to question) did not reveal any significant deviation from normal; thus, cardiovascular and respiratory responses were normal throughout, as were the Blood Sugar tests, Blood Counts, Liver

/function tests

Liver/ function tests, and Urinary constituents. Himwich has expressed the view that although Meratran is a stimulant and, therefore, presumably resembles, e.g., the Amphetamine group of drugs in some of its action, yet it cannot be considered sympathomimetic, for its administration does not evoke the over-activity of the Sympathetic Nervous System characterized by dilated pupils, sweating, tachycardia, and increased blood pressure. Experience in this group confirms the view of Himwich that the stimulant effect of Meratran, however produced, is not due to an action on the Sympathetic Nervous System peripherally or otherwise. I must comment again on the absence of depression or "hang-over" effect so frequently seen following the termination of the period of action of the Amphetamines. The experience of American workers is confirmed on this point and will be dwelt on again when the therapeutic and physiological actions of Meratran, such as are known, are compared with other stimulants.

ELECTRO-ENCEPHALOGRAPHY.

The effect of Meratran on the E.E.G. records was elicited in only four patients; experience therefore, is very limited. The drug would appear to alter the resting pattern, the Electro-encephalogram assuming the faster frequencies and lower amplitude characteristic of the alerting response. I have mentioned already the view of Himwich and Rinaldi, that the site of action of Meratran is mainly the Reticular Substance of the Tegmentum which, they say, is stimulated, and then in turn stimulates the cortex, resulting in the E.E.G. change. Whether this view has been substantiated I do not know - I can offer no relevant opinion.

I am afraid that, following the exhibition of the drug to the Normal Group for the period of three weeks mentioned, the immediately-gratifying results and observations which were provided, were seized on as firm evidence for proceeding with the treatment of abnormals with Meratran. As experience with the drug widened, types of response began to clarify and I found myself unwittingly dwelling on the normals. Perhaps more is being read into the few untoward responses which occurred than should strictly be allowed. Some months later, armed and re-orientated by what was, comparatively, a wealth of knowledge and experience, I re-interviewed the group of twenty Normals; by then I knew what to look for and, probably, was determined to find it. I quote my findings briefly for what they are worth, in view of a large, subjective, distorting factor.

I was primarily interested in the two patients who developed initial insomnia, and the two who did not report any effect at all. I am convinced that insomnia as a side effect of Meratran is, in reality, an exacerbation or "blow-up" of anxiety which may, or may not, have been recognised in mixed depressive pictures. I am convinced, also, that the drug rarely creates anxiety per se, but only exacerbates pre-existing anxiety. This observation, which is not at present stressed by the Americans, is of extreme importance. If anxiety is recognised before giving the drug, there are ways of preventing "blow-up" - Both those patients who developed insomnia proved, on belated scrutiny, to be constitutionally anxious individuals.

Of the two who were unaffected by the drug, examination of them in space and time provided ample evidence of marked hysterical traits. It has been my experience that frequently such persons either tolerate large doses of this drug with equanimity, or they exhibit "toxic" effects, which for lack of knowledge we brand empirically as dissociative or even, as I have seen, paradoxical, e.g., pronounced somnolence. These findings retrospectively discovered in the Normals will be further discussed when the use of the drug in Abnormals is covered.

DOSAGE. Antos has described his self-experiments with Meratran when only the results of animal investigation were known. Various doses from .1 mgm. up to 5 mgms. were tried at first; later, high doses were given. After a few days of hit-or-miss trials it was established that the average dosage was 1-2 mgms. Initially only one daily dose was given; latterly, the tendency to divide into three administrations was used. The Americans then generally recommend a dosage of 3-6 mgms. per day in the Reactive Depressions which are suitable for Meratran Therapy, and larger doses in Endogenous Depressions. In the series of Reactive Depressions which I treated, the optimum dosage seemed to be between 3 and 7.5mgms. per day, given as 1- 2.5 mgms. thrice daily. I would regard the figure of 7.5 mgms. of Meratran daily as the extreme upper limit in any Depressive Neurotice Reactive, however therapeutically ideal the case might seem.

In the fairlyelarge number of cases of Depression of all kinds which are included in, and which have formed the basis for this work, certain facts have emerged which are at variance with those formulated in America and reported in the American Journals. Perhaps American workers, in the light of further experience, have altered their views and these will, in time, be propagated. I may, if further experience dictates, radically alter mine. I am bewildered by the bipolarity of the findings and can only hope that, as experience accrues, reconciliation will occur. The difference in approach and orientation of the psychiatrist surely do not account for it all; if, indeed, they do I have been sadly misguided these several years.

It is my experience that Meratran should never be given to any Depression in doses of more than 1 mgm. thrice daily at the maximum while commencing treatment. It is generally wiser to start with doses of 1 mgm. b.d.

It is the American contention that where diurnal Mood Swing is marked the drug should be given in amounts which vary directly with the intensity of the depressive affect. This sounds very reasonable; if the patient is most depressed in the morning then, naturally, the heavier dose should be given to coincide and initial morning doses of up to and beyond 6 mgms. are recommended.

My experience has been that it is much less dangerous to give relatively-large doses to Reactive Depressions than to Endogenous Affective Psychoses, and that the results of Meratran Therapy, in all but a very few types of Endogenous Depression - which require very careful selection - are not only poor but sometimes extremely harmful. American workers have claimed over 50% improvement (Fabing, H.D.; Hawkins, J.R.: Moulton, J.A.L.; address to the American Psychiatric Association, St. Louis, 3rd. May, 1954). This certainly is not confirmed in my experience.

Controversy over the origin and inter-relation of the Depressions seems endless; Lewis and Curran have opined that there is no real difference between endogenous and Reactive Depressions; Lewis in 1934, Curran in 1941. Tredgold also propounded the same view in 1941. For close on twenty-two weary years known to me, the conflict has raged; now bursting forth to lacerate the whole contemporary scene, then rumbling on the fringe, our little world's echo; flickering into print, the announcing or departing glow, of psychiatric stars.

By self-denial I can accept that there is no real difference between Reactive and Endogenous Depression. I do accept it, and in so doing I never intend to forget that, although there is no real difference between them they occur in vastly different types of human being; moreover, this is true also within the limits of any one of these two major subdivisions itself. The Endogenous Group alone occurrs in a variety of constitutional settings, largely genetically determined, and each with totally different affiliations, in the realms of pathology, both physical and psychical.

The modest findings resulting from my work with Meratran, even they hint at some wide cleavage. The above view, perhaps a psychiatric truism, hints at wider issues. We cannot expect any body, even professional, to do other than reflect, in its most hackneyed daily activities, the prevalent bias of the community which it invariably claims to serve.

The application of Genetic, and even more total concepts, to the problem of the Depressions, presuming that such a radical alteration of outlook, the most difficult of all human achievements, could be effected, even in a group which considers itself enlightened, would be a major achievement. Unfortunately, depression occurrs in human beings; total alteration of approach cannot be directed solely to the morbid; moreover, as history advises us to consult our prejudices, we should do so more often; they will even produce figures for us.

A more relevant conclusion - in the use of Meratran in Endogenous Depressions, such few as are suitable for this form of therapy - response is to minimal doses of the drug and that nothing but harm results from immoderate use.

In the variety of conditions for which I have found this drug useful, oftimes dosage varies markedly, in my experience. I know of no special reference in the Literature, but I have found the drug of marked value in the treatment of the Anergia which sometimes persists following modified leucotomy operations for many years. The optimum dosage in this condition would appear to be from 12-14 mgms. per day. This finding was from a small series of five such cases.

In Spasmodic Torticollis, for which the drug seems very useful, the optimum dosage appears to be (from a series of five cases) in the region of 20 mgms. daily. This finding, both with regard to the effectiveness and the dosage, is in accord with the results of American investigations. One case of Blepharospasm was treated, and an encouraging response was obtained, on a high dosage. In my opinion the dosage in these conditions is of particular importance. The toleration of comparatively large amounts of Meratran by those with hysterical facets of personality has previously been commented on. I have seen the drug dismissed as valueless in Spasmodic Torticollis after a dosage of 5 mgms. per day was reach; generally the aim should be to reach the optimum dosage within seven days from the commencement of treatment. Any improvement is generally apparent within a few days, and almost certainly within a week. I have found this generally true in all conditions, including Depression, for which the drug is valuable. The therapeutic response occurs soon or not at all. This has been previously stressed.

Any other important modification of dosage will be mentioned appropriately.

It is my experience that Depression attributed as a reaction to physical illness responds, in particular, to small doses (3 mgms. daily) of the drug.

USE IN THE DEPRESSIONS.

Despite almost certainly having created the impression of insistence on sharp diagnostic groupings in this difficult field, I nevertheless appreciate the difficulties involved and fully recognise the frequent occurrence of mixed and atypical pictures. These facts are axiomatic: but if we are ever to assess the value of a particular physical method of psychiatric treatment the first essential, surely, is to acknowledge those newer clinical concepts, the fruits of painstaking efforts and meticulous observation, which by their objectivity are now open to every clinician, and should introduce a semblance of agreement, both diagnostic and therapeutic, in the management of cases of depression.

The elicitation of such ostensibly-blatant features as the presence of daily mood swing, type of insomnia - initial or terminal - pre-psychotic personality, age of onset, presence of agitation, degree and type of hypochondriasis intermingled, detailed family history, (there are many others) will introduce a surprising degree of order in the light of recent knowledge. If it is my contention that the less commonly occurring, simple-retarded, purely affective depression of the early Senilium responds to Meratran, this then should convey a wealth of knowledge and agreement, and perhaps ensure a fair estimation of the drug; for the obvious immediate cause of the discrepencies in results is different diagnostic criteria.

The Endogenous Group of Depressions treated contained sixty-five patients. They had been referred inthe first instance to the E.C.T. Clinic, and in the normal course of events would almost all have been given thistreatment; whereas the sixty-nine patients who were considered to be suffering from Depression, largely Reactive in origin, were drawn from the Out-Patient Clinics and normally would have been treated by Psychotherapy, Stimulants such as Amphetamine alone or in combination, or in a few cases probably Electroplexy. This latter group were referred specifically for Meratran treatment.

In the Endogenous Group the results were certainly very much lower than in the Reactive; of sixty-five patients only fourteen obtained any lasting benefit from the drug, and in view of the self-limiting cyclical course of many of these illnesses, the correct figures may well have been lower. A further seven cases in this series showed transient elevation of mood, lasting usually for a day or so; in one instance this lasted as long as a fortnight.

Sometimes a depressed patient, not previously showing obvious anxiety, would become acutely anxious, agitated and deeply depressed. Frequent suicidal ideas developed where they had previously been absent as the condition worsened over a period of a few days. Although this was, possibly, part of the normal course of the illness, investigation of the relevant factors did not leave this impression generally.

In my opinion the worsening was attributable directly to the drug. Fabing has warned against giving it where E.C.T. is the correct treatment, and experience with this group amply confirms his view. In one case of Involutional Depression with Obsessional doubts, the doubts took on temporarily the quality of delusions, the patient suddenly remarking "That it all fitted in". He was totally unable to elaborate on this remark, a schizophrenic flavour entering the picture. Another patient, who had steeped himself in the works of Blake and Jung, described a large amount of archaic material in the form of visual images which he was able to recall to his mind at will. It is of interest to quote here briefly case histories to illustrate the effects that may follow the use of Meratran in Endogenous Depressions which are unsuitable for this form of treatment.

Case 1: A middle-aged Civil Servant complained of lack of energy, and tiredness, associated with Ruminative fears of organic disease. He had previously been seen by a physician and investigated for vague, atypical abdominal symptoms. No organic pathology had been found and he had been re-assured and advised to take a simple stomach mixture. He had always displayed obsessional traits of character and was asthenic in physique. Apparently his habitual self-effacing modesty had cloaked from the physician the urgency of his fears of disease and when I saw him he was depressed, tense and very anxious. He had for many years a varying degree of difficulty in getting off to sleep but now, in addition, he was awakening early and then his anxiety was worse. He stated that he was a failure in life and that its richness and fullness had eluded him. He was full of self-reproach and guilt for his professional failure - more imaginary than real.

He was given 2 mgms. of Meratran to be taken in the morning at 8 a.m., then again in the early afternoon. The next day he returned to the hospital in a state of great agitation with marked pressure of talk and stated that he had not slept all night; more depressed and self-reproachful than ever, he was with difficulty restrained from handing in his resignation on the spot.

Case 2: A professional woman in her late thirties, who was unmarried, was receiving in-patient treatment for an Endogenous Depressive Episode associated with Depersonalization and Derealization, was given up to 4 mgms. of Meratran daily. She had a meticulous, exacting, tidy, and somewhat withdrawn personality. In the course of a few days she became more deeply depressed and exhibited marked agitation and Terminal Insomnia. Suicidal thoughts, previously unmentioned, appeared and one was struck by the intensification of the Psychotic picture resulting from the drug. She recovered after receiving E.C.T.

Case 3: A married woman in her forties complained of fear-contaminations, especially by insects, accompanied by compulsive washing and destruction of contaminated articles, with feelings of depression which were worse in the morning; she received gradually-increasing doses of Meratran without any apparent change until a dosage of 7.5 mgms. per day was reached. She then became extremely depressed, agitated and suicidal. Her compulsions, which had died down while she was in hospital, returned with all their old force.

Case 4: A skilled worker in his late thirties complained of depression which was worse in the mornings, insomnia which was terminal in type, lack of energy and interest of three weeks' duration, was given 1 mgm. of Meratran twice daily and referred for four days. On his second appearance he stated that although he was no better he was certainly no worse; the dose of Meratran was increased to 1 mgm. t.i.d. It transpired that he had previously had an attack of depression some six years before and that he had been given E.C.T. as a Voluntary Patient and subsequently recovered, the duration of that attack being six months. He recognised the present illness as almost identical with the first and so had sought treatment much more quickly. A rather plethoric, pyknic individual, he stated that he had always been cheerful, energetic and optimistic, and this was confirmed by his wife. Questioned about his parents, the information gathered - although non-specific - confirmed the clinical impression of an Endogenous Depression of the Manic-Depressive Group in a constitutionally-hypomanic personality.

A week later he made a tardy appearance at the Out-Patient Clinic, having been brought there - under protest - by his wife. He was in a state of almost continuous agitation and acutely hallucinated, the voices accusing him of various sexual misdemeanours. Strangely enough, he did not associate these occurrences with the tablets which had been prescribed for him and he had continued to take them throughout. He stated that if the voices continued in their accusations he would have to do something drastic; consequently, he was committed for a period of observation. The hallucinatory, paranoid state subsided within forthy-eight hours of the discontinuation of the drug, and the depression remitted with three E.C.T's.

Extensive enquiry into this case indicates that this certainly was not an exacerbation of a mis-diagnosed schizophrenic psychosis. It was seen in a recurrent depressive episode of the manic depressive type and must, I think, be attributed directly to the drug itself. It resulted from the administration of very small doses of Meratran over a period of fourteen days in all, and appeared suddenly and dramatically, without any warning whatsoever.

There had not been any "blow-up" of anxiety, as far as it was possible to tell, and the agitation present was secondary to the content of the hallucinatory voices. He had absolutely no insight into these, the clinical picture resembling that seen in acute schizophrenic episodes.

It seems that it is not possible to predict this type of reaction to Meratran in the present state of our knowledge and that, although this was the only case which showed this pathological response, its significance can hardly be over-stressed.

Of the fourteen patients who received lasting benefit from the drug, the clinical impression was that these were almost all depressions of the manic-depressive type, and that the effect of Meratran was to expedite slightly the remission of cases of depression which were already undergoing spontaneous self-termination.

ILLUSTRATIVE CASES.

Case 1: An ex-Naval Petty Officer in his late fifties complained of atypical headache of ten months' duration, which was associated with early waking and difficulty in concentrating or making decisions. His condition was more or less static and had not increased really in severity since the onset. Though tallish he was extremely powerfully built and of frank and open personality. There was no previous history of depression and he was unable to adduce any factor which might be responsible for it. I had no doubt of its endogenous nature: if one looks carefully, one will find few depressions, relatively, which do not contain an element of anxiety, however superficially absent it may seem. It may be present as the terror associated with early waking only, or it may be in the form of inner restlessness which is present, but rarely complained of as such.

As scrutiny excluded these features he was given 1 mgm. of Meratran t.i.d. for two days, then re-assessed. He stated that he had improved remarkably and that he now felt very well. In particular, he was impressed with the disappearance of the headache and the increase of confidence and energy output which had resulted almost instantly from ingestion of the drug. He still found it rather difficult to get going in the morning, but this speedily disappeared shortly after taking his morning dose of Meratran. He was advised to continue his treatment and took the dose of 3 mgms. daily for a period of three months, under protest, that as he felt so well there really was no necessity to continue with it. He has now been without the drug for two months and has remained very well.

Case 2: A man of 42 complained of depression, which was worse in the morning, headache and constipation; he also complained of early waking and noted that he dithered over shaving and dressing; in particular, when he was engaged in these activities he noticed that he had difficulty in remembering where he had put things, and stated that it often took fifteen minutes to collect his shaving gear from

/various

from/
various places. He was athletic in physique and in his previous personality he had exhibited prolonged endogenous mood swings. He had difficulty in making eventhe most trivial decision.

This particular episode had lasted for eight months, and there was a history of a similar episode eleven years before, for which he had not had any particular treatment and which had remitted spontaneously after six months. He felt that this attack of depression was more severe and its slightly-longer duration had caused him to seek advice.

He was reassured as to the outcome of his illness and given Meratran rather than E.C.T. because of the absence of anxiety, and because it was felt that the attack would soon terminate. Within a week of receiving 1 mgm. of Meratran t.i.d. he was almost his old self, and said that he had improved right from taking the first tablet. He took this dose of the drug for ten weeks. It was discontinued six weeks ago and he has remained well.

Case 3: A thick-set married woman of 38 complained of Depression of four months' duration and which she attributed to the fact that her marriage was barren. She had, fairly recently, been investigated for sterility and had been given a disappointing prognosis. Questioning revealed that her depression was worse in the morning and that it was accompanied by Terminal Insomnia. The illness had already lasted for four months and, although she attributed it to her circumstances, and it was conceded that reactive features were present, in view of the previous personality, body build, type of sleep disturbance in addition to the variation in the intensity of the mood disturbance from morning to evening, it was considered largely endogenous. She was given Meratran in doses initially of 1 mgm. b.d., rising within a few days to 2 mgms. b.d. She immediately improved, and within a week felt very well; with superficial psychotherapy she radically altered her view of her difficulties. More optimistic, she regained her previous vivacity. She continued to take the drug for three weeks without other than beneficial effect.

Case 4: A retired manufacturer had become very depressed immediately following the death of a favourite niece. He was aged 72 and the apparent precipitating cause had occurred four months previously, his niece having been killed outright in a car accident. The depression took the form of a rapid and complete withdrawal of interest from outside events with marked terminal insomnia and a fair degree of psychomotor retardation. His wife remarked that in the course of a few days he had become an old man, yet his immediate domestic circle considered that the change was warranted in view of the intensity of his attachment to his niece. His General Practitioner, too, for a long time accepted this phenomenon for what it appeared to be.

The degree of passive acceptance of what are considered the normal vicissitudes of life is quite astonishing, and my experiences in General Practice have convinced me that many commonly-occurring psychiatric syndromes are simply not recognised, and often when they are, a frequent reaction is to ignore them.

He was seen four months from the onset when it was still apparent that the intensity of the reaction was out of all keeping to the precipitating cause, and that the depth of mood variation was psychotic in degree. Examination showed that his memory was intact, his reasoning clear and no other signs of deterioration were apparent. It is not commonly appreciated that endogenous depressions of the manic depressive type occur for the first time late in life, and such a clinical entity this was considered to be; the previous personality was quite in keeping with this concept.

Because of the duration, and the picture of simple retardation without anxiety or agitation, he was given 1 mgm. of Meratran t.i.d. with marked improvement. His depression disappeared over a period of three days, he slept better, and started to regain his old interests. The retardation conspicuously vanished. He continued to take the drug for three months, after which it was stopped without relapse.

There is little doubt in my mind that Meratran has little part to play in the treatment of Endogenous Depression, and I cannot substantiate the American findings of over 50% improvement. Such value as it has in this group of conditions is, in my view, confined to those of Manic Depressive origin and this, I believe, has never been stressed, the American workers simply lumping all the Endogenous Depressions as one clinical entity. Moreover, the depressions should be free from features of anxiety generally speaking, although this can be controlled, and by their duration the clinician should suspect that natural remission is probably in the offing. It should not be used as a substitute for E.C.T. for, indeed, it is not. Involutional depressions, especially those commonly seen occurring in obsessional and constitutionally-anxious individuals, are in my view totally unsuitable for Meratran; very frequently it is harmful. Here again it should not be used where E.C.T. is indicated.

Many depressed patients complain of sleep disturbances, and these can prove a valuable guide in clarifying the clinical syndrome. Frequently the sleep disturbance is a dominant feature as far as the patient is concerned, and it is my experience that Meratran can safely be combined with the usual Barbiturate Sedatives. IfTerminal Insomnia is present it can be given in conjunction with Medinal, grs. V-X, half to three-quarters of an hour before retiring. The occasional hang-over effect of this drug should be remembered as it can intensify the depression of patients, although this effect is by no means universal. It can also be combined with safety with Sodium Amytal, Amytal, or Nembutal, in the usual hypnotic doses, as also in my experience with Chloral Hydrate or Carbrital.

This is not stressed in the Literature. In my view, these combinations are often helpful and rarely harmful.

USE IN REACTIVE DEPRESSIONS.

This group contained sixty-nine patients, who were specifically referred as likely to benefit from Meratran therapy and who were drawn from those attending the Out-Patient Clinics. In the normal course of events they would probably have been treated with Amphetamines, alone or incombination, or, for example, Psychotherapy, or insome instances by Electroplexy.

It is with this type of patient that Meratran was claimed by the American workers to be most useful, and so we can consider it the most relevant group treated. Moreover, it is in Reactive Depressions that Amphetamines are so useful, and we can gauge whether Meratran has therapeutic effects superior to the above-mentioned group of drugs.

It is of interest, in view of the increasing occurrence of milder, depressive reactions, to elaborate some of the conclusions which were apparent from a study of this group.

Depressed patients almost always complain of physical disturbances, and failure to enquire about any mood change present can result in complete misleading of the practitioner. The physical complaints are wide and varied, including headaches, dizziness, a variety of undefined aches and pains, as well as disturbance of alimentary and cardiovascular function. There is no doubt that these manifestations are actually due to the depression and it is of common occurrence to find that these patients have been treated for a physical complaint before being referred to the psychiatrist. Many of these disturbances seem rooted in a disorder of function of the autonomic nervous system.

It is common to find a history indicating a break in the pattern of life and outlook. Individuals who generally had a warm, active interest in persons and events lost their enthusiasms and their energies, and frequently complained of difficulty in concentrating, an inability to face the future, or to cope with day-to-day events. Many, about 50%, gave a history of a similar attack previously and frequently adumbrated their potentialities in their previous personalities, an inordinate sensitivity to the difficulties of life or, perhaps, they were mildly pessimistic in outlook and tended to magnify their difficulties. Features of anxiety, hysteria or neurasthenia were often intermingled.

Insomnia was an almost constant feature and, commonly in the Reactive Depressions, was initial in type, the patient complaining that he could not get to sleep. The affective disturbance was not of sustained intensity and generally they could be made to laugh by some amusing allusion. If anything, their depression was worse in the evening. This, however, was not commonly remarked upon and they stated that they felt depressed all the time.

For purposes of therapeutic trials this group of sixty-nine patients was further sub-divided. The limitations and presumptions of this are appreciated; nevertheless, it was felt that more light could be thrown on the drug's properties in this fashion. Thus, twenty-seven of these cases were considered relatively free of obsessional anxiety or hysterical features, and were considered pure Reactive Depressions although, of course, the existence of such a clinical entity is doubted by some. It was in this group that the results of Meratran Therapy were most encouraging, and of these twenty-seven patients twenty-three, i.e, 85%, were improved, four, i.e., 14% were not improved, yet none considered themselves worse as a result of the drug.

ILLUSTRATIVE CASES.

Case 1: A youngish, recently-married man complained of "tension" headache associated with irritability and low spirits, more marked in the evenings and associated with difficulty in getting off to sleep. The onset of the condition occurred three months previously and he attributed it directly to his marriage. He stated that his wife was stupid and bored him, and that he could not understand why he had married her. His parents had been opposed to the match, his mother having informed him bluntly that he had married beneath him.

He was given 1 mgm. of Meratran B.D. initially and, as he tolerated this well, after three days the dose was increased to 1 mgm. t.i.d. He improved almost immediately with the drug; he lost his irritability, became more cheerful and optimistic. He appreciated, with a little psychotherapy, his wife's virtues (of which she had many) and learnt to minimise her failings. His insomnia, however, remained but did not become any more troublesome. It was easily countered by small, hypnotic doses of Sodium Amytal. He received Meratran for six weeks; following its discontinuance he remained well.

Case 2: An unmarried man of twenty-seven, employed as a salesman with a large wholesale provision company, complained of depression of six months' duration with marked feelings of inadequancy and slight insomnia. He felt that his inability to concentrate would jeopardize his job, and he attributed his condition to the unpleasantness and hectoring manner of his immediate superior at work. He stated that if his condition did not improve he would have to seek other employment. He admitted that he had always been easily upset by the difficulties of interpersonal relationships which other people appeared to take in their stride.

He was re-assured and given 1 mgm. of Meratran twice daily in conjunction with Sodium Amytal, grs. 3 at night. He improved immediately, felt much more optimistic about his prospects and more able to cope with his day-to-day difficulties. His energy and ability as a salesman increased and he directly attributed this to the heightened confidence he experienced from the drug. After one month he was able to sleep without sedatives and he received from then a maintenance dose of 1 mgm. of Meratran daily. He has continued to take this amount for many months now without feeling any necessity to increase the dose, and with considerable benefit.

It is in this group of patients that Meratran is of considerable value and appears, by its absence of untoward side-effects, e.g., insomnia or anorexia, to be of more value than the Amphetamines.

REACTIVE DEPRESSIONS WITH ANXIETY FEATURES.

The speedy realisation of the general unsuitability of this group for Meratran Therapy resulted in a deliberate curtailment of its size. Some seven patients only were included and the results were poor. Moreover, the tendency of the drug to exacerbate anxiety was clearly demonstrated. Of these seven patients, three were only very slightly improved, one was not improved, and three were very much worse.

I wish to recapitulate my view that the drug does not create anxiety where it does not already exist. It may, or may not, have been recognised as it is extremely difficult to differentiate to what extent this entity is present when depression also exists. It is also my impression that Insomnia, when it results from the exhibition of this drug, is also a manifestation of "blow-up" of anxiety not previously recognised.

ILLUSTRATIVE CASES.

Case 1: A rather asthenic male of twenty-eight complained of depression of two months' duration associated with insomnia and intense irritability, accompanied by bouts ofTachycardia and sweating. He had first attended the Tavistock Clinic at the age of fourteen, and was regarded as suffering from a chronic anxiety state. Nevertheless, the depressive element was paramount, in his view, and he attributed it to the fact that he was at present obliged to live with his mother-in-law, who interfered officiously in his marriage.

In view of his constitutional anxiety he was given - in spite of doubts - 1 mgm. of Meratran B.D. He returned two days later to hospital in a state of great Tension and complained that he had not slept at all in the previous two nights. There was no increase in his somatic manifestations, but mentally he was greatly accelerated, with marked pressure of Talk. His depression had markedly increased. Meratran was immediately discontinued and he was sedated with Largactil, 50 mgms. t.i.d. with, in addition, Sodium Amytal grs. 6 at night. He settled gradually over the next few days. His depression has persisted and was not relieved by E.C.T.

Case 2: A single woman of 42 had had a modified leucotomy operation performed six years previously for a chronic tension state, with a fair degree of relief of her symptoms.

When I saw her she was still rather tense and was complaining of depression of six weeks' duration, which she attributed to worry about her sister's health, and consequent difficulties in her work as a secretary.

With some dubiety she was given 1 mgm. of Meratran B.D. She failed to keep her first appointment, but turned up a week later. Her Tension was very much increased, she wrung her hands and contorted herself in her chair stating that her habitual insomnia was worse. Her stream of Talk was under greater pressure. Nevertheless, she was very well satisfied with the result, her mood level being considerably raised, even though her Tension was worse.

It is my later experience and, as yet to my knowledge, there is not any reference in the Literature to the fact that in such cases as the above the management and result can be considerably ameliorated by combining Meratran with Sedative Drugs or Tranquillizers.

Where Anxiety is openly apparent, or its latency suspected, the risk of flare-up is readily prevented by combination of Meratran with Largactil (25/75 mgms. to each dose) or .25/1 mgm. of Serpersil in suitable cases. Equally effective is its combination with Amytal, grs. $\frac{3}{4}$ to each 1 mgm. of Meratran, or Sodium Amytal, grs. $1\frac{1}{2}$, to each 1 mgm. of Meratran.

This is an important finding, as the chief drawback of the drug appears to be the tendency to "blow-up" anxiety and, if this can be combated, the therapeutic scope of the drug is considerably enhanced.

REACTIVE DEPRESSIONS WITH HYSTERICAL FEATURES.

Some twenty-two of the total sixty-nine patients with primarily Reactive Depressions were regarded as falling within the limits of this group. Eleven patients (50%) considered that they were improved as a result of the drug, eight patients were not improved, and three (13%) were worse. It seemed characteristic of this group that almost all of the 50% who were helped did not complain of any specific sleep disturbance as part of their depression.

It was also in this group that bizarre effects, undoubtedly dissociative, were seen in the 13% who were made worse by the drug. These effects included Micropsia, Aphonia, Transcient Paresis of limbs, and the paradoxical reaction of Somnolence. This last was the commonest, and I have also seen it result from Intravenous Methedrine in disposed individuals.

ILLUSTRATIVE CASES.

Case 1: Miss A.M., aged 32, was referred from the Department of Physical Medicine, where she had been receiving treatment for low back pain for over one year. She complained to me of depression of three months' duration which, however, was not accompanied by sleep disturbance, and which she attributed to her back condition and its interference with her normal life. There was no characteristic diurnal mood swing, and she stated that she was depressed all the time. She did not exhibit the Belle Indifférence of Janet; nevertheless, there was a suggestive blandness of her affect. She volunteered that she had lost the use of her right arm for several weeks when she was fourteen.

She was given, in a way to minimise any influence of suggestion, 1 mgm. of Meratran t.i.d., and in a week's time she reported that she was no longer depressed but, rather, optimistic and cheerful. Although her physiotherapy had been interrupted her backache was less severe. She has continued to receive Meratran,

/3 mgms. daily

Meratran/

3 mgms. daily over these last three months, and has remained very well.

Case 2: J.W. was a divorced woman who had received prolonged Methedrine (Intravenous) Treatment for a hysterical paralysis of her right hand, and whose marriage had broken up on account of her frigidity. She complained of Depression of two months' duration, again without any characteristic daily mood variation, and unaccompanied by Insomnia.

She attributed her depression to the paralysis of her right hand, which seriously affected her professional capacity as a Journalist. She had considerable insight into her disability and was highly intelligent.

She was given Meratran up to 4 mgms. daily in two doses without any upset, and with considerable benefit both with regard to the depression and the functional disturbance of her hand, which almost completely disappeared. She continued on this Therapy for one month, when she discharged herself as cured.

Case 3: T.S., a male aged 40, had been regarded as a Hysterical Hypochondriac for some eight years. He was referred to me complaining of persistent, flatulent dyspepsia, which in the past month had become more severe and was associated with Depression. Physical and Radiological Examination were essentially negative. His Depression was continuous and unvarying in severity. He stated that he did not get any sleep at all now; nevertheless, he looked remarkably fresh.

He was tentatively given 1 mgm. of Meratran .B.D. Two days later he 'phoned to say that he had not been able to get out of bed since he commenced this treatment. He complained of excessive somnolence, and that everything looked small and far away. He was reassured and told to stop taking the drug. When I saw him last, ten days ago, his condition certainly had not altered for the better; indeed, it was his contention that my treatment had been so drastic that all chance of his ever being cured had now evaporated.

REACTIVE DEPRESSION ASSOCIATED WITH ORGANIC DISEASE.

Meratran proved fairly useful with this group: of thirteen cases of Depression associated with organic disease, all but two of these cases were improved, and it is of interest to note that, in general, a dose of up to 3 mgms. a day of the drug was generally efficacious. Frequently there was a fair degree of alleviation of physical symptoms such as dyspnoea in addition to elevation of mood. Of these thirteen cases five were Post-Influenzal Depressions, one was a case of depression following Infective Hepatitis, three were

/Depressions

three were/

Depressions associated with a greater or lesser degree of Cardiac Failure, one case was associated with Paralysis Agitans, two associated with Chronic Bronchitis and Emphysema, one associated with a Lympho-Sarcoma of the Cervical Glands.

The two cases which were not improved were
(a) In association with Paralysis Agitans,
(b) One Post-Influenzal Depression.

ILLUSTRATIVE CASES.

Case 1: R. B., a man of thirty-eight years, was admitted early in a second attack of Congestive Failure precipitated by a mild upper respiratory Tract Infection. He suffered from Rheumatic Valvular Disease and exhibited a wealth of physical signs. He had a marked praecordial heave due to enlargement of his right ventricle, the right border of his heart by percussion being almost at the mid-clavicular line; the left border was in the sixth interspace beyond the mid-clavicular line. When I saw him he exhibited controlled fibrillation; he had a blowing, systolic murmur at the apex, high-pitched and propagated to the left axilla and to the back of his chest, in addition to a sharply-localized mid-diastolic murmur at the mitral area. Tricuspid, Systolic and Aortic Diastolic murmurs were also present. His liver was enlarged and pulsated. He was considered as suffering from Mitral Stenosis and incompetence, with Aortic and Tricuspid Incompetence.

Despite the improvement in his physical condition effected by treatment, he was hopelessly depressed and complained of terrifying dreams. The marked palpitation which he experienced and the liver pulsation, of which he was acutely conscious, he considered the main factors for, as he said, they constantly reminded him of the precariousness of his hold on life.

He was ordered 1 mgm. of Meratran thrice daily, to be given at 8 and 11 a.m., then again at 2 p.m. His mood improved remarkably after one day and, characteristically, he stated that his depression was less marked. The change in mood was very marked and he entertained me with facetious remarks about the examinations, in the clinical part of which he had figured for the appraisal of candidates. Although he has been in hospital for these last two months he has remained optimistic and cheerful, and has continued to take 3 mgms. of Meratran daily without harmful effect.

Case 2: Miss M. K., aged 59, suffered from Paralysis Agitans, which had been diagnosed some ten months before. She complained of Depression with suicidal thoughts, the onset of which had occurred some two months previously and which was accompanied by bouts of agitation and crying. In these attacks she continually reiterated that she had nothing to be depressed about, and this feature almost amounted to palilalia. In the fourteen days prior to that date on which she was first interviewed, she had received 200 mgms. daily of Ethopropazine Hydrochloride (Lysivane). I have observed the tendency of this drug to cause Depression; consequently, following her admission it was stopped, and she was given Artane, 2 mgms.t.i.d. in combination with Meratran, 1 mgm. t.i.d.

The effect of this therapy was to increase her Depression and Agitation; it increased her suicidal ruminations; consequently, it was stopped after two days. She has shown temporary improvement as a result of Electroplexy, but over these last three months she has required maintenance E.C.T. at fortnightly intervals. Unfortunately, I have not sufficient experience of Mental Disturbance associated with Paralysis Agitans to fully appraise this case. She presented more as an Involutional Depression with the characteristic agitation; her personality before the onset was obsessional, as is frequently the case in Involutional Psychoses. Many of these, however, respond poorly to Electroplexy. The exact connection with the organic changes of Paralysis Agitans is obscure.

This case, despite the complexity of the factors involved, helps to confirm the impression that Involutional Depressions should not receive this drug.

Case 3: A. L., a male of twenty-seven, complained of atypical headache, lassitude, lack of interest in his surroundings and mild depression which was continuous. He stated that he had failed to "pick up" after influenza, the onset of which had occurred five weeks before, and for which he had been treated with M & B tablets. Enquiry revealed that he had had a febrile illness associated with aching limbs and cough, and for which he had received, as far as I could ascertain, 30 grams of Sulphatriad, following which he said he felt utterly prostrated physically and mentally. His previous personality was rather obsessional, and his physique good. It was felt that a combination of Influenza and Sulphonamides, both of which are frequently followed by depression, had produced the clinical picture.

He was given 2.5 mgms. of Meratran twice daily and improved immediately after the first dose. His interest brightened, his energy output increased, and his vague headache resolved.

This drug was continued for one month. He remained perfectly well for the two subsequent months and was discharged as recovered.

The Post-Influenzal Depression which failed to respond to the drug presented rather as that of the Manic Depressive Type which had been triggered off by the febrile illness, and which was not a true picture of the syndrome described as Organic Neuresthenia which follows Influenza, the administration of Sulphonamides, and Infective Hepatitis.

SPASMODIC TORTICOLLIS.

Five cases of this distressing condition were treated with Meratran, four of whom were improved, One patient received 37.5 mgms. of the drug per day without any improvement initially, although subsequently it was possible to combine the drug with intravenous Methedrine, with fair benefit to the patient. The optimum dosage of the drug in this condition appears to be in the region of 20 mgms. per day. In this group the results varied with the duration of the illness, and the degree of integration and development of the personality. Those with a good previous personality and a short history responded best to the drug, and vice versa. Generally speaking, such therapeutic response as is going to occur manifests itself in the first few days of treatment.

ILLUSTRATIVE CASES.

Case 1: S.L., a stockbroker's clerk of forty-one, had suffered from Spasmodic Torticollis of one year's duration and of sudden onset. He exhibited marked clonic spasm of the right Sterno-Mastoid muscle, with severe pain and, of course, deviation of his head to the left. He attributed it to repeated movements of his head while answering a battery of telephones in the Stock Sxchange. He nursed a sense of grievance against his employer, feeling that men of lesser ability had been promoted over his head while his hard work and reliability has passed unnoticed. He stated that during his absence from work, which had lasted for one year, three other individuals were employed on the work which he had managed alone. He lived in a dormitory suburb and travelled to the City daily. He was hard-pressed to maintain his growing family and sustain the payments on his house mortgage. He had served as a Captain in the Sudanese Camel Corps, and made invidious comparisons between being one of the twelve millions in the Greater London area struggling to pay a house mortgage, and being passed over at work, and the freedom which he nostalgically accredited the pagans of Equatoria, although subsequent events have disenchanted him.

His previous personality was good. He had received a variety of treatments without effect, yet his affect was intense and deep. His distress, I am certain, was heartfelt.

He received from me intensive daily psychotherapy of an explanatory and re-educative type with some success, so that in combination with oral Methedrine, mgms. 5, B.D. (I had immediately discontinued the thrice-weekly injections of Methedrine, 50 mgms., which gave him temporary relief), he was able to go back to work. This return to employment resulted in immediate and catastrophic relapse.

He was nonchalantly prescribed Meratran 2.5 mgms. t.i.d. with immediate improvement, the dose being raised over four days to 20 mgms. daily, given in four doses of 5 mgms. each. He has been symptom-free except immediately on awakening in the morning, and has continued to take this amount of the drug. He states that the main effect is to relieve pain and spasm; he notices very little cerebral stimulation, although he complained of initial insomnia, which was easily controlled by small doses of Sodium Amytal.

Case 2: A. R., a male executive of 56, had complained of Spasmodic Torticollis of three years' duration, of sudden onset, and for which he had received a variety of treatments without avail. His marriage was not a success; he is impotent. His outlook was one of bored, bland sophistication and he had at one time given psychoanalysis - as he said - "a whirl". He occupied a remunerative post as an advertising agent to a large Petroleum Company. He told me that he had failed to fulfil the early promise as a writer which he had exhibited in his Cambridge days. His demanding, widowed, Clergyman father who had dominated him until he died (when the patient was 28) had, he maintained, made him indelibly what he was.

He was given Meratran in doses of 5 mgms. daily initially, and this was raised over ten days to 37.5 mgms. without any alleviation of the man's condition, and with a slight increase of pain and spasm.

The Meratran was then discontinued and he commenced a course of Intra-Venous Methedrine Injections given at twice-weekly intervals in doses of up to 50 mgms. This was accompanied by considerable relief following each injection for a period of twenty-four hours. This, however, was followed by intensification of his symptoms, with a degree of depression. It was found possible to counter this "let-down" by Meratran in doses of up to 7.5 mgms. daily, in the intervals between the Methedrine Injections. He has continued this form of treatment for six weeks and has improved considerably on this regime.

BLEPHAROSPASM.

As in Spasmodic Torticollis, Meratran seems of considerable value in the treatment of Hysterical Blepharospasm. One case only was treated: it was seen in an elderly lady who had bilateral spasm of the orbicularis oculi, and which occasioned her much inconveniece. The condition was of some twenty months' duration. She has been helped immensely by a stabilising dose of 14 mgms. of Meratran daily and, although tic-like movements of the orbicularis oculi still occur, they are much less severe than formerly.

POST-LEUCOTOMY ANERGIC STATES.

Five such cases were treated: the optimum dosage of Meratran in this condition, as I have said, appears to be between 12 mgms. and 14 mgms. daily. These patients had had leucotomies performed for a variety of conditions. Two of them had been performed in the early 1940's and were Standard Operations involving both upper and lower quadrants. These had been followed by considerable lethargy and lack of interest, into which the patients had sufficient insight to complain, and which had persisted for years despite the administration of various stimulants. It was in this group that the results were best, the patients volunteering that Meratran was vastly superior, in its stimulant properties, to the Amphetamines stressing, in particular, the insidious, sustained action and the absence of "hang-over" effects. The other three patients had had relatively-recently performed lower quadrant Sections, and two of them were given the drug in the almost-immediate post-operative period, in doses of up to 14 mgms. per day. The results were highly encouraging, although not so marked as in the long-standing group.

USE IN COMBINATION WITH RESERPINE.

It has been reported that Meratran is of particular value in combating the lethargy frequently associated in hypertensive subjects with the administration of Serpasil. Two such patients were given Meratran, with encouraging results and without affecting the hypotensive action of the Rauwolfia preparation. In these cases the American practice was followed, the dose in mgms. of Meratran being half that of Serpasil. This would seem a relatively-promising use for this particular drug.

My experience suggests that Meratran is also of value in combating the lethargy resulting from the use of anti-convulsants in Epilepsy.

USE IN PREVENTION OF MIGRAINE.

Two such cases were treated but, though the severity of the attacks was diminished, no essential feature was altered or, indeed, abolished. This resulted solely from the prophylactic administration of the drug. Since the part of vascular disturbance is well recognised in migraine, such knowledge as we have of the action of Meratran would not encourage us in any optimism we might have about its value in this condition. The little inference one can admit from only two cases would seem to suggest that such value as it has is in raising the mood and mitigating psychogenic precipitating factors in the condition.

Each of these two patients was given 1 mgm. t.i.d. for a period of two months. The attacks were less frequent and less severe, but in no wise different from usual. The value in this condition is only limited.

TOXIC AND SIDE EFFECTS.

Undoubtedly, the chief toxic effect of this drug is its tendency to exacerbate the pre-existing anxiety, and this feature depends largely on the personality setting. It is just as likely to occur with minimal doses of the drug as with the larger, and this untoward action, as I have said, depends primarily on personality. This cannot be over-stressed and is one of its real dangers. This is especially true in the Depressions of the involutional period, which are so frequently seen in an obsessional personality, and accompanied by agitation and anxiety. In these cases the depth of the depression is frequently augmented, and suicidal ideas which may have been latent become prominent. In the Reactive Depressions complicated by this feature, exacerbation is also likely to occur and prove exceedingly alarming both to the patient and his relatives. In such persons the complaint is of great irritability and restlessness, with marked pressure of talk, frequently insomnia, exacerbating to a degree bordering on that of panic. Visceral manifestations are very rare.

A few patients complain of feeling "muzzy-headed" and I have taken this to mean the minimal degree of vertigo subjectively experienced. Likewise, nausea is rarely complained of. One patient, of all this series treated, developed a macular rash on the flexor aspects of his arms and on his trunk. This disappeared completely within twenty-four hours of discontinuance of the drug. As far as is known, the drug does not alter the urinary constituents and has no effect on liver function or bone marrow. There is no mention of jaundice in the Literature and I have never encountered it.

Unfortunately, I must report the occurrence of a psychotic episode which can only be attributed to the drug itself and concerning which, to date, there is no mention in the Literature. We have seen the intensification of doubts into delusions, the adding of a schizophrenic flavour to an Involutional Depression: this is not the most sinister effect, since it is recognised by some authorities that certain of the Involutional Depressions are related to the Schizophrenias.

The most distressing feature was the appearance of an Acute Hallucinatory Paranoid State in an Endogenous Depression of the Manic Depressive Group in a long-standing illness (the history extended back over seven years) and which could not clinically, by any method of enquiry, be attributed to a misdiagnosed schizophrenic psychosis. It occurred following the administration of 3 mgms. of the drug for fourteen days. Its onset was acute and it subsided within forty-eight hours of discontinuance of Meratran. The most disconcerting feature is the total inability to predict this type of Reaction in the present state of our knowledge, and this is a very real danger. The visceral manifestations of over-stimulation are absent with this drug, so there is no warning whatsoever.

Insomnia is relatively rare, and it is my strong impression that when it occurs as a result of Meratran it is, in reality, a manifestation of the "blow-up" of pre-existing anxiety which one has failed to recognise in the mixed picture so common in the psychoneuroses. Initial insomnia may suggest its otherwise-hidden presence, but not always; a family history may put one on guard.

Anorexia is also very rare and I have not encountered it as a dominant feature. It has been claimed by some American workers that the drug is of use in the control of obesity, since by its stimulant powers it augments decision, thus facilitating self-control of appetite. This, I think, is a rather contentious and involved concept and really too loose to be confirmed or denied. I have not personally investigated this claim; it admits of too many fallacies.

Discretion should be exercised in administering Meratran to theblatantly-hysterical, as the side effects, which it is convenient to regard as dissociative and concerning which we know very little, can be extremely distressing and alarming for the patients; thus, I have seen in this series somnolence, transient paresis of limbs, and micropsia. Paradoxical though it may be, they can utterly destroy any rapport created, and may add symptoms to those already in existence. This can be a major catastrophe in hysterical patients and should always be borne in mind when exhibiting any relatively-powerful drug

The drug was given to one blatantly-obsessional patient in addition to Case 3 cited amongst the Endogenous Depressive group. This was a deliberate curtailment on my part, for I had

/little

for I had/

little doubt, following my initial experience with the drug, that such patients would be made worse. In Case 3 of the Group cited above, we note the increase of the depth of the depressive effect, with extreme agitation. The other patient cited developed a marked increase in the tendency to ruminate obsessively, both the subjective feelings of tension and internal resistance which they habitually feel being markedly increased with resultant agitation and insomnia.

The tendency of the drug to "blow-up" anxiety in the Involutional Group and the few Obsessionals given it, was a great as in the constitutionally-anxious. In the Obsessionals, the "inner-restlessness" engendered by the drug, and which may be much greater than the degree of agitation or anxiety might lead one to suppose, can be literally overwhelming for the patient, so that he may feel as if his mind were being rent in pieces.

CONTROL OF SIDE EFFECTS.

This has previously beenmentioned and requires little elaboration. The effective combination with Largactil and the Barbiturates is often sufficient to prevent "blow-up" of anxiety. This is of particular consequence in the Reactive Depressions. It should not be utilised in Involutional Depressions or any Endogenous Depression showing great agitation, as Meratran is unsuitable for the treatment of these cases and, moreover, even in combination in this latter group the depth of involvement of the psyche is so great that the response is poor. It is of interest to point out - and I believe that this has not already been done - how Serpersil is of use in combating the Anxiety induced by Meratran and, conversely, the value of Meratran in combating the lethargy of Serpersil. This latter action has, I believe, been remarked upon by American workers but not (shall I say) the reciprocity of action of these two drugs.

I wish also to point out that combination of Meratran with the Scandinavian Tranquillizer "Suavitil" seems definitely encouraging. In some respects this combination is more potent than combination with Largactil or Serpersil. This finding, however, requires further study. It should be mentioned that the combination with Barbiturates, in the light of later experience, is not so successful as the combination with the other drugs and that the anxiety-dampening effect of the Barbiturates seems to wear off in a few months. The dose of Barbiturates in such instances was not increased, as the danger of addiction with these drugs is now well recognised. Generally they were withdrawn gradually and one of the other drugs mentioned substituted. Moreover, that the prolonged use of Barbiturates can result in a Tension State is well recognised.

Nausea resulting from Meratran is rarely severe and disappears almost immediately the drug is stopped. One patient developed a skin eruption which disappeared rapidly on discontinuance of the drug. Itching of the eruption was not complained of and I did not consider it necessary to order any specific treatment. The preventative treatment of "flare-up" has been mentioned. When one encounters a similar "flare-up" which has not been anticipated the drug must immediately be discontinued and the individual sedated. The most useful drug, I find, is Largactil in doses of 50-100mgms. thrice daily. If Insomnia is marked and specifically complained of, it is advisable to concentrate the dose of Largactil towards the evening. If Barbiturate sedatives are ordered the potentiating qualities of Chlorpromazine must be constantly borne in mind, and it is advisable to ensure considerable time interval between the last dose of Largactil and the Hypnotic.

In Endogenous Depressions, Agitation, and deepening of depression as a result of injudicious Meratran Therapy may call for immediate E.C.T., especially if suicidal ideas are prominent.

In patients with hysterical tendencies the dissociative phenomena resulting from Meratran are usually ephemeral if adequate reassureance and explanation are immediately forthcoming; if necessary, combined with adequate sedation, usually Barbiturate. It is of great importance that they be dealt with quickly lest they become fixed. It may be necessary to heighten suggestibility by using Intravenous Sodium Amytal or Pentothal, and I have seen hypnosis successfully employed by a colleague in such a case. At any rate, it is extremely important to maintain rapport so that the effectiveness of any alteration in treatment required is not impaired. This can be particularly difficult where paradoxical reactions have occurred. One patient of this particular series demanded Meratran to make her sleep and keep her quietened.

The acute hallucinatory paranoid state reported in this series necessitated admission to an observation ward, with immediate cessation of the drug. Enquiry revealed that intra-muscular Largactil, in doses of 50 mgms. t.i.d., had a remarkably-calming effect on the patient.

TOLERANCE.

Clinical trials of Meratran were first instituted in the United States in February, 1953 and, as far as I am aware, the drug has been undergoing investigation in this country for over a year.

To date, from the literature and from my personal experience, there is little evidence to show that tolerance is developing. A few patients mentioned that the effect tended to wear off with time. This is by no means common, and in my experience of this series only five patients have remarked that the morning dose of the drug was tending to produce rather less effect. This was complained of only after periods of several months.

There seems to be a considerable variation in the amount of the drug which can be tolerated by different persons. Persons with hysterical traits of personality would appear to tolerate large doses with little upset. I have not seen any real indication of tolerance in any condition, despite the fact that some patients have received the drug for many months. It was in the Depressions that a falling-off in action was remarked on. I have no experience of administering the drug to psychopathic individuals, worth mentioning, so I cannot state whether the toleration of Amphetamines by explosive and aggressive psychopaths is being mirrored in the case of Meratran.

So far, there is no evidence of addiction to Meratran, either from the Literature or from experience of this series. Our experience is, however, very limited in time; judgement must be reserved on these issues.

INDICATIONS AND CONTRA-INDICATIONS.

The great difficulty in defining the range of therapeutic value of a drug by one particular individual can readily be appreciated. Nevertheless, as a result of consistent use of the drug in a fairly-large series of cases over a period of many months to the exclusion of any but related activities, certain very definite conceptions of its application and limitations have been formulated. The drug is primarily indicated in these Reactive Depressions uncomplicated by features of Anxiety, Hysteria, or Obsessional trends. A very large percentage of such patients regain their normal state of well-being on Meratran. Generally, the response is almost immediate and no good result is delayed longer than one week from commencement.

Reactive Depressions with hysterical features vary in their response; only about half respond well. Absence of sleep-disturbance indicates a good response, and the drug can be given with confidence to such patients.

In reactive depressions with features of anxiety, the drug is unsuitable except in combination; this is particularly true of depression seen in obsessional individuals. Phobic fears, in particular, are a warning not to give the drug.

Depressions reactive to physical illness are a definite indication for the drug. Occasionally, despite appearing superficially reactive, they are in reality endogenous; these should be avoided. The drug helps to relieve physical symptoms.

Endogenous Depressions are unsuitable for Meratran Therapy, especially the Involutional Depressions, or Depressions accompanied by anxiety or agitation. A few Endogenous Depressions repond fairly well; these are Remitting Depressions of the Manic Depressive type.

Spasmodic Torticollis and Blepharospasm are definite indications for the drug. The shorter the history, the stronger the indication; the younger the patient, the more definite the indication. A good response will appear within a week. Should the drug fail by itself it can, with advantage, be combined with Intra-Venous Methedrine.

The drug is definitely indicated in post-leucotomy Anergia. The optimum dosage is 12-14 mgms. daily. The more radical the leucotomy, the more striking the result, probably because lethargy is more marked.

The drug is of value in relieving the lethargy induced by Reserpine in severe hypertensives, and it is indicated to relieve the lethargy induced by anti-convulsants in Epilepsy.

There is a slight indication for the drug in migraine, especially if psychogenic precipitating factors are marked, e.g, depression. The results are rather disappointing.

Slight experience indicates that it is of value in relieving the "hang-over" effects of alcohol.

The presence of Anxiety is a precluding feature as far as Meratran is concerned, and this has been repeatedly stressed.

Psychotic trends are a definite contra-indication, e.g., paranoid delusions.

Meratran should never be given where E.C.T. is properly indicated.

COMPARISON WITH AMERICAN FINDINGS.

The value of the drug in Reactive Depressions is generally confirmed, and its superiority to the Amphetamines by the absence of "hang-over" effect, and by the absence of Insomnia and Anorexia is substantiated. It was found possible to sub-divide these cases and thereby delineate more exact indications than pointed out by American workers.

The claims of American workers that 50% and over of Endogenous Depressions are improved are not substantiated. Involutional Depressions, in particular, are made worse by the drug. The Americans have not stressed this fact in particular, nor have they pointed out that it seems to be only of use in those Depressions of the Manic Depressive Type which are undergoing self-termination.

They do not point out how the "blow-up" of Anxiety can be prevented by combination with other drugs; this is an important finding.

The use of the drug in Post-Leucotomy Anergia is not reported by American workers.

The value of the drug in Depression associated with Organic disease is confirmed.

The value of the drug in Hysterical Torticollis is confirmed, also Blepharospasm.

The rapidity of the Therapeutic Response is not stressed by the American workers.

Its value in combating the Lethargy resulting from Reserpine is confirmed.

Psychotic Disturbances arising purely from the use of Meratran are reported in this series. This is not mentioned by American workers.

The finding of Fabing that it should never be used where E.C.T. is indicated is confirmed.

The value in combating the "hang-over" effect of the Amphetamines has been demonstrated, e.g., I.V. Methedrine. This is not mentioned by American workers.

COMPARISON WITH AMPHETAMINE.

It is relevant to consider the actions of Amphetamine which has been exhaustively investigated since the initial work by Piness and co-workers in 1930. Amphetamine, racemic B Phenyl-isopropylamine, is closely allied in chemical structure to ephedrine, phenylpropanolamine methamphetamine, and hydroxyamphetamine. The pharmacological differences between amphetamine and adrenalin are due especially to the fact that the former drug possesses an alpha methyl substitution and lacks phenolic hydroxyl groups. The structure of amphetamine confers on it resistance to enzymatic destruction in the body, as a result of which it is effective after oral ingestion and has a prolonged duration of action and the ability to stimulate the Central Nervous System. Due to the presence of an asymmetric carbon atom in the molecule B-phenylisopropylamine exists in three forms, namely d-, l- and dl-beta-phenylisopropylamine. The dextrarotatory form is approximately twice as potent as the racemic form on the basis of clinical tests on normal individuals and in patients with Narcolepsy and postural hypertension. The Laevorotatory form is the least potent of the three, This is particularly interesting, because in most instances laevorotatory compounds possess more pharmacological activity than Dextrarotatory or racemic compounds.

It is highly probable that the sympathomimetic effects of Amphetamine are the result of direct action of the drug on the receptors of muscle and gland cells innervated by adrenergic fibres. It has been suggested that it acts by inhibiting amine oxidase, but this is by no means substantiated.

The mechanism of the central stimulation produced by Amphetamine has not been elucidated, although the chemical structural basis for this action is fairly-well understood. The drug has no ability to increase the respiration of the brain cells inhibited by anaesthetic drugs, or to increase oxygen consumption of normal brain tissue. The stimulant effects of Amphetamine on normal and anaesthetized brains is largely unexplained; it is doubtful whether the peripheral actions of Amphetamine can be profitably correlated at the present time with the excitatory effects of the drug on the Central Nervous System.

ACTION ON CENTRAL NERVOUS SYSTEM.

Amphetamine is a potent agent for stimulating the Respiratory Centre, lessening the degree of central depression caused by anaesthetics or narcotics. Animals receiving large doses of Amphetamine exhibit tremor, restlessness, increased motor activity, agitation and sleeplessness, to a marked degree. These effects are thought to result from cortical stimulation by the drug but they may also result, in part, from an action on the Reticular formation of the brain stem. Unlike pentylenetetrazol (Cardiazol) and certain other analeptics, Amphetamine does not produce seizure or sub-convulsive dysrhythmias in normal animals. In man, the response depends upon the mental state and personality of the individual and the dose administered. Following the ingestion of 10-30 mgms. of the drug by mouth we notice wakefulness and alertness, increased initiative, and euphoria amounting almost to elation; increased motor and speech activity, increased ability to concentrate. The effect on psychomotor performance is such that more work may be accomplished, but the number of errors is not necessarily decreased.

The psychic effects of Amphetamine are not always as described. The salutary or pleasurable effects may be reversed by over-dosage or repeated medication. Many patients may experience headache, palpitation, dizziness, vaso-motor disturbances, agitation, confusion, apprehension, delirium, depression or fatigue. Following stimulation patients almost always complain of fatigue and depression. The effect of the drug on the E.E.G. is to accelerate and desynchronize the resting rhythm. The drug also has a stimulating effect on the spinal cord. The action of Amphetamine in producing anorexia is almost certainly a central effect and has been correlated with the depression of sense of taste and smell resulting from the drug. This, however, does not completely explain the phenomenon. Addiction to this drug is well recognised and occurs primarily in psychopaths. The drug may be obtained from inhalers. Alcohol and Barbiturate addicts frequently abuse Amphetamine. The usual single dose taken by the addict is 100-250 mgms. and it may be repeated once or twice a day. Such amounts cause anorexia, insomnia, marked restlessness, irritability and aggressiveness. Toxic psychoses may occur and are characterized by agitation, auditory and visual hallucinations (similar to those of cocaine intoxication), and paranoid delusions.

A characteristic abstinence syndrome does not develop when Amphetamine is abruptly withdrawn, but depression tremors weaken and gastro-intestinal symptoms have been observed in some individuals.

Tolerance is well recognised, and one individual cited in the literature took 250 mgms. a day for five years, but then developed an acute hallucinosis.

Meratran, from our studies, by comparison with the Amphetamines appears to have a much more insidious action and the stimulating effect, although not quite so great, is more sustained. The effects of the drug wear off insidiously as well, and the depression and "let-down" of Amphetamine is conspicuously absent. The insidiousness of action is apt to conceal the intense stimulation which does occur.

Meratran has little or no effect on appetite and rarely causes insomnia, which is such a frequent, undesirable side-effect of the Amphetamines. It does not appear to have any of the sympathamimetic properties of Amphetamine and these are conspicuously absent. Talkativeness, which so frequently accompanies even therapeutic doses of Amphetamine, is rarely seen in Meratran Therapy and then usually in the constitutionally-anxious.

The site of action of Meratran would appear to be confined to the sub-cortical centres, whereas in addition to its peripheral action Amphetamine acts on the cortex.

Both drugs can cause disturbances which are similar to those encountered in the psychoses. My experience is that this tendency is only displayed on very large doses of Amphetamine, whereas in the present work the most intense disturbance resulted from small, therapeutic dosage of Meratran. Even in dosage which is sufficient to cause a "blow-up" of anxiety, or in a constitutionally-disposed person, Meratran very rarely causes any of the bodily manifestations of anxiety. Tolerance to Meratran is very slight and, as yet, addiction is unknown.

A comparison of the Therapeutic Range is interesting and, despite the recency of Meratran, it is rapidly enlarging in therapeutic scope.

The Americans (Fabing) have reported the effective use of Meratran in Narcolepsy, but I have not been able to confirm this due to lack of clinical material. It is claimed that the drug is even more effective than the Amphetamines. The effectiveness of Amphetamine in the treatment of the physical disturbances, e.g., Oculo-gyral crises of paralysis agitans, is not rivalled by Meratran. So far as is known, Meratran is of no value in this condition per se.

Meratran seems superior, in my experience, to Amphetamines in the treatment of Spasmodic Torticollis and Blepharospasm.

Amphetamine is of use in the treatment of chronic alcoholism in assisting patients to abstain. This claim is also made for Meratran. I am unable to assess their respective value in this condition, as I have little experience. So, also, for the relief of Alcoholic "hang-over". Both drugs have their main field in the treatment of Reactive Depression. They can both be used in combination. Both are largely unsuitable for use in Endogenous Depression.

The Amphetamines have been found useful in a whole range of Abreactive procedures, alone or in combination with CO_2 or ether, e.g., the Traumatic Hysterical Syndrome, or Anxiety States in an obsessional setting. Work along these lines is proceeding, but so far no information can be adduced to show that Meratran has any real abreactive possibilities.

Amphetamines Intra-Venously have been found useful as a purely physical treatment of chronic skin conditions. So far, the analogous value of Meratran is uhknown. Amphetamines Intra-Venously have a value in the diagnosis of Stupor and may release heretofore-hidden schizophrenic symptoms. The value of Meratran here is unknown. Meratran is superior, in my experience, to Amphetamines in the treatment of Post-Leucotomy Anergia.

It is also superior in combating the Lethargy of Reserpine since, unlike the Amphetamines, it does not elevate the blood pressure.

Amphetamines are of value in the treatment of poisoning by depressants: no information is available on the value of Meratran in such cases.

Amphetamines, by their tendence to produce Insomnia and stave off fatigue, were found of value in the exigenices of war. It is doubtful if Meratran is of any value under such circumstances. The value of Amphetamines in reducing obesity is not paralleled by any similar action of Meratran as it does not affect the appetite.

Amphetamines have a wide use due to a local vaso-constrictive action in the treatment of congestion of the mucosa of the respiratory tract. Such therapy is widely employed in hay-fever, acute coryza, acute sinusitis and vasomotor rhinitis. They are also of value in Orthostatic Hypotension. Amphetamines are of value in the treatment of enuresis. Meratran has also been used in this condition without definite conclusive result.

The value of Amphetamines in petit mal as an adjuvant is well known.

Meratran has no comparable action, but its value in combating the lethargy of anti-convulsants is recognised.

Amphetamine is of definite value in the treatment of Behaviour Disorders in children with E.E.G. abnormalities.

It is of similar value in the Dysrhythmic Aggressive Behaviour Disorder of Adults. No knowledge is available about Meratran in such conditions. Both drugs have very little preventive value in Migraine.

The value of Amphetamine in Dysmenorrhoea and the Nausea and Vomiting of Early Pregnancy is recognised. The action of Meratran in these conditions is unknown.

SUMMARY OF FINDINGS.

There seems little doubt that in Meratran a valuable therapeutic agent has been discovered which, by the absence of side-effects, promises to be superior to any similar drug at present available. The drug, however, has serious limitations; in particular, its tendency to exacerbate anxiety, and the necessity for exact diagnostic findings before it is exhibited; moreover, the occurrence of psychotic disturbance on even minimal dosage of the drug is reported. Nevertheless, the drug seems superior in the treatment, for example, of Spasmodic Torticollis, Post-Leucotomy Anergia, Blepharospasm, and certain Reactive Depressions, to any other substance at present available. Likewise, its value is apparent in the treatment of Depression resulting from physical disease. Its value in the treatment of Endogenous Depression is not confirmed; however, this does not severely restrict its use as more-or-less effective methods of treatment are available in such conditions.

In the present state of our knowledge the problem would appear to be whether this drug should be made available generally, and widespread use advocated. My feeling in the matter is that such a move is premature, and that further investigation of its properties should be undertaken. I feel that the anxiety-exacerbating propensities of this drug, despite the effectiveness of combination to prevent this, mitigates against its general use (although it is at present widely available in America). The occurrence of psychotic disturbance, I feel, enhances the relevancy of the stressing of its dangers.

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