

PROGNOSTIC FACTORS IN THE TREATMENT
OF DEPRESSION

with special reference to the use of E.C.T.

by

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Leeds, 1958.



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ACKNOWLEDGEMENTS

It is a pleasure to record my indebtedness to many who have helped this investigation in various ways. I am grateful to Professor G. R. Hargreaves for his advice, encouragement and continued interest, and for permission to study patients in the General Infirmary at Leeds. My thanks are due to Dr. J. Valentine, Scalebor Park Hospital, Burley-in-Wharfedale, and Dr. M. Leahy, St. James's Hospital, Leeds, for the co-operation and facilities they afforded me to see patients under their care, and to the nursing staff of the three hospitals concerned. I wish to thank also Dr. M. J. Parsonage for permission to use the E.E.G. apparatus at Leeds Infirmary, and Miss M. S. Todd for patient technical assistance in this connexion; Dr. A. S. Douglas, Director of the Leeds University Computing Laboratory and Miss Winifred Ashton, Research Assistant, who gave invaluable advice and help with the more laborious calculating involved in the investigation; my colleagues, Dr. B. Ward and Dr. H. H. Grosser for their helpful co-operation in clinical matters; and Miss S. A. Thackeray, Miss E. A. Barker and Miss R. Ziff for their secretarial assistance.

I am particularly indebted to Dr. Max Hamilton Senior Research Fellow in the University of Leeds

Department of Psychiatry, whose unstinted advice, practical assistance and helpful criticism at all stages of this work, especially with regard to experimental planning and statistical evaluation of the results, have contributed in no small way to any merits which it may possess.

Finally, but by no means least, I would record my gratitude to the 54 patients who made this investigation possible.

J. M. R.

Leeds, August, 1958.

REVIEW OF PREVIOUS WORK

"I hold that it is an excellent thing for the physician to practise forecasting He will carry out the treatment best if he know beforehand from the present symptoms what will take place later." Hippocrates (quoted by J. A. Ryle)

Introduction

A new era of therapeutic progress in psychological medicine began in the 1930's with the introduction of physical methods of treatment - first insulin coma in 1932, metrazol convulsive treatment in 1934, prefrontal leucotomy in 1935, and finally the introduction of electro-convulsive therapy (E.C.T., electroshock) in 1938.

In the succeeding 20 years, E.C.T. has become probably the most widely applied form of physical treatment in psychiatry, despite the fact that its method and site of action are still not precisely known. It has been applied in a variety of psychiatric syndromes, not always with success and occasionally with deleterious effects. For this reason, numerous investigations have been undertaken in the attempt to delineate more clearly the indications for its use. A good measure of agreement has been reached on the value of E.C.T. in depressive states and certain schizophrenic

syndromes, but even in the former, where results are generally acknowledged to be best of all in mental illness, there is still a paucity of evidence on which firm criteria for the prediction of outcome to treatment can be based. This is not altogether surprising in view of the probable non-specific cerebral action of electroshock, a theme elaborated by Roth (1951). Furthermore, until comparatively recently, little attention has been paid to the search for more specific prognostic indicators other than those based upon empirical clinical observations during the course of routine psychiatric practice. The majority of such studies appeared in the decade succeeding the introduction of E.C.T.; despite their great value, the fact that they have not in themselves been sufficient for accurate prognostication is emphasized by the continuation and changing pattern of such investigations in the last decade. These have included more intensive and precise investigations based on possible psychological, physiological, biochemical and pharmacological indices of capacity to respond to electroshock, many involving new techniques or new avenues of approach.

Some of the more recent methods have not yet been fully appraised. It is with these researches, as well as those based on the clinical features of history and examination which preceded them, that

this review is concerned, and it is convenient to utilize this chronological development as a basis for classification of the literature dealing with the prognosis of depressive states treated by electroshock.

- A) General prognostic factors from history and symptomatology.
- B) Specific prognostic indices:
 - I - Psychological Tests.
 - II - Tests of Autonomic Function.
 - III - Tests based on response to drugs.
 - IV - E.E.G. studies.
 - V - Miscellaneous indices - endocrine biochemical and other.

A) GENERAL PROGNOSTIC FACTORS

In a survey of the published work touching upon conventional clinical prognostic studies in the electroshock therapy of depressive states, difficulties in the selection of material for consideration are soon encountered. The literature is a considerable one, with, for example, frequent overlapping in diagnostic categories, many studies being concerned with schizophrenics also; in some of these, conclusions regarding the depressed patients are not stated separately. Many accounts of the use of E.C.T. in affective disorders merely give the bald results of treatment,

such as percentages of the total classed as "improved" or unimproved", without other information about clinical status than a diagnostic label; this precludes any assessment of individual clinical features as prognostic guides. Such reports on the results of treatment are, by implication, statements on the prognosis of the condition treated from the short-term aspect; they are of great help in assessing the value of electroshock in various broad groupings of psychiatric disorders, but may give little aid as to the probable outcome in the case of an individual patient. Especially is this so in the patient who, whilst being quite properly included in a general diagnostic category, exhibits anomalous or unusual features which may affect the outcome with treatment in a way markedly different from the rest of the group.

Another major difficulty is the question of diagnosis of the various depressive conditions. Excluding depressive symptoms as secondary manifestations in such diverse conditions as schizophrenia and organic brain disease, the classification and terminology of affective states leaves much to be desired. Little has been added since Lewis's classic historical survey of 'melancholia' was published in 1934, although a good deal of

argument both preceded and succeeded it, particularly with regard to the concepts of "reactive" versus "endogenous" depression ("neurotic" versus "psychotic"). The debates on this theme have been admirably reviewed by Partridge (1949), and the main trend which has developed since then has been towards the "separatist" school of thought, as exemplified particularly by such authors as Mayer-Gross (1954a). He believes that it is possible in the majority of cases to make a clear distinction between "reactive" or neurotic depressive states and endogenous depressive illnesses, on the basis of history and clinical features; it is probable that a majority of British psychiatrists subscribe to this view.

In America the trend is less clear, and there appears to be more support for such criticisms of the concept of neurotic depression as were put forward by Ascher (1952). Following a review of 97 patients with so-called 'neurotic depressive reactions', he felt that neither the course of the illness, the therapeutic success of various procedures nor the danger of suicide were ~~not~~ consistently dependent on factors such as reactivity, psychogenesis, neurosis, psychosis, and so on. The apparent different response of various depressive reactions to electroshock therapy was, he considered, more dependent on the

relative prominence of depressive mood in the total clinical picture than on a neurotic or psychotic nature of the condition. Differences are got round by some authors, e.g. Skottowe (1953) by the inclusion of such clinical categories as "the minor depressive syndromes", or "mixed depressive states", "depressions with anxiety", "psychotic depression - unspecified", "hysterical depression" and so on.

The existence of "involutional depression" or "involutional melancholia" as a nosological entity has also been increasingly called into doubt in recent years. Although considered as a separate clinical entity by many, and described recently as such by, for example, Henderson and Gillespie (1950), disagreement with this view has frequently been expressed. Drobnes (1943) in a review of 51 cases of involutional psychoses concluded that they might properly be diagnosed either as manic-depressives or schizophrenia, occurring later in life. Mayer-Gross (1954b) suggested that involutional affective psychoses are a somewhat heterogenous group not easily distinguished clinically. A recent study of initial psychiatric illness in 54 involutional women (Tait et al., 1957) has led the authors to conclude that "the boundaries of this traditional syndrome (i.e. involutional melancholia) are more

nebulous than those of other diagnostic groupings."

The deceptive simplicity of current classification of depressive illnesses was again emphasized by Lewis (1938), and also the difficulty of singling out the effects of heredity and environment in individual cases. He proposed assessment of each patient on six points of clinical judgement as well as observation:

- (a) Is the illness mild or severe?
- (b) Does it depend on physical disease, and how completely?
- (c) What happened in any previous attack?
- (d) What are the discoverable influences, both constitutional and environmental?
- (e) Has the process gone on to autonomy, with inveterate bodily and mental habits?
- (f) Have the patient's character and surroundings worked to advantage or not during the illness?

These points were put forward as a basis for a working classification, using the broad symptomatic conception of depressive states introduced in his earlier papers on the subject (1934a and b): Jarvie (1950), in the light of 130 case-studies, has suggested that this conception now requires emphasis and extension particularly since the advent of E.C.T. which has shifted the emphasis

from more advanced and florid clinical pictures to the earlier or more atypical cases.

Garmany (1958) studied 525 patients suffering from depression seen at the Westminster Hospital. They included both males and females and all age groups were represented. He concluded that the distinction between reactive, endogenous and involuntional forms of the illness was an unreal one, particularly in relation to the reactive and endogenous varieties. In these groups he found a similar incidence of such factors as constitutional predisposition and personal and domestic stress. He considered the traditional distinction to be between depressions showing more dependence on external circumstances, of less severity, and requiring E.C.T. less often, and those with the reverse features. In Garmany's view, this resolves itself into a distinction between mild and severe depression - a quantitative, rather than a qualitative difference. The fact that some depressions show less "reactivity" to outside stimuli than others is thus taken to indicate that the depression is deeper rather than that it is 'more endogenous', and this same quantitative difference was taken to account for the fact that E.C.T. was administered more frequently in this type of case.

It is clear therefore, that prognostic studies based upon broad discontinuous clinical groupings such as the current diagnostic categories are extremely difficult to compare because of the variation of diagnostic criteria and the differing conceptions of depressive illnesses which are held.

It may fairly be said that there is more disagreement than agreement as far as aetiology and nosology are concerned in this field. There are a few comparatively clearly defined clinical syndromes which are generally recognised when examples occur in classical form, for example, manic-depressive depression occurring in a person of pyknic physique, with a family history of the malady and a personal history of previous attacks of depression or mania without obvious precipitation, and so on. Regarding such a patient there is little argument, but relatively few depressives present so typically a Kraepelinian description.

In comparing results of electroshock treatment, and thereby prognosis, temporal relationships are of considerable importance in at least two respects. Firstly with regard to the stage of the illness at which treatment is applied, there now exists a good deal of evidence to suggest that treatment is more effective, in manic-depressive

psychosis at least, when the nadir of the depressive downswing has been reached or passed; given earlier in the cycle the patient may fail to respond. This point is emphasized in practical treatment manuals, such as that by Sargant and Slater (1954), and this manifestation of the tendency to spontaneous recovery which affective disorders frequently show may thus be of considerable moment. Secondly, it was made clear by the studies of Alexander (1944, 1945) that a time factor for the evaluation of treatment results must be set, and failure to take this into account could introduce serious errors in estimates of therapeutic efficacy of electroshock. He assessed the results of the treatment with and without a 30 day time factor in 100 consecutive patients (including about 50 depressives), and found considerable differences in the number showing 'social recovery', varying with the time elapsed since treatment. This degree of improvement in depressives was found in 87% of cases assessed from one to three months after E.C.T., but only in 49% when the assessment was within 30 days. Similar though less striking results were obtained with schizophrenics.

The good response of depressive illnesses to convulsive therapy was soon observed after the introduction of the treatment. One of the

earliest critical reviews of the treatment in this country was that of Kennedy (1940), who summed-up the current indications for its use to which little has been really added since:-

"It is more helpful to regard convulsion-therapy, not as a specific remedy for a single type of psychosomatic disorder, but rather as acting on a mental symptom-complex which is common to most of the conditions which it can affect favourably. The exact features of this symptom-complex must vary according to its setting, but inhibition and a depressive affect are certainly two of the features prominent in cases which benefit from convulsion-therapy."

The exigencies of war seriously curtailed further reports for a time, with, of course, a serious gap in French, German and other Continental studies on electroshock, but it was not long before a steady stream of papers in British and American journals began to appear as more experience with the treatment accrued.

Batt (1943) described the results of E.C.T. in 100 consecutive female depressives considered ill enough to warrant its use. Various diagnostic groupings were used, including classification into cases of 'first attack', 'recurrent cases', 'manic-depressive group', 'menopausal type' and

'senile class'; the ambiguity of this method is manifest, and no details were given on the time interval or criteria for assessing response to treatment. 'Success' was claimed in 87% of cases and 'failure' in 13%; no prognostic value was to be found in the symptoms of those responding after 4 treatments and those requiring more, and chronicity of the illness per se was not found to be important.

Fitzgerald (1944) studied 92 females and 58 males suffering from 'psychotic depression' who were treated by E.C.T. All were "psychotic" and showed characteristically melancholic symptoms such as severe depression, retardation and agitation", and all were regarded as of manic-depressive or involuntional types. 78% were discharged from hospital as 'recovered', 4% discharged 'improved', 10% remained in hospital, and a further 8% discharged for a time but later re-admitted on relapse. This author gained the impression that grouping of depressive cases according to pre-psychotic personality was more likely to yield valuable prognostic criteria than the more usual system of drawing distinctions between the 'involuntional cases' and the manic and melancholic phases of manic-depressive psychosis. However, he gave no figures for this. He suggested that, other factors such as duration of illness

being equal, depressive states should be grouped in the following prognostic order of favourability for treatment:-

- (a) Melancholics in whom previous personality showed evidence of melancholic trends (defined as severe depression, retardation, agitation, delusions of guilt).
- (b) Those without previous 'melancholic trends'.

The clinical material quoted, however, gave no worthwhile evidence in support of this hypothesis.

A fairly large number of other reports on the use of electroshock therapy in various conditions were also published in the early 1940's but the specific prognostic factors were mentioned in few. In an excellent review of convulsion therapy up to that time, Cook (1943) surveyed the results which had been published on schizophrenia and affective psychoses. Widespread agreement on the value of E.C.T. in depressive states was reported, and a few clinical pointers to outcome were noted; the presence of marked anxiety, compulsive features and schizophrenic features in a depressive setting were reported by various authors as being associated with a poorer prognosis. A duration of illness of under 3 years was also regarded as being unimportant, thus confirming Batt's finding in this respect.

A comparative study and evaluation of electroshock in depressive states, reporting very favourable results, was made by Tillotson and Sulzbach (1945). Seventy patients with various clinical types of depression - manic-depressive, involution and 'reactive' were treated by E.C.T. and followed-up for a period of up to 45 months; a clinically comparable group of 68 patients who did not receive electroshock was used as a control. Improvement rate was 30%, and recovery rate 44%, and this was higher in the group receiving treatment with maximal therapeutic gain in the group of involutional depressives. What the authors call "the factors generally said to be significant for the prognosis in shock therapy", such as chronicity of illness, age, previous attacks and pre-psychotic personality, were reviewed in the two groups, but the findings in this respect were reported as 'rather bewildering' each factor varying too capriciously to have any practical prognostic value. This appears to have been a carefully planned and executed investigation, although full clinical information about the selection and diagnosis of the patient population is not given.

Another investigation using a control group not given convulsion treatment was reported by the Ziskinds (1945), who treated 88 patients suffering

from various types of affective psychosis: mania and depression of the manic-depressive cycle, and involuntional melancholia. 78% obtained full remission, 18% were improved and only 4% failed to respond when assessed, apparently after a 3 to 6 week period. Therapeutic results were said to be the same for all these sub-types of affective disturbance - a finding not substantiated by others, especially with regard to mania - and the only prognostic factor of significance was found to be age, with an immediate recovery rate of 75% for treated patients under 60 years, and only 56% for those over. The influences of possible organic factors to account for this difference does not appear to have been fully appreciated; two kinds of convulsion therapy were employed in this study, metrazol and E.C.T., which introduces a further variable in assessing results. Metrazol is still considered by some to have slightly superior effects in certain psychiatric illnesses in comparison with electroshock, but the point is a difficult one to prove or disprove. This introduces a further point for consideration in comparing treatment results and prognosis, for various kinds of E.C.T. apparatus have been used in different series reported on, delivering varying quantities of electrical energy, together with qualitative differences in some, e.g. square waves,

sine waves, half-sine waves etc. Specific claims have been made for particular therapeutic efficacy, freedom from side effects such as memory disturbance, etc., attending the use of these different techniques, but the general consensus of opinion is that it is doubtful if any particular advantage is to be gained by their use in most cases. The introduction of muscle-relaxants raises a further issue, especially as the use of thiopentone and a rapid-acting relaxant has become routine in many centres. Experienced mental nurses have for some time expressed the conviction that the modified form of electroshock, whilst pleasanter for the patient and also for those administering the treatment, was not as effective therapeutically as unmodified convulsive therapy. A short controlled experiment to investigate this point was made by Seager (1958) comparing the results of modified and unmodified E.C.T.; his statistics suggest that those treated by the unmodified method were in hospital a shorter period, received less treatments, and were more likely to remain well than those given the modified form. A confirmatory study is obviously desirable.

Huston and Locher (1948) also compared two groups of manic-depressive patients, using E.C.T. in 74 cases, with a comparable control group of 80, carefully matched in relation to various

clinical features such as age, duration of illness, symptomatology, etc., both groups being followed-up for a maximum period of four years. Electroshock was demonstrated to have been responsible for shortening the duration of the illness by six months in the treated group. Family history, prepsychotic personality, acuteness of onset, number of previous attacks, age, sex, and other factors were investigated, but none showed any significant relationship to outcome in the treated group; there was some evidence that first attacks responded better than a second or third, and also the somewhat unusual finding that 'atypical' cases appeared to do better than 'typical'. No specific factors were found to characterize those depressives who did not respond to E.C.T. These authors concluded that the factors related to shock response were unknown. Again details are lacking as to diagnostic criteria for initial classification and selection, so that a resulting possible group heterogeneity may have masked potential prognostic factors.

Studying the problem from the reverse direction, Rickles and Polan (1948) investigated clinical features associated with 38 patients, of various diagnostic categories, who had not maintained satisfactory improvement for at least one year after electroshock or insulin coma. The

number of cases is small (involving at least two major illnesses) from which to draw valid conclusions, and no precise figures for their results are given. In this series, E.C.T. was regarded as apt to fail in association with a previously suspicious and socially inadequate personality, if there had been a longstanding psychoneurotic type of response to life situations, in the patient who had lost a marital partner on whom he or she was very dependent (particularly in the menopausal and post-menopausal epochs), and in the person who for years had sought adjustment in life through strong religious identifications. A previous history of treatment with E.C.T. was found not to be necessarily unfavourable. Clearly no firm conclusions can really be drawn from this report: a more ambitious one was by Bennett (1944), based on a study of 103 patients with affective psychoses who had relapsed within 90 days of completing E.C.T. He considered that those with paranoid trends, marked hypochondriasis, extreme agitation and suicidal tendencies were likely to be refractory to treatment. The reference to paranoid trends again raises the probability that this series contained a number of involuntional psychotics who would probably be now regarded as paraphrenics, and not basically as depressive; this is a constantly recurring difficulty in

assessing work in this field, and one which might well give rise to considerable discrepancies between various reports.

A publication which aroused considerable controversy, coming after so many concurring reports of the efficacy of electroshock in the majority of depressive syndromes, was that of Karagulla (1950), on a comparison of nearly 1000 shock-treated depressives, treated in Edinburgh, with a control group of patients treated conservatively. The results apparently showed that the percentage rate of recovery did not vary greatly with or without E.C.T., and the treatment did not shorten the duration of hospitalization, or prevent recurrences and readmission. This latter conclusion has never been seriously contested by the protagonists of electroshock, but the other two conclusions were quite at variance with common clinical experience. Slater (1951) was able to discover a significant bias in the statistics used for calculating the general trends, and was able to propose that in fact the contraries of Karagulla's first two propositions were correct, electroshock both increasing the recovery rate and reducing the period of hospitalization. This lends special emphasis to a potential pitfall inherent in planning the use of statistical methods in clinical research; in the original paper 177

deaths were omitted from further consideration in the series of depressive patients reviewed, which was sufficient to obscure the real state of affairs. Bellak (1952) in a book devoted to summaries of a good deal of the literature relating to manic-depressive psychosis, commented that he was deeply impressed by the amount of work and journal space wasted because of the absence of any methodological sophistication in a large proportion of the contributions by doctors. Such deficiencies happily are becoming less noticeable, and indeed any reviewer of medical publications in the past decade cannot fail to be impressed by the improvement in research work brought about by the application of scientific methodology to the problems of clinical medicine.

In recent years a more marked difference between British and American publications has become apparent as far as immediate prognosis with electroshock is concerned. In this country more and more emphasis has been laid on E.C.T. as the treatment of choice, with better short-term prognosis, in depressions characterized by retardation, early morning waking, and diurnal variation of mood. These are features of 'endogenous' or 'psychotic' depression in the view of Mayer-Gross, Partridge (1954) and others. The poorer results with E.C.T. in depressions

associated with much anxiety, insomnia of early type, and precipitation by external events - the 'neurotic' or 'reactive' depression of many authors - have also been stressed, although Garmany (1951) reported considerable improvement with electroshock in 49 out of 58 such patients.

American literature, however, abounds with such statements as that of Kalinowsky and Hoch (1952), in a book dealing exclusively with the use of shock treatments in psychiatry: "the responses of the various types of depression are so similar that it is safe to assume a close relation or even the same underlying process in manic-depressive depressions, involuntional depressions, senile depressions and even the so-called psychoneurotic depressions; they all react to approximately 4 - 6 convulsions". L. Alexander (1953) states: "This effect (of electroshock) is independent of whether or not the depression is of manic-depressive type, involuntional, or reactive". This author has attempted to explain physiological mechanisms on the basis of psychoanalytical theory - a somewhat uneasy partnership of very doubtful validity - and suggests that electroshock is likely to be effective only in conditions, such as depressions, in which 'ego defences are either insufficient or inoperative'.

Others have reported findings more in keeping with many British ones; Regan (1957) studied the effectiveness of E.C.T. in 200 patients, including 62 depressives of the manic-depressive type, and found that these cases responded best to electroshock. Psychoneurotic reactions with depressions did well, but to a lesser degree. Depression associated with anxiety, agitation, fear or ideas with a sexual content yielded better results than in patients whose depressive associations included hostility, fear or excessive body concern.

Attempts have been made in some recent investigations to avoid the use of formal nosological concepts; instead of using rigid differentiation of clinical types, individual clinical features, or combinations of them, have been assessed and their influence on the outcome with treatment observed. Jarvie (1954), for example, reported on the response to electroshock of 97 patients, of both sexes, age 21 to 78 (the majority over 50 years) who were suffering from depressive illnesses which would have been covered only by a variety of diagnostic classifications. He concluded that E.C.T. was an effective form of treatment in most cases, but that its limitations in some 30 - 40% of cases should be recognised. These 'hard core' cases consisted of 2 categories - those where little or no improvement

occurred despite adequate treatment, and those where amelioration of symptoms was followed by early and recurrent relapses. No attempt was made in this study to differentiate the E.C.T. failures on clinical or other grounds.

A more elaborate and carefully devised investigation was performed by Hobson (1953), who attempted the statistical assessment of particular clinical features in regard to outcome with electro shock in 127 patients treated at the Maudsley Hospital. These were a selected group, mostly depressed, but including many with neurotic traits; the presence or absence of 121 clinical items was recorded in each case, two improvement ratings being used - those well or having only slight symptoms, and those still with marked symptoms and social handicap. Cases were classified into these two groups a fortnight after the end of treatment, and the relative frequency of occurrence of the individual clinical items in each group evaluated statistically.

Favourable features (with the level of statistical significance in parentheses)

Sudden onset	(1%)
Obsessional previous personality	(2%)
Self-reproach: duration of illness of under 1 year	(5%)
(Pronounced retardation: not significant but very suggestive).	

Unfavourable features

Mild or moderate hypochondriasis:

depersonalization (1%)

Emotional ability (2%)

Neurotic traits in childhood and in adult life: hysterical attitude to illness: Above-average intelligence fluctuating course: (5%)

(Hysterical or ill-adjusted previous personality - very suggestive).

The rest of the 121 clinical items showed no significant associations.

A scoring method based on the presence or absence of the items listed was devised to predict the outcome to E.C.T.; this was found to be reasonably accurate, only 21% of cases being misclassified.

This work is noteworthy for its methodological sophistication and its attempts to avoid ambiguity by careful definition of the clinical terms employed, although purely objective estimations of many clinical psychiatric items is, of course, impossible.

Thomas (1954) reviewed the response of 307 depressed patients to electroshock in terms of 'recovered', 'much improved', 'improved' and

'unchanged'. Conventional diagnostic criteria, along the lines of the 'endogenous-psychotic' - 'reactive-neurotic' dichotomy and 'involutional depression' were employed: 219 were males and 88 females. Of these, 69% were regarded as recovered or much improved after treatment, 28% improved and only 3% unchanged. 'Reactive depressions' did least well, 'endogenous depression' with hysterical or obsessional symptoms less well than other forms, and of those in this group without special features, 81% were recovered or much improved. Involutional depression, depression with hypochondriasis and agitated depressions reacted similarly. In 26% of all cases recovery was not smooth or sustained, and this interruption of recovery was reported as being of prognostic significance as regards recurrence, which bore no relationship to the degree of recovery achieved by treatment. Thus 41% of those who required further E.C.T. after a period of 7 days or more without it had relapsed during an ensuing follow-up period of a year, as opposed to only 16% of those with an uninterrupted recovery originally.

Some criticism of those who found existing nosology unsatisfactory was made in this paper, Thomas considering that conventional diagnosis

categories were sufficiently accurate for broad prognostic purposes. This would, of course, be very satisfactory if the same diagnostic groupings were uniformly employed and thus comparable, which is manifestly untrue.

In a review of 47 female patients who suffered from depressive illness in the involutional period and who failed to respond to electroshock therapy, Cameron et al. (1954) considered that an approach to the problem in terms of symptomatology was inadequate in explaining resistance to treatment. These authors suggested that both an external "socio-psychiatric" and an internal psychological factor must be taken into account in estimating prognosis: the former, such events as death of a relative, or physical illness; the latter, the degree of fear of the destructive force of anger and hate. The psychoanalytic theories of the aetiology of depressive states by Freud and Abraham were used in this connexion, and the authors conclude that a) the more isolated is the patient, and the fewer the social contacts, the worse the prognosis, with or without E.C.T., and b) the prognosis is also poorer where there is little capacity to tolerate aggressive feelings which may be released or flare up with electroshock.

In view of the contention that electroshock treatment is only effective in cases with a good prognosis ordinarily, it is of considerable interest to examine briefly the suggested clinical prognostic indications in depressive states before the advent of convulsion therapy. Here the problem is somewhat complicated by the question of long-term prognosis as compared with treatment results, which are primarily indications of short-term prognosis of the immediate episode. Differing diagnostic concepts also cause difficulty in comparing the findings of various authors, so that only the more important publications which specifically mention individual clinical features in regard to prognosis, rather than those linking the two by diagnostic labels alone, have been selected. As Lewis (1936) pointed out, most of the earlier writers on prognosis in manic-depressive disease, from Kraepelin onwards, and including such authorities as Lange and Bleuler, used the method of adopting rigid criteria for a diagnostic grouping, collecting as many such cases as possible, and seeing what became of them. This method of obtaining the 'general drift' of the malady, whilst holding good for large numbers, does not permit of accurate prognosis in the individual case but merely states a probability of recovery

or otherwise for that diagnostic group alone.

As might be expected, considerable differences of opinion are apparent in such a selection of the relevant literature, but it is possible also to find a good deal of agreement on certain points.

Strecker et al. (1931), in a study of 166 manic-depressives, found that those with age of onset after 40, the appearance of projection mechanisms, hallucinations, and somatic complaints did less well than others. Rennie (1942), who followed up 208 patients, also found the prognosis worse when attacks occurred after 40; Anderson (1936) made a clinical survey of 50 female depressives over the age of 40, and concluded that the outcome of such depressions was, on the whole, poor. Guiding factors in prognosis were few, and in most cases vague; he thought multiple previous attacks, grossly absurd ideas, paranoid ideas, hallucinations and the presence of ideas of negation were all associated to some extent with a bad outcome. Lewis and Hubbard (1931), whose case material admittedly included a proportion of schizophrenic patients, found that persistent depersonalization, dominant hypochondriacal ideas, bizarre delusions and paranoid ideas all bespoke a bad prognosis. Steen (1933) in a follow-up of 493

manic-depressives, examined the influence on outcome of a large number of clinical variables: an abnormal previous personality, positive heredity, gradual onset of depression and the presence of delusions and hallucinations all militated against recovery. Lewis (1936) reported on prognosis in the group of 61 depressives he had previously described. This was a detailed and careful study, the results of which led to his conclusion that from an examination of the history and clinical features there were no unequivocal prognostic signs, either as to duration of the current attack or to the subsequent history. Certain features did, however, emerge as favourable or unfavourable, although they were not constant. Thus general retardation, stupor, puerperal precipitation, adaptability and affectively labile personality tended to be of good omen, whilst agitation, incessant talk, self-reproach, ideas of influencing others, voracious eating, vascular and endocrine disease, disorders of perception, denial of illness and obsessional symptoms and previous personality were bad. He concluded by remarking that "Manic-depressive psychosis is a provisional group of heterogeneous disorders. It is not surprising or disconcerting that we cannot find a clear and easy answer to our questions about the future in such an illness".

It may be added somewhat wryly that the advent of electroshock has not changed the pertinacity of this statement, but we have at least advanced some way beyond the stage epitomized by the statement attributed to K^repelin that "if it gets better, it is depression; if it doesn't, it is schizophrenia, paranoia or what you will".

Duncan (1936) found that the presence or absence of mental defect had no influence on prognosis as far as manic-depressive patients were concerned. Other studies have dealt with the group described as involuntional psychoses, although here one is struck by the apparent frequent inclusion of late schizophrenic syndromes in the clinical descriptions, a factor which tends to obscure prognostic features as far as depression is concerned. Hoch and MacCurdy (1922) reported that patients with 'involuntional melancholia' recovered as a general rule, unless they showed as dominant symptoms: marked insufficiency of affect, peevish or auto-erotic behaviour, ridiculous hypochondriacal delusions (usually alimentary). These features may, however, be present for a short time at the beginning of the illness without necessarily having serious import.

Drobnes (1943), in a series of 51 involuntional

illnesses not given electroshock again noted that any suggestion of schizophrenic-like symptoms led usually to an unfavourable outcome. Palmer and Sherman (1938) felt that a lifelong rigidity and constriction of personality characterized the involuntional melancholic, and the more marked this was the more malignant the illness. On the other hand, Brew and Davidoff (1940) considered that prognosis in involuntional patients varied little with the presence or absence of unhealthy personality traits; in a review of 176 patients they found no significant relationship between outcome and the presence of introversion or extraversion, poorly integrated and rigid personalities and those well adjusted.

From such a survey it is possible to abstract certain factors which are agreed upon by several investigators to have some bearing on prognosis, either good or bad, though many contradictions remain. Presaging a poor outcome in depressives before shock treatment were such features as older age of onset of illness, poor or ill-adjusted previous personality (especially of a neurotic kind), the presence of anxiety, depersonalization, and nihilistic ideas, schizophrenic and especially marked paranoid features, hysterical symptoms and hypochondriasis. According to some, a family

reports suggested that the presence of hypochondriacal ideas or delusions were associated with a poor outcome: Hobson's investigation confirmed this for mild and moderate degrees of hypochondriasis, but was in agreement with Drobnes (1943) that more severe and delusional hypochondriacal symptoms carried a good prognosis.

Similarly, Hobson reported favourably on the presence of obsessional features in the pre-morbid personality in electroshock-treated cases, a finding at odds with Lewis's observations in 1936.

Conclusions

From the foregoing review it may be seen that the literature on prognosis in depressive states, with or without electroshock, is both considerable and yet on many points, inconclusive. It is apparent that there are a number of major reasons for these findings which have been touched upon in the context, but may be summarized as:

- (1) Difficulties of objective assessments of clinical status, both qualitative and quantitative.

Qualitatively, Kraepelinian diagnostic terms lack sufficient precision, reliability and validity for the purpose of comparing

results of treatment etc. Diagnostic criteria vary from hospital to hospital and from clinician to clinician: this is a dilemma of modern psychiatry, for despite dissatisfaction with current nosology there is, so far, nothing better with which to replace it.

Quantitatively, estimations of degree of improvement in clinical status are also lacking in standard and comparable methods of assessment and description. Even the evaluation of one treatment given to a single diagnostic grouping of patients by different investigators may be of uncertain value. For example, a category of 'improvement' may refer to symptom-amelioration, increase in social adaptability, or a combination of these and so on. The use of behavioural and symptom rating scales is a method increasingly applied as an attempt to surmount these difficulties.

- (2) Neglect, until recent years, except in certain instances, of initial planning of investigations. This is important in enabling simple tests of statistical significance to be applied to the results, and for the avoidance of some of the commoner

potential pitfalls. These include the taking into account of such variables as the mode of application of treatment, possible influence of adjuvant therapy (e.g. drugs), the time factor in both commencing treatment and assessing its effects, and possible bias in the investigator.

B) SPECIFIC PROGNOSTIC INDICES.

I. PSYCHOLOGICAL TESTS

There is no dearth of prognostic studies which attempt to relate performance on various psychological tests to the eventual outcome of psychiatric disorders, with or without the application of specific treatments. Relatively few have been concerned with depressed patients and their response to electroshock treatment, and the unsatisfactory nature of many investigations in this field was pointed out by Malamud (1946). He drew attention to the difficulty of achieving standard and comparable methods of clinical assessment of patients, the general lack of careful experimental planning, and the small use of appropriate statistical techniques in evaluating the results.

A comprehensive survey and critique of the use of psychological tests for prognostic purposes was that of Windle (1952), who observed that

investigations in this field appeared "discouragingly unorganized". Much of the work reviewed involved other diagnostic categories than depression, and very few studies appear worth serious attention. Frequently diagnostic groups of uncertain differentiation were employed, results from several types of therapy were lumped together or not even specified, and failure to cross-validate results or to use comparable standards and criteria of improvement were widespread.

The psychological test most used in the earlier prognostic studies has been the Rorschach, but as might be expected in a test so dependent upon subjective assessments in the tester, very few of the reported results have been favourable to the use of this technique as a prognostic guide. Few of the published researches refer to depressives treated by electroshock, and of these even fewer are free from serious methodological defects. Positive results are scanty when variables such as chance and validity are taken into account, and it would appear that the test has no useful place as a prognostic indicator.

Other projective tests such as Thematic Apperception Test and free-drawing, have been used, as well as various miscellaneous techniques e.g. the mosaic test, measures of aggression,

but mostly with schizophrenic patients and not with depressives. Tests of mental ability, including I.Q., have given very varying results as prognostic guides and no firm conclusions can be drawn from their use.

Clinical estimates of behavioural or personality traits have also been related to outcome, again with no clear leads other than the attempts of Wittman and Steinberg (1944) with the Elgin Scale. This contained 50 weighted factors derived from numerous psychological and clinical characteristics of patient groups; prognostic indications given by this scale were distinctly better than those given by the clinical staff, but this appeared to be only significantly so for the schizophrenic patients. Little work has been done on depressives with this scale, which clearly is more suitable for the more severely disturbed psychotics.

The most promising technique for prognostic use has appeared to be the Minnesota Multiphasic Personality Inventory (M.M.P.I.) or derivatives of it. It has been widely applied, but the same objections to much of the work hold good, especially with regard to the lack of specific information regarding the patient populations studied, and the statistical evaluation of the

results. Pacella, Piotrowski and Lewis (1947) administered the M.M.P.I. to various diagnostic groups of patients before and after E.C.T., and reported that the test was a failure as a prognostic aid in the group of depressives tested. This work followed a similar study by Harris (1945), who had reported some success in estimating outcome to insulin coma or E.C.T. in schizophrenics, depressives and severe psychoneurotic patients; such criteria as high score patterns in the psychotic scales and clinical diagnoses of schizophrenia being associated with a poorer response to treatment. The prognostic concordance suggested by this work was certainly not high and it is not surprising to find an inability on the part of later workers to confirm it. These disappointing results led to a search for M.M.P.I. derivatives which might be more helpful for prognosis, such as the selected scale - profiles or signs reported by Pearson (1950) which appeared to have predictive value for the E.C.T. response of schizophrenics. Welsh (1952) described an "anxiety index" and an "internalization ratio" obtained from M.M.P.I. responses, alleging the latter to be an indication of degree of internalized aggressive tendencies, said to be greater in patients who responded less well to treatment.

A new scale, empirically derived from the M.M.P.I. and called the "Ps scale", was described by Feldman (1951), for use in prognosis with insulin and electric shock treatments independently of diagnosis. This consisted of 52 items selected by item analysis of the records of patients who were assessed improved or unimproved after shock therapy, and is one of the few studies in this field in which the results have been cross-validated. The resulting Ps scale had a uniformly high positive correlation with the psychotic scales, little relationship to the neurotic ones and a high negative correlation with the "lie" scale. Feldman found that high scores on this test were significantly associated with unimprovement in treated patient groups, the scores not being affected materially either by the type of shock treatment or the diagnosis; he concluded that the "inherent propensity to improve" of the patient was the main variable affecting scores, and that those who did better were persons still struggling to maintain object relations and with motivation to improve.

Carpenter (1953) made an experimental test of this Ps scale by mixing the 52 items with an equal number of randomly chosen ones and asking 20 persons to sort the total for their ideas of "relevance and direction to a specification of externally

directed aggression, unacceptable to the ego". The Ps items were chosen significantly more often than the dummy ones, with better than chance agreement in direction. This kind of experiment, however, is itself open to criticism; more helpful is the further attempt at validation of predictive tests is the work of Pumroy and Kogan (1958), who applied 4 different M.M.P.I. measures which purported to predict the efficacy of E.C.T. to a sample of 23 male psychiatric patients before treatment. The measures were Feldman's Ps Scale, Welsh's Anxiety and Internalization ratios, and Pearson's signs; two criteria of improvement were used - ratings by psychiatrists about one month after finishing electroshock, and the number of treatments administered. The only statistically significant relationship was that between the internalization ratio of Welsh and the number of treatments - a negative correlation of 0.42, significant at the 5% level. In general the measures were considered unable to predict the efficacy of E.C.T. in that sample. This last qualification is important, as the total number of patients was small and little clinical information about them was given.

Feldman himself (1958) has more recently modified some of his original claims regarding the Ps Scale; this has been enlarged to 62 M.M.P.I.

items, called the "Evaluation Scale for Shock Therapy" (E.V.S.) which he considered moderately valid only as a prognostic guide; the validity was mainly impaired because a sizeable proportion of unimproved patients obtained favourable test scores. In the main, Feldman concluded that the E.V.S. item content reflected symptoms and not interpersonal relationships, which suggested to him that improvement with shock therapy was largely a process of symptom abatement without real changes in interpersonal relations.

Conclusions

Despite the large volume of work in this field, the place of psychological tests as prognostic aids in psychiatric treatment is by no means secure; to date only tests derived from the M.M.P.I. appear to have any usefulness at all as far as shock treatments are concerned, and even these are seemingly of limited value.

II. TESTS OF AUTONOMIC FUNCTION

Psychosomatic relationships - using the term in its broadest sense - have been extensively studied in various psychiatric conditions, both psychoses and neuroses, and autonomic functions were among the earliest to receive attention. Much of the work on autonomic regulation, homeostasis, and its dysfunctions has been carried out on schizophrenics, although an apparent reduction in parasympathetic activity in depressed patients was reported by Henry in 1931, and Strongin and Hinsie in 1938, in relation to gastro-intestinal activity and parotid gland secretion. These observations were regarded as of more interest for diagnostic purposes and little attempt seems to have been made to explain their possible significance in terms of aetiology; more recently Campbell (1953) has attempted to explain the whole aetiology of manic-depressive disorders on the basis of hypothalamic-central-autonomic dysfunction, although with little new evidence.

More sophisticated studies of autonomic functioning, such as those of Wenger (1947) utilized a battery of tests and physiological observations of blood-pressure, psycho-galvanic reflexes, vaso-motor responses etc. in various stress-situations; Recent attention has also

turned to physiological responses to sympathetic and parasympathetic drugs administered to various patient populations. Some of these investigations, such as those of Hoffer (1954) using atropin, appear to have little clinical application or have not been confirmed, but since 1948 a considerable volume of work has been published by Funkenstein and his colleagues in Boston on the diagnostic and prognostic aspects of a test of autonomic functioning using injections of adrenaline and methacholine.

The Adrenaline-Methacholine Test (Funkenstein)

This test was originally performed by studying the subjective psychological changes and the systolic blood-pressure variations to a standard intravenous injection of synthetic l-adrenaline and intramuscular injection of methacholine chloride (10 mgm.) under resting and fasting conditions. A "basal B.P. reading" was first established for each subject, and on the basis of the B.P. responses to the drugs and the occurrence or otherwise of anxiety during the test, 7 patterns of response were described as far as B.P. changes were concerned, and 4 groups of subjective emotional response.

Group I Adrenaline - rise in systolic pressure of 50 mm. +.

Methacholine - slight fall in systolic B.P. with early rise above pre-injection level during 25 min. observation period.

Group II Adrenaline - rise of 75 mm. +.

Methacholine - moderate or slight fall with or without slight rise above basal level but with establishment of homeostasis i.e. return to, and maintenance of, pre-injection level within 25 min.

Group III Adrenaline - rise of 75 mm. or less.

Methacholine - as for Group II.

Group IV Adrenaline - rise of 50 mm. +.

Methacholine - moderate fall with marked compensatory delayed rise before homeostasis within 25 min. period.

Group V Adrenaline - rise of 50 mm. or less.

Methacholine - fall with failure to reach basal level within 25 min. period.

Group VI Adrenaline - rise of 50 mm. +.

Methacholine - fall with failure to reach basal level within 25 min. period.

Group VII included all cases in which a "chill" (shivering, rigors) occurred after methacholine.

The test was administered in a standardized fashion; a test injection of intravenous normal saline was given after the resting systolic B.P. in the fasting state had been taken. This was followed next day by intravenous l-adrenaline 0.025 mgm. in 1 ml. water, and the B.P. recorded every 15 seconds for 2 min. When the rise had subsided, intramuscular methacholine 10 mgm. was given and the B.P. followed at $\frac{1}{2}$, 1 and 2 min. intervals at various stages of a 25 min. period. The results were then plotted on graph paper, time v. systolic pressure.

Following the original paper by Funkenstein, Greenblatt and Solomon in 1948, in which they reported some changes in B.P. responses after electroshock treatment, various modifications and refinements of technique were introduced.

In 1950 these authors reported on the correlations obtained between the test and the clinical outcome of 100 patients treated with electroshock, when it was found that patients whose test results could be classified into groups VI and VII appeared to have a better outcome to treatment than patients in other groups. It also appeared that the clinical outcome was poorer when the intravenous adrenaline injection provoked anxiety in the patient.

Following these observations, together with further work on the test in relation to asthma (1950), additional studies of the apparent prognostic value of the test were undertaken (Funkenstein et al., 1952), 188 patients forming the experimental population. These included males and females, ages 15-60 years, and clinical diagnoses covered schizophrenia, manic-depression, involutional psychosis, and psychoneurosis.

Five mathematical measures derived from the graphs were used in the statistical handling of the test data and correlated with the clinical global assessments of "improved" and "unimproved" after electroshock. These were:-

- 1) Basal B.P. - the resting pressure before any drug was given.
- 2) Height of B.P. rise after adrenaline.
- 3) Time of homeostasis after methacholine
- 4) Area of total fall to methacholine.
- 5) Maximum fall after methacholine.

In addition Groups II and III were amalgamated into one group.

Results showed that outcome to treatment was highly significantly related (better than 0.01% level of statistical significance) to the pattern of B.P. responses, Groups VI and VII being

associated with a favourable outcome, and Groups I and II-III with poor treatment response.

A high basal pressure, large fall and prolongation of hypotension to methacholine were clearly associated with "improvement" and a low basal B.P., low fall and short hypotensive response to methacholine were linked with "unimprovement"; all were at better than 0.01% level of statistical significance. Height of B.P. rise to adrenaline was unrelated to clinical outcome, but adrenaline-precipitated anxiety was associated with a poorer treatment response.

A modification of the general test technique was introduced in this study for patients with a resting B.P. of 140 mm. or over; only the methacholine portion of the test was used, and the profoundly hypotensive effect of the drug in this group of patients was noted. Two sub-groups were distinguished by the B.P. responses - Group A, whose systolic pressure failed to return to the resting level during the 25 min. period, and Group B, whose pressure returned fairly rapidly. A difference in outcome to electroshock was observed between the two groups, A showing a significantly better response than B. When the hypotensive effect was accompanied by "chills" the prognosis with treatment was considered even better.

A point of particular interest was that the test results had a higher relationship with response to electroshock than the clinical diagnosis employed, i.e. the test appeared to cut across diagnostic categories. On the basis of earlier studies the authors suggested that those patients showing a marked hypotensive response to methacholine and who tended to do well with E.C.T. (Groups V, VI and VII) showed evidence of excessive secretion of an adrenaline-like substance. Although the test results tended to override diagnostic groupings, most of the patients in Group VI and who were supposed to have excessive adrenaline-like secretion were in fact found to be depressions of a manic-depressive or involutional type: the schizophrenics in this group had a marked depressive affective component in their illness. Funkenstein and Meade (1954) in a study of adrenaline-like and nor-adrenaline-like substances and the elevation of the blood pressure in acute stress situations offered further experimental findings in support of their theoretical explanation of the test results, but an alternative, and certainly superficially more plausible rationale was put forward by the neuro-physiologist Gellhorn (1952). His views were derived from animal studies, using anaesthetized

cats. In Gellhorn's view, any procedure leading to a marked fall in B.P. (e.g. administering methacholine) induces a sympathetico-adrenal discharge via the sino-aortic reflexes and a central sympathetic reflex; his cat studies demonstrated that the degree and duration of the hypotensive action of methacholine and the reflexly induced sympathetico-adrenal discharges as an attempt to maintain homeostasis appeared to depend upon the intact state of the posterior hypothalamus.

In the light of these findings the original groups described by Funkenstein were reviewed by Gellhorn, and on the basis of the methacholine responses only were re-classified into three distinct patterns; a theoretical explanation for the differences was advanced.

Group I (Funkenstein's Groups I and IV) -
slight to moderate fall to methacholine
rapid return to basal levels and subsequent secondary B.P. rise.

Group II (Funkenstein's Groups II and III)
Slight to moderate hypotension, with
return to control levels usually by
about 10 min. and no overshooting.

Group III (Funkenstein's Groups V, VI, VII)

Marked hypotension with delayed return to basal levels, often 25 min. or more of continuous hypotension being observed.

Gellhorn regarded the Group I responses as representing an increase in central (i.e. posterior hypothalamic) sympathetic reactivity, so that the injection of a parasympathomimetic drug called forth an exaggerated sympathetic response in the attempt to restore autonomic equilibrium. Group II had a normal degree of central sympathetic reactivity, with rapid homeostasis, and Group III represented decreased central reactivity; in these subjects, reflexly induced sympathetic activity was diminished and parasympathetic effects thus predominated for a longer period than normal. In Gellhorn's view therefore, patients showing increased central sympathetic reactivity (C.S.R.) were made worse by electroshock treatment, which tended to increase C.S.R.; thus the treatment was predictably effective in those patients showing decreased C.S.R. This also fitted in with the observations of Funkenstein that physiological improvement tended to occur together.

This explanation appeals because of its

apparent simplicity and seemingly logical deductions on the basis of animal experimental work. It has received some support from the work of Schneider (1955) who investigated the effects of reserpine and amylobarbitone on the methacholine test, and found the results appeared to "establish the validity of the test as a measure of G.S.R. in the intact organism." Some doubt has been cast upon Gellhorn's hypothesis by investigations on adrenal responsiveness during methacholine administration (Sloane, Saffran and Cleghorn, 1958). In a series of psychiatric patients - including 9 with what was described as 'overt but non-psychotic depression' - the eosinophil response and urinary excretion of free 17-keto-steroids were compared after the injection of methacholine and corticotrophin (A.C.T.H.). No evidence of enhanced adrenal activity was found after the former drug, and on this basis the authors concluded that methacholine did not serve as an indicator of central responsivity at the hypothalamic or other higher C.N.S. level. Clearly much more investigation is required.

Alexander (1955), Brothers and Bennett (1954) among others, have reported favourably on the methacholine test, particularly with regard to its use in deciding on treatment and in predicting



the outcome. Confirmation of the efficacy of E.C.T. in patients showing diminished C.S.R. came from Jones (1956), who used the test 747 times on 465 patients in an American State hospital. Unfortunately no accurate figures are reported in this paper, but the author states that central sympathetic hypo-reactivity was "invariably" (sic) seen in retarded (manic-depressive) depressed patients and involuntional melancholia; patients with agitated depressions "customarily demonstrated C.S. hyper-reactivity".

Blumberg, Cohen and Miller (1956) also reported a better response to electroshock where a "lower level of sympathetic tone" was demonstrable by the methacholine test; they also reported a correlation with age, the old patients showing a proportionately greater hypotensive response to the drug. This latter finding has more recently been amply confirmed by Nelson and Gellhorn (1958).

The relationship of the methacholine response to what the authors termed "adequacy of affect" was investigated by Pasquarelli et al. (1956), who found that Funkenstein's groups correlated with depth and sufficiency of emotional responses appearing during diagnostic and psychotherapeutic

interviews. They reported a clear correlation between adequate affect, good outcome to psychotherapy, and hypotensive response to methacholine, but this work appears open to various objections on the grounds of insufficient objective clinical assessment of the patients before and after psychotherapy. One point of interest was that they omitted the adrenaline portion of the test as it "failed to give any meaningful information", a practice which has been followed by a number of other workers in this field.

Stemmerman and Owen (1957) carried out serial testing on 125 patients at 2-4 week intervals; they reported that the test predicted with accuracy whether patients would benefit from E.C.T., and that the more quickly abnormal B.P. response curves were altered in the direction of normal, the less malignant was the illness.

L. Alexander (1958), on the basis of his own clinical experience of the test, has also suggested condensing Funkenstein's original groups as follows:

- (1) An adrenergic (nicotinic) overshooting above the pre-injection level.

Sub-types 1) lasting most of the 25 min. observation period.

- ii) sporadic, and
- iii) delayed and on the rebound.

(2) Enhanced and prolonged cholinergic (muscarinic) reaction to methacholine with marked fall over the 25 min. period, with or without a chill.

(3) An inadequate response to adrenaline.

According to Alexander, the adrenergic overreaction is most commonly seen in obsessive-compulsives, paranoid patients, anxiety states and schizophrenics, and in his experience the results of E.C.T. in this group are less related to the particular test pattern than to the clinical diagnosis. The cholinergic overreaction is alleged to be 'typical of depressions', especially at the involutinal period, as well as in manic-depressive depression; some schizophrenics, those with schizo-affective psychoses and neurotics (not defined) also are included. The general tendency is to react well to E.C.T. In the third group of inadequate adrenaline-response (this is not defined further) Alexander has never seen patients do well either with E.C.T. or other forms of treatment, including psychotherapy.

Little British evaluation of the test seems to have been performed for some time; Montagu

and Davies (1955) found it of no prognostic help in the electro-stimulatory treatment of anxiety states, and the work of Sloane and Lewis (1956) cast considerable doubt on the usefulness of the procedure where E.C.T. was concerned. Using a modified version of the original technique omitting the initial saline and by giving the other drugs on separate days in many cases, they tested 111 patients prior to E.C.T. The majority of these were of mixed diagnosis, with a preponderance of depression, and were found to exhibit the same range of responses as a group of normal cases; some suspicion was aroused as to the possible unsatisfactory nature of the one-day test results. In this series patients with B.P. responses similar to those of the normal controls showed the best outcome to E.C.T. - the opposite of previous reports - and the overreaction to methacholine was not found to be significantly associated with a good prognosis. Where anxiety was precipitated by both drugs the treatment response was particularly poor.

As this work appears to have been carefully carried out and statistical pitfalls avoided in the evaluation of the results, the different findings are difficult to explain. Nurses (experienced in sphygmomanometry) made the B.P.

recordings; this may have introduced a source of error due to lack of training in scientific observation. A possible explanation of the differences reported by Sloane and Lewis may have been in the methacholine preparation used, as unless a fairly freshly prepared aqueous solution is employed, results may be fallacious.

Further studies by Sloane, Lewis and Slater (1957a and b) were on the reliability of the test and its diagnostic use. Although Funkenstein had found that it cut across diagnostic categories, the above workers found that the test differentiated a group of endogenous depressives from one of schizophrenics by showing a lower rise of B.P. to adrenaline and a greater and longer hypotensive effect with methacholine in the former group. The schizophrenics, in turn, were differentiated from a group of neurotic patients by showing a pronounced secondary rise in B.P. following the initial drop produced by methacholine. Multiple correlations obtained from the B.P. response curves were found promising for diagnostic purposes, the B.P. variations being measured in terms of 8 variables. These included the following methacholine responses:

- 1) Maximum fall.
- 2) Time of return to basal level.

- 3) Area of fall till homeostasis
- 4) Total area of rise to methacholine.
- 5) Maximum rise to methacholine.

A further complication which appears to relate chiefly to schizophrenic patients is that duration of stay in hospital, and thereby chronicity of illness in many, is important in determining the autonomic response; recent admissions have a different distribution of response curves from the longer-stay patients (Funkenstein, 1956, Geocaris and Kooiker, 1956). It is unlikely that this is important in the case of depressives, whose length of stay in hospital is usually comparatively short.

The test-retest reliability was commented on favourably by Geocaris (1956) and Weckowicz (1956), chiefly working with schizophrenics, but again the most careful work in this field is that of Sloane et al. (1957 b), who not only examined the reliability but also the influence of various administration techniques. Methacholine alone or as the first drug of the day they found to have fair correlations with B.P. fall ($r = 0.6 - 0.77$), with a moderate amount of misclassification into Funkenstein's arbitrary groups but a good degree of prognostic concordance of the two tests. The prior administration of adrenaline greatly

reduced the reliability of the methacholine variables, and they suggested that the drugs should be administered on separate days, or only the methacholine used. If the latter course is followed the procedure is certainly simplified in several ways; what was a fairly time-consuming and at times technically difficult test is reduced to a reasonably short and simple procedure, disturbance to the patient is less (especially where the adrenaline precipitated distressing anxiety symptoms), the test reliability is apparently increased and the multiple groupings of Funkenstein can be condensed. An interesting point regarding reliability was raised by Maas (1958), who investigated the methacholine test by giving it to 20 male patients on alternate days, administered by a physician or trained orderly. What he described as 'disparate results' were obtained, which were regarded as a function of the tester and the patient's perception of him. To obtain consistent results on repeating the test, it would obviously seem desirable that the same examiner should be employed each time.

Conclusions

From this survey of the relevant information on the methacholine test the following conclusions

may be drawn:-

- 1) Provided certain technical and methodological precautions are observed, the test appears to be reasonably reliable measure of certain aspects of autonomic functioning.
- 2) Disturbances of autonomic function appear to occur in psychiatric patients considerably more frequently than in normals, but their relationship to clinical diagnostic categories is unclear.
- 3) Several neurophysiological theories to explain the observed differences in autonomic response are available; that of Gellhorn has some experimental animal studies to support his suggestion that the test is an indication of the degree of central (posterior hypothalamic) sympathetic reactivity.
- 4) The weight of experimental evidence so far available suggests a relationship between the B.P. response to methacholine and the outcome with E.C.T., but the degree of this association is undecided at present.
- 5) Factors of age, length of hospital stay (at least as far as schizophrenics are concerned) and the height of the "basal B.P." have to be

taken into account in assessing the response to the test.

- 6) Current methods of scoring the responses are rather arbitrary, and further modifications may well be found desirable or helpful.
- 7) There is clearly further scope for carefully planned investigations into both the diagnostic and prognostic relationships of the test in patients undergoing electroshock therapy.

III. RESPONSE TO SEDATIVE AND STIMULANT DRUGS

Although the first of these tests described originally utilized the E.E.G., the primary factor is the effect of the barbiturate employed, so that the account is given under this heading.

1) "Sedation Threshold" Studies

This test was originally described by Shagass (1954), working at Montreal, and was developed from the widely known clinical observation that, by and large, the more tense and anxious a patient, the greater the amount of sedative drug required to produce relaxation. From this the hypothesis was propounded that the amount of sedative required to attain a specific index of sedation could be used as a quantitative indicator of tension.

Making use of the observations of Brazier and Finesinger (1945) on the effects of barbiturates in increasing the amplitude of frontal fast activity in the electroencephalogram, a technique was developed in which amylobarbitone sodium was injected intravenously at the rate of 0.5 mgm. per kilo body weight every 40 seconds. 25 seconds after each injection the subject was asked to repeat various words and phrases in order to detect the occurrence of slurred speech;

E.E.G. recordings of frontal activity were made throughout. The amplitude of all the 15-30 c.p.s. activity from sample periods before and after each injection was then measured (at first by hand ruler, later by a specifically designed additive ruler) and a mean amplitude in microvolts calculated for each injection period. Amplitude was then plotted against amount of amylobarbitone sodium injected. Shagass claimed that the resultant graph was usually S-shaped, with a definite inflexion point where the rate of increase of amplitude suddenly lessened; this usually coincided, or nearly coincided, with the clinical observation of slurring of speech.

The 'Sedation threshold' was then defined as the amount of sodium amylobarbitone, in mgm. per kilo body weight, required to produce an inflexion point in the amplitude curve of the E.E.G. frontal fast activity; this inflexion point must have occurred within 80 seconds of the onset of slurred speech to be meaningful.

A series of papers later attempted to develop and explain the use of the sedation threshold estimation, and this further work led to considerable revision of the earlier theoretical interpretation of the findings.

The threshold was initially considered to

correlate highly with clinically assessed "tension" using psychoneurotic and control subjects. In view of the ambiguity attaching to the term "tension", this was changed to "manifest anxiety", and a further hypothesis was developed on the lines that the greatest amount of such anxiety should be found in subjects suffering from anxiety states and the least in conversion hysterics; psychoneurotic patients showing features of both were expected to occupy an intermediate position. Shagass and Naiman (1955, 1956) found that this prediction was confirmed, using different neurotic groups, and also found that the majority of their patients with anxiety states had obsessional personalities whilst those with hysterical personalities, like the ones with conversion symptoms, tended to have lower sedation thresholds. These findings were interpreted along the lines of Eysenck's (1947) theory of an introversion-extraversion continuum.

When the test was applied to schizophrenics, the correlation between 'manifest anxiety' and the threshold was not found to be significant, but recent acute patients had a lower threshold than chronic ones. This difference was interpreted in terms of the vague concept of "impairment of ego function", and it was considered that "in acute psychoses, ego functions are thought to be more

impaired than in non-deteriorated psychoses of long duration in which reparative processes have taken place". Using this somewhat shaky theoretical foundation, the threshold was postulated as lowest in those cases showing the greatest impairment of ego functioning. Investigations on selected groups of patients again fitted in with this hypothesis, organic cases having the lowest thresholds, then acute schizophrenics, agitated depressives and chronic schizophrenics in that order. (Shagass, 1956)

Attention was then turned to depressed patients (Shagass et al., 1956); 182 patients were classified into fairly rigid diagnostic groups comprising "psychotic depression", "schizo-affective psychosis with depression", "hysterical depression", "neurotic depression" and "anxiety state". Sedation threshold estimations were made and the following observations made from examination of the data.

- a) The sedation threshold was low in "psychotic" depression, high in "neurotic" depression, differentiating between the two in this series with 95% accuracy.
- b) Thresholds for patients with anxiety states were similar (high) to those with "neurotic" depressions.

- c) Patients with high thresholds (anxiety and "neurotic" depressive patients) were treated with E.C.T. much less frequently than those with low thresholds ("psychotic" and "hysterical" depressives).
- d) The short-term results with E.C.T. were significantly better in the low-threshold group than the other.

It was concluded that the concept distinguishing "psychotic" and "neurotic" depressions was a valid one, that the relationship between the threshold and depression was probably secondary to the degree of "impairment of ego functioning", and that the sedation threshold appeared to have some validity for predicting the outcome of E.C.T.

Further studies (Shagass, 1957 a and b) found that in test-retest estimations on 40 patients the retest results were almost identical with the initial threshold estimations; where significant clinical improvement had occurred, abnormally high thresholds were definitely decreased ("normal" threshold was regarded as about 3.5 - 4.0 mgm. drug per kilo). It was concluded that the test had high reliability and reflected significant clinical psychiatric changes, that the threshold was not fixed and thus was probably a representation of affective change rather than of enduring

personality factors. A further conclusion, based on the testing of 399 patients and 45 normal controls was that the sedation threshold was a function of rate of depressant action of amylo-barbitone, possibly measuring a time characteristic of neuronal activity which was probably an important factor influencing cerebral excitability.

Shagass's observations on the apparent lowering of high thresholds when affective disturbances decreased led him to suggest that the test be regarded as "an objective index of therapeutic change".

Further observations on 750 consecutive psychiatric admissions (Shagass and Jones, 1958) and 45 non-patient normal controls were reported as confirming previous findings of statistically significant differences between the thresholds of various diagnostic groups. Further modifications of technique were used, including an automatic integrator summing all E.E.G. activity between 17-25 c.p.s. The observed differences between diagnostic groupings suggested to the authors the use of the sedation threshold for clarification of a number of problems, which they specified as:-

- a) Measurement of the degree of manifest anxiety,
- b) Differentiation between hysterical and obsessional personality traits;

- c) Confirmation of the presence of organic psychosis;
- d) Differentiation of acute from chronic schizophrenia;
- e) Differentiation of neurotic from psychotic depression;
- f) Prediction of the therapeutic outcome with E.C.T.

This last use of the test is presumably an extension of e) above, depending upon diagnostic differentiation of depression. In the case of 292 patients of all types who were apparently studied from the point of view of outcome with E.C.T., the degree of improvement was graded as 'marked', 'moderate' and 'slight or none'. No further information was provided about the actual method of assessment, although the authors did in fact mention the possibility that other workers "might disagree as to whether a particular case was markedly or moderately improved." The only time-relationship to treatment mentioned was that of "short-term", the patient's clinical status being reviewed at the time of discharge from hospital; but as Alexander (1945) has shown, the timing of post-electroshock assessments may be of great importance in determining the efficacy or

otherwise of the treatment. Shagass and Jones have claimed that the chance of a given patient benefitting from E.C.T. diminished as the sedation threshold increased; there appeared to be a critical point between 3.5 and 4.0 mgm. per kilo, which the authors had previously found to be also the critical point in distinguishing "neurotic" from "psychotic" depression.

Several groups of investigators have criticized various aspects of this work from Montreal. Thorpe and Barker (1957) made sedation threshold estimations on 7 patients, recording the proceedings on tape and playing them back to a group of 16 mental hospital professional staff; they reported "a marked inability to agree on the slur-point". This criticism is not perhaps as trenchant as might at first appear, for the group was quite unpractised in the technique, and the estimations of one experienced observer in a series of cases could conceivably attain a much higher degree of accuracy once some facility had been acquired.

Bradley and Jeavons (1957) investigating the effects of chlorpromazine and reserpine on the sedation threshold in schizophrenic patients, found that the method described by Shagass was technically difficult and liable to inaccuracies, particularly in low voltage E.E.G. tracings. They

found great difficulty in many cases in distinguishing a definite inflexion point, and finally used a modification of the technique, taking the threshold as the point where the amplitude of the drug-induced fast activity reached a maximum and was followed by a flattening of the curve; this they reported as much more satisfactory.

More serious objections were those of Ackner and Pampiglione (1958), who made a study of the relationship of the sedation threshold to

- 1) the maximum vasodilation during barbiturate-induced sleep (recorded by a finger plethysmograph)
- 2) the affective state of the individual at the time of the test, and
- 3) the diagnostic category.

Several sophisticated modifications of the original technique were employed, including a preliminary trial E.E.G. to reduce test anxiety, the use of Gordh's needle to facilitate injections and the recording of the subject's responses on tape, synchronized with the E.E.G. and plethysmograph records: injections of sodium amylobarbitone were continued until there was no verbal response from the patient.

They found that many of the growth-curves of barbiturate-induced fast activity were much more

complex than those originally described; others showed no definite inflexion points. For these reasons, and doubts over the clinical slur-points in some cases, a clear-cut threshold (as defined) could be determined in only one-third of their 56 psychiatric patients; it was doubtful in one-third, and impossible to fix in the remainder by E.E.G. alone.

Using three gradings according to severity of clinical anxiety in these patients, no significant differences were found between those with minimal and those with severe anxiety as far as the sedation thresholds were concerned.

Diagnostic groups of:-

- a) anxiety and neurotic depression
- b) obsessional states
- c) mixed neuroses,
- d) endogenous depressions
- e) hysteria

were utilized, and the mean threshold found to be the same (6 mgm. per kilo) for both the anxiety and neurotic depression group and those with hysteria. The mean threshold for the other 3 groups was 5 mgm. per kilo. These results were quite at variance with the findings of Shagass, and therefore failed to confirm his reported experimental link with personality theory.

Ackner and his colleague considered the slur-

point essential in deciding which of possibly several E.E.G. amplitude-curve inflexions should be used to fix the sedation threshold, and were quite unable to agree that the E.E.G. findings alone were a more accurate method of indicating the threshold than that afforded by speech-slurring. No correlation was found between the sedation threshold and vasomotor finger changes which they had previously found to reflect changes in emotional tension.

This investigation appears to have been carried out with great care and attention to detail, and the results must therefore carry considerable weight, although the number of patients studied is very much smaller than the Montreal series. Shagass, singly or with others, has published no less than 7 papers in a relatively short period on the sedation threshold, a number of which differ from each other only in detail; one is left with the impression that a smaller volume of publication with a higher degree of critical selectivity might have proved more useful in the long run. The suggested "impairment of ego awareness", to attempt to explain certain observed differences in thresholds between the groups of patients which Shagass reported, must impress some as an uneasy and unsatisfying attempt to link

neurophysiology with dynamic psychological theory; the result in this case is singularly unconvincing.

Conclusions

It would appear that the original E.E.G. technique of estimating the sedation threshold, if the concept itself is a valid one, is open to criticism on the score of its technical difficulty and liability to considerable error.

There is clearly a need for further investigation of the sedation threshold, particularly in regard to depressed patients. If the claims of Shagass are upheld, and the test does differentiate between diagnostic categories of depressive illness, this may well have prognostic significance, especially as he has reported that "E.C.T. was significantly more effective in the patient with psychotic than neurotic depression". (Shagass, 1957 c)

2) Clinical Response to Sodium Amylobarbitone

Barbiturate drugs have a wide field of application in psychiatry, not only for sedation but for abreactive, exploratory and diagnostic purposes in a broad range of conditions. Sodium amylobarbitone ("sodium amytal") has been one of

the most extensively employed, and some claim has been made for its possible prognostic help in various conditions also.

Clark, Kiefer and Gerson (1945) first claimed some degree of association between the effect of sodium amytal narcosis in relieving psychotic symptoms and the results of convulsive shock treatment (E.C.T.). Using a 10% solution of the drug on 40 psychotics, administered intravenously, before treatment, they concluded that the procedure was of some value in predicting the outcome to shock treatment. The test population consisted of 35 schizophrenics, 1 paranoid state, 1 involuntional depressive and 3 endogenous depressives, so that little reliance could be placed upon their findings as far as depressive states are concerned, even if the results on this group were completely favourable. As it was, however, they quote one depressed patient (i.e. 25% of this group!) who responded poorly to the drug but showed a good result with electroshock.

An apparently more efficient prognostic indicator to electroshock, using sodium amylo-barbitone, was described by Kahn, Fink and Weinstein (1956). This was based on earlier observations of two of the authors (Weinstein et al., 1953) on the effects of organic brain disease

in producing characteristic alterations in reply to questioning under the drug. They questioned 88 patients with proven brain disease and who on clinical observation showed no disturbances of behaviour, on their orientation for time, place and person, awareness of their illness and insight into it. No gross disturbances of thought processes were found. Sodium amylobarbitone was then given intravenously until nystagmus, slurring of speech and errors in counting backwards appeared, and the questions repeated. Of the 88 subjects, 57 showed patterns of disorientation for time, place and person, often with lack of awareness of their disability amounting to complete denial of illness. No similar changes were observed under the drug in any of 50 control patients with psychoneurosis or peripheral nerve lesions.

Kahn et al. then gave this 'amytal test' as a standardized procedure to a consecutive series of 24 patients referred for E.C.T. (14 depressives, 9 schizophrenics, 1 manic, ages 24-68, median 47 years). It was repeated at regular intervals during and after their treatment, and 'positive' reactions of various grades were noted. A close relationship was found between the short-term response to treatment and the results of the test,

those patients much improved by electroshock showing early, persistent and increasingly positive reactions during their course of treatment. Unimproved patients showed infrequent, inconsistent or no positive reactions, with a middle group, showing moderate clinical amelioration and more positive reaction than the unimproved one, but many less than the much improved group. The authors concluded that their observations indicated that "clinical improvement in electroshock requires the creations of conditions of altered brain function in which new patterns of symbolic adaptation can be maintained".

Conclusions

This work is more of interest in its possible relationship to at least part of the mode of action of electroshock, rather than as a purely prognostic test.

3) Response to Amphetamine Derivatives

The use of amphetamine sulphate ("Benzedrine") in the treatment of mild depressive states dates from the mid-1930's; since then various derivatives have been employed, notably dexamphetamine ("Dexedrine") and methylamphetamine ("Methedrine"). The more powerful cerebral stimulatory activity of

the latter drug was described by Simon and Taube in 1946, who noted its usefulness for diagnostic purposes. Its effects in producing relaxation, euphoria, increased alertness and relief of tension in neurotic patients, with, on the other hand, intensification of delusions and florid phantasies, increased psychomotor activity and emotional discharge in a group of psychotics were described by Levine et al. (1948).

The more widespread use of methylamphetamine in the treatment of depressive states was urged by Rudolph in a series of papers. In 1949 he described the results of treatment by the oral use of the drug in 42 depressives of all kinds, ranging in age from 24-39 years and of both sexes, and found an identical improvement with a separate group of depressed patients given E.C.T. Monro and Conitzer (1950), in a similar study of 34 patients given methylamphetamine and 200 given E.C.T. found a very significantly greater degree of improvement in the electroshock group.

Rudolph (1956) pointed out various difficulties inherent in the comparison of these results, as different dosages of the drug were employed, and the sub-groups probably differed considerably in the severity of the depressive illness. He then went on to compare the results of treatment

with methylamphetamine and E.C.T. according to the clinical type of depression diagnosed. This is in some ways an unsatisfactory study, for the author has taken reported results from a large number of sources, and himself admits that "all authors do not give full details of diagnosis or results"; this makes it difficult to attach much importance to the findings quoted. Summation of results from a variety of sources, with incomplete information regarding diagnostic criteria and other important data may be misleading. Results did suggest, however, that a higher proportion of 'involuntional depressives' and 'depressives with anxiety' showed a good response to treatment with E.C.T. rather than with methylamphetamine, whilst 'reactive depressions' did better with the drug; no apparent difference in outcome with the two treatments was observed in 'depressives with hysteria'. No tests of statistical significance were reported, and these results must be treated with reserve: they did suggest some difference in response to methylamphetamine in various diagnostic groupings of depressed patients, but it was not made clear as to whether this difference was quantitative, qualitative, or both.

Further studies with this drug have shed further light on its possible mode and site of

action: Liddell and Weil-Malherbe (1953) reported increased blood-adrenaline levels after its administration. Rothballer (1957) after experiments on unanaesthetized cats with coagulation lesions in the mid-reticular system has postulated that methylamphetamine produces its stimulant action on the C.N.S. by a sensitizing effect upon an adrenergic (adrenaline-sensitive) component of the reticular activating system. Other studies of the depressive effects of reserpine, and the euphoriant action of iproniazid (an inhibitor of amine-oxidase) on depressive states (Ayd, 1957) point in the same direction.

Conclusions

The results of the administration of methylamphetamine in various depressive states, with some suggestion of clinical differentiation into diagnostic groups gives reasonable grounds for supposing that it might be suitable as the basis of a prognostic test.

IV ELECTRO-ENCEPHALOGRAPHIC STUDIES

E.E.G. studies in depressed patients, unrelated to treatment, have not on the whole provided any useful information or shown any specific abnormalities. Studies by Shagass (1955 a and b) in attempting to differentiate anxiety from depression by means of photic-driving of the E.E.G. have suggested a quantitative difference between the two, anxiety patients being associated with a relatively greater degree of driving at faster rates than was the case in depressives. No corroboration or extension of this work seems to have been forthcoming. Since the introduction of electroshock a number of investigations have been carried out on E.E.G. changes produced by the treatment, and although these have chiefly contributed to theory on its mode of action, some prognostic observations have also been made on these changes.

Proctor and Goodwin (1945) compared unidirectional fluctuating current with alternating current in administering E.C.T., using a group of 129 patients, about half of the total receiving each type of electroshock. Both schizophrenics and affectively disturbed patients were included, but unfortunately no indication is given of the numbers of each diagnostic category separately.

They found that the widespread appearance of slow wave activity towards the end of a series of treatments was associated with little or no clinical improvement as far as the use of the unidirectional current was concerned; with alternating current this slow activity appeared to be very much less. The significance of these findings was not clear.

Hoagland, Malamud, Kaufman, and Pincus (1946) studied intensively 13 women with agitated depression before, during and after 8-15 E.C.T. They reported a good correlation between daily ratings on the Malamud rating scale and fast (greater than 13 per sec.) E.E.G. activity. As the patients improved with treatment, the percentage of time this fast activity was present decreased, but tended to return on relapse. This was not an invariable finding, however, and the same pattern was observed in some patients who responded well to electroshock.

A more recent investigation was that of Fink and Kahn (1957) who analysed the relationship between the degree of shock-induced delta (1-4 c.p.s.) activity and clinical assessments. A preliminary study showed a significant positive correlation between the early appearance of slow activity and marked clinical improvement; further

work on 54 patients undergoing E.C.T. taking records in the 2nd and 3rd weeks of treatment confirmed this and the conclusion was that "early induction and persistence of high degree delta activity were related to the short-term clinical evaluation".

Others (e.g. Kennard and Willner, 1948) also noted slow activity resulting from E.C.T., but this was by no means invariable in its appearance, even after effective treatments; Roth (1951) first described a technique using serial E.E.G. studies under thiopentone anaesthesia which would consistently reveal E.E.G. changes earlier and more effectively than waking records. These changes - the appearance of runs of delta activity - were found either to coincide with, or precede, signs of clinical improvement, although they were not specific to depression. Inasmuch as they also appeared in neurotic subjects, they were described as "invariable concomitants of clinical improvement".

These observations were made the basis of further investigations (Roth, Kay, Shaw and Green 1957) on 41 patients with "unequivocal endogenous depressions". Using a standard technique and measuring the delta activity produced by E.C.T. appearing under thiopentone (3-4 hours after a convulsion), the percentage of time occupied by

these slow waves in the 300 sec. following their first appearance was plotted as its value changed during treatment. A wide range of variation was found, but a close association noted between this measurement and the clinical improvement or relapse with the treatment. Patients with peak values of 40% or less showed significantly higher relapse rates, at 3 and 6 months after treatment, than those with values of 40% +. The conclusion was reached that cases of endogenous depression with values of less than 35% time had not acquired an adequate physiological basis for recovery; this basis was postulated as probably a derangement of function of the thalamo-frontal projection system.

Conclusion

This work is of great interest, not only for its predictive value but as a contribution to further knowledge of the rationale of E.C.T. It is, however, necessarily more of a research technique than a practical clinical prognostic test for widespread application.

V MISCELLANEOUS PROGNOSTIC INDICES

A number of specific items in relation to outcome of depressive states have been described from time to time, most of which do not seem to have been followed-up despite the usefulness claimed for many of them. The use of a hyperglycaemic index was suggested by McCowan (1936), based on various blood-sugar estimations, fasting and after administration of glucose. He considered a high index an unfavourable prognostic sign, regarding the index as a measure of the patient's emotional tension. In view of the difficulty of establishing satisfactory norms, and the great variation in blood-sugar findings, it is not surprising to find that this work does not appear to have been followed up until recently when more suitable techniques became available. Pryce (1958) used an intravenous test which gave a numerical index for glucose tolerance and applied it to 19 depressed patients and 9 controls. A highly significant decrease in glucose tolerance and body-weight was found in the depressives, particularly in the 8 cases diagnosed as 'involuntional melancholia', but no explanation for this was forthcoming from the data available. No prognostic studies have yet been made using this technique.

Other biochemical indices have also been utilized. Serum calcium levels were studied before and after E.C.T. by Gour and Chaudhry (1957) in patients with schizophrenia and depressive illnesses; transient post-ictal hypercalcaemia was found, with the observation that the calcium rise and subsequent fall were greater in those patients showing marked clinical improvement. The authors suggested that by studying the pattern of calcium response to E.C.T. after the first 2-3 treatments, and comparing it with a "minimal standard fluctuation curve" it might be possible to assess the chances of a good response to further therapy. No probability calculations were made on their figures, and the method appears laborious, necessitating the application of several treatments before any conclusions at all can be drawn.

A far more important investigation was that of Dawson, Hullin and Crocket (1956) into metabolic variations in manic-depressive psychosis. They found blood levels of acetylmethylcarbinol (A.M.C.) to vary considerably between manic and depressive phases of the illness in the same patients, high levels of this substance being found in depression. Further studies of variations in A.M.C. levels in different diagnostic depressive groups have been made

(Dawson, 1958) and norms for the usual levels of this compound determined. Dawson now believes that the level of A.M.C. will differentiate diagnostically "endogenous" and "reactive" depression, the former being characterized by high levels and the latter by normal levels; low levels are found in manics. There appears to be a prognostic significance in A.M.C. estimations, as those patients with normal levels do not appear to do as well with electroshock treatment as those characterized by high levels, and further work on this point is proceeding at the present time.

A prognostic index based upon adrenocortical activity has been described by Faure et al. (1957); various biochemical and haematological variables which are indicators of adrenal activity were studied before and after an injection of 25 mgms. adrenocorticotrophic hormone (A.C.T.H.) in depressed patients about to receive electroshock therapy. The reactions studied included lymphocytes, neutrophils, eosinophils, 17-ketosteroids, 11-oxysteroids, creatinine, uric acid, phosphorus, sodium and potassium; a definite correlation found between adrenocortical response to A.C.T.H. and the clinical response to E.C.T. Those patients who showed the most marked response in endocrine activity before E.C.T.

also did better with the treatment, and vice versa. Only 12 patients were studied - this is not surprising in view of the complexity of the undertaking - and the method is clearly unsuitable for routine use unless a simple indicator of adrenal activity became available.

The value of morphological indices for prognosis have been investigated chiefly in schizophrenic patients; the original observations of Kretschmer on the frequency of asthenic physique in schizophrenia and pyknic build in manic-depressive psychosis gave these investigations their initial impetus. Studies of differences in body-build and their association with differences in outcome have more usually stressed the better prognosis for patients of pyknic than asthenic habitus, but a number of investigators have not found any significant relationship between body-build and outcome. Many of these studies have in the past been based upon general impression of physique rather than actual measurements; the technique of somatotyping introduced by Sheldon (1940) has made researches in this field much more scientific, although it involves photography and multiple measurements. A simpler index of somatic morphology is that suggested by Rees (1950) and called the "Body Index"; this was obtained by

the factor analysis of intercorrelations between 15 anthropometric variables measured on 200 women neurotics. By various statistical treatments of the information collected in this way, a regression equation containing 4 simple measurements, duly weighted, was used as the body index.

Stature, height to the symphysis pubic and chest and hip circumferences were employed giving the equation:

$$\begin{aligned} \text{B.I.} &= 0.59 \text{ stature} + 0.47 \text{ symphysis ht.} \\ \text{(F)} & - 0.31 \text{ chest circumf.} - 0.64 \text{ hip} \\ & \text{circumf.} \end{aligned}$$

(Measurements expressed in standard measure).

On the basis of this index, patients were classified into three groups as leptomorphs, mesomorphs and eurymorphs; leptomorphy was found to be associated with dysthmic traits of anxiety and depression (Rees, 1950), lending some support to the observations of Pullar-Strecker (1936) that patients whose leg-length was more than 50% of the total body-length were more prone to suicide. Rees has, however, emphasized that the correlation between physique and psychological studies is probably too small for clinical use in diagnosis or prognosis, and that the relationships involved are complex ones.

In investigation of capacity for recovery

from psychosis, based upon biochemical and morphological studies, was based on the preliminary work of Gildea, Kahn and Man (1936), who demonstrated that the levels of serum lipoids (fatty acids and serum cholesterol) showed an association with physique. In normal people it was observed that high serum lipoids were found in conjunction with what the authors called "pykno-philic" qualities such as pyknic body-build and high energy output; low lipoid levels were associated with the "leptophilic" factors of leptosomatic or asthenic physique and low energy output. In manic-depressives, these further studies (Gildea et al. 1940) showed that those patients who possessed "pyknophilic potentialities" usually had considerably higher serum lipoids than schizophrenics, and led the authors to regard the triad of pyknic physique, uncomplicated symptoms of manic-depressive psychosis and high serum lipoids as evidences of a strong capacity for recovery. An extension of this work to include 142 patients - 90 manic-depressives, 52 schizophrenic - was later reported (Gildea and Man, 1942), and serum lipoid estimations were concluded to be a promising adjunct to conventional clinical methods in assessing capacity for recovery. The manic-depressive patients were, however, carefully selected as 'presenting

relatively clear-cut and uncomplicated examples of the manic-depressive syndrome'; 81% of this group were doing well 5 to 10 years after the onset of the illness. High lipid levels occurred in most patients who subsequently recovered, and vice-versa.

This work is of great interest and underlines the importance of constitutional factors in the two psychoses where genetic influences are known to be most important. It is, of course, well recognised that the short-term prognosis in 'classical' manic-depressive attacks is, on the whole good, and it is in other forms of depressive illnesses that outcome is more uncertain. It is in precisely these conditions that this method of assessing recovery-potential is unlikely to be of much assistance, as many patients tended to have average serum-lipoid values of uncertain significance. In the 142 patients studied there was a relatively large overlap of both diagnostic groups of patients as far as body-build only was concerned; 16% of a group of 74 manic-depressives who showed good capacity for improvement were of leptosomatic physique, and 10% of a group of 30 schizophrenics of poor improvement potential had pyknic physiques. Here diagnostic criteria - especially as far as the schizophrenics were concerned - may have played a

part in the discrepancies, but the results again demonstrate the limitations of physique alone as a criterion for prognosis.

DESIGN OF THE PRESENT INVESTIGATION

DESIGN OF THE PRESENT INVESTIGATION

Introduction

The conclusion that ample scope still existed for further prognostic studies in depressive illnesses sprang not only from a survey of the relevant literature, but also from personal experience of the difficulties sometimes encountered in forecasting the probable results of electroshock treatment.

Two broad avenues of approach to the problem are possible. The first, like studies of Kraepelin and Bleuler, is to take a large number of cases, using rigid diagnostic criteria, and see what becomes of them after treatment; the second method is to make a more intensive and comprehensive study of a much smaller number of patients, without emphasis on diagnostic categories, and to determine the relationship of various specific clinical and other features to outcome by means of standard statistical methods. Both approaches have their advantages and disadvantages; in the first, practical considerations of the availability of sufficient clinical material make this method more suitable when large numbers of patients are accessible, because of the rigid selection of cases to conform to specific diagnostic criteria. From

such a study, broad trends only are apparent, of less applicability to prognosis in the individual patient, especially in the case where atypical clinical features may be present. The second method depends for its effectiveness on sound planning and attention to methodology, is often laborious and time-consuming, and is more open to bias on the part of the observer. It is, however, capable of yielding useful results on a comparatively small number of cases - results which may be more applicable to estimation of outcome in the individual patient. Further, information as to the probable usefulness of specific physiological and other tests as an aid to forecasting may be obtained comparatively rapidly in order to decide whether an extended investigation would be worth while.

It was felt that this second method was more suitable, partly because of practical considerations regarding the availability of eligible patients, but chiefly because this 'deep' type of investigation is designed to detect and assess the influence of specific factors in relation to short-term prognosis, with the possibility of immediate therapeutic guidance. Furthermore, Hobson's (1953) investigation furnished a convenient starting point: an attempt at validating his findings together with an assessment of other

specific prognostic indices seemed a worthwhile study.

Such an investigation should clearly fulfil a number of requirements in order to avoid serious errors, and the most important were considered to be as follows:-

- a) Because of the ambiguity often attending the use of diagnostic groupings, attention should be paid to the presence or absence of specific clinical features as such, within very broad diagnostic limits.
- b) An attempt to quantify depressive symptoms and manifestations, rather than the use of 'global' assessments, was felt to be desirable; for this purpose a symptom rating-scale seemed appropriate.
- c) As far as possible clinical terms, criteria, etc., should be defined as closely as possible.
- d) A definite time interval should be set for the assessment of the results of treatment.
- e) Other variables such as age, technique of treatment etc., should be controlled as far as possible, with overall attention to methodological planning so that standard statistical methods could be applied in the assessment of results.

f) Clinical features alleged to be of prognostic significance should be particularly noted, together with the application of a number of tests, psychological, physiological and pharmacological, which it was thought might increase accuracy in predicting outcome.

The Overall Purpose and Plan of the Investigation

The general purpose of the investigation was summarized as: 'What prognostic factors can be gleaned from clinical, psychological, physiological and pharmacological studies of the electroshock treatment of depressive states?'

In brief the investigation took the following form:

50 female patients, aged 40-60 inclusive, and suffering from primary depressive illnesses of sufficient severity, were carefully examined and their depressive symptoms assessed on an appropriate rating scale. Physical measurements were taken, a psychological test derived from the M.M.P.I. was administered, systolic blood pressure response to methacholine noted, the sedation threshold (Shagass) to sodium amylobarbitone estimated, and an empirical dose of methylamphetamine given and its effects observed. Electroshock therapy was then given; the patient's clinical condition was

again assessed on the rating scale at one month and 3 months after the completion of treatment, and the influence of specific clinical factors on the quantitative symptom scores were calculated.

1. Selection of Patients

In order to reduce the number of variable factors, the choice of patients for the investigation was carefully made within certain limits. Chiefly because of the increased incidence of depressive states in women, only females were selected for study, and only those between the ages of 40 - 60 years. The age limits were set so as to include the involutinal period, when many minor or atypical depressions occur, and to exclude older patients where the increasing complication of organic factors might introduce other difficulties.

Only those patients considered to be suffering from a depressive illness of sufficient severity to warrant the application of E.C.T. were included: a 'depressive illness' was defined as a sustained primary mood disturbance, leading to subjective or objective inefficiency of mental activities experienced in a mood of sadness, and usually with a diffuse persistent lowering of interests and activity. The need for E.C.T. was considered established where symptoms were

sufficiently severe to render the patient unfit for her normal occupation, or constituted a serious social handicap, or had led to what was considered as a genuine attempt at suicide.

Patients showing depressive symptoms in relation to organic mental syndromes, or schizophrenia, paraphrenia, etc., were excluded, as were those who had received electroshock treatment in the twelve months preceding their current illness. No attempt was made initially to place patients within more narrowly defined diagnostic categories, any otherwise suitable patient showing a sufficient degree of sustained primary affective change in a depressive direction being included.

Patients were seen and treated in three hospitals - psychiatric beds in the medical wards of the teaching hospital, the General Infirmary at Leeds; in the psychiatric unit of a large general hospital, St. James's Hospital, Leeds; and in a small (350 bed) mental hospital nearby, Scalebor Park Hospital, Burley-in-Wharfedale. Although this introduced certain obvious disadvantages, it was essential in order to obtain sufficiently varied clinical material for the study. For one reason or another, quite a number of otherwise suitable depressives could not be included, so that a larger patient population

than that available in the teaching hospital only was necessary. The use of three hospitals had the advantage of increasing the representation in the sample of the more severely depressed patients, as the teaching hospital tended to receive either the milder cases (particularly those with neurotic features) or those who had made suicidal attempts and who were often transferred after resuscitation. 54 patients were initially investigated, and a total of 50 included in the final assessments after treatment.

2. Clinical Examination and Assessment.

All patients were seen personally, and if considered potentially suitable for inclusion in the investigation, were then studied in more detail. The history-taking paid special attention to the various clinical items considered by Hobson to be of prognostic significance and these were carefully noted as present or absent. Apart from the general history-sheet, these items (along with later test results) were also entered on a special pro forma for convenience (Appendix B); as far as possible standard criteria and definitions for various clinical items were adhered to (Appendix C). Clearly objective estimations from the patient were not always possible, but gaps or doubtful points were filled in or clarified by

additional information from relatives and other medical sources or appropriate agencies.

Routine physical examination was carried out on all patients to exclude gross physical disease. In view of the later use of intramuscular methacholine, patients suffering from asthma or heart-disease were excluded, although essential hypertension of moderately severe degree was not considered a contraindication unless there was evidence of cerebral, cardiac or renal involvement. Opportunity was taken at this stage to measure and record the body weight and the necessary measurements for the calculation of the Rees-Eysenck body index - the height, chest circumference at the xiphisternal level midway between inspiration and expiration, hip circumference at the level of the iliac crests, and the height to the upper border of the symphysis pubic. The standard anthropometric techniques of measurement described by Hrdlicka (1947) were used.

The mental examination covered the usual points of appearance, behaviour, mood, thought content, orientation, memory, insight etc., including a rough assessment of the intelligence level based on simple memory, comprehension and general knowledge tests, together with school and employment attainments. Particular attention

was paid to the clinical features of anxiety and depression, and an attempt made to quantify these by rating on an appropriate scale.

Rating Scale for Depressive Symptoms

During the course of clinical trial of a tranquillizing drug, benactyzine, experience had been gained in the use of a symptom rating scale for assessing anxiety, using 13 headings for symptom-grouping with a 5-point scale of severity of manifestation. With 3 psychiatrists working in pairs in combination, an overall interphysician correlation on these assessments of 0.89 was found, indicative of a very high measure of agreement (Hargreaves, Hamilton & Roberts, 1957).

A gloss of various depressive symptoms was first prepared, using many sources in the literature including most of the standard text-books. These were next arranged in appropriate groupings, in approximate order of their significance for the severity of the depressive illness (Appendix B) and the groupings summarized under the following headings on a separate sheet:-

- 1) Depressive mood.
- 2) Depressive guilt-feelings.
- 3) Depressive suicidal features.
- 4) Insomnia - early (i.e. difficulty in falling asleep)

middle (restless or disturbed
sleep, nightmares)

late (early wakening inability to
get off again)

- 5) Diurnal variation of mood.
- 6) Interference with work and activities.
- 7) Degree of retardation.
- 8) Agitation.
- 9) Anxiety - psychic manifestations.
somatic manifestations.
- 10) Depersonalization, rerealization, nihilistic
ideas.
- 11) Paranoid symptoms.
- 12) Obsessional - compulsive symptoms.
- 13) Hypochondriacal symptoms.
- 14) Somatic depressive symptoms (e.g. abdominal
discomfort, backache)
- 15) Loss of weight
- 16) Degree of insight into illness.

The scale has been shown to have a high degree of reliability between observers (Hamilton, 1958a); the one used in this study was a slightly modified version.

Those features which could usually be assessed simply as 'present' or 'absent' were scored '2' or '0' appropriately, occasionally '1' when slight or doubtful. Features with a varying

distribution, such as depressive mood, guilt feeling, anxiety, etc. were scored on a 5-point scale, ranging from '0' - absent, 1 - mild or trivial, 2 & 3 - moderately severe and 4 - severe.

A number of difficulties of various kinds were encountered in the use of this scale: initial trials with a number of patients (not included in the series under investigation) were made and various modifications introduced, the final result taking the form outlined above. Various difficulties remained; an example was the handling of the symptoms of delusions and/or hallucinations - should there be a separate category for these manifestations of some depressions, or could they justifiably be included in the scale according to their content? After deliberation it was decided to include, for example, somatic hypochondriacal delusions as a '4' rating under the group heading of 'hypochondriasis', and the presence of delusions of guilt under a similar rating of 'depressive guilt'. Admittedly such inclusion tends to mask the possible significance of these features in some respects, but their separate assessment in terms of content in a rating scale would add considerably to it and make it unwieldy. Similarly assessments of suicidal manifestations caused some difficulty, particularly in those cases where suicidal attempts had been

made. Where these were clearly deliberate efforts directed to self injury in such a way that the patient might reasonably have expected death to ensue, they were scored '4' under the 'depressive-suicide' heading. In other cases, bearing in mind the thesis of Stengel (1952) on the "cry for help" significance of many suicidal attempts, rather than as deliberate efforts to end life, various other factors were considered in the assessment. These included the tendency towards histrionic forms of behaviour and the timing of the attempt. Where genuine doubt as to the strength of the suicide drive existed, they were classed as genuine.

The use of such a rating scale allows a higher degree of accuracy than overall clinical judgements in assessing and comparing the results of treatment, as well as furnishing a quantitative expression of symptoms capable of being handled by simple statistical methods. It was noted with considerable interest that a completely independent clinical item card, drawn up by Watts (1958) for the assessment of depressives in his Leicestershire general practice, was remarkably like the scale described above.

3) Application of Specific Tests

Psychological Test - The Feldman "Ps" Scale

Before starting treatment, the patient was asked to sort the relevant 52 items of the M.M.P.I. which go to make up the scale, into the appropriate group of 'true', 'false' or 'don't know', with instructions to keep the number in the latter category as few as possible. The cards were then checked against Feldman's groupings and a total 'prognostic score' derived on the basis of 1 point for each item answered in a prognostically unfavourable direction.

Considerable difficulties were encountered in the use of this procedure, the chief one being the inability or unwillingness of some patients to attempt it. This was usually due to agitation, retardation or indecisiveness, and in a number of cases it proved quite impossible to obtain a completed series of sortings: in other cases the test was finished only with persuasion from doctor or nurse, and in some it was obvious that the results were unreliable because of inattention, poor concentration and the general inability of the depressed patient to persist at the task. Even before the results could be assessed the value of this test (assuming a validity for it which is by no means certain) was clearly

jeopardized by these factors. A further source of difficulty was the tendency of some patients to include up to 10 or 12 items in the 'don't know' category, which could not be scored.

Autonomic Function - Methacholine Test

Before treatment was begun, a modified version of the test of autonomic function, introduced by Funkenstein, was applied. Trials with various forms of this test were used on depressed patients, firstly using the techniques originally described with intravenous normal saline, intravenous synthetic 1-adrenaline and intramuscular methacholine chloride, 10 mg. Various difficulties were encountered: with the adrenaline administration, it was extremely difficult technically to obtain reliable systolic blood-pressure readings every 15 seconds for two minutes, and great variation in the resulting rise in B.P. was found. Also patients found it disturbing, with the frequent production of markedly unpleasant anxiety symptoms, so that in order to simplify procedure this portion of the original test was omitted in the patients investigated later, particularly as the methacholine portion of the test has been alleged by other workers to be the more useful for prognosis.

With the methacholine response an entirely

different difficulty arose. An oily solution of methacholine chloride, marketed in the United Kingdom by a British drug firm, was the only preparation at first available and many tests were carried out with this. The results were somewhat variable, but by and large very little hypotensive response was noted after injection, and suspicion arose as to the potency and activity of the preparation. The manufacturers then prepared an aqueous solution of the drug, date-stamped and said to be reliably active for one month: results with this were very different, and approximated much more to the American reports. Finally a supply of the drug in dry powdered form was obtained from an American firm whose product was used in the original investigations, and this was used for the cases in this series, freshly prepared with water before each test was carried out.

The technique for the test finally adopted was based on that used by Sloane and Lewis (1957) as follows:

In the morning, and under fasting conditions, the systolic B.P. was taken after the patient had been lying down for at least half an hour. Readings were taken for at least five minutes at about half-minute intervals until five consecutive

readings within 8 mm. of mercury were obtained; the average of these last five was taken as the "basal B.P."

10 mgm. of aqueous methacholine chloride solution, freshly prepared, was then injected intramuscularly, and the systolic B.P. recorded every half-minute for seven minutes, every minute for the next five minutes, and then every two minutes until a total of 25 minutes had elapsed, or the B.P. had returned to the basal level and remained there for at least five minutes.

Atropine sulphate gr. 1/100 was kept at hand to check apparently dangerous parasympathetic overactivity, but was only used on one occasion to relieve distress after the 25 min. test period had elapsed.

During the course of the test, a note was also made as to the occurrence and severity of parasympathetic and other phenomena, such as marked facial flushing (almost invariable), lacrimation, shivering or rigors, anxiety, restlessness and agitation.

No major difficulties were encountered with this technique once a routine had been established; the test was repeated in the case of two patients because of apparently unsatisfactory absorption of

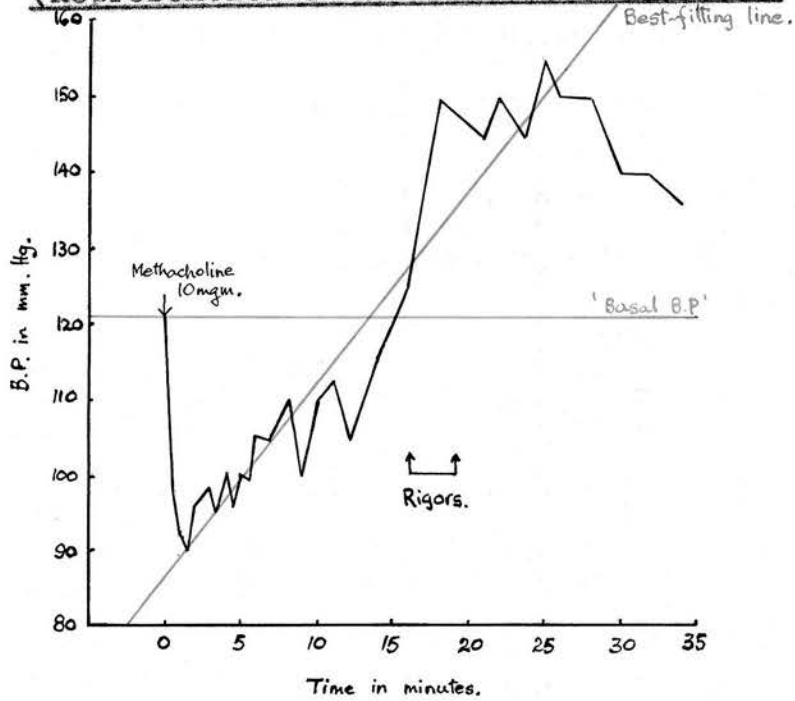
of the drug, which had presumably inadvertently been injected into fat. The profound hypotensive effect of methacholine in patients with a high resting B.P. was confirmed, but no complication resulted.

The problem of the scoring and interpretation of the results of this test was considered at some length; the arbitrary nature of some of the original variables used in assessment (e.g. the 25 min. observation period - why not 30 minutes? or 20 minutes?) suggested that other methods of scoring might yield added information and for this reason the results were treated in three different ways.

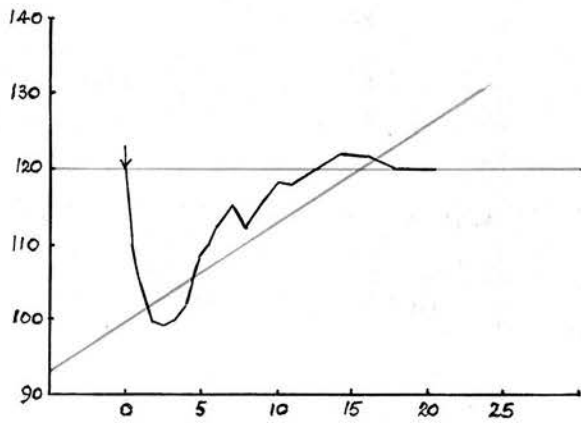
Initially the information obtained from each patient was transcribed into graph form, on 1 m.m squared paper, systolic B.P. in m.m. Hg. on the ordinate and time in minutes on the abscissa (See Figure 1). The basal B.P. was also indicated so that the pressure variations and return to resting levels were clearly visible.

1) For this first method of assessment, the graphs were then examined individually and sorted into three groups according to the following criteria:-
Group I : cases with an initial fall in B.P. to methacholine followed by a fairly rapid return to the basal level and a subsequent marked secondary

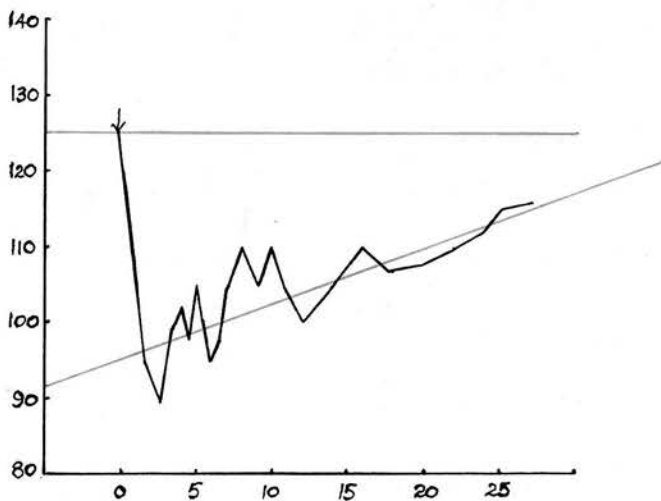
FIGURE 1
(Representative Methacholine Responses)



GROUP I
(Series no. 30)



GROUP II
(Series no. 26)



GROUP III
(Series no. 6)

rise.

Group II : graphs showing an initial fall - small, moderate or marked - with re-established homeostasis within the 25 min. observation period (often within 8-12 minutes).

Group III : those with an initial fall - often of marked degree - and failure to return to the basal level within the 25 min. period.

Following this sorting, the mean symptom-scores one month after treatment were calculated for each group separately and compared. In addition the correlations between the maximum B.P. fall observed and the symptom-score at the one month interval, and between the time in minutes to the re-establishment of homeostasis and the same scores, were also calculated.

2) A second method of assessment was used, devised in the University of Leeds Department of Psychiatry (Hamilton, 1958 b). It is based on the fact that the relation between systolic B.P. and time can be roughly represented by a straight line. Such a relationship is capable of being expressed by means of the simple mathematical equation:

$$y = ax + b,$$

where y is the blood pressure, x the time after the injection, a is the slope of the line and b

a suitable constant.

In practice, the points defined by observation rarely lie exactly upon a straight line, so that the technique of finding the 'best-fitting' straight line is used. This minimized the sum of the squared vertical deviations of the points from the line, involving a number of calculations in each case - simple if tedious ones.

Such a line, by minimizing momentary fluctuations, would give a more accurate indication of the general trend towards the re-establishment of the basal pressure which was noted in all cases, and the use of measurements based on the line might well yield more accurate criteria for comparison between cases and their outcome with treatment. This would involve separate calculations, an average of about 20 for each patient, and over 1,000 for the 50 patients under investigation - a laborious process in the extreme had not special facilities been available in the form of the Leeds University electronic computing machine. After the necessary data had been punched on to tape and, with the relevant instructions, fed into the computer, the regression equation for the best-fitting line for each set of observations on the 50 patients was automatically typed out, the whole process taking little over 15 minutes computing time.

The first B.P. reading used for purposes of computing was that at the fourth half-minute interval from the beginning of the test: it was observed from the initial graphs that the maximum fall of pressure was reached by about this time in the majority of cases, and the use of prior estimations taken while the B.P. was still falling rapidly would have introduced a serious bias in the calculation of the best-fitting line expressing the return to basal pressure. From the information supplied by the computer, the straight line was drawn in on each methacholine test graph for each patient; the relevant B.P. was calculated automatically for the fourth $\frac{1}{2}$ minute period (y_4) for one point on the line, and the regression equation enabled a convenient point further along to be calculated easily.

The graphs were now once more sorted into the same three groups as method (1), this time using the point where the regression line intersected with the basal pressure line as the criterion for the timing re-establishment of homeostasis, and again the means of the symptom-scores after treatment were compared.

3) In this method the information yielded by the regression lines only was utilized, and correlation coefficients were calculated for a number of

variables derived therefrom with the one month symptom-scores. These included the fall in B.P. from the resting (basal) level to the level on the line at the fourth half-minute, and the constant representing the slope of each line - an expression of the speed with which basal pressures were re-attained. In addition the correlations with outcome for age and basal pressure were made and the intercorrelations between these variables themselves calculated.

Sedation Threshold Estimation

Experience was first gained with a short trial series of patients using the method originally described by Shagass, and this was also used for the first 10 patients in the investigation.

With the patient lying down, and having had no drugs of any sort during the preceding twelve hours, a resting electroencephalographic recording was made, using 4 frontal electrodes across the scalp. When this was satisfactory - to facilitate later measurement, the recording amplitudes were usually boosted in size - a needle was inserted into a suitable vein of the arm and an injection of sodium amytal solution begun when the disturbance of the procedure had subsided. The drug was made up in a strength equivalent to 0.5 mgm.

sodium amytal per kilo body-weight for each patient, 1 ml. being injected rapidly every 40 seconds. The rate was controlled by an assistant with a stop-watch who gave an appropriate signal at the correct interval, when a mark was made on the recording: a second signal was given 25 seconds after each injection time (i.e. 15 seconds before the next 1 ml. was due), and the patient then asked to repeat such phrases as "5-6-7", "77", "British Constitution", "Methodist episcopal". When slurring of speech was first noted, the record was marked by the assistant at the appropriate point, and a further mark made when unequivocal slurring was apparent. The injections were usually continued for two or three further 40 sec. intervals after the appearance of slurred speech.

The E.E.G. recording was then examined, and sample periods of two seconds duration marked where the 15-30 cycles per second fast activity appeared maximal; these were chosen from periods of 15 seconds before and 10 seconds after each injection point. Twenty samples of the 15-30 c.p.s. wave activity in each two second period were measured by hand, using a finely engraved ruler, and the mean amplitude calculated for each injection point. These mean measurements were then plotted on graph paper against the amount of sodium amytal injected, and a mark made on the

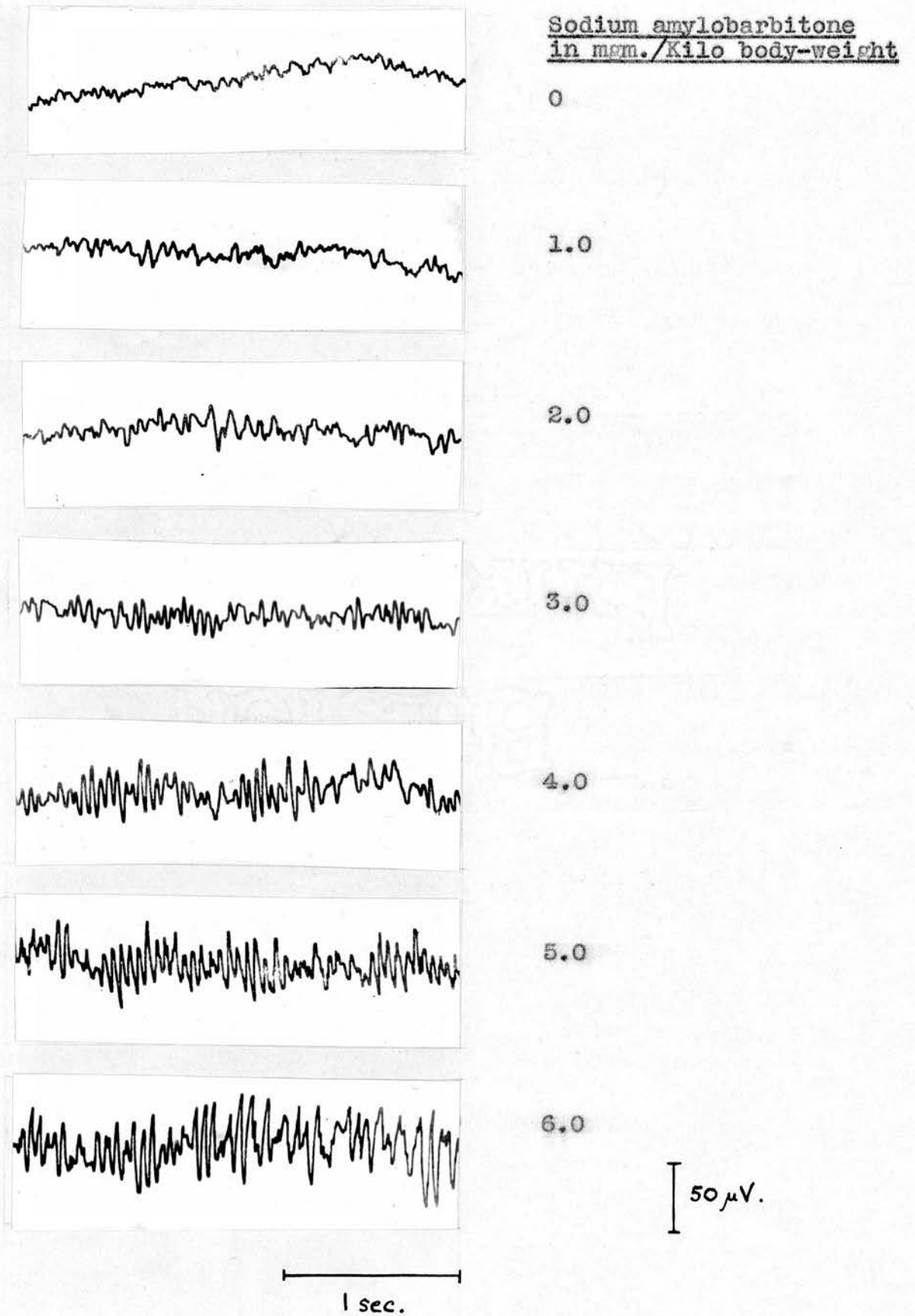
graph corresponding to the clinically observed slur-point. The general trend of the results was in accordance with Shagass's observations, the frontal fast activity being at a minimum to begin with and gradually increasing in amplitude as the amount of drug in circulation increased; eventually a maximum was reached, but this was after the slur-point had been passed in almost all cases (Figure 2).

A number of technical difficulties were encountered, most of them of a minor nature, during the actual performance of the test. These included faulty E.E.G. recordings due to poor scalp electrode contact, excessive artefact as a result of eye-movement, muscle tension or restlessness in some patients; some records had to be discarded on account of one or more of these faults, or occasional difficulty with the injection because of poor veins.

A rather different problem was posed by the fact that only one E.E.G. apparatus was available for the whole of the Hospital Board region, so that access to it was limited by consideration of heavy demand, waiting-list etc., and the necessity of bringing patients for the test from other hospitals, all of which led on occasion to administrative difficulties.

FIGURE 2

Effects of barbiturate on frontal E.E.G.



The assessment of the slur-point also led to some difficulty; patients varied a good deal in this effect of the drug, articulation in becoming slower and more hesitant, whilst in others speech was continued at the same speed, but became thicker. Occasionally a patient would clearly slur, and then articulation would improve markedly for a while before sustained slurring was apparent. With experience, however, it was felt that the onset of slurred speech was noted reasonably accurately in most patients, and where there was doubt, the practice of marking the record "?S" at that point, and "S+" when slurring was unequivocal, helped considerably in fixing the point afterwards. Slurring was not considered to be present until there was a definite change in articulation, apart from such changes as slowness or hesitancy.

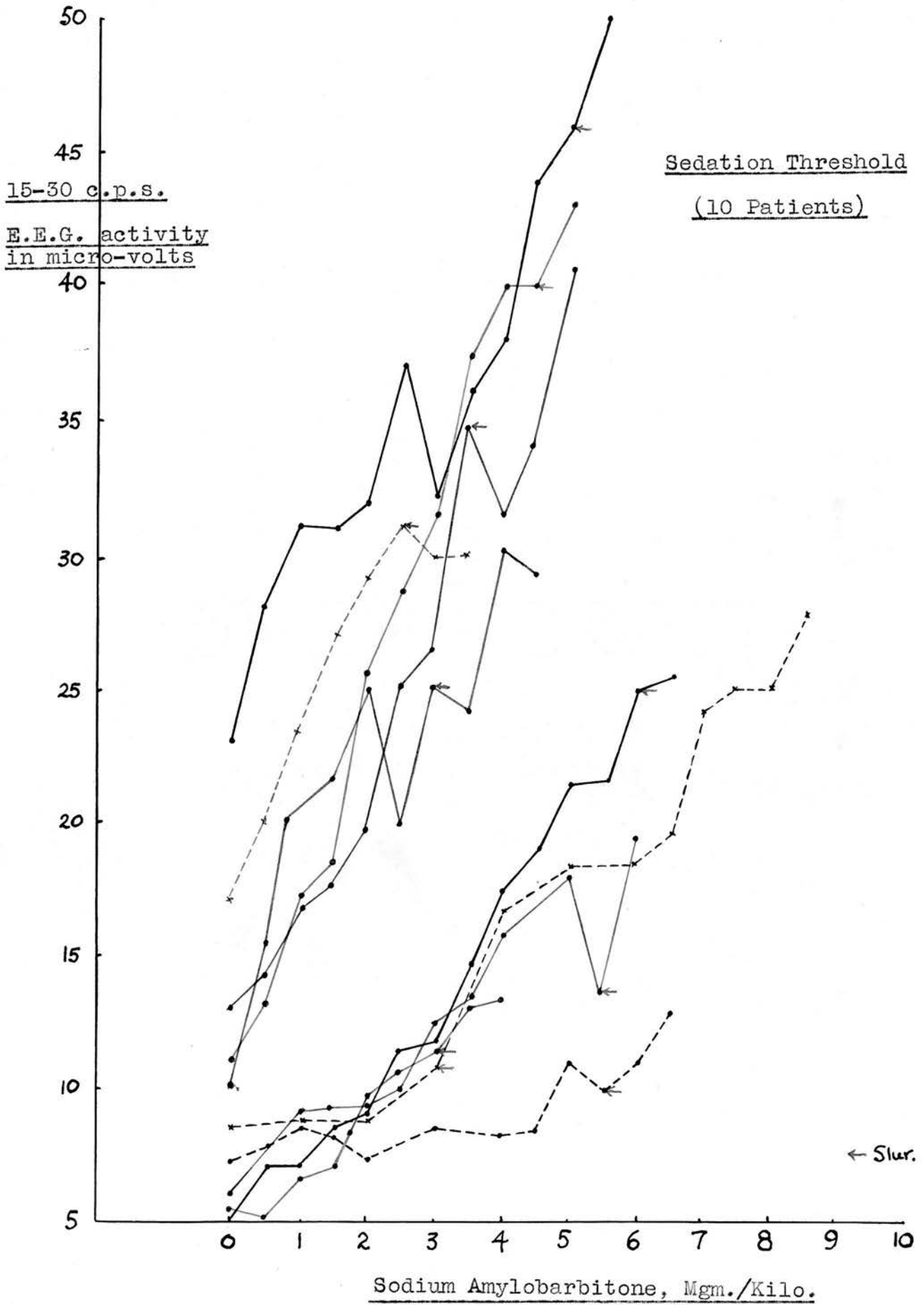
The main difficulties experienced with this test were in the measurement of the amplitude of fast activity and the subsequent assessment of the "sedation threshold" based on the combination of E.E.G. changes (alteration in the gradient of barbiturate-induced fast activity) and the clinical slur-point, the former to occur within 80 secs., of the latter to be significant.

An automatic frequency-analyser was not

available for this study, so that all measurements were made by hand-ruler; this was extremely tedious and time-consuming, although not technically difficult, and the measurement and calculation of the mean fast-activity amplitudes in one channel of a recording took 2-3 hours or longer. On three records these measurements were re-checked some time later, and differences of 10-15% were found; not perhaps particularly large considering the special factors in the field of E.E.G. study, but large enough to give some concern.

The fast-activity amplitude in microvolts was then plotted against the injected amount of sodium amytal per kilo body weight for ten cases (see Figure 3). Although an S-shaped curve was apparent in some cases, in most there were a number of "inflexion points", even sharp dips in the graph rather than a plateau, and several such dips or plateaux could occur in a single plotting. This variation was more noticeable in those cases where the injection had been continued at the same rate for several minutes after the clinical slur-point; where a dip or flattening of gradient occurred one 40 second (i.e. one 0.5 mgm. per kilo of drug) period on either side of the slur-point, the sedation threshold as defined by Shagass could be assessed, but this was not always possible; in

FIGURE 3



a few cases no appropriate amplitude change was noted within these limits. In any case, it became quite apparent that accurate localization of the threshold by E.E.G. criteria alone was not possible, because of the appearance of more than one flattening of amplitude-dose gradient in many records, and that the clinical slur-point was necessary to decide which E.E.G. inflexion point was to be used.

In view of these difficulties, together with the extremely laborious and time-consuming hand measurements necessary because of the lack of a frequency analyser, it was decided to omit the E.E.G. recordings, and use the clinical slur-point alone as an approximate index of the sedation threshold. It was appreciated that this might well detract from the accuracy of the estimation, particularly as the slurring of speech tended to be manifested a little later than the nearest E.E.G. inflexion point on the record, but at least these sources of possible error would occur in all patients tested. Thus it should still be possible to obtain some information as to the potential predictive value of the sedation threshold in order to determine the advisability of further studies.

Response to Methylamphetamine

Usually later on the same day as the methacholine test, the patient was given 15 mgm. methylamphetamine intravenously. The dose was chosen after considerable experience with this drug in a variety of conditions, this amount being insufficient in most cases to cause marked disturbances of behaviour, yet sufficient to have a clear effect upon mood and symptoms.

The general effects upon behaviour, mood and symptoms were closely observed over the subsequent 2-3 hours, and it was found that these fell roughly into two fairly distinct categories, depending upon whether the patient's mood and symptoms were changed in the direction of normality or the reverse. With a number of patients the commonly observed initial phase of weeping, pressure of talk and emotional lability quickly settled into a more sustained period of general uplift of mood and feeling of greater well-being, and these reactions were classified under the 'return to normality' heading. Others showed an immediate, or almost immediate, intensification of symptoms, particularly a worsening of any agitation present, often together with a deepening of the depressive affect, increased self-deprecation and so on.

The response was classified as one which brought the patient nearer to her normal self by reduction of symptoms - an 'N' response, or one which intensified symptoms - an 'I' response. Where more than very temporary fluctuations of mood, etc. occurred, the predominant reaction over the succeeding 2-3 hours was used as the criterion for classification.

In two patients a different reaction to the drug occurred, manifested by a mild degree of prostration, occasional vomiting, complaints of headache and trembling, and accompanied by a markedly hysterical attitude to these drug induced symptoms. Both patients had clear evidence of hysterical traits in their previous personality.

3) Treatment and Follow-Up

With patients who were being treated in three separate hospitals, there were clearly a number of random variable influences at work in treatment other than the application of electroshock. These included the use of sedative drugs, especially at night, varying facilities for social relationships with other patients, occupational therapy, and more personal contact with doctors and nurses; no attempt was made to utilize any method of formal psychotherapy other than the usual pleasant

doctor-patient relationship, together with superficial discussion of personal difficulties, reassurance etc., in some cases. In view of the randomness of these factors it was felt that they could legitimately be ignored.

Electroshock treatment was in all cases administered by the same type of apparatus (the "Ectron"), using a half-sine wave current of about 115 volts for approximately one second's duration; no form of counter-stimulation was employed in any of the patients investigated, who all received the treatment as in-patients.

In all cases an intramuscular injection of atropin sulphate gr. 1/100 - 1/75, was given 30-45 minutes before treatment, followed later by 0.2 - 0.5 gramme of thiopentone by rapid intravenous injection. Immediately afterwards suxamethonium chloride ("Scoline") 25-50 mgm. was administered through the same needle, and the current passed at the time of maximal muscular relaxation. Insufflation with oxygen by means of a hand positive-pressure apparatus was then carried out until normal spontaneous respiration was restored.

No case of difficulty or complications was noted with this technique during the investigation.

Electroshock treatment thus administered was usually given twice per week (occasionally three times per week for 1-2 weeks in more severely depressed patients) and continued until it was felt that maximum benefit had been obtained from the treatment, or that nothing further was to be gained by its continuation: no "course" or fixed number was used.

A careful note was made of the number of treatments given and the date of the last one; most patients were discharged from hospital within a matter of 2-3 weeks at most following the cessation of treatment.

Reassessment was then carried out personally on every patient at approximately 30 days after the last electroshock, using the rating scale; where it was not feasible or convenient for the patient to visit the out-patient clinic where most of these interviews were conducted, in a few cases the patient was visited in her own home or occasionally in hospital again.

Patients were again reassessed approximately two months later, i.e. three months altogether after completion of treatment.

Further reassessments at six and twelve month intervals are also being made with a view to more

accurate long-term information about the course
of these patients' illnesses.

RESULTS OF THE PRESENT INVESTIGATION

RESULTS OF THE PRESENT INVESTIGATION

1) AGE

The ages of the 50 patients ranged from 41-60 years, with a mean age for the group of 51.1 years.

The relationship between age and outcome with electroshock treatment at one and three months respectively was assessed by the calculation of the Pearson product-moment coefficient of correlation (r), using the age in years and the total symptom-scores derived from the rating scale.

At 1 month after treatment $r = -.298$, ($P = .05$.)

At 3 months " " $r = -.118$, (not significant)

($n = 50$, degrees of freedom = 48)

Referring to Fisher's standard Statistical Tables it is apparent that the correlation for the one month post-treatment period is statistically significant at the 5% level of significance; that at three months is not significant.

This negative correlation indicates a tendency for the older patients to have a lower symptom-score after treatment, i.e. to have a better short-term prognosis, and the reverse for the younger ones. This trend is not a very marked one, however, and in a fairly small series of 50

cases may be partly due to bias introduced in the initial selection of patients. There is a non-significant correlation ($r = 0.265$) between age and the initial (before treatment) symptom-score in this series, however, which does not suggest a marked bias.

This finding, although the association is not sustained at the three month interval, is of interest as it tends to confirm other studies which have suggested the reversal of the worsening influence of increasing age on prognosis in depressives since the introduction of E.C.T.

2) PHYSIQUE

The body-index regression equation for females (Rees), expressed in standard measure, was first converted into an equation in which raw measurements from the patients could be used directly; this was calculated from the means and standard deviations given by Rees (1950) in the original work. The necessary adjustment to convert centimetres to inches, in which the measurements of this series were made, was also undertaken. The resulting equation did not give a sufficiently wide discrimination between patients of different physique, so that the original regression equation was multiplied 15 times to increase its standard deviation accordingly. From this a further equation

was obtained which proved satisfactory; an arbitrary figure of 100 was added to each index-figure in order to obviate negative numbers.

The final equation was:-

$$\begin{aligned} \text{B.I. (F)} &= 3.59 \text{ stature} + 3.77 \text{ symphysis ht.} - \\ & 1.91 \text{ chest circumf.} - 3.73 \text{ hip circumf.} \\ & - 159.39 \text{ (measurements in inches)} \end{aligned}$$

The index ranged between 19 and 151; the distribution is shown in Table 1.

TABLE 1

Distribution of Body-Index (female)

Body Index	0-20	21-40	41-60	61-80	81-100	101-120	121-140	141-160
Number	1	1	4	9	18	12	3	2

n = 50

This is a normal distribution with a slight positive skew, and provides no evidence to suggest that an undue proportion of patients of a particular physique have been included in the series.

The indices were then correlated with the symptom-scores at one and three months respectively, the results being:-

	Symptom-score 1 month	Symptom-score 3 months
Body-index (F): r =	+0.617	+0.767

Both significant at the 0.001% level)

These are surprisingly high correlations, and on a small series of patients must be treated with reserve. The inference is clear however, that depressed patients with a lower body-index, i.e. those tending towards a more pyknic type of physique, have a better outcome with electroshock than those of more leptosomatic habitus, and the trend is enhanced three months after treatment.

Rees (1950), in his series of 400 female neurotic patients, also found an association between leptomorphy and the depthymic personality traits and symptoms of anxiety and depression; there was also a higher incidence of autonomic dysfunction in this group.

3) CLINICAL FEATURES AND ASSESSMENTS

Clinical Item Scores

In addition to the three clinical assessments on the rating-scale for depression, a scoring method devised by Hobson (1953), based on the presence or absence of various clinical items, was also used. These items had been found to be significantly associated with the immediate outcome with electroshock.

For each of the following allegedly favourable clinical features, a score of 1 was given if it was absent:

Sudden onset.

Good insight.

Obsessional traits in the previous personality.

Self-reproach (here taken as a score of 2 or more on the 'guilt' rating).

Duration of illness of less than a year.

Pronounced retardation (taken as a score of more than 2 on the rating-scale).

For each of the following allegedly unfavourable features, a score of 1 was given if it was present:

Mild or moderate hypochondriasis (taken as a rating of less than 3)

Depersonalization.

Emotional lability.

Neurotic traits in childhood.

Neurotic traits in adult life.

Hysterical attitude towards symptoms.

Intelligence above average.

Fluctuating course since onset.

Ill-adjusted or hysterical previous personality.

Thus for each patient a clinical item score was made, furnishing a simple numerical assessment which could be compared with outcome: a high rating denoted a presumably poorer prognosis than a low one.

Ratings by this method ranged from 0 - 12;

their distribution and the mean symptom-scores at 1 and 3 months after treatment for each rating are shown in Table 2.

TABLE 2

Scoring on Clinical Items (Hobson) and
Mean Symptom-Scores after Treatment.

Clinical Item Score	0	1	2	3	4	5	6	7	8	9	10	11	12
No. with each Rating	1	4	7	4	3	10	3	3	7	4	2	1	1
Mean Symptom Score at 1 month	1.0	2.75	3.3	1.2	4.6	5.3	7.3	6.0	8.0	9.2	13.0	13.0	10.0
Mean Symptom Score at 3 months	1.0	4.75	2.8	1.3	5.2	5.9	4.6	11.3	9.1	13.0	11.5	12.0	18.0

n = 50

The distribution is an uneven one, but this is not necessarily of much significance in a comparatively small series of 50 patients.

The mean symptom-score at one month after E.C.T. show a remarkably consistent rise (apart from 3 minor exceptions) *pari passu* with the clinical item score, and this is reflected in a correlation of + 0.727 between them (significant at the 0.001% level for 48 degrees of freedom).

A symptom-score at one month of less than 5 points may be regarded as an indication of a 'good' result of treatment, and a score of over 6 as 'moderately good' to 'poor'.

Table 2 shows the distribution of cases with these symptom-scores in relation to the item-scores.

TABLE 3

Scoring of Clinical Items (Hobson)
and Degree of Recovery

Clinical Item Score (Hobson)	0	1	2	3	4	5	6	7	8	9	10	11	12
No. of pts. with Symptom-Score (1 mth.) 0-5	1	5	5	4	2	6	1	2	2	0	0	0	0
Ditto. 6+	0	0	1	0	1	4	2	1	5	4	2	1	1

n = 50

From this table, an item-score of 5.5 points may be taken as an index of a good degree of recovery with treatment. Using this criterion, 11 cases are seen to be misclassified, or 22% of the total. This is in close accord with Hobson's own figure of 21% of his total of 127 patients who were similarly misclassified.

The close association between the clinical item scoring of Hobson and the symptom score is less marked at three months after treatment, (Table 1), the correlation being +0.666 (significant at the 0.001% level).

The relationship between the various clinical assessments which were made, i.e. the rating-scale assessments before treatment, at one and three months after E.C.T., and the scores on clinical items (Hobson) are demonstrated in Table 4.

TABLE 4

Correlations between Clinical Assessments

	Clinical Item Score (Hobson)	Initial Symptom Score	1 month Symptom Score	3 month Symptom Score
Clinical Item Score (Hobson)	1.0	+.498	+.727	+.666
Initial Symptom Score	+.498	1.0	+.353	+.318
1 month Symptom Score	+.727	+.353	1.0	+.582
3 month Symptom Score	+.666	+.318	+.582	1.0

Initial Assessment and Improvement

The initial symptom-scores before treatment show a closely similar negative correlation between the re-assessments at one and three months after electroshock: $r = +.353$ and $+318$ respectively (significant at the 2% and 5% levels respectively).

There is therefore a clear tendency for those patients with high symptom-scores initially to respond rather better to treatment, and vice versa; this is the more so at one month afterwards than at three months. Two explanations for these findings are possible. Either the difference is a quantitative one, as Garmany and others believe, and the more severe depressives respond better to E.C.T. than milder ones, or there is a qualitative difference, with a variety or group of varieties of depression which are characterized by a higher initial symptom-score and a good response to electroshock and a variety showing the reverse features.

Examination of the relationship between initial assessments and the clinical item score of Hobson gives a correlation of $+498$ (significant at the 0.001% level). Thus there is an even clearer tendency for the higher initial symptom-scores to

be accompanied by low clinical-item ratings and vice versa. To obtain a high score on the clinical item assessment a fairly large number of neurotic features must be present: Hobson has commented on the high proportion of neurotic traits in his series. If the differences noted above were due merely to different degrees of intensity of depression, it seems unlikely that marked neurotic traits should be so much commoner in the less severely depressed. The evidence here suggests, although it by no means proves, that there may well be a qualitative difference, and that there is a variety of depression, characterized by lower initial symptom-scores for depression on the rating-scale, a higher incidence of neurotic features and thus a higher clinical-item score (Hobson), and a tendency to do less well with E.C.T. Similarly there is a variety, or group, in which the opposite features are found.

These clearly correspond to "neurotic" or "reactive", and "psychotic" or "endogenous" depressions. (The terms "reactive" and "endogenous" to imply mutual exclusion and specificity are misleading, as a psychotic depression may be "reactive" in some senses, and endogenous constitutional predisposition is present in many depressions regarded as "non-endogenous"). The

50 case-histories and clinical records were carefully scrutinized, and the diagnosis of 'psychotic' or 'neurotic' depression made on the criteria laid down by Mayer-Gross (1954). Some difficulties were experienced in a number of cases, most of which could be satisfactorily resolved after discussion with experienced colleagues, and by taking into account the predominating clinical features. Three cases remained where no clear-cut diagnostic differentiation could be made. The 'psychotic' group contained 20 patients and the 'neurotic' group 27. The number in each diagnostic category was then compared with the clinical-item score of Hobson (Table 5).

TABLE 5

Diagnostic Groups and Clinical Item Scores

Clinical Item Score (Hobson)	0	1	2	3	4	5	6	7	8	9	10	11	12
'Psychotic'	1	4	7	2	2	4	0	0	0	0	0	0	0
'Neurotic'	0	0	0	1	1	5	2	3	7	4	2	1	1
Unclassified	0	0	0	1	0	1	1	0	0	0	0	0	0
Totals	1	4	7	4	3	10	3	3	7	4	2	1	1

n = 50

This shows clearly a differentiation into two groups, with a fairly small degree of overlap.

Conclusions

It may be concluded that the clinical item scoring method derived by Hobson is a reasonably reliable method of predicting short-term outcome with electroshock in depressive states generally: a high score appears to reflect marked neurotic traits, and the higher scores (5 and above) tend markedly to cluster in relation to the diagnostic category of 'neurotic' depression. There are, of course, many possible sources of error in the present investigation, but the evidence presented in Tables 2 to 5 is sufficiently striking as to suggest a practical clinical value.

It is not suggested that prognosis can be reduced to a few simple figures, however, and the individual variations and general complexity of the problem are obvious. Nevertheless it is felt that Hobson's claim for his investigation is justified - that the results "can be of practical assistance in the formulation, treatment, and prognosis by indicating the significance of certain features".

Post-treatment Symptom Scores.

These have been chiefly utilized as a convenient yardstick for comparing other clinical information (v. infra). The assessments at one

month show a higher correlation than those at three months with all the items where the association has been investigated, although this difference is of very small degree in some.

The two symptom-scores themselves show a correlation of $+0.582$ (significant at the 0.001% level), showing a general tendency for improvement to be maintained at the three month interval.

Hysterectomy

Of the 50 patients, 11 (22%) had had this operation, all except 2 in the 3 years preceding their depressive illness. Although this seems a high proportion, it must be remembered that all the women were between 41 - 60 years, the age-range in which hysterectomy is most frequently performed; it is not known what proportion of non-depressed women of this age have also had the operation.

No significant differences in mean symptom-scores at 1 and 3 months after treatment, or in diagnostic category, were found between the women who had had a hysterectomy and those who had not.

Number of E.C.T.

The average number of treatments given to each patient was between 7 and 8. No significant differences were observed in the mean symptom-

scores of those requiring more or less than this number.

4) Ps SCALE (FELDMAN)

The difficulties attending the use of this test have already been commented upon, and 9 patients did not complete it for various reasons. Of the 41 patients who sorted all the cards, the results were of doubtful value in 11 because of the high number of "don't know" responses which could not be scored.

The scores obtained from the 41 subjects were correlated with the symptom scores at one and three months after treatment, with the following result:

	1 month rating	3 month rating
Ps score	+.236	+.225

In neither case is r significant at even the 10% level, and it is concluded that as far as the present series of patients is concerned, the test is of no practical prognostic value in the treatment of depressive states by electroshock.

5) THE SEDATION THRESHOLD.

The distribution of the sedation threshold to sodium amytal, assessed in the majority of cases

by the onset of slurring of speech, was as follows:

TABLE 6

Distribution of Sedation Thresholds

Threshold (mgm./Kilo)	2.5- 3.4	3.5- 4.4	4.5- 5.4	5.5- 6.4	6.5- 7.4	7.5- 8.4	8.5- 9.4
No. of Pts. (Total=50)	6	7	11	12	8	5	1

This table shows a continuous distribution without any clear tendency to clustering which would suggest two or more separate groupings for the threshold.

The association between the threshold and the various symptom and clinical item scores is shown in Table 7.

TABLE 7

Correlations between Sedation Threshold
and Symptom and Item Scores

	Sedation Threshold	Symptom Score 1 month	Symptom Score 3 months	Clinical Item Score
Sedation Threshold (mgm./k)	1.0	+.491	+.424	+.556
Symptom Score at 1 month	+.491	1.0	+.582	+.727
Symptom Score at 3 months	+.424	+.582	1.0	+.666
Clinical Item Score (Hobson)	+.556	+.727	+.666	1.0

There is a fairly well-marked relationship between the threshold and the symptom-scores at one and three months ($r = +.491$ and $+.424$, respectively, both significant at the 0.001% levels): there is the usual falling off at three months in the strength of the association, although in this case the difference is slight. This tendency for a higher threshold to accompany a higher symptom-score after treatment is in line with the findings of Shagass, although the trend is not as clear as his work has suggested, and the reasons for the agreement may not be the same. Shagass has claimed that a higher threshold over the critical value of about 4 mgm./Kilo will differentiate 'neurotic' and 'psychotic' depression with 95% accuracy: the higher clinical-item scores, which have been shown to contain more neurotic traits, should thus be expected to show a fairly high positive correlation with the sedation-threshold if Shagass's theories are correct.

In the present series, the reverse is true, and there is a highly significant negative correlation between the two ($r = -.556$, significant at the 0.001% level). There is thus a tendency for the higher sedation thresholds to be associated with lower clinical item scores. The reason for this is not clear, and it is certainly not in

keeping with expectation based upon Shagass's findings.

Comparison of sedation thresholds with diagnostic category gives the following information:

"Neurotic" depressions	= 27 cases.
Mean sedation threshold	= <u>5.4</u> mgm./kilo.
"Psychotic" depressions	= 20 cases.
Mean sedation threshold	= <u>5.1</u> mgm/kilo
"Unclassified" depressions	= 3 cases
Mean sedation threshold	= <u>6.0</u> mgm/kilo

There is obviously no significant difference between the mean thresholds for the two main groups, and a 't' test is unnecessary. The numbers in the third group are too small for valid conclusions to be drawn.

These results again do not confirm the reports by Shagass and his colleagues on the diagnostic, and thereby prognostic, aspects of this test in depression. They are very similar to the findings of Ackner and Pampiglione, who were also unable to confirm the work from Montreal.

It is appreciated that the present method used for determining the sedation threshold based on speech changes alone is open to criticism, and that another observer might have differed con-

siderably in the estimations. Nevertheless the original E.E.G. technique was given a fair trial also, and found to be unsatisfactory. It is concluded that even if the concept of the threshold is a valid one, serious doubts exist as to its practical value both as a diagnostic and prognostic aid in depressive states.

6) THE METHACHOLINE RESPONSE

Method 1.

Initially the raw data were plotted on graph-paper and sorted into three main groups; the height of the "basal B.P." was not considered here. (Figure 1).

Group I: characterized by initial B.P. fall and subsequent marked secondary rise.

'Increased central sympathetic reactivity' (Gellhorn).

Group II: initial fall and re-establishment of homeostasis within 25 minutes. Normal central sympathetic reactivity (Gellhorn). 26 responses were of this type.

Group III initial fall (often marked) and failure to return to 'basal level' within 25 minutes. 'Decreased central sympathetic reactivity' (Gellhorn). 26 responses were of this type.

The accompanying table shows the mean symptom scores at one and three months respectively for each group.

TABLE 8

Methacholine Response Groupings and Mean Symptom-Score at 1 and 3 months

Methacholine Response	Mean Symptom-Score at 1 month	Mean Symptom-Score at 3 months
Group I (4)	5.5	8.7
Group II (26)	6.1	7.2
Group III (20)	5.4	5.5

As far as the symptom-scores at the one month interval are concerned, the means of the three groups show no significant differences.

At the three month interval, there is some tendency for those in Group I (after-rise of B.P.) and Group II (homeostasis within 25 minutes) to have worsened slightly. This is more marked in Group I, but as the present series only contained 4 patients of this category no valid conclusion is possible. The mean symptom-scores for Group III patients remained similar throughout, and the difference between the means for Groups II and III is not significant (F ratio 1:19.)

Funkenstein treated cases with a resting B.P. of over 140 m.m. separately: those in whom

homeostasis was re-attained within the observation period were reported to have a worse response to treatment than those in whom the drug-induced hypotension persisted.

The present series of 50 patients included 13 in whom the basal B.P. was over 140 m.m. These were sub-divided into two further groups on the criterion of return to basal levels: Group A where homeostasis was reached within 25 minutes, and Group B, where hypotension persisted.

Group A - 4 cases. Mean symptom-score at one month = 7.1 points

Group B - 9 cases. Mean symptom-score at one month = 6.0 points.

Although there is a slight tendency for the Group A patients to respond less well to electro-shock, the trend is very small and not significant in view of the small numbers involved.

Maximum B.P. Fall

This was next examined in relation to outcome. The maximum fall was calculated from the 'basal' reading to the lowest reading noted at any time during the test (usually within the first $2\frac{1}{2}$ minutes).

Correlation (r) between maximum fall and one month symptom-score = +.572. (This is significant (d.f. = 48) at the 0.001% level).

This is a moderately high degree of association and tends to confirm Funkenstein's finding that a marked drop of B.P. to methacholine is a favourable prognostic sign. In view of other factors found to be related to the fall in pressure, notably age and basal pressure (v. infra) this finding is almost certainly not merely a reflection of the action of methacholine alone.

Time of Homeostasis.

This was assessed from the graphs, and was taken as the time in minutes for the B.P. to return to the basal level, or within 4 m.m. of it, after the initial fall, and remaining there for three consecutive minutes. Four patients (Group I) showing a pronounced secondary rise were excluded from consideration.

Correlation (r) between time of homeostasis and 1 month symptom-score (46 cases) = +.358.

(This is significant at the 2% level).

This denotes a trend for those patients in whom basal pressures are quickly re-attained to do less well, but it is not sufficiently well marked to be of practical prognostic use.

Diagnostic Categories.

A comparison of the methacholine response

groups and clinical diagnostic category is made in Table 9.

TABLE 9

Methacholine Response and
Clinical Diagnostic Groups.

Methacholine Responses	'Neurotic'	'Psychotic'	Unclassified
Group I	3	1	0
Group II	13	10	1
Group III	11	9	2
Totals (n=50)	27	20	3

No clear relationship appears to exist as far as the present series of depressed patients is concerned.

Conclusions

The results of this method of assessing methacholine responses in the present series of patients lend no clear confirmatory support to the claim made as to the prognostic value of the test.

Method 2.

In this method of assessing the methacholine responses, the best-fitting straight line to express each graph was drawn in after the appropriate regression equations had been calculated.

The graphs were then re-sorted into three groups corresponding to the ones described under Method 1; the mean symptom-scores for each group were then calculated. The point at which the best-fitting line intersected the basal B.P. axis was taken as the criterion for assessing the time of homeostasis. Instead of the maximum fall, the drop in B.P. where the regression line intersected the axis of the fourth half-minute (y_4) line was used. This was found in fact to differ very little from the maximum observed fall in the majority of cases ($r = +.965$).

Little difference in the sorting of the graphs was observed with this method, and the mean-symptom scores at one month are shown in the accompanying table.

TABLE 10

Methacholine Groups (Regression Line)
and Mean Symptom-Score at One Month.

Methacholine Response	Mean Symptom-Score 1 month
Group I (4)	5.5
Group II (25)	6.1
Group III (21)	5.5

This table is practically identical with the corresponding portions of Table 8, the use of the regression line resulting in a re-classification of only one case.

The B.P. drop at y4 (i.e. at two minutes after the beginning of the test) and the symptom-score at one month gave the correlation:

$$r = +.667 \text{ (significant at the 0.001\% level)}$$

This is clearly better than the association when the observed maximum fall was used ($r = +.572$), but the same reservations apply regarding the influence of age and the basal B.P. levels. As far as this method of assessing the results is concerned, no real advantage is to be gained from the use of the best fitting straight V line.

Method 3

By this method variables obtained from the use of the regression lines were correlated with one another and the factors of age, basal B.P. and symptom-score at one month, as shown in Table 11.

TABLE 11

Methacholine Response Variables (Regression line)
Outcome and Intercorrelations

	Age	Basal B.P.	Fall y4	Slope	Symptom-Score 1 mth.
Age	1.0	+.517*	+.488*	+.393	+.298
Basal B.P.	+.517*	1.0	+.700*	+.413	+.168
Fall (y4)	+.488*	+.700*	1.0	+.625*	+.667*
Slope	+.393	+.413	+.625*	1.0	+.165
Symptom score 1 month	+.298	+.168	+.667*	+.165	1.0

* Significant at the 0.001% level.

Fall in B.P.

This, measured at the 4th half-minute, is seen to correlate fairly highly with age ($r = .488$), and even more highly with the level of the 'basal' B.P. ($r = 0.700$).

The association with symptom-score at one month ($r = +.667$) is also clear, and whilst suggesting a general tendency for patients who show a bigger drop in pressure to have a lower symptom-score, i.e. to have a better immediate outcome, the higher falls are also partly accounted for by increasing age and higher basal pressures, especially the latter.

Slope of Regression Line

This reflects the speed with which homeostasis is re-attained, a steep slope representing a rapid return to basal pressure and vice versa. In view of the prognostic claims made partly in respect of this time factor, it is disappointing to find such a small negative correlation between slope and symptom score ($r = -.165$, not significant). Slope and fall of B.P. are moderately highly correlated, however, ($r = 0.625$, significant at the 0.001% level).

General Conclusions

The only variables of the methacholine

response which show a sufficiently high association with outcome to be of potential prognostic aid are the basal B.P. and fall in pressure (whether this is the maximum observed drop, or that calculated at two minutes from the regression line). Both are also closely related to each other, and to a lesser extent, to the patient's age.

An incidental clinical observation of interest was that in all four cases of Group I (after-rise to methacholine) a tendency to develop marked post-E.C.T. anxiety was observed, which in 2 cases took several weeks to subside. This total is a small one, but the observation, if confirmed, would have practical clinical application.

7) METHEDRINE RESPONSE

These were recorded as 'N' or 'I' response, depending on whether the patient felt either more normal or her symptoms were intensified. Two other cases were excluded from general consideration as their responses were clearly atypical: because of the smallness of this particular sample, it was not felt that any valid conclusions could be drawn from their separate consideration.

The mean initial symptom-scores for the two main groups, together with the mean symptom-scores

at one and three months respectively, are shown in the accompanying table.

TABLE 12

Methedrine Responses and Mean Symptom-Scores

	Initial Symptom Score	Mean Symptom Score 1 month	Mean Symptom Score 3 months
'N' Response (31)	22.2	6.9	7.4
'I' Response (17)	31.5	6.6	3.9

n = 48.

At one month there is no meaningful difference in symptom-score between the two groups, but the 'N' response group has a considerably higher symptom-score at three months after treatment i.e. are less well after that interval. This difference is statistically significant at the 1% level (F ratio = 7:19).

The relationship of the methedrine responses to clinical diagnostic categories are indicated in Table 13. (overleaf)

This indicates a striking difference in response to methedrine between diagnostic categories, hardly to be expected if the difference between clinical varieties of depression was purely one of degree.

TABLE 13

Methedrine Responses and Diagnostic Category

Diagnostic Category	'Neurotic'	'Psychotic'	Unclassified	Totals
'N' response	25	3	3	31
'I' response	1	16	0	17
Atypical	2	0	0	2
Totals	28	19	3	50

Conclusion

The response to intravenous methedrine in the present series appears to have more application as a diagnostic help in some cases rather than as an aid to prognosis.

SUMMARY

- 1) The importance and historical development of the search for reliable prognostic guides for the electroshock treatment of depressive states is indicated.
- 2) A review of the literature since 1938 on this theme is given: in it are included prognostic items from the clinical history and examination, as well as specific psychological, physiological and pharmacological indices of alleged value for prediction. A brief examination of relevant similar work before the introduction of E.C.T. is added for comparison, and throughout points of agreement and disagreement are noted and the practical value of the various findings assessed.
- 3) It is concluded that important defects of methodology are present in much of the earlier, and some of the later, published work. There is particular disagreement on the question of clinical classification and the nosology of depressive illnesses which have a bearing on prognosis.
- 4) The aims and outline of the present investigation into specific prognostic factors are given, and the points requiring particular

attention which emerged from a study of the literature are noted.

- 5) The design of the experiment, the criteria for selection of patients, and the clinical assessments made are described in detail, together with a note on the use of a^a rating-scale for depressive symptoms.
- 6) The application of individual psychological, physiological and pharmacological tests, with their evaluation and assessment, is described.
- 7) 50 female patients aged 40 - 60 years and suffering from depressive illnesses were investigated; difficulties encountered are discussed, and details of the subsequent electroshock treatment and follow-up are given.
- 8) The association between the alleged prognostic factors investigated and the outcome assessed at 1 and 3 months after treatment is examined statistically; the findings are described, their meaning considered and their relation to previous studies discussed.

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APPENDICES

APPENDIX A.

INFORMATION SUMMARY, 50 PATIENTS

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	49	+	+	+	1	0	36	2	0	98	14	N	III	6.0	N	8	26	9	5
2	49	+	+	++	1	0	24	2	0	97	-	N	III	5.5	N	6	21	5	6
3	40	+	+	0	1	0	24	1	0	114	12	N	II	6.5	N	9	23	10	11
4	57	+	+	0	1	0	12	1	0	116	-	N	III	5.0	N	8	20	8	8
5	52	+	+	0	1	0	24	1	+	44	31	-	III	3.0	N	9	25	10	19
6	47	+	+	++	0	1	3	2	0	105	21	I	III	5.0	P	5	37	9	5
7	48	0	0	+	0	1	12	1	0	103	24	I	II	6.0	P	2	27	4	4
8	58	0	0	0	0	1	2	1	+	76	17	I	II	6.5	P	1	30	1	3
9	59	0	0	+	0	1	6	1	0	128	9	N	II	7.0	P	1	30	5	3
10	48	+	+	+	0	1	9	1	+	85	30	I	II	7.5	P	5	31	6	2
11	41	+	+	++	1	0	15	2	0	95	17	N	III	7.0	N	7	25	4	13
12	53	0	0	0	0	1	3	1	0	72	16	I	I	2.5	P	2	25	2	5
13	57	+	+	++	0	1	1	1	0	87	18	I	II	4.5	P	4	45	2	11
14	44	+	+	0	1	0	36	0	+	105	26	-	II	3.0	N	12	20	10	18
15	48	0	0	0	0	0	2	1	0	69	17	N	III	5.5	N	3	18	2	0
16	58	+	+	0	0	1	2	1	0	59	-	N	II	4.5	P	5	20	5	5
17	60	+	+	0	0	1	5	1	0	19	-	I	III	3.5	P	5	36	3	1
18	53	0	0	+	0	1	7	1	0	112	16	I	III	8.0	P	1	31	4	2
19	58	+	+	+	0	0	40	1	0	127	21	N	II	6.5	N	7	18	3	9
20	43	0	0	0	0	1	1	1	0	138	-	N	III	8.5	?	3	33	1	1
21	51	0	0	0	1	0	10	0	+	86	13	N	II	5.0	?	6	23	11	2
22	56	0	0	+	0	1	5	1	0	86	12	I	III	5.5	P	2	40	4	2
23	49	+	+	0	1	0	20	1	0	100	16	N	II	5.5	N	10	21	13	11
24	47	0	0	0	1	0	24	1	0	86	26	N	III	3.5	N	5	18	5	5
25	41	+	+	0	1	0	12	0	0	115	26	N	III	6.0	N	11	20	13	12
26	48	+	+	+	0	0	30	1	0	106	30	N	II	8.0	N	8	23	9	15

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
27	59	+	+	0	0	1	12	1	0	79	36	I	II	3.0	P	4	24	2	10
28	59	0	0	0	1	0	30	1	0	60	17	N	III	4.5	?	5	20	1	1
29	60	0	0	0	0	1	2	1	0	87	10	I	III	3.0	P	1	24	1	11
30	52	+	+	0	1	0	20	0	+	103	-	N	I	6.0	N	9	22	6	10
31	60	0	0	+	1	1	8	1	+	113	8	I	II	6.5	P	2	39	0	0
32	49	0	0	+	0	1	1	1	0	151	11	N	III	5.5	P	0	25	1	1
33	51	+	+	+	1	0	12	1	0	101	26	N	III	2.5	N	8	21	15	14
34	49	+	+	0	1	0	20	0	+	60	24	N	II	3.5	N	8	20	7	6
35	44	0	0	0	1	0	3	1	0	94	25	N	III	5.5	N	4	21	10	0
36	49	0	0	0	1	0	12	1	0	63	12	N	II	4.0	N	5	22	4	9
37	53	0	0	0	0	1	3	1	0	75	-	I	III	3.5	P	2	32	3	0
38	47	+	+	0	0	1	1	0	0	27	-	N	III	5.0	N	6	22	6	6
39	47	0	0	+	1	0	6	2	0	90	7	N	I	8.0	N	5	24	10	14
40	55	0	0	+	0	1	4	1	+	88	23	I	II	5.0	P	2	25	4	1
41	43	+	+	0	1	0	36	1	0	100	23	N	II	4.0	N	9	23	11	12
42	58	0	0	0	1	0	15	1	0	96	-	N	II	8.0	N	10	21	13	12
43	42	+	+	0	1	0	8	2	+	90	25	N	II	5.0	N	8	21	4	2
44	48	0	0	0	0	1	3	1	0	116	10	I	II	6.5	P	3	28	1	1
45	48	0	0	0	1	1	7	1	0	97	10	I	III	3.5	P	3	31	1	2
46	55	0	0	0	0	1	3	1	0	79	7	I	III	5.5	P	2	31	6	6
47	55	0	0	+	1	0	7	1	0	107	13	N	II	7.0	N	5	22	6	11
48	53	+	+	++	1	0	40	1	+	64	21	N	II	5.0	N	8	22	4	7
49	60	+	+	0	1	0	15	1	0	62	10	N	II	6.0	N	7	24	11	12
50	46	0	0	0	1	0	24	1	0	87	16	N	I	4.5	N	5	18	4	6

Totals

2556

4547 736

265.5

266
1268

289 332

KEY

Column

- 1 = Series no. of patient.
- 2 = Age in years.
- 3 = Neurotic traits, childhood (0 or +)
- 4 = Neurotic traits, adult (0 or +)
- 5 = Obsessional traits (0, + ++)
- 6 = Onset (sudden 0, gradual 1)
- 7 = Course (fluctuating 0, progressive 1)
- 8 = Duration in months
- 9 = I.Q. (below 0, average 1, above 2)
- 10 = Hysterectomy (0 or +)
- 11 = Body Index
- 12 = Ps scale score
- 13 = Methedrine Response (N or I)
- 14 = Methacholine Response Group
- 15 = Sedation threshold (mgm./Kilo)
- 16 = Diagnostic Group (Neurotic N, Psychotic P)
- 17 = Clinical Item Score (Hobson)
- 18 = Initial symptom score
- 19 = 1 month symptom score
- 20 = 3 months symptom score

Retardation Slowness of thought, speech and
 activity
 Stupor

Agitation Purposeless motor activity
 associated with anxiety

Depersonalization & Derealization

 Nihilistic ideas
 Perplexity

Paranoid Symptoms

 Suspicious (Not with a
 Ideas of reference / depressive
 Delusions of reference / colouring)
 and persecution

Obsessional Symptoms

 Obsessive thoughts and compulsions

Anxiety

Psychic symptoms, worrying, fears
 tension, etc.

Somatic symptoms, G.I., C.V., G.U.,
 resp., etc.

Somatic Symptoms of depressive type

 Anorexia
 Indigestion and abdominal pains
 Constipation
 Backache
 Heavy limbs
 Pressure in head or chest

Fatiguability

Menstrual disturbance

Loss of libido

Hypochondriasis

Self-absorption (bodily)

Pre-occupation with health

Querulous attitude

Hypochondriacal delusions

Loss Of Weight

Loss of Insight

APPENDIX B
RATING SCALE

Name

Series No.

0 Absent
1 Mild or trivial
2 & 3 Moderate
4 Severe

0 Absent
1 Slight, doubtful
2 Clearly present

Item No.	Score Range	Symptom	Initial	One Month	Three Months
1	0 - 4	Depressive Mood			
2	0 - 4	" Guilt			
3	0 - 4	" Suicide			
4	0 - 2	(Early			
5	0 - 2	Insomnia (Middle			
6	0 - 2	(Late			
7	0 - 2	Diurnal variation			
8	0 - 4	Work & Activities			
9	0 - 4	Retardation			
10	0 - 2	Agitation			
11	0 - 4	Anxiety (Psychic			
12	0 - 4	" (Somatic			
13	0 - 4	Depersonalization etc.			
14	0 - 4	Paranoid symptoms			
15	0 - 2	Obsessional symptoms			
16	0 - 4	Hypochondriasis			
17	0 - 2	Somatic symptoms			
18	0 - 4	Loss of weight			
19	2 - 0	Insight			

APPENDIX B

PRO FORMA

PROGNOSIS IN DEPRESSIVE STATES

Name: _____ Series No.: _____
Age: _____ Date of 1st interview: _____ Place: _____
Family History 0. +. Previous depression 0 +
Neurotic Traits in childhood 0 + in adult life 0 +
Previous Personality: _____

Onset: sudden 0. gradual 1
Physical precipitations: 0 +
Psychological precipitation: 0 +
Course: fluctuating 0 progressive 1
Duration: _____ months
Intelligence: below 0 average 1 above 2

Weight = _____ st. _____ lbs. = Kilos.
Body Index:
Stature _____ symp. ht. _____ Chest circumf. _____ Hip circumf. _____
Index = _____
Ps Scale Score - _____
Methacholine Response _____
Methedrine response - N I 'Basal B.P.' _____
Sedation Threshold - _____
Diagnostic Category _____
Additional Comments
(e.g. Hysterectomy, 0 +)

APPENDIX C

DEFINITIONS OF TERMS EMPLOYED

Neurotic traits in childhood: recorded as positive where 3 or more of the following traits were present, or one present in severe degree:- night terrors, nightmares, sleep-walking, enuresis, excessive timidity, nail-biting, stammering, severe or frequent tantrums.

Neurotic traits in adult life: the presence of abnormal psychological reactions, not requiring treatment and not part of definite psychiatric illness. A marked degree of any of the following, or the presence of several of lesser severity, led to inclusion under this heading:- clear anxiety, out of proportion to stresses encountered, specific fears and phobias, excessive timidity, frequent nightmares, hypochondriacal worries.

Ill-adjusted personality: the person unable to maintain satisfactory social or occupational relationships because of emotional factors, leading to frequent job-changes, marriage-failures, etc.

Hysterical previous personality: those showing excessive emotional responses

to situations, often with a wish-fulfilling or pain-avoiding motivation leading to behaviour designed to manipulate the environment to their own advantage. Usually persons showing superficial relationships with others, immature and histrionic in emotional reactions and innately egocentric.

Obsessional personality traits: marked as positive when several of the following features were present, or a few in marked degree: meticulous perfectionism & conscientiousness, excessive orderliness & tidiness, rigidity of behaviour patterns and emotional responses, obstinacy or marked submission, tendency to indecision and doubts, general dependence on an ordered routine.

Sudden onset: a rapid deterioration to the condition when first seen within the space of 8 weeks.

Insight: defined as a patient's capacity to appreciate the fact that she is ill, the nature of the illness and to be classed as 'good' must include some understanding of the more obvious causative factors operating.

Emotional Lability: rapid mood-changes within the space of a few hours.

Self-reproach: unwarranted tendency to blame oneself, particularly in a moral sense or with regard to capabilities and personality assets.

Retardation: slowing up of mental activity, manifested as difficulty in thinking, in initiating and in executing motor actions.

Depersonalization: including feelings of unreality. Defined as a feeling of subjective or environmental change in a patient's personal relationship with the outside world compared with the normal state.

Hypochondriasis: preoccupation, with bodily function in the absence of disease in its milder forms: more severe forms showed some belief in the existence of physical illness up to the settled conviction of gross disease, usually of an incurable or unpleasant nature (e.g. V.D., cancer).

Hysterical attitude to symptoms: usually seen in the hysterical personality: excessive emotional response to symptoms, which may be used in a manipulative fashion to dominate the environment.