SLEEP THRESHOLDS IN DEPRESSION

By

IRENE MARTIN

and

BRIAN M. DAVIES

INTRODUCTION

THERE are conflicting psychiatric opinions about the value of separating depressive illnesses into several syndromes on clinical grounds, and so far experimental attempts to reach a classification of depression by distinguishing physiological or biochemical features which characterize one group rather than another have had only limited success. One interesting series of experiments in this area has been that of Shagass and his colleagues on the sedation threshold (Shagass *et al.*, 1956, Shagass and Naiman, 1956, Shagass, 1954); they report that neurotic and psychotic depressions can be differentiated by means of EEG and other reactions to sodium amytal (amylobarbitone sodium) neurotics requiring greater amounts of the drug to reach the sedation threshold.

These and allied data have been handled by means of the hypothesis that depression is a central inhibitory process, and that the degree of inhibition is much greater in psychotic than in neurotic depressives (Shagass *et al.*, 1956). On the assumption that the sedation threshold is one way of measuring certain excitability characteristics of the central nervous system (C.N.S.) Shagass' results to date only partially support the hypothesis.

Although Shagass' view seems to imply that "excitation" and conversely "inhibition" are gross unitary factors, there are of course many ways of assessing C.N.S. excitability in the sense of measuring different *aspects* of C.N.S. activity. It seems equally likely that such measures as autonomic and skeletal muscle activity also relate to C.N.S. "excitability", and, incidentally, to clinical assessments of anxiety and tension. So far there have been relatively few studies which specifically investigate autonomic activity in depressed patients, although certain positive findings in this area have been reported (Busfield and Wechsler, 1961; Davies and Gurland, 1961). The significant changes in blood pressure responses to methacholine with changes in the mental state reported by Funkenstein *et al.*, 1951, have not been confirmed by other reports (Davies, 1960). It seemed of interest, therefore, to obtain recordings of autonomic activity from our subjects to observe whether there were different levels of activity between clinical groups and what kinds of changes might occur under sodium amytal. This drug undoubtedly has a selective effect upon specific levels within the C.N.S. such as the cortex and the reticular system, both of which have connections with peripheral autonomic activity.

In our study, then, we attempted first to reproduce Shagass' findings as a whole by using his technique of administering sodium amytal to depressed patients to obtain their sleep thresholds. At the same time we obtained several autonomic and skeletal muscle recordings, as well as a number of ratings and questionnaire scores which could be correlated with the sleep threshold measures.

Some of the patients were studied throughout the course of their illness.

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first when they were severely depressed and later after treatment, when they were symptom free. The autonomic and test-retest data will be reported in two subsequent papers; the present paper will deal with the relationship of the sodium amytal sleep threshold to diagnosis, clinical ratings, and scores on personality questionnaires.

It has been claimed that patients with depressive illness can be differentiated by the amounts of intravenous sodium amytal required to reach certain physiological and behavioural endpoints. One such endpoint is the sedation threshold (Shagass *et al.*, 1956) which is determined by assessing EEG changes and slurring of speech; another is the sleep threshold (Shagass and Kerenyi, 1958), defined as the point when the subject no longer responds to verbal stimulation. The amount of sodium amytal necessary to reach these criteria is calculated in terms of mg./kg. body weight, and on this basis "neurotic depressives" had higher thresholds (i.e., required greater amounts of the drug) than "psychotic depressives".

Both types of threshold—sedation and sleep—correlate together significantly, though not perfectly, and since sleep thresholds require no elaborate EEG facilities it was proposed by Shagass and Kerenyi that they might prove a simple and effective means of classifying cases of depression. The present study was carried out to check this hypothesis.

Shagass' techniques and findings have aroused widespread interest, both from the practical implications of sedating patients and relating such data to different therapies, and from various theoretical views which link drug tolerance with personality, "inhibition", or other concepts. Unfortunately, the attempts made by several investigators to confirm Shagass' findings have not met with any great success, and the reasons why this is so are fairly clear. In this kind of experimental procedure there are a number of methodological problems, two major ones being the classification of subjects and the establishment of objective and reliable sedation end-points. It is well-recognized that psychiatric classification is often unreliable, being very dependent upon the views of the diagnostician. The same is largely true of clinical ratings of such features as "anxiety" and "tension" (Kreitman *et al.*, 1961). In connection with criteria determining sedation end-points, a number of studies have reported that EEG changes are not clear-cut nor easy to quantify (Ackner and Pampiglione, 1959; Boudreau, 1958; Seager, 1960), and that little agreement could be reached by independent judges on the occurrence of slurred speech (Thorpe and Barker, 1957; Ackner and Pampiglione, 1959). Far from being precise, objective criteria, they seem to be most difficult to reproduce.

These two problems of classification and sedation criteria are of course relevant to the present study. So far as the problem of assessing patients goes, we decided to employ a number of methods, including psychiatric diagnosis, clinical ratings and personality questionnaires. On the question of the criterion of verbal unresponsiveness as the sleep threshold, some modification of Shagass' method seemed desirable. In the Shagass and Kerenyi experiment their subjects were simply asked to repeat sibilant phrases at regular intervals, and it seems very likely that such factors as the firmness and loudness of the examiner's voice, or the number of repetitions involved, would affect the nature of the subject's responses (Ackner and Pampiglione, 1959).

An improved and more objective technique of assessing verbal responses during sedation was recently reported by Claridge and Herrington (1960); they recorded a series of digits on tape which were played back to the subject during

the injection procedure. Subjects were requested to respond to each number by doubling it, and the sedation end-point was defined at the occurrence of several consecutive errors. The authors claimed that clear-cut effects of the drug on the task of doubling numbers were obtained.

In the present study, then, Shagass' general procedure was followed of administering intravenous sodium amytal at a pre-determined rate to groups of depressed patients and normals, but with additional modifications which seemed likely to make for greater objectivity. Thus, apart from psychiatric classifications and ratings, subjects were given the Maudsley Personality Inventory (M.P.I.) to provide scores on factors of neuroticism and introversion-extraversion (Eysenck, 1956) and the Taylor Manifest Anxiety Scale (M.A.S.) (Taylor, 1953); the digit doubling task of Claridge and Herrington was included so that a continuous assessment of the subject's verbal behaviour during sedation could be made under standard conditions.

Selection and Description of Subjects

The patients studied were 30 consecutive admissions to one female ward of Bethlem Royal Hospital, in whom a diagnosis of a primary depressive illness was made at the initial ward conference and where the subsequent course of events was consistent with this diagnosis. The patients' ages ranged from 18–59 years (mean 41·2). They had all developed symptoms within the three months prior to their hospital admission and in the majority of cases had been ill for less than four weeks. Patients were first tested between 7 and 10 days after admission. By this time they had become used to ward routine, initial anxieties had been allayed and a full psychiatric history had been taken; yet no specific anti-depressive treatment had been given. No drugs were given for 24 hours before testing.

The clinical features of retardation, agitation and anxiety were rated on a 5-point scale, as was the severity of the depressive illness as a whole. In addition, a number of variables relating to depression were scored from the Item Sheet of the Institute of Psychiatry, used within the Maudsley and Bethlem Royal Hospitals, and on which numerous aspects of each in-patient's illness are recorded by the doctor responsible for the patient.

This procedure followed a study by Trouton and Maxwell (1956) in which 45 items were selected from the total number of 500 or so in the Item Sheet, and were factor-analysed; of the resulting factors, one (Factor 3) had high negative loadings for symptoms such as "delusions of guilt", "depressed", "anxious", etc., and was considered descriptive of psychotic depression. We therefore went through the Item Sheets of the depressed patients in the present study, and recorded the presence or absence of those symptoms (there were 10 in number) which had high negative loadings on this factor, hoping by this means to distinguish a group of subjects having high scores on the factor of "psychotic depression".

It was not possible to derive a corresponding score for "neurotic depression" since no such specific factor was extracted from the original matrix of inter-correlations. Instead a general factor of neuroticism was identified, but it was not considered useful for the present purposes to work out subjects' scores on this factor since it is well known that within this kind of dimensional system psychotics, as well as neurotics, have elevated scores on neuroticism (Eysenck, 1960, p. 16).

After the patient had left hospital and the response to treatment was there-

fore known, the whole case history was reviewed. The family history, previous personality, past illnesses, precipitating factors and clinical features of the illness were assessed, and the depressive illness classified into three groups: (*i*) mainly endogenous (N=12), (*ii*) mainly reactive (N=9), and an indeterminate group (N=9). Patients who showed the features conventionally classified as endogenous or reactive were so classified, but others who had features of both types were considered to be "indeterminate".

The normal subjects were all volunteer women (N=12). They were not taking drugs, and their ages ranged from 24–40 years (mean 28·0). Thus the groups differ with respect to age, as can be seen in Table I, endogenous depressives being significantly older than the other three groups.

Experimental Procedure

The procedure was carried out in a standard ward bedroom. Subjects rested on a hospital bed, were reassured, and given details of the test they were to have. Electrodes were fitted for recording skin resistance, heart rate, and forehead muscle tension, and continuous records were obtained throughout the whole procedure: these data will be reported separately.

After an initial period of rest to accommodate the subject to the situation, the sodium amytal solution was injected intravenously at the rate of 0·5 mg./kg. body weight every 40-seconds, and the tape recorder started on which digits were played back at the rate of one every two seconds. Subjects had previously been instructed to respond by doubling each number and to continue with this task for as long as possible. The responses to the numbers were noted so that errors, omissions, etc., could be counted.

Results

(i) *Assessment of the Sleep Threshold*

It was hoped that the method of assessing errors and verbal unresponsiveness to the numbers would provide a relatively clear-cut end-point, but this was not the case. Subjects showed a great deal of variation in their verbal efficiency at all times during the task. Some retarded depressives barely responded at all; others managed to do so intermittently. In the case of non-responders (there were only three) general clinical criteria of sleep had to be applied. Of those who co-operated well in responding, some showed drug effects by a slowing of response time or slurring, some by increasing errors, others by stopping and starting at short intervals. It seemed in many cases as if "consciousness" waxes and wanes before the subject becomes so sedated that verbal responses truly cease. It was therefore not possible to apply the Claridge and Herrington criterion of approximately five consecutive errors with any confidence. Instead a less stringent system of scoring was used of 20 consecutive *failures* to respond (i.e. 40 seconds of verbal unresponsiveness); this point was taken as our sleep threshold and in fact coincided with the appearance of sleep. The amount of drug administered was determined and converted to a measure of mg./kg. body weight.

(ii) *Group Differences*

Diagnostic categories: In view of the different ages of the groups, a correlation was first calculated between age and the sleep threshold; this was −·05 and was not significant. An analysis of variance was then carried out on the amount of sodium amytal required to reach the sleep threshold, but as can be

seen in Table I, there were no significant differences between groups. Thus the results do not support Shagass' data which show a high differentiation between neurotic and psychotic patients on the sleep threshold. There is a slight tendency for reactive depressives to have higher thresholds, and there is also some evidence that, taken as a whole, the depressive patients have a wider range of thresholds than normals.

TABLE I

Analyses of variance between depressive and normal groups on age, sleep thresholds and personality scores from the M.P.I. and M.A.S.

		Mean Scores				
Groups	N	Age (years)	Sleep thresholds (mg./kg.)	Neurot.	Extrav.	Anxiety
1. Endogenous depressives	12	47·5	9·4	27·09	16·91	23·89
2. Indeterminate ,,	9	37·5	9·3	33·88	18·88	34·88
3. Reactive ,,	9	35·6	10·2	33·38	22·25	34·25
4. Normal controls	12	28·0	8·8	17·67	29·33	11·71
F ratios:		5·7737	0·3851	3·819	3·054	10·795
'p's		0·05	NS	0·05	0·05	0·01

A/V tables:

Source	df	Sum Sqrs	MSV
Age:			
Between groups	3	2203·27	734·42
Within ,,	40	5088·17	127·20
	43	7291·44	*F=5·7737*
Sleep Thresholds			
Between groups	3	11·14	3·7133
Within ,,	38	366·37	9·6413
	41	377·51	*F=0·3851*
Neuroticism			
Between groups	3	1472·66	490·8867
Within ,,	32	4113·65	128·5516
	35	5586·31	*F=3·819*
Extraversion			
Between groups	3	843·03	281·01
Within ,,	32	2945·28	92·04
	35	3788·31	*F=3·054*
Anxiety Scale			
Between groups	3	2633·18	877·73
Within ,,	28	2276·69	81·31
	31	4909·87	*F=10·795*

The actual figures obtained for the sleep thresholds are considerably higher in our sample of subjects than those of Shagass and Kerenyi (1958). Their patients' sleep thresholds range from 2·5 to 9 mg./kg.; ours range from 5·0 to 17·8 mg./kg. These higher figures agree very closely with those obtained by Ackner and Pampiglione (1959).

Psychiatric ratings: No consistent findings were observed between ratings of agitation, anxiety, retardation, or severity of depression, and the dose of sodium amytal required to reach the sleep threshold.

As described earlier, a number of variables were extracted from the Item Sheets so that scores could be obtained for our patients on a factor of psychotic depression, following the procedure of Trouton and Maxwell (1956). The patient group was then split into two, one sub-group having high factor scores, the other low scores, with the expectation (following Shagass) that subjects high on psychoticism would have low sleep thresholds; in fact, the thresholds were very similar and not even in the predicted direction, being 10·1 mg./kg. (N=13), and 8·9 mg./kg. (N=11) for high and low psychoticism sub-groups respectively.

Personality questionnaires: The M.P.I. and M.A.S. were administered to all subjects; the mean scores for each group on the neuroticism, extraversion, and anxiety scales are given in Table I. As would be expected, there are marked differences between the normals and patients on all scales. Subsequent "t" tests showed the normal group to score significantly lower on neuroticism and anxiety, and higher on extraversion; and indeterminate and reactive depressives significantly higher than both endogenous and normal groups on the Anxiety scale. These findings are in agreement with many others on neurotic and normal groups.

Product-moment correlations between sleep thresholds and neuroticism, extraversion, and anxiety scale scores were calculated over the total number of subjects. The correlation between the sleep threshold and neuroticism was +·1871, between sleep threshold and extraversion −·0072, and between sleep threshold and the anxiety score −·0202. None of these correlations approaches statistical significance. Although the numbers in each group were small, further correlations were calculated between sleep thresholds and personality scores on each group separately. These correlations, too, failed to reach statistical significance.

Discussion

Our data provide no support for many aspects of the original findings reported by Shagass and his colleagues; for example, (*i*) he claimed highly significant differences between psychotic and neurotic depressives, whereas in our sample the groups do not differ significantly or even approach statistical significance either when psychiatric diagnosis or psychoticism factor scores are used to classify the groups; and (*ii*) Shagass found significant correlations between ratings of anxiety and tension and sedation thresholds; there is no evidence in our data of such a relationship. Further, there appear to be no trends in our data to support the view that the personality measures obtained from the questionnaires are related to sleep thresholds.

Taken as a whole, the findings are not particularly encouraging so far as the relationship between tolerance to sodium amytal and psychiatric diagnosis, ratings, or personality scores are concerned. As many investigators have already pointed out, criteria for classifying groups are difficult to define, but whether subjective or objective, none of the methods we employed related to the sleep thresholds of the subjects. We had also hoped that the method employed of recording verbal behaviour during sedation would increase the objectivity of the criterion of sleep, but it served instead to reflect the variability of subjects' verbal responses. It is somewhat surprising that these results should differ so much from those of Claridge and Herrington (1961) who obtained a clear-cut decrement in performance as a result of injecting sodium amytal; it should be

noted, however, that their sample consisted of male army patients, whereas ours were depressed women admitted to a psychiatric hospital; moreover, their technique was different in that they used a continuous intravenous infusion of sodium amytal at the rate of 0·1 G/min. Our findings are in line with recent data on nitrous oxide administration to normal subjects by Rodnight and Gooch (1962).

The method of giving sodium amytal every 40-seconds from a syringe makes environmental control impossible, as the patient is aware of stimuli from the doctor and also knows when the drug is being given. At present, studying the effects of a fixed amount of sodium amytal on autonomic functioning, we give the drug *via* an intravenous infusion set up in an adjacent room. This control of the environment improves the objectivity of the method. (Results will be reported at a later date).

The many kinds of response decrement observed in verbal behaviour during the digit-doubling task—slowness, slurring, errors and omissions—do not suggest any simple or single method of determining a sedation end-point by means of verbal behaviour, except by some rather loose criterion such as the relatively lengthy period of unresponsiveness used in this study. The fact that sleep thresholds determined in this way do not correlate with diagnosis or with personality scores raises many questions. There is no means of deciding on the available evidence whether it is the criterion, the method of classification, or any one of a host of factors which, if improved, might result in more significant relationships.

The questionnaires used (the M.P.I. and the M.A.S.) discriminated between the groups, but failed to show any significant correlations with the sleep threshold. In this respect the results correspond with those of Kawi (1958) but not with those of Claridge and Herrington (1961) who found significant correlations between sleep thresholds and both neuroticism and anxiety scores.

There are by now sufficient studies to show that many aspects of the sleep and sedation threshold procedures are not reproducible when carried out by independent investigators on different samples. Yet other aspects of the studies do agree: the sleep thresholds of the present study, of Ackner and Pampiglione (1958) and of Claridge and Herrington (1960) are all uniformly higher than those of Shagass and Kerenyi (1958). Similarly, the neuroticism and extraversion (M.P.I.) scores of Claridge and Herrington's dysthymic and normal groups compare quite closely with the present reactive depressive and normal means even though the numbers in all groups are small.

It is difficult, therefore, to invoke sample differences or criterion differences as sources of explanation when some general aspects of the data can be reproduced. That individuals vary in tolerance to sodium amytal is a statement of the obvious; but how these differences relate to personality and psychiatric illness is as yet uncertain.

Summary

1. Sleep thresholds for intravenous sodium amytal were determined in 30 depressed patients and 12 normal subjects, the criterion of sleep being that of verbal unresponsiveness to stimuli. The depressed patients were classified on clinical grounds into an endogenous, a reactive, and an indeterminate group.

2. There were no significant differences between the groups on the amount of sodium amytal required to reach the sleep threshold. Similarly, there was no significant correlation between the sleep threshold and clinical ratings of

agitation, retardation, anxiety, severity of depression, or with factor scores from a factor of "psychotic depression".

3. Scores on the M.P.I. and the M.A.S. showed that in general the patient groups were higher on neuroticism and anxiety and lower on extraversion than the normals. The personality scores did not, however, correlate significantly with the sleep threshold data.

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REFERENCES

ACKNER, B., and PAMPIGLIONE, G. (1959). "An evaluation of the sedation threshold test", *J. Psychosom. Res.*, **3**, 271–281.

BOUDREAU, D. (1958). "Evaluation of the sedation threshold test", *A.M.A. Arch. Neur. Psychiat.*, **80**, 771–775.

BUSFIELD, B. L., and WECHSLER, M. (1961). "Studies of salivation in depression", *Arch. Gen. Psychiat.*, **4**, 10.

CLARIDGE, G. S., and HERRINGTON, R. N. (1960). "Sedation threshold, personality, and the theory of neurosis", *J. Ment. Sci.*, **106**, 1568–1583.

DAVIES, B. M. (1960). "The methacholine test in depressive states", *A.M.A. Arch. Gen. Psychiat.*, **3**, 14–16.

DAVIES, B. M., and GURLAND, J. B. (1961). "Salivary secretion in depressive illness", *J. Psychosom. Res.*, **5**, 269–271.

EYSENCK, H. J. (1956). "The questionnaire measurement of neuroticism and extraversion", *Riv. di Psicologia*, **50**, 133–140.

Idem (1960). "Classification and the problem of diagnosis", in Eysenck, H. J. (Ed.) *Handbook of Abnormal Psychology*. London: Pitman, pp. 1–31.

FUNKENSTEIN, D. H., GREENBLATT, M., and SOLOMON, H. C. (1951). "Autonomic changes paralleling psychologic changes in mentally ill patients", *J. Nerv. Ment. Dis.*, **114**, 1–18.

KAWI, ALI A. (1958). "The sedation threshold. Its concept and use for comparative studies on drug-induced phenomena", *Arch. Neur. Psychiat.*, **80**, 232–236.

KREITMAN, N., SAINSBURY, P., MORRISSEY, J., TOWERS, J., and SCRIVENER, J. (1961). "The reliability of psychiatric assessment. An analysis", *J. Ment. Sci.*, **107**, 887–908.

RODNIGHT, EMER, and GOOCH, R. N. "A new method for the determination of individual differences in susceptibility to a depressant drug". In *Experiments with Drugs* (Ed. H. J. Eysenck). Oxford: Pergamon Press (to appear 1962).

SEAGER, C. P. (1960). "Problems in technique concerning the sedation threshold", *EEG and Clin. Neurophysiol.*, **12**, 910.

SHAGASS, C. (1954). "The sedation threshold. A method for estimating tension in psychiatric patients", *EEG and Clin. Neurophysiol.*, **6**, 221–233.

Idem, and NAIMAN, JAMES (1956). "The sedation threshold as an objective index of manifest anxiety in psycho-neurosis", *J. Psychosom. Res.*, **1**, 49–57.

Iidem, and MIHALIK, JOSEPH (1956). "An objective test which differentiates between neurotic and psychotic depression", *A.M.A. Arch. Neurol. Psychiat.*, **75**, 461–471.

SHAGASS, CHARLES, and KERENYI, ALBERT (1958). "The 'sleep' threshold. A simple form of the sedation threshold for clinical use", *Canad. Psychiat. J.*, **3**, 101–109.

TAYLOR, JANET A. (1953). "A personality scale of manifest anxiety", *J. Abn. and Soc. Psychol.*, **48**, 285–290.

THORPE, J. G., and BARKER, J. C. (1957). "Objectivity of the sedation threshold", *A.M.A. Arch. Neur. Psychiat.*, **78**, 194–196.

TROUTON, D. S., and MAXWELL, A. E. (1956). "The relation between neurosis and psychosis", *J. Ment. Sci.*, **102**, 1–21.

Irene Martin, B.A., Ph.D., Dip.Psych., *Honorary Lecturer, Institute of Psychiatry, University of London*

Brian M. Davies, M.D., M.R.C.P., D.P.M., D.C.H., *Senior Registrar, Bethlem Royal and Maudsley Hospitals, London*