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A Neurophysiological Tool for Psychosomatic Research

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SEVERAL recent neurophysiological advances, such as the elucidation of reticular system functions,^{12,13} seem highly relevant to the understanding of brain mechanisms involved in psychological disorders. Most of this information has come from the animal laboratory or from patients subjected to surgical operations. Pertinent methods for neurophysiological study of the *intact human subject* are needed to provide closer links between the data of the psychiatric clinic and the neurophysiology laboratory. This paper deals with one such method, the sedation threshold.

The sedation threshold is an objective pharmacological determination, which depends upon the electroencephalographic (EEG) and speech changes produced by intravenous Sodium Amytal.¹⁹ Starting from the common clinical impression that effective sedative dosage is correlated with the degree of tension, the method was originally developed to measure tension or manifest anxiety. After the realization of this initial aim, continued research revealed additional psychological cor-

relates of the sedation threshold. The results indicated that the method has important potentialities as a tool in psychiatric and psychosomatic research.

The purpose of this paper is to present the evidence which supports the statement that the sedation threshold is a valid clinical neurophysiological approach to the investigation of psychopathological problems.

Method

Test Procedure

Sodium Amytal is injected intravenously at the rate of 0.5 mg./Kg. body weight every 40 seconds. The EEG is recorded continuously. The injection solution is made up so that 1 cc. contains 0.5 mg./Kg.; 1 cc. is given as rapidly as possible at the beginning of every 40-second interval. Twenty-five seconds after each injection the subject is asked to repeat sibilants, such as 567, 77, etc. The Sodium Amytal generally produces marked increase of the EEG fast frequency activity (15- to 30-cps). This effect is greatest in the frontal areas and is best recorded from bifrontal electrodes. Since the bifrontal recording is particularly subject to contamination by muscle artifact, a record from sagittal frontocentral electrodes is also taken routinely. The latter usually contains less muscle artifact and is measured if the bifrontal tracing is obscured. The left-hand side of Fig. 1 shows the effect of Sodium Amytal on the bifrontal tracing. The amplitude of the 15- to 30-cps activity is measured, and a dosage-response curve is plotted. The right-hand side of Fig. 1 shows a typical curve. Usually the curve is S-shaped and contains a fairly clear inflection point, preceding

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which the amplitude rises quite sharply, and following which the curve tends to plateau. This inflection point usually coincides with the onset of slurred speech. The sedation threshold is defined as the amount of Sodium Amytal, in mg./Kg., which is required to produce the inflection point in the amplitude curve of frontal 15- to 30-cps activity; the inflection point must occur within 80 seconds of the clinical observation of slurred speech. The slurred speech is thus used as a rough

vious sedative consumption. However, this conclusion must be qualified, since addicts, alcoholics, and patients receiving exceptionally heavy doses of sedatives were not included in these studies.

Body surface was calculated in 60 patients and the threshold worked out in terms of milligrams per square meter. The correlation between thresholds based upon body weight and those based upon body surface was 0.91. This indicates that little would be gained if

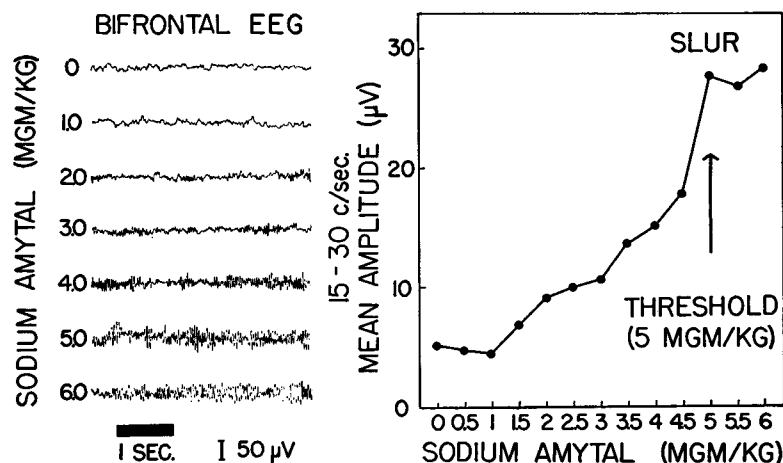


Fig. 1. Illustrates effect of Sodium Amytal on bifrontal EEG. Note progressive increase of the fast-frequency amplitude. Arrow points to inflection point in the amplitude curve which indicates sedation threshold.

guide to the threshold and the EEG change as a precise guide.

Technical Data

More than 700 tests on about 600 subjects have been carried out to date. All data have not yet been fully analyzed; much of the present material comes from a full analysis of the first 340 technically valid tests on 320 subjects. Somewhat less than 1 in 10 tests is invalid for technical reasons.

The effects of age, sex, and previous intake of sedatives were assessed by determining whether there was any correlation between these factors and the threshold. No significant correlations were found. It was surprising to find that the threshold was unaffected by pre-

body surface were to replace body weight as a base for calculating the threshold. As regards repeatability, the correlation between initial and repeat determinations, carried out after time intervals, averaging 30 days and as great as 15 months, was 0.91 in a group of 20 subjects. Ninety per cent of repeat determinations were within 0.5 mg./Kg. of the initial threshold.

Measurement of the EEG has so far been done on samples by a precise hand method. This yields results comparable to those obtained with an automatic frequency analyzer,¹⁹ but is laborious. An electronic device, incorporating the analyzer principle, but much smaller, is now giving promising initial results, and may replace the hand method.

Clinical Criteria

These have included numerical ratings of tension based upon specially directed interviews, the Saslow Screening Test¹⁸ in control subjects, and assessments based upon conventional psychiatric diagnostic interviews and hospital case records. It has been our impression that the most reliable criterion available to us was obtained by combining the diagnostic interviews of at least two psychiatrists with the hospital record of the course and outcome of a hospital stay averaging 5 weeks in duration.

Results

Anxiety

The following results bear upon the correlation between the sedation threshold and degree of manifest anxiety.*

1. If the threshold is correlated with the degree of manifest anxiety, it should be significantly higher in a group of psychoneurotics than in a nonpatient control group. The mean threshold of 121 psychoneurotic patients was 4.15 mg./Kg., as compared with the mean of 3.09 mg./Kg. in 45 control subjects.²² The difference was highly significant statistically.

2. Sixty-five nonpsychotic patients were rated by two psychiatrists on a 5-point scale for degree of "tension," which, as defined, was equivalent to what we now call "manifest anxiety."¹⁹ The correlation between the sedation threshold and the average tension rating was 0.72. This coefficient was almost as high as that for agreement between the two raters, which was 0.78.

3. Clinically, one would expect the different psychoneuroses to differ in degree of manifest anxiety. The greatest amount of anxiety would be expected in anxiety states and the least in conversion hysterics; mixed neuroses should

* It is difficult to select a completely acceptable term for the phenomena here called "manifest anxiety." Originally it was thought that "tension" would be suitable. However, psychotic depressives, who appeared very tense clinically, were later found to have low sedation thresholds. The qualifying term "manifest," is used here to avoid confusion with concepts of "unconscious anxiety."

be intermediate. Sedation thresholds of the different neurotic groups were found to conform to clinical expectation. A sample of 121 psychoneurotics was classified according to fairly definite clinical criteria.²² Mean thresholds in the diagnostic groups were as follows: anxiety state, 5.4; neurotic depression, 4.6; obsessive compulsive, 4.3; anxiety hysteria, 4.0; mixed neurosis, 3.7; conversion hysteria and hysterical personality, 2.9. Most of the intergroup differences were statistically significant, indicating that the threshold differentiated well between these groups.

4. A nonpatient control group, containing 45 subjects, was interviewed clinically and given the Saslow Screening Inventory prior to sedation threshold determination.²² Significant correlations were found between the sedation threshold and the number of anxiety symptoms elicited during interview and in the inventory.

These data lead to the conclusion that the sedation threshold is highly correlated with degree of manifest anxiety in psychoneurotic patients and in nonpatient control subjects. Studies of psychotic patients did not give similar results. The only statistically significant relationship between the threshold and anxiety in psychotics was found in a group of chronic ambulatory schizophrenics.²³ A probable explanation for the results in psychotics will be considered in a following section.

Hysterical-Obsessional Personality Traits

In the study of psychoneurotic patients, it became evident that the sedation threshold was correlated not only with degree of manifest anxiety but with related personality manifestations. The thresholds of hysterical patients, either with conversion symptoms or hysterical personalities, or both, were almost invariably in the lower half of the scale, while those of patients with obsessional personalities were almost always high. Patients with both obsessional and hysterical personality characteristics were most often diagnosed as having a mixed neurosis, and their thresholds usually fell into the intermediate range.

Figure 2 shows the proportion of high and

low thresholds in four diagnostic groups which were selected because they represent well-defined points on the hysterical-obsessional continuum. All 23 conversion hysterics had major somatosensory conversion symptoms. The 12 obsessive-compulsives all had rituals or constant ruminations, or both. The 41 anxiety states presented severe anxiety and nearly all had obsessional personalities, although they were not true obsessive-compulsives. These data show that the more obsessive

this group, but it was noted that the recent and acute cases had lower thresholds than equally tense chronic ones. This difference between acute and chronic schizophrenics provided a clue to a factor, other than degree of anxiety, which might influence the sedation threshold. 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. This concept led to the hypothesis that the

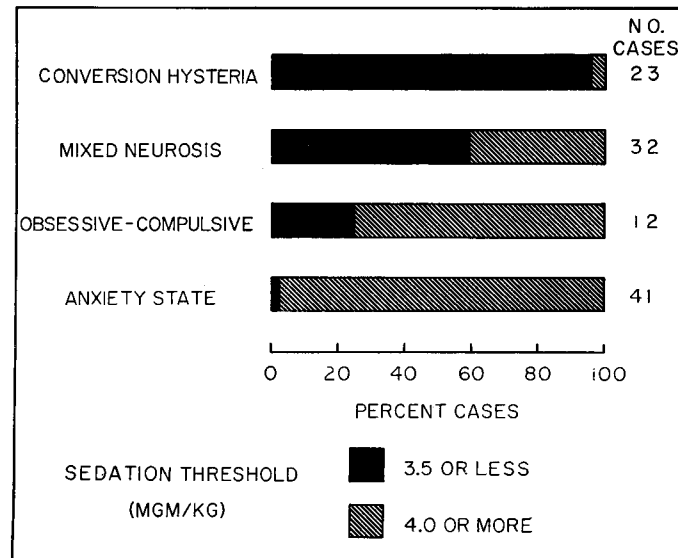


Fig. 2. Relationship between sedation threshold and predominance of hysterical or obsessional characteristics.

the personality, the higher the sedation threshold. However, average thresholds of the true obsessive-compulsives were actually lower than those of the anxiety states. This suggests that in the presence of frank obsessive-compulsive symptoms, there may be less anxiety than when such symptoms do not develop in the obsessional. This would be in accord with the postulated "anxiety-binding" function of compulsions and obsessions.

Impairment of Ego Functioning

There were 11 schizophrenics in the experimental population of the first sedation threshold study.¹⁹ The threshold was not significantly correlated with degree of tension in

sedation threshold was negatively correlated with degree of impairment of ego functions. According to this hypothesis, the greater the degree of ego impairment, the lower the threshold.

Since adequate methods of measuring ego impairment are not available, it was not possible to test this hypothesis directly. However, certain predictions, based on the hypothesis, could be checked. Two such predictions were tested in one study.²³ The first was that the thresholds of chronic schizophrenics, who were ambulatory and did not show significant evidence of personality deterioration, should be significantly higher than those of acute schizophrenics or agitated depressions, who

were equally tense but whose psychosis was of brief duration. The second prediction concerned the organic psychoses. The cardinal signs of organic psychosis are gross impairments of such ego functions as memory, judgment, and attention. Since ego functions are impaired to the greatest extent in organic psychoses, it was predicted that the thresholds of these patients should be lower than those of

Figure 3 also contains data for a group of "borderline states." Patients in this group generally presented neurotic symptoms, but were found to have one or two of the following symptoms: ideas of reference, depersonalization, derealization, distortion of the body percept, paranoid trend. These patients probably would fall into the pseudoneurotic schizophrenia classification of Hoch and Polatin.

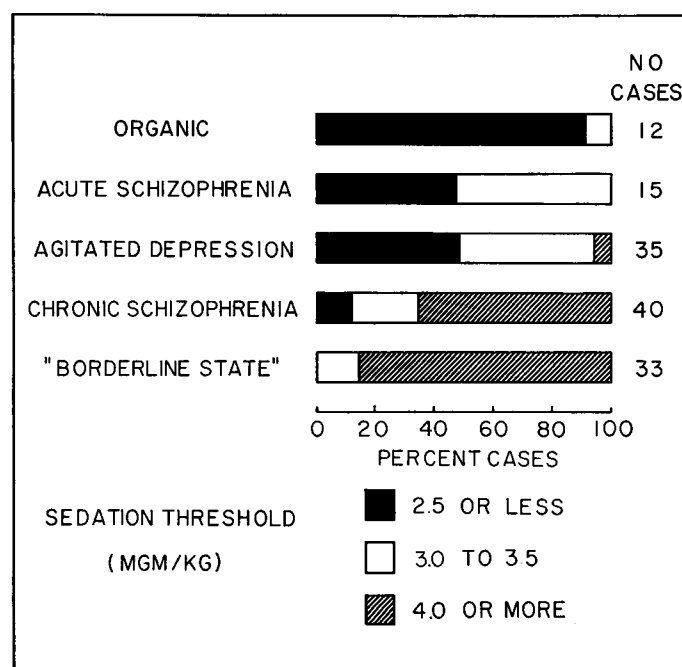


Fig. 3. Relationship between sedation threshold and degree of ego impairment, as represented by different psychotic groups, ranging from greatest impairment in organic psychoses to least in "borderline" psychoses.

all other subjects. The results confirmed both predictions.

The data for organic psychoses, acute and chronic schizophrenias, and agitated depressions, shown in Fig. 3, are those of the original study on ego impairment, supplemented by additional cases. Thresholds of the chronic schizophrenics were significantly higher than those of the acute "functional" psychoses; thresholds of the latter groups were, in turn, significantly higher than those of the organic psychoses.

This group was included here to test a third prediction from the ego-impairment hypothesis. Of the various psychotic groups in Fig. 3, the borderline schizophrenic group would be considered to have the least degree of ego impairment; consequently their sedation thresholds should be highest. The data verified this prediction. The mean threshold of the borderline group was 4.9, compared with 4.1 for the chronic schizophrenic group. This difference was significant at the 1 per cent level of confidence.

These data indicate that gross impairment of ego functions lowers the sedation threshold, while manifest anxiety raises it.

Differential Diagnosis of Depression

Differentiation between psychotic and neurotic depressive reactions is often difficult, particularly if a rapid decision is needed. From the factors related to the sedation threshold, it would follow that psychotic depressions should have low thresholds, whereas neurotic depressions, providing they do not occur in severe hysterics, should have high ones. Fig-

tion threshold is meaningfully related to several important psychopathological phenomena. It may therefore be regarded as a valid clinical neurophysiological approach to study of these phenomena. Some practical and theoretical implications of the data will be considered under the following headings: clinical and research applications, neurophysiological aspects, and relation to personality theory.

Clinical Applications

The sedation threshold is now used as a routine clinical test at Allan Memorial Insti-

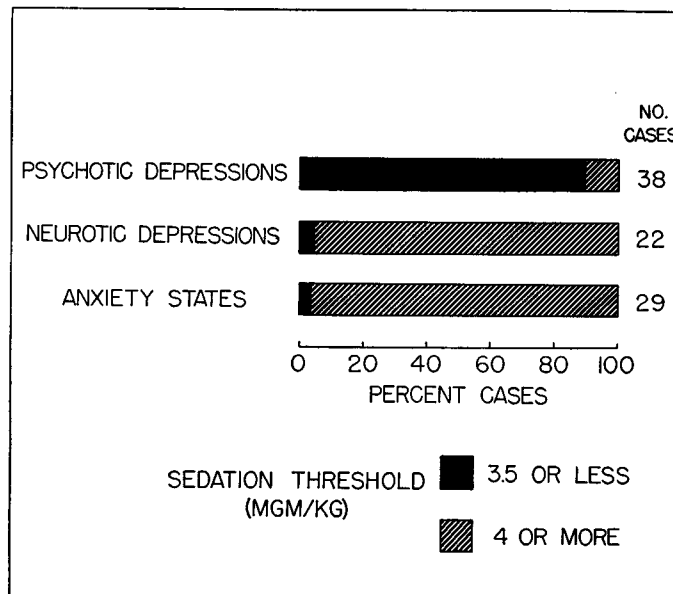


Fig. 4. Differentiation of psychotic depressions from neurotic depressions and anxiety states by the sedation threshold.

ure 4 shows the distribution of sedation thresholds above and below the patient median in all the psychotic depressions, neurotic depressions, and anxiety states, among the first 275 patients tested. It is clear that the threshold differentiated between psychotic depressions and neurotic depressions or anxiety states with a very high degree of accuracy. This finding has proved of considerable practical clinical value.

Discussion

The preceding results show that the seda-

tute. Like any test, it gives information which is meaningful only in a context of clinical differential diagnosis. It is most frequently employed to help distinguish between neurotic and psychotic depression and to estimate degree of anxiety. In connection with the latter application, a low threshold in an apparently severe anxiety state may lead to a fruitful review of the communicative, hysterical aspects of the case. An example has been cited elsewhere.²² Another cause for an unexpectedly low threshold in an apparent anxiety state may be an oncoming psychotic episode.

An extremely low threshold may point to an organic mental state. The Amytal test for organic brain disease, developed by Weinstein *et al.*, may be combined with the sedation threshold as a further diagnostic measure in such cases. When a high threshold is found in an apparently acute schizophrenic patient, recheck of the history usually reveals that the illness has been of a considerably long duration.

Research Applications

The sedation threshold holds a number of possibilities for application to psychiatric and psychosomatic research problems. A few investigations utilizing it have already been undertaken at this Institute. The test has been used to select subjects at the low and high extremes of the anxiety scale for electromyographic studies.³ Investigations are in progress on the effect of certain drugs, electroconvulsive therapy, and brief psychotherapy on the threshold. Practically no work has been done with the classical psychosomatic syndromes, except for study of a small number of hyperthyroid cases. In these the thresholds were generally high and tended to decrease when thyroid function was normalized.

It seems likely that the sedation threshold could provide objective data relevant to some hypotheses concerning psychosomatic disorders. Suppose the thresholds of adequate samples of patients suffering from different disorders were determined. Would the distributions resemble those of a normal group or a neurotic group? Would the distributions be similar for all disorders, or would they differ from one to the other? If they differed, would the differences agree with prevailing concepts about associated emotional state and personality patterns? For example, certain conditions, such as arterial hypertension⁸ and Raynaud's disease¹⁴ have been associated with obsessional personality traits or compared with anxiety attacks. Other conditions, notably certain skin disorders, have been regarded as depressive equivalents or as hysterical symptoms.^{1, 17} One would expect high thresholds in the former cases and low thresholds in the latter.

Neurophysiological Aspects

Since Sodium Amytal is a central nervous system depressant, which should quantitatively counteract excitatory processes, the sedation threshold may be regarded as a measure of cerebral excitability. This view is reinforced by evidence obtained by Gastaut and his co-workers in a study of the cortical excitability cycle. They showed that barbiturates diminish the amplitude of cortical responsiveness to photic stimuli, and lengthen the time it takes to recover normal excitability.

Anxiety, associated with a high sedation threshold, probably reflects increased cerebral excitability. In psychotic depression, associated with a low threshold, the neural processes seem to be different from those involved in anxiety. Some of the main clinical features of depression suggest that it involves inhibitory processes.² This is supported by studies in progress on the effect of electroconvulsive therapy on the sedation threshold. Results so far indicate that this treatment, in relieving depression, also increases the threshold. Additional evidence that anxiety and depression are neurophysiologically different was obtained in two recent studies of the EEG response to intermittent photic stimulation, which showed that these affects were associated with different response characteristics.^{20, 21}

Rothballer has recently found that a component of the reticular system responds to epinephrine by producing arousal. He found this adrenergic component to be particularly sensitive to barbiturates and to other depressants. Indeed, it was more sensitive than other parts of the reticular system which, as a whole, is especially sensitive to barbiturates.⁶ These facts, in conjunction with present data, suggest that excessive excitatory activity of the adrenergic component of the reticular system may be a key mechanism in the mediation of anxiety.

The capacity to attend to external stimuli, which is essential for adequate ego functioning, depends upon intact reticular system function.¹² Barbiturates in sufficient dosage impair ego functioning. When they are used for day-

time sedation one attempts to find a dose which will reduce anxiety without impairing ego functions. The fact that this can frequently be done favors the concept that the reticular system contains a number of functional components. It also suggests that different components are involved in anxiety and in the maintenance of ego functioning.

Relation to Personality Theory

The relationship of the sedation threshold to relative predominance of hysterical or obsessional personality traits suggests the possibility that the threshold may reflect some basic neurophysiological aspect of personality organization. Since significant personality factors must be consistent over long periods of time, such a hypothesis would be supported by evidence that the threshold is a relatively enduring biological characteristic of the individual. This is not yet proved, but is in agreement with available data. These data include the high test-retest reliability, and the fact that relatively quick changes in the threshold have so far been produced only by such major agents as severe toxicity and electroconvulsive therapy; even these changes are apparently temporary. The data relating the threshold to symptomatic variables, like anxiety, can easily be fitted into the personality context, since proneness to certain kinds of symptoms may be regarded as a personality characteristic.

Several personality typologies of the past have been based on a concept similar to the hysterical-obsessional continuum. Eysenck⁴ provided strong experimental support for the validity of this concept. He factor-analyzed several kinds of objective data on large groups of subjects and derived three dimensions of personality. One of these, the introversion-extraversion dimension, is equivalent to the hysterical-obsessional continuum. The hysteric is the extreme extravert, the obsessional or dysthymic, the extreme introvert. No direct studies have so far been done, which correlate the sedation threshold with measured introversion-extraversion, but there is strong indirect evidence that they may be closely related. This evidence comes from a study by one of Eysenck's students, Hildebrand, who meas-

ured introversion-extraversion by means of six psychometric tests and a body index. Subjects were a group of psychoneurotics who were classified in much the same way as those studied here. The introversion-extraversion scores arranged the various neuroses in an order which was almost the same as that in which they were arranged by the sedation threshold.

There is another point in favor of assuming a close relationship between the sedation threshold and Eysenck's introversion-extraversion dimension. Eysenck⁵ has recently proposed a theory of anxiety and hysteria, in which he distinguishes between hysterics and dysthymics in terms of differences in reactive inhibition. Reactive inhibition is a term borrowed from Hull, but Eysenck's theory has its origin in Pavlov's attempt to classify the nervous systems of experimentally neurotic dogs according to predominance of excitatory or inhibitory process. According to Eysenck's theory, hysterics should generate reactive inhibition more quickly and strongly than dysthymics, and should dissipate it more slowly. He also postulated that brain injury should increase reactive inhibition and extraversion, and drew attention to the extraverting effects of inhibitory drugs like alcohol and Sodium Amytal. If one follows Eysenck in equating reactive inhibition with the inhibitory effects of Sodium Amytal, one would predict lower sedation thresholds in hysterics and organic psychotics than in dysthymics, a prediction in accord with the results. Thus, not only the order but also the direction of sedation threshold differences agrees with Eysenck's data and theory on introversion-extraversion.

In another approach to personality investigation, that of Sheldon and Stevens, high resistance to alcohol is listed as one of the criteria for the cerebrotonic temperament. This would lead one to expect high sedation thresholds in cerebrotonics. Since cerebrotonics seem very similar to obsessionals or dysthymics, this expectation also agrees with present results. It is unusual and encouraging to find such apparent agreement between results of personality investigations which differ widely in method and theoretical orientation. The vari-

ous methods appear to be tapping different aspects of some process common to all.

The foregoing discussion implies that the sedation threshold measures neural processes which may be important determinants of personality. These processes could be considered to influence proneness toward development of one or another kind of character trait or neurotic symptom. Although it is easy to think of such processes as constitutional factors, there is no evidence which would allow one to speculate about the relative importance of heredity or environment in their development. However, it should be technically feasible to obtain data on this point, e.g., by determining the sedation thresholds of identical twins.

Summary

1. The sedation threshold is an objective pharmacological determination which represents the amount of intravenous Sodium Amytal required to elicit certain EEG and speech changes. The purpose of this paper was to present the evidence which bears on the validity of this method as a clinical neurophysiological approach to investigation of psychopathological problems.

2. Data were drawn from tests on over 500 psychiatric patients and 45 nonpatient controls. The following general results were obtained: (a) The sedation threshold was positively correlated with degree of manifest anxiety in nonpsychotic subjects. The greater the manifest anxiety in psychoneurotics or control subjects, the higher the threshold. (b) Obsessional personality characteristics tended to be associated with a high threshold, hysterical characteristics with a low threshold. (c) The sedation threshold was negatively correlated with degree of gross impairment of ego functioning in psychotics. The greater the ego impairment, the lower the threshold. (d) The threshold differentiated between neurotic and psychotic depressions with a high degree of accuracy. Thresholds were low in psychotic depressions and high in neurotic depressions.

3. It was concluded that the sedation threshold was meaningfully related to several important psychopathological phenomena, and that

the results supported its validity as an investigative approach. The findings were discussed from the following standpoints: clinical and research applications; some neurophysiological aspects of anxiety, depression, and ego functioning; and relation to personality theory, with special emphasis upon Eysenck's theory.

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