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LATERAL GAZE NYSTAGMUS AS AN INDEX OF THE SEDATION THRESHOLD [1]

MAX FINK, M.D.
With the technical assistance of
HANNAH MOSQUERA
Department of Experimental Psychiatry, Hillside Hospital, Glen Oaks, N.Y.

(Received for publication: October 17, 1957)

On reading the report of Thorpe and Barker (1957) in the recent issue of the *Archives,* we were moved to assess our own experiences with the sedation threshold, and to report a clinical guide to the "inflection point" that we have found useful.

Following the initial description of the technique by Shagass (1954), we modified our tests which included the administration of the amobarbital test for brain dysfunction (Weinstein *et al.* 1953) to obtain a measurement of the sedation threshold as well. Our technique was identical to that of Shagass, with the addition of the measurement of nystagmus on lateral gaze which the latter test required. The change in beta amplitude in the EEG was measured visually in consecutive samples of record, using the additive ruler described by Shagass.

In the initial group of patients, two observers were unable to identify the onset of slurred speech with consistency. Disagreement led to administration of amounts of amobarbital greater than was required, with the frequent induction of sleep. As we were also obtaining a record of the induction of nystagmus on lateral gaze, we became aware that this index was reliably agreed upon by the two observers, and a correlation with the sedation threshold was sought.

We, therefore, omitted the instructions regarding counting and substituted the following instructions. Subjects were told that at periodic intervals they would be requested to open their eyes and to look first to one side and then to the other at pre-arranged fixation points. This was repeated twice in each direction, usually within ten seconds, while the observer noted the development of sustained regular nystagmus on lateral gaze. Such observation was repeated after each injection of 1 cc. of amobarbital solution, between the 25th and 40th sec. of the injection period. The administration of barbiturates continued until nystagmus was observed, and then an additional 2 cc. were given.

RESULTS

To date, we have 91 measurements. The following table notes the difference between the number of milligrams of amobarbital per kilogram body weight for the EEG measure (the sedation threshold) and for the onset of nystagmus. Differences greater than one unit did not occur in this series. The two measurements are seen to be reliably related by a unit of 0.5 or less in more than 90 per cent of the observations.

TABLE I

Frequency Distribution of Difference in Amount of Amobarbital Necessary to Induce EEG Change and Nystagmus (mg. amobarbital/kg. body weight)

	—1.0	—0.5	0	+0.5	+1.0
No. Tests (91)	1	12	47	27	4

Test-Retest Reliability:

During these studies we have also had the opportunity to repeat the sedation threshold measurement three to five times in the same patient at weekly intervals. These measurements were done in randomly selected patients receiving subconvulsive doses of electric current under barbiturate premedication as part of a study of convulsive-subconvulsive electroshock. The behavioral changes in this group were small — 14 of the 16 were referred for grand mal electroshock within 4 weeks after the subconvulsive treatment period.

The range of sedation threshold measurements under these conditions is noted in table II.

TABLE II

Absolute Range of S.T. Values

Range	0	0.5	1.0	1.5	2.0	>2.5
No. Subjects (16)	0	2	6	2	4	2

1 Supported by the Board of Directors' Research Fund of the Society of the Hillside Hospital.

Being unable to ascribe greater validity to one reading than to any other, we determined the mean sedation threshold for each subject, and the range of variability about the mean. In table III we have listed the subjects in each range of variability about the individual mean value.

Thus, the intra-patient inter-test variability for this test in this series is considerable. The test reliability of nystagmus as an index of the electroencephalographic change is well within the retest variability of the test in these subjects.

TABLE III

Range of S.T. Values from the Mean

Range	0	0.1—0.5	0.6—1.0	1.1—1.5	1.6—2.0	>2.0
No. Subjects (16)	0	6	4	4	1	1

CONCLUSION

The appearance of nystagmus on lateral gaze is a clinical guide to the sedation threshold, with a variability from the measured EEG index well within the test-retest reliability of the test itself. It is recommended as a substitute, therefore, for the onset of slurred speech. Further studies of the retest reliability of the sedation threshold are necessary.

RÉSUMÉ

L'apparition d'un nystagmus dans le regard latéral est une mesure clinique de la sédation qui montre une bonne corrélation avec l'index électroencéphalographique mesuré chez ces malades et dont la validité a été démontrée. Il est recommandé d'utiliser cette méthode en remplacement de celle qui est basée sur l'apparence de troubles dysarthriques.

ZUSAMMENFASSUNG

Das Auftreten von Nystagmus mit lateralem Blick ist ein klinisches Mass für die Sedationsschwelle, welche gut mit dem gemessenen EEG-Index übereinstimmt und dessen Verlässlichkeit nachgewiesen werden konnte. Gebrauch dieser Methode wird daher empfohlen als Ersatz für diejenige basiert auf dem Auftreten von verwischter Sprache.

REFERENCES

SHAGASS, C. The sedation threshold. A method for estimating tension in psychiatric patients. *EEG Clin. Neurophysiol.*, **1954**, *6*: 221-233.

THORPE, J. G. and BARKER, J. C. Objectivity of the sedation threshold. *A.M.A. Arch. Neurol. Psychiat.*, **1957**, *78*: 194-196.

WEINSTEIN, E. A., KAHN, R. L., SUGARMAN, L. and LINN, L. The diagnostic use of amobarbital sodium (''Amytal Sodium'') in brain disease. *Amer. J. Psychiat.*, **1953**, *109*: 889-895.

Reference: FINK, M. Lateral gaze nystagmus as an index of the sedation threshold. *EEG Clin. Neurophysiol.*, **1958**, *10*: 162-163.

EEG Clen. Neurophl.

Lateral Gaze Nystagmus as an Index of the Sedation Threshold

Max Fink M.D.

With the technical assistance of

Hannah Mosquera

From the Department of Experimental Psychiatry, Hillside Hospital, Glen Oaks, N.Y.

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9-13-57

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1. Thorpe, J.G. and Barker, J.C.: Objectivity of the Sedation Threshold, A.M.A. Arch. Neurol. & Psychia. 78: 194-196, (Aug) 1957.

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Department of Experimental Psychiatry

September 13, 1957.

Dr. Roy Grinker,
Editor, Section of Psychiatry,
A.M.A. Archives Neurology & Psychiatry,
29th Street & Ellis Avenue,
Chicago, 16, Illinois.

Dear Dr. Grinker:

In reading the recent article of Thorpe and Barker on the "Objectivity of the Sedation Threshold," we were moved to describe our parallel experiences with this test, as well as our solution to the problem. The enclosed short clinical note may be of help to other investigators who are attempting an assessment of the significance of this test.

If the format of this note is improper for the Archives, I would be pleased to follow your suggestions.

Sincerely yours,

Max Fink, M.D.

MF: JB

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Institute for Psychosomatic and Psychiatric Research
29th Street and Ellis Avenue, Chicago 16

September 20, 1957

Max Fink, M.D.
Department of Experimental Psychiatry
Hillside Hospital
75-59 263rd Street
Glen Oaks, New York

Dear Doctor Fink:

I am very sorry, but it will not be possible to publish your paper in the ARCHIVES. We have a large backlog, and we like to have a wide selection of papers on many subjects and feel that we have published already all that seems important on the sedation threshold test as devised by Shagass.

Regretfully yours,

Roy R. Grinker

Roy R. Grinker, M.D.
Editor-in-Chief for Psychiatry

RRG:jm
enclosure

September 24, 1957.

Dr. Robert S. Schwab,
Massachusetts General Hospital,
Box #743,
Boston, 14, Mass.

Dear Dr. Schwab:

In reading a recent article on the "Objectivity of the Sedation Threshold" in the Archives of Neurology and Psychiatry, we were moved to describe our parallel experiences with this test, as well as our solution to the problem. I would appreciate your consideration of this short clinical note for the Section of Clinical and Laboratory Notes of the EEG Journal.

Sincerely yours,

Max Fink, M.D.

Department of Experimental Psychiatry.

MF: JB

TEL. LAFAYETTE 3-8200
EXT. 380

ROBERT S. SCHWAB, M.D.
MASSACHUSETTS GENERAL HOSPITAL
BOSTON 14

September 27, 1957

Dr. Max Fink
75-59 263rd Street
Hillside Hospital
Glen Oaks, New York

C.N. #61

Dear Dr. Fink:

Your manuscript has been received and I would like to conditionally accept it for Clinical Notes in the EEG Journal as it stands subject to the approval of the Editor-in-Chief, Herbert Jasper.

Yours very sincerely,

Robert S. Schwab

Robert S. Schwab, M.D.

RSS:mc

J. Peters

McGILL UNIVERSITY
MONTREAL

Department of
Electrophysiology

Allan Memorial Institute,
1025 Pine Avenue West,
Montreal.

September 30 1957

Dr.Max Fink,
Hillside Hospital,
75-59 263rd Street,
Glen Oaks,
New York.

Dear Max,

Thank you for your note on the nystagmus. It was nice to see you at Zurich, and I hope that we shall be able to meet again soon.

My best regards.

Sincerely,

Charles

CS/ef

C. Shagass, M.D.

12/3/58

Discussion: Dr. Shagass

Dr. M. Fink - Hillside Hospital

Dr. Thompson, Members and Guests:

It is always a pleasure to read another chapter in the unfolding saga of sedative tolerance tests as they have been developed by Dr. Shagass. This study, like its predecessors, relates neurophysiologic indices to behavioral measures - and in this area of psychiatry, reflects a welcome application of basic science to clinical problems.

It seems appropriate to examine this report in the perspective of recent concepts in experimental psychiatry. During the 1930's, when electroencephalography was a new science considerable effort was expended in relating EEG patterns to "personality types" or "diagnoses," without success. With more refined instrumentation, there have been sporadic re-assessments without noticeable success.

In the sedation threshold, however, Dr. Shagass, did succeed in achieving such a relationship. In these earlier studies, he related the amount of barbiturate necessary, under standard conditions of rate of administration and concentration, to induce a specific EEG voltage and frequency change, to the personality profiles of the Mandsley-Eysenchian school. It is important to note that the relationship was not between any fixed aspect or index of the EEG and behavior but betweem a measure of reactivity or responsivity of the EEG and clinical behavior.

We may carry this description a bit further. The electro-encephalogram is a reflection of central or brain neurochemistry, and the reactivity of the electroencephalogram to any chemical stress, a measure of the reactivity, or responsivity, or buffering

of the biochemical enzymatic systems that make up the nervous system.

It is in this organismic biochemistry that much activity is now directed in experimental psychiatry. The wide variety of phrenotropic agents, the new and more potent hallucinogens, and the expanding technics of enzyme and steroid chemistry are providing experimental psychiatry with research tools of considerable adaptability. One application of these technics was highlighted yesterday by Dr. Gottlieb and his co-workers at the Lafayette Clinic, who reported their initial observations on the significant relationships between schizophrenic behavior and the reactivity of the glucose-enzyme systems to the stress of insulin. These authors carefully noted that there was no relationship between the initial levels of their biochemical measures and behavior.

Dr. Shagass' earlier studies of the sedation threshold - using an EEG end-point - are clearly within this tradition. His report today is also in this general tradition, but instead of a neurophysiologic index of clear definition has utilized a clinical index - lack of a verbal motor response to a verbal command - as the end-point. In the report today, he has related the amount of pentothal necessary to induce this state of lack of response (which is defined as "sleep") with the affective state of the individual at the time of the experiment. He has observed that the more fearful, disturbed, tense, angry and worried a subject is, the more barbiturate is necessary to induce

sleep. The quieter, more indifferent, inactive and retarded a patient is, the less barbiturate is necessary for sleep. He is thus achieving a biochemical titration, and is, in essence, measuring the subject's responsivity or reactivity to barbiturate. By repeating the studies seriatim, he is able to report shifts in this state of reactivity.

In his desire to extend the sedation threshold technic to situations in which the EEG was not available, and provide for greater clinical applicability, some of the precision of the earlier studies has been forfeited. It is not unexpected, considering the lack of precise definition of behavior as well as the end-point of titration, that the reactivity-clinical relationships are somewhat cloudy. I have noted two puzzling relationships. Incfeasing sleep thresholds are associated, on the one hand, with excitement, worry, restlessness and anger; but also, with clinical improvement in a course of convulsive therapy. Also, in one patient, a transient LSD induced psychosis is associated with a sharp drop in threshold, while in the same patient, fear of treatment, restlessness and increased tension are associated with rising thresholds. I would suspect that these apparent discrepancies arise from the non-specific nature of behavioral response to neuro-physiologic change and to the poverty of our descriptive language for behavioral change. I would wonder what shape the curves would take if the change in sleep threshold were plotted against other indices of brain function as predominant EEG frequency pattern or degree of synchronization; or such psychologic indices of brain function as the perception of embedded figures or CFF; or such behavioral indices as dyadic or syntactic linguistic

analyses. Alternatively, more precise,- operational measures of the behavioral subsumed under "anger," restlessness," "worry" may provide, again, the relationships indicated earlier by the sedation threshold studies.

Lest these comments be misconstrued, let me say, in closing, that Dr. Shagass is to be warmly congratulated in these studies which are providing a firm basis for the developing neurophysiologic-adaptive hypothesis of behavior. His demonstrations of central neurophysiologic reactivity in the sedation threshold are in the best experimental traditions. We are eagerly looking forward to further experimental neurophysiologic studies from his new laboratories in Iowa.

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orig + 2
D.S.

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References:

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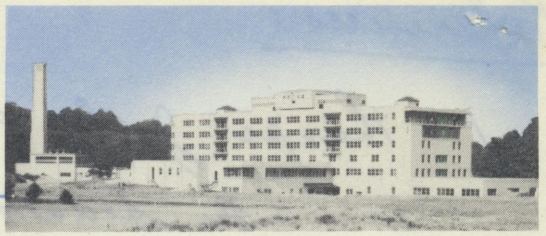

THE LONG ISLAND JEWISH HOSPITAL

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Department of
MEDICINE

September 21, 1961

Martin M. Katz, Ph.D.
Research Psychologist
Psychopharmacology Service Center
National Institute of Mental Health
Bethesda 14, Md.

Dear Martin,

Your letter regarding a review of the sedation threshold struck a sympathetic chord, and I am encouraged to share my views with you. However, the problem is complex and perhaps we can set aside some time in Washington for a detailed discussion.

My interest in the sedation threshold was occasioned by my earlier interest in the use of intravenous amobarbital as a test for brain dysfunction. (Weinstein and Kahn: Denial of Illness, C.C. Thomas, 1955) In the course of electroshock studies, we carried out many estimates of the S.T. and came to the conclusion that the test was physiologically and technically sound. Finding dysarthria a difficult end-point, I substituted nystogmus; but in reality, this too can be dispensed with, since the measured end-point is the EEG response.

The critics who have carped about dysarthria, are correct as far as they have gone, but this difficulty is not insurmountable, and bears no significant relation to the value of the test.

The questions at issue are:

1. Is the test stable in the same individual overtime?
2. Is there a characteristic response which bears a significantly high correlation with a behavioral variable - namely, the classification by psychiatrists of subjects into nosologic groups?

3. Thirdly, your question, "if true, it (S.T.) obviously can be very useful in treatment prediction studies".

1. Our own experience indicates that a high intra-individual variability; a limited range of values for the test (twelve points from 1-6 in half steps); and an equivocal EEG end-point in 10-20% of tests serve to make the reliable determination of the S.T. difficult. These variables seem inherent in the test design, and are not, in my opinion, a lack of know-how by the observers.

2. No. My negative answer to this question is partly based on (1); and partly on the usual difficulties of nosology. It is somewhat simple-minded to expect a high correlation between a "simple" physiologic reactivity measure and a "complex" hypothetic construct with so much inherent ambiguity and variability.

3. Even though the S.T. may not be related to diagnosis, can the S.T. be useful in treatment prediction? I think it may be, -- not for the logical reasons, usually given, but because of the value of the test as a "reactivity" measure. In the past few years various indices have been shown to bear some relation to treatment or to diagnosis -- and each index is best subsumed under the term of a "reactivity index". We stated that patients who showed two or more language changes after intravenous amobarbital were more likely to show early EEG changes after electroshock, and to show greater degrees of behavioral change and improvement (Psychopathology of Communication, 126 - 139, 1958). Goldman has repeatedly suggested that EEG pentothal bursts are slow in appearance in schizophrenic subjects, and has used this test prognostically. Similar statements have been made, in more quantitative studies, by Itil (Erlangen) and Cazzulo (Milan), who have related the changed EEG patterns to cerebral atrophy on pneumoencephalography. In another type of studies, the blood pressure responses to mecholyl and to adrenalin have been repeatedly suggested as a diagnostic and prognostic index. A common basis in these studies is that a lack of reactivity or a slow reactivity is generally equated with schizophrenia or brain atrophy -- a poor prognostic sign for the available therapies; while high reactivity is equated with depressive syndromes -- a good prognostic sign with available therapies. Thus, low reactivity may be invoked as an index of poor prognosis; but high reactivity will bear a high correlation with behavioral change, and a variable one with improvement ratings. (See

our views of behavioral change and improvement ratings, Arch. Gen. Psychiat. 4: 259, and 5: 30, 1961)

Thus, there is much merit in Shagass S.T. -- not, in my view as a diagnostic index (for age is much more reliable and easier to ascertain), but as one guide to neurophysiologic reactivity -- a subject that needs further study as a prognostic and as a nosological tool.

I trust this is responsive to your inquiry. I would like to discuss it more fully in Washington (October 16-17 ?) and would recommend that if you do get interested in the S.T., that you consider a series of meetings on various reactivity measures in psychiatry -- the mecholyl test, the S.T. and the Goldman as examples of the more explicit.

My regards.

Sincerely yours,

MF:dts

Max Fink, M.D.

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September 12, 1957.

Dr. Roy Grinker,
Editor, Section of Psychiatry,
A.M.A. Archives Neurology & Psychiatry,
29th Street & Ellis Avenue,
Chicago, 16, Illinois.

Dear Dr. Grinker:

In reading the report of Thorpe and Barker in the latest (August) issue of the Archives, we were moved to assess our own experiences with the sedation threshold, and to report another clinical guide to the "inflection point" that we have found useful.

During the past two years we have included a measurement of the sedation threshold in our tests of brain function. We initially followed the technique described by Shagass (EEG Clin. Neurophysiol. 6: 221-233, 1954). Measurement of the beta amplitude response is done visually in several samples of record using the additive ruler described by Shagass.

In the initial group of patients, two observers were unable to identify the onset of slurred speech with any consistency. We, therefore, gradually omitted this step, and continued drug administration until drowsiness was clearly manifest, combined by a statement by the technician that an increase in beta amplitude in the record had occurred at least 1½ minutes before.

This technique had the drawback that occasionally amounts of amobarbital inadequate to reach an inflection point were administered. We, therefore, began to note the onset of nystagmus on lateral gaze as a guide to the sedation threshold.

Subjects were told that at periodic intervals they would be requested to open their eyes and to look first to one side and then to the other at pre-arranged fixation points. This was repeated twice in each direction, usually within ten seconds, while the observer noted the development of sustained regular nystagmus on lateral gaze. The administration of barbiturates continued until nystagmus was observed, and then 2 cc more were given. The EEG records were then measured for the inflection point by the visual method.

To date, we have 91 such measurements. In the following table, the difference between the point of onset of nystagmus (nystagmus index) and the inflection point of beta amplitude change (EEG index) is reported.

Difference - EEG Index - Nystagmus Index

-1.0	-0.5	0	+.5	+1.0
1	12	47	27	4

Differences greater than 1.0 unit did not occur. It is apparent that the nystagmus end point for the sedation threshold is reliably related to the EEG end point by a unit of $\frac{1}{2}$ in more than 90% of the trials. Since the error of the sedation threshold under test - retest conditions is between 0.5 and 1.0 units, this nystagmus index is a satisfactory guide to the sedation threshold, as defined by Shagass.

In our continuing studies of the sedation threshold, we have, therefore, ceased measurement of slurred speech or drowsiness, but have relied on the onset of nystagmus as the clinical guide to this index.

I trust that this data may be helpful to other investigators.

Sincerely yours,

Max Fink

Max Fink, M.D.

MF:JB