# Experimental Studies of Convulsive and Drug Therapies in Psychiatry: Theoretic Implications

Max Fink M.D.

Robert L. Kahn Ph.D.

and

Martin A. Green M.D.

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

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# Experimental Studies of Convulsive and Drug Therapies in Psychiatry: Theoretic Implications

The proper role of the physiodynamic or somatic therapies in psychiatry remains poorly defined. This results, in part, from the lack of an adequate formulation of their mode of action. In the past six years increasing evidence for a neurophysiologic-adaptive view of electroshock therapy has been presented by Weinstein and Kahn, Roth, and Ulett. In this view, the therapeutic process in electroshock is ascribed to a persistent alteration in cerebral function which provides the milieu for a change in adaptation of the subject in his environment.

During the past four years in the laboratories of Hillside Hospital, we have studied the relation between alteration in various indices of brain function and the behavioral response of psychiatric patients to three of the physiodynamic therapies - electroshock, insulin coma and "tranquilizers." The neurophysiologic-adaptive view of electroshock has been supported and amplified in these studies; and evidence for a similar view of insulin coma has been presented. Recently, the concept has been fruitfully extended to the newer "tranquilizers." These studies provide the basis for a generalization

concerning the mode of action of these therapies. It is our purpose tonight to examine the experimental evidence to determine whether or not the mode of action of these therapies may result from their ability to induce sustained alteration in cerebral function; and the corollary question, whether measurable alteration in cerebral function is a necessary condition for the efficacy of these therapies, or whether such changes in brain function are a "complication" or "untoward effect."

We have used various indices of brain function including memor scales, visual and tactile perceptual tasks, and changes in orientation patterns of language both clinically and after intravenous amobarbital which is generally known as the "Amytal Test." In electroencephalographic studies, changes in the delta index in unactivated records have been found to be a sensitive index of altered brain function. For this review, changes in this latter index will be stressed.

In the initial studies of consecutive patients referred for convulsive therapy, electroencephalograms were obtained before, and on a day after a treatment at weekly intervals during therapy. The patients received grand mal therapy three times a week, for a total of 12-20 applications.

During convulsive therapy, serial electroencephalograms consistently demonstrate slow wave activity. In the initial series, we quantitatively measured the amount of induced delta activity during each week of treatment by determining the per cent time of such activity, the slowest frequency, the highest voltage and the duration of bursts in selected leads. The records were then ranked and the upper third were classed as "high," the second third as "middle," and the lower third as "low" degrees of delta activity. Examples of such records are noted in the figures.

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Figs. 1, 2, 3

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During and after the course of treatment, the patients were independently rated for their short term clinical response (2-3 weeks post treatment) using conventional psychiatric criteria, and were classed as "much improved," "moderately improved" and "unimproved."

In the first series of patients, a significant relationship between the early induction of high degrees of delta activity, and clinical ratings of "much improved" was observed. Eighty per cent of the records in the

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Fig. 4

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much improved group were high degree delta by the 4-6 treatment; and the percentage was sustained at 90% in the third and fourth weeks. In contrast, none of the unimproved patients developed high degree delta records in the first three weeks, and only 20% of the records in the fourth week were so classified.

Based on these observations, a predictive study was undertaken. EEG records obtained during the second and third weeks of treatment were analyzed for the degree of induced delta activity, and it was anticipated that those patients who had high degrees of delta activity during these two periods would show better ratings of "improvement" than patients in whom

such degrees of delta activity were not induced. This prediction was

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Fig. 5

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indeed true, as 67% of the patients with high degree records on both occasions were "much improved," while of patients without such records, 70% were "unimproved" or "moderately improved."

Further corroboration was obtained in a convulsive-subconvulsive control study. Consecutive electrotherapy referrals were placed either on convulsive or on subconvulsive therapy on a random basis. Of 27 patients who received subconvulsive treatments, none demonstrated slow wave EEG activity of middle or high degree in any week of treatment. Of 28 subjects receiving convulsive therapy, high degree records were observed in 20 during the second to fourth weeks of treatment.

Of the 27 subconvulsive patients, no change in behavior was noted in 23, and of these, 19 were referred for a second course of treatment. Grand mal electroshock induced high degrees of delta activity in 14 of these, and in each, a significant behavioral change was noted. In the five patients

without such delta change, only two showed a significant behavioral response.

These studies of convulsive therapy indicate that EEG slow wave activity is an index of the changes in cerebral function which are a prerequisite to the behavioral change in this form of therapy.

(b) Tranquilizing Drugs:

When the newer psychopharmacologic agents are studied from the viewpoint of their electroencephalographic and clinical neurologic effects, a meaningful relationship between the degree and type of induced change in cerebral function and the clinical behavioral response is observed. The ability of the newer tranquilizing agents to induce signs of central nervous system dysfunction, as motor rigidity, depression, excitement and seizures are well known.

Based on observations made in acute experiments and in chronic administration of various drugs in adult psychiatric patients, EEG changes have also been noted. These EEG effects may be classified according to predominant changes in the frequency spectrum, and are of three broad types:

I. Increased slow wave activity with hypersynchrony.

II. Increased high voltage fast activity.

III. Desynchronization with voltage and frequency irregularity and irregular theta activity.

Of the drugs that induce increased slow wave activity the phenothiazine derivatives, chlorpromazine, promazine and perphenazine are clear examples. Each drug also induces seizures in non-epileptics, exaggerates seizures in epileptic subjects, and induces clinical parkinsonian neurologic patterns. In the clinical service at Hillside Hospital, parkinsonism has been induced in all patients receiving chlorpromazine, and seizures have been observed in 10% of psychotic patients without a previous history of seizures.

Reserpine also evokes delta activity, but only when given in large doses. At high dosage levels, it also exaggerates seizures in epileptics, and induces seizures in animals, and clinical parkinsonism in man.

Of drugs that induce increased high voltage fast activity, barbiturates and meprobamate are clearest examples. These agents differ from the phenothiazines and resperine in not producing parkinsonism, or clinical seizures. Indeed their anticonvulsant activity is measurable.

Habituation is readily achieved, and withdrawal phenomena of agitation and seizures have been observed.

Various drugs induce EEG desynchronization with varying degrees of efficacy. Mepazine and diethazine, two phenothiazine derivatives, and benactyzine induced desynchronization with small amounts of theta activity. Delta activity has not been observed with those drugs, nor have we found reports either of seizures or parkinsonism in the clinical literature. Furthermore, in acute experiments, diethazine and benactyzine have been shown to desynchronize the EEG delta records of patients undergoing electroshock therapy.

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Fig. 6, 7, 8, 9

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Of these newer tranquilizers, chlorpromazine, perphenazine and reserpine have been consistently clinically reported as most useful in altering gross psychotic behavior patterns. These are also the drugs that induce the shift in EEG frequencies to the delta range. Meprobamate, mepazine and benactyzine

are clinically less useful. These are the agents that produce EEG changes in the direction of fast frequencies or desynchronization. Thus, in the tranquilizers, as in convulsive therapy, an EEG frequency shift in the delta range is a concomitant of significant behavioral effects.

(c) Insulin Coma Therapy:

The effects of insulin coma therapy may be analyzed in a similar fashion. During each coma, EEG delta activity is induced, which usually persists for minutes to a few hours after gavage. Not infrequently, in approximately one third of patients receiving deep coma therapy in this hospital, seizures, aphasia or prolonged coma results. After such events EEG changes of delta activity persist for days, and in cases of prolonged coma, for weeks and months.

The relation between prolonged coma, altered brain function and behavioral response has been discussed at length by various authors who conclude that improvement is related to the induction of organic brain damage. We have observed a similar relationship, and reported one such case study. A 34 year old schizophrenic patient with paranoid ideation

developed a left hemiplegia during insulin coma therapy. With the onset of neurologic signs there was a marked change in speech and behavior. His former paranoid - withdrawal type pattern was replaced by a friendly cooperative attitude. These changes were accompanied by delta changes in the EEG.

(d) Lobotomy:

While we have not had the personal opportunity to study lobotomy patients from the point of view of this summary, the reports of numerous observers clearly document a similar relationship. EEG changes of delta activity are present in all subjects post-operatively and persist for varying periods, up to three years. Furthermore, post-operative seizures are a frequent complication, being variously reported as occurring in 3 to 20% of subjects.

DISCUSSION:

Thus, when various physiodynamic therapies are essayed from the point of view of an alteration in brain function, we may infer a common mode of action. These therapies represent devices for the induction of changes in brain function with resultant changes in behavior.

EEG analysis of the effects of these modalities permits a more explicit definition of the induced alteration in brain function. Changes in cerebral function reflected by a shift in the spectrum of EEG frequencies toward the delta range, with an increase in synchronization, provides the milieu change which is most effective in altering psychotic behavior. The significance of the delta shift has been clearly demonstrated in electroconvulsive therapy; and can be inferred from the available data for the newer psycho-pharmacologic agents, lobotomy and insulin coma.

That a shift in EEG frequencies towards increased synchronization, especially slowing, has some specificity is seen in the analyses of the drug effects. Those drugs that induce a delta shift - the phenothiazines and reserpine - have been consistently reported as effective modifiers of psychotic behavior, and also as potent anti-hallucinogens.

Agents that induce a change in brain function reflected by increased synchronization in the beta range, as barbiturates and meprobamate also have effects of sedation and tranquilization, but are less potent. Drugs that induce EEG desynchronization, as benactyzine, diethazine and mepazine, in contrast, are poor tranquilizers; and in high dosage induce anxiety, tension and illusory phenomena. These observations are clearly consistent with those of Wikler ( ) who concluded in his studies of morphine and mescaline that " . . regardless of the nature of the drug administered, shifts in the pattern of the electroencephalogram in the direction of desynchronization occurred in association with anxiety, hallucinations, fantasies, illusions or tremors, and in the direction of synchronization with euphoria, relaxation or drowsiness."

How persistent changes in cerebral function affect behavior is not clear. Psychotic behavior is not 'reversed' or 'obliterated.' Rather, with an alteration in the central nervous system milieu, there is an alteration in all aspects of behavior including perception, mood, affect, memory, judgment and attitude. The adaptive response under these conditions is variable

for each subject and is dependent on numerous historical and environmental factors. Premorbid personality, environmental situation and expectations, and the duration of the alteration in brain function have recently been discussed as determinants of the individual behavioral response.

The induced changes in behavior are evaluated by the psychiatrist as to the degree of "improvement." These ratings are value judgments, based upon such factors as the type of induced behavioral response, the environmental tolerance, and the observer's expectations. In this context, the physiodynamic therapies do not induce 'improvement' - rather, they induce a behavioral change which is evaluated as improvement. The alteration of cerebral function is therefore not a 'complication' or an 'untoward effect' but the desired goal of these forms of therapy. Of the many 'organic' therapies introduced during the past thirty years, none apparently, has been a specific agent for the therapy of psychoses (in the sense that penicillin is specific for neurosyphilis and nicotinic acid for pellagra dementia), but rather devices with greater or lesser degrees of applicability and efficacy in altering behavior by altering the cerebral milieu.

In summary, we have examined the neurophysiologic aspects of various physiodynamic therapies, and have concluded that the therapeutic process of electroshock, insulin coma, lobotomy and tranquilizers may be ascribed to the induction of a persistent alteration in cerebral function which provides the milieu for a change in adaptation of the subject to his environment. The efficacy of each treatment method is related to its ability to induce a persistent change in cerebral function, of which the delta shift in the EEG spectrum with increased synchronization may be a significant index. Such a concept has applicability in the management of each of these therapies; to the screening of new psychopharmacologic agents, and as a frame of reference for further study of behavior and neurophysiology.