Role of EEG Frequency Shift in Behavioral Effects of Drugs

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During the past few years we have been interested in the interrelationship of changes in various measures of brain function and the behavioral response of psychiatric patients to somatic therapies. Our initial studies were devoted to the changes in tactile perceptual tasks in patients with organic psychoses. This study, carried out at Bellevue Psychiatric Hospital, demonstrated that patients with active organic psychotic reactions made repeated errors in the simple task of reporting two simultaneously applied cutaneous stimuli. The persistence of such errors was interpreted as an index to the presence of an "organic mental syndrome."

In the initial studies at Hillside Hospital in 1952, the same patterns of errors were observed in patients receiving convulsive therapy. We then became interested in the role of altered brain function in the "improvement" induced by convulsive therapy. In our first group of patients we followed consecutive electroshock referrals with weekly measures of changes in brain function and clinical interviews. We used four indices of brain function: memory tests, simultaneous tactile tests, the amobarbital test for organic brain disease described by Weinstein and Kahn, and the degree of induced delta activity in the EEG. It was soon apparent that neither the memory scales nor the tactile tests were sufficiently sensitive indicators of alteration in brain function to be satisfactory for our purposes. The amobarbital test, however, was a sensitive indicator. In this test, the subject is asked a series of questions regarding his illness

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and orientation for place, date, time and person. Following the administration of intravenous amobarbital until the patient has nystagmus, the questions are repeated. Errors of confabulation and disorientation are scored as "positive" tests, and have been found almost exclusively in subjects with active cerebral dysfunction. In the patients in the electroshock series, a significant relationship was observed between changes in this test and improvement ratings in convulsive therapy.

Fig. I

Amobarbital Test - Improvement

EST #1

We also measured the changes in the degree of induced delta activity in the EEG. Examination of a series of preliminary records, as well as the description in the literature, demonstrated the early development and persistence of slow wave activity in the EEG during convulsive therapy. With this preliminary information, we obtained weekly records during and after a course of treatment. We measured specified leads for the per-cent time delta, the slowest frequency, highest voltage of delta and the duration of burst activity. Using these quantitative indices we ranked the initial 180 records in 24 patients according to the extent of the induced delta activity. The upper third were classed as "high degree delta records," the middle third as "middle or moderate degree delta" and the lowest third as "low degree delta activity."

Figs. 2, 3, 5

High, Middle and Low Delta - EST #1

When we related the development of high degree delta activity to improvement rating, a significant relationship was again demonstrated.

Fig. 5

EEG Delta - Improvement - EST #1

In subsequent months we embarked on a predictive study, relating the development of high degrees of EEG delta activity during the second and third weeks of treatment to improvement ratings. In the next table, we have summarized these observations in the next 54 patients.

Fig. 6

Table: Patients High Delta 2nd, 3rd weeks of Treatment

EST 2, 3, 4

By this time we believed that EEG delta activity was related to the behavioral changes in convulsive therapy, and its significance was tested in a control convulsive-subconvulsive study. Of consecutive convulsive therapy referrals, randomly selected patients were subjected to a course of subconvulsive therapy instead of the convulsive therapy. This substitution was unknown to the patients or their therapists. Of the 47 subjects who received convulsive therapy in this series, high degree delta activity records were observed in 34 during the second to the fourth weeks of treatment. Of the 27 subjects who received subconvulsive therapy, however, none demonstrated either high or middle degree delta activity

EEG records during any week of treatment. In concurrent behavioral evaluations, 42 of the 47 subjects in the convulsive group showed marked behavioral change, while only 3 of the 27 in the subconvulsive group showed such a change. In clinical improvement ratings, 24 of 47 were rated "recovered" and "much improved;" 15 as "improved" and 8 as "unimproved or worse." But of the subconvulsive group, only 3 were rated "recovered" and "much improved," 5 as "improved" and 19 as "unimproved or worse."

We were now convinced that high degree of EEG delta activity reflected the physiologic changes essential to the behavioral change in convulsive therapy. An alteration in brain function, sufficient and of the kind to induce considerable EEG slow wave activity appeared to be the prerequisite, - a necessary, though not sufficient factor - in the convulsive therapy process. Perhaps a similar relationship was observable in other somatic therapies?

We next examined insulin coma therapy. During each coma, EEG delta activity is induced, which usually persists for a few minutes to a few hours after gavage. Not infrequently - in approximately 1/3 of patients receiving deep coma insulin therapy in our hospital, seizures, aphasia or prolonged coma result. 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 by numerous authors. Revitch reported eight cases and concluded that improvement was related to the induction of organic brain damage, similar to lobotomy. Yaeger et al

noted a correlation between length of coma, degree of organic confusion, remission of mental symptoms and degree of EEG abnormality in 12 cases of prolonged coma. In reviewing our insulin coma experiences, we noted that our best clinical results have been observed in prolonged coma cases. As a result, it has been the intention of our staff to induce such a state. Persistent EEG delta activity has been observed in a small number of our coma subjects, and only in those with prolonged coma or persistent neurologic signs. Thus, in insulin coma also, a relation between EEG delta change and behavioral response is indicated.

Concurrent with these investigations, we had begun clinical investigations with the newer tranquilizers. Initial study of Raudixin in 1953 failed to indicate any clinical efficacy. With reserpine, however, we were able to administer large doses - up to 10 mgm. At these levels, behavioral change become prominent but so also did neurologic complications. Parkinsonism was readily induced, and seizure induction and increased clinical depression became prominent. The EEG changes on chronic administration were small. With our doses, desynchronization was apparent, but at higher dosage hypersynchrony was also noted.

With chlorpromazine, however, we were more fortunate. We had undertaken a control insulin-coma-chlorpromazine study, in which the experimental dosage called for levels sufficient to induce clinical parkinsonism. In three of the thirty patients grand mal seizures were induced. In all patients significant changes were observed in serial EEGs. These consisted of increased modulation, increase in per-cent time alpha, and in twenty patients low voltage theta and delta activity. On hyperventilation, delta

burst activity was observed.

In reviewing the experiences of others, we noted numerous reports of chlorpromazine inducing seizures; exaggerating seizure activity in epileptics; and activating seizure EEG records. Similar reports are available for reserpine.

A review of the electroencephalographic effects of various phrenotropics demonstrated that not all newer agents induced slow wave activity. Meprobamate, in clinical doses, induces an increase in EEG fast activity, with increased voltage and spindling. The records are most similar to barbiturate records.

Benactyzine (or suavitil) induced neither slow nor fast wave activity but desynchronized the record, with flattening of voltages and loss of whatever rhythmicity was present.

From our clinical experience we were impressed that chlorpromazine and reserpine were the most effective modifiers of psychotic behavior, with benactyzine and meprobamate as relatively inefficient agents. It seemed appropriate therefore to extend the neurophysiologic adaptive hypothesis of the mode of action of convulsive and insulin coma therapies; it was suggested therefore, that agents that induce a change in brain function reflected by a shift in EEG frequencies to the delta range would be most active in modifying psychotic behavior; while those that induce a shift to the beta range, or desynchronize the record would be less effective. As a corollary it was suggested that agents that induce no change in brain function or changes so small as not to be reflected in serial EEGs would have little behavioral effect. Thus, a classification of newer phrenotropic

drugs based on their EEG effects was suggested:

(a) Increased slow wave activity with hypersynchrony

(b) Desynchronization with voltage and frequency irregularity, and irregular theta

(c) Increased high voltage fast activity

In reviewing the available literature reports of promazine and perphenazine would indicate that these agents induce a shift in the EEG spectrum to the delta range. Mepazine has minimal EEG effects, and these are largely desynchronization. Information regarding other newer agents was not available.

We have undertaken two studies based on this hypothesis relating EEG changes to behavior. One is serial EEG studies of patients now receiving chronic tranquilizer medication at the hospital. A second is a study of the relation between the EEG and the behavioral effects on acute administration: the data of our chronic administration studies are not yet available, but the acute studies have progressed sufficiently to demonstrate the applicability of the hypothesis.

Following the observations by Denber that one of the phenothiazine derivatives, diethazine, when administered with chlorpromazine, would elicit slow wave activity similar to convulsive therapy, we undertook some explorations of this compound. In the EEG laboratory with continuous EEG recording, varying amounts of diethazine from 100 to 250 mg. were administered intravenously over a 10 minute period in psychiatric patients at various stages of the convulsive therapy process. Instead of hypersynchrony, patients who were pretreatment and without EEG delta activity, demonstrated significant desynchronization of the record.

Fig. 7, 8

EEG - Diethazine - Pretreatment

Most interesting, however, was the effect of diethazine in patients with increased slow wave activity during convulsive therapy. Here, too, desynchronization became manifest, and there was a decrease in the voltage and per-cent time of the induced delta activity.

Fig. 9, 10

EEG - Diethazine - Delta Activity

Concurrent with these EEG effects, we observed distinctive behavioral changes. Patients became more irritable and restless; they complained of sensations of unreality, and of dysesthesias of the extremities. In some, visual illusory phenomena and delusional thoughts about their illness, the setting of the test procedures or our identity. There were changes in their language patterns opposite to that previously described for amobarbital, so that denial, minimization, cliches, third person mode and past tense were less prominent. The duration of these behavioral and language changes was from one to five hours. The EEG changes were of similar duration - appearing during the period of drug administration and disappearing when the behavior had apparently reverted to the pretreatment state.

The ability of diethazine to induce illusory and hallucinatory activity led to an evaluation of other known hallucinogens. In checking

the literature we noted that Denber and Merlis had previously described that mescaline reversed the EEG changes induced by electroshock, in a fashion identical with diethazine. Pennes had observed hallucinogenic activity for another experimental compound Win 2299. We obtained some of this material, and repeated our diethazine studies. Here, too, Win 2299 induced EEG desynchronization associated with clinical patterns of restlessness, excitement, hallucinatory and illusory activity.

Fig. 11, 12

Win 2299 - EEG

We repeated these studies with LSD, and again the same patterns. There was a difference in the time constant, but concurrent with the behavioral effects we observed EEG changes.

Fig. 13, 14, 15

LSD - EEG

Recalling the ability of benactyzine to desynchronize records, we administered this compound intravenously, and again, we observed the same EEG pattern of desynchronization, associated with restlessness and excitement. While we did not observe the illusory and hallucinatory patterns, we did note the same kinds of language changes in these patients that we observed with diethazine.

Fig. 16, 17

Benactyzine - EEG

The chemistry of these compounds is noted in the next figure:

Fig. 18

Thus, from each of these agents, EEG desynchronization was induced, and hallucinogenic or excitatory activity was observed.

We can now amplify our initial hypothesis to encompass hallucinogens. In this regard, I would like to refer first to conclusions described in 1954 by Wikler in a study of the effects of mescaline, n-allylnormorphine and morphine in man, in which he stated: ".... regardless of the drug administered, shifts in the pattern of 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." We would now generalize our observations of EEG changes and behavior to note that agents that induce EEG synchronization and shift to the delta range are potent agents in the control of psychotic behavior. Agents that induce synchronization in the beta range are relaxant, euphoriant and sedative, while agents that desynchronize the record tend to be hallucinogenic.

This hypothesis lends itself to a variety of applications. It provides a bases for the understanding of the mode of action of various organic

therapies in psychiatry. EEG analysis may also provide a basis for the assay of new drugs and therapy procedures. Finally, these observations permit a more rational management of the somatic therapies. I would like to explore each application in summary fashion.

The application of the neurophysiologic adaptive hypothesis - for that is the rubric under which we subsume the relationship between the changes in brain function, reflected by the EEG, and the changes in behavior - to insulin coma therapy has already been described. We have applied this concept to our studies of phrenotropic agents, and have been able, both predictively and retrospectively, to assess new agents. It is possible to understand lobotomy therapy, and sleep therapy, within this framework.

As for the assay of new drugs, our explorations into hallucinogens is one example. We have recently noted that each of the potent hallucinogens have a biochemical similarity in a common tertiary amine radical connected by an ethyl linkage to a large nucleus. On this basis, we sought for compounds with this linkage. One group are known anti-parkinson agents with anti-cholinergic properties as parsidol, artane, kemadrin, panparnit and benadryl. We have not yet tested these compounds for their EEG or clinical effects. Recently, Pfeiffer reported at the Academy of Neurology that these compounds, in trained subjects, were identified most with LSD. In 1956, Gottlieb reported that benadryl desynchronized the EEG of electro-shock patients, much as we saw this evening. Thus, some confirmation is available in the literature.

With regard to the third application - the management of somatic therapies - this hypothesis may be of considerable help. In convulsive therapy and in drug therapies, the patient who responds in a favorable fashion is no problem. But what of the patients who responds poorly, or not at all? Could the failure of response be related to inadequate dosage? In electroshock, when a patient manifests paranoid or withdrawal behavior, or no significant change, an EEG provides a guide to management. If the record fails to demonstrate high voltage slow wave activity, then we may assume that treatment has been inadequate, and continue the treatment course or increase the frequency or alter the convulsant method. If EEG changes are present, then we would assume that other factors - personality, sociologic or interpersonal - are not conducive to "improvement" by electroshock, and other remedies sought. Similar applications are possible for phrenotropic agents.

In summary, we believe that somatic therapies in psychiatry exert their effects primarily by altering brain function. Changes in the EEG spectrum are one reflection of such alteration and are useful as a guide to the mode of action, effectiveness and application of somatic therapies.