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A UNIFIED THEORY OF THE ACTION OF PHYSIODYNAMIC THERAPIES[1]

MAX FINK, M.D.[2]

The proper role of the physiodynamic therapies (convulsive, insulin coma and lobotomy) in psychiatry remains poorly defined. In part, this results 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 electroconvulsive therapy has been presented (41, 32, 38, 1). This view ascribes the therapeutic process in electroshock to a persistent alteration in cerebral function which provides the milieu for a change in adaptation of the subject to his environment. The type of adaptation evoked is dependent upon the personality of the subject, the environmental situation, and the duration of the induced alteration in cerebral function. Concurrently, an awareness of a similar mode of action in insulin coma (31) and lobotomy (40) has developed.

During the past four years we have studied the relation between alteration in various indices of brain function and the behavioral response of psychiatric patients to therapy. The neurophysiologic-adaptive view of electroshock has been supported and amplified (11, 12, 13, 19, 21); evidence for a similar view of insulin coma has been presented (22); and recently the concept has been extended to the newer "tranquilizers" (9). These studies provide the basis for a generalization concerning the efficacy of these therapies. It is our purpose in this report to examine the experimental evidence to determine whether or not the mode of action of each of these thera-

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

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pies 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 a "complication" or "untoward effect."

The indices of brain function used in these studies have varied. These include memory scales (26), visual (20) and tactile (10) perceptual tasks, and changes in language patterns of orientation both clinically (19) and after intravenous amobarbital (21). In electroencephalographic studies of this problem, changes in the delta index, both in routine records (11, 12) and after activation by intravenous thiopentone (32, 33), and in the beta index (16) have been applied successfully. For this review, two indices will be stressed: changes in the delta index of the unactivated EEG, and clinical neurologic signs. These indices have been selected because of their successful application in the analysis of the electroshock process, and because data is available for each of the therapeutic modalities.

Observations

(a) *Electroshock*

The following notes summarize our experimental studies of the role of changes in EEG delta activity in the response of subjects to electroshock (11, 13). In these studies, electroencephalograms were obtained before treatment, and at weekly intervals on a day after a treatment in consecutive electroshock referrals. Grand mal treatments were administered three times a week, for twelve to twenty treatments. The EEG records were quantitatively analyzed for the amount of induced delta activity, and classified into categories of "high," "moderate" and "low" degrees of delta activity. At the end of treatment, the patients were independently rated for their short-term clinical response into the categories of "much improved," "moderately improved" and "unimproved."

In the initial 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 much improved group were high degree delta by the fourth to sixth treatment; and the percentage was sustained at 90 per cent 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 per cent of the records in the fourth week were so classified.

In a subsequent predictive study, the EEG records during the

second and third weeks of treatment were analyzed. Of the patients who had high degree delta records on both occasions, 67 per cent were rated as much improved, while of the patients without such records, 70 per cent were in the unimproved and moderately improved categories.

Roth (32, 33), studying the EEG delta activity evoked by intravenous thiopentone after electroshock, has related both the stability and the rate of remission of patients with endogenous depressions to the peak value of the induced slow activity. He concluded that patients not attaining a specified delta activity level "have not acquired an adequate physiological basis for recovery," and recommended measurement of delta activity levels after thiopentone as a guide to the clinical management of patients.

Further information is obtained from convulsive-subconvulsive control studies. While convulsive electroshock induces degrees of delta activity that vary from low to high, subconvulsive therapy rarely alters EEG patterns or induces low degrees of delta activity (13). In their comparative study of different convulsive and subconvulsive techniques, Ulett, Smith and Gleser (38) demonstrated a significantly greater recovery rate for the convulsive than the subconvulsive group.

In a similar study (13) recently completed here, twenty-seven patients received a course of subconvulsive therapy. Electroencephalograms, taken at weekly intervals, demonstrated minimal changes—none of the records were scored as middle or high delta activity. Of the twenty-seven patients, no change in behavior was noted in twenty-three, and of these, nineteen were referred for a second course of treatment. Grand mal electroshock induced a high degree of delta activity in fourteen. All patients in this group showed significant changes in behavior, while of the five who did not show the delta response, only two showed a behavioral change.

(b) *Tranquilizing Drugs*

When the newer drug therapies are studied from the viewpoint of their electroencephalographic and clinical neurologic effects, a meaningful classification emerges. Furthermore, a relationship between the degree and type of induced change in cerebral function and therapeutic efficacy may be noted. The ability of these agents to induce such signs of central nervous system dysfunction as motor rigidity, depression, excitement and seizures are well known. Less well documented, however, are the clearly definable electroencephalographic patterns. Based on observations made in chronic admin-

istration of drugs in adult psychiatric patients, the EEG changes may be classified according to predominant changes in the frequency spectrum. There are three broad types:

I. Increased slow wave activity with hypersynchrony ("bursts")—"delta shift"
II. Desynchronization with voltage and frequency irregularity and irregular theta activity—"desynchronization"
III. Increased high voltage fast activity—"beta shift."

Of the group of drugs inducing a delta shift, the phenothiazine derivatives chlorpromazine, promazine, and perphenazine are clear examples. Each drug induces seizures in nonepileptics or exaggerates seizures in epileptic patients (7, 8, 15, 29, 37). Each drug induces clinical parkinsonian neurologic patterns when given in adequate dosage. In our laboratories, we have induced parkinsonism in all patients receiving chlorpromazine (14) and have observed seizures in 10 per cent of a group of psychotic patients without previous history of seizures. Induced delta activity, including burst activity, was observed in more than half the patients in this series.

Reserpine also evokes delta activity when given in large doses (2). At high dosage levels, it exaggerates seizures in epileptics and induces seizures in animals (35). At the usual clinical dosages, however, reserpine induces desynchronization of frequencies with a moderate increase in theta activity (28), without seizure induction but with definite motor rigidities. In a series of patients treated here (39), parkinsonism was induced in all patients. EEG changes were limited to desynchronization only, without delta burst activity.

The primary response of two other drugs, mepazine and benactyzine, is the induction of EEG desynchronization. Mepazine, a phenothiazine derivative, induces desynchronization with small amounts of theta activity (7). Delta activity has not been described, nor have we found reports either of seizures or parkinsonism in the clinical literature. Benactyzine, a potent anticholinergic compound, induces a blocking of alpha, flattening of the record and occasional theta activity (5, 17). Neither seizures nor parkinsonism have been described for this agent.

Meprobamate is the clearest example of the group of drugs inducing a beta shift in the EEG (3). This agent further differs from the phenothiazines and reserpine in not producing parkinsonism and not only are clinical seizures not induced, but definite antiepileptic activity has been described (30). Habituation is readily

achieved, and withdrawal phenomena of agitation and seizures have been observed (42). In these actions, meprobamate is more like barbiturates than like the other new tranquilizers.

If we determine the clinical efficacy of these agents, we note a parallel between the induced EEG effects and their potency in altering behavior. The drugs that most readily induce a delta shift in EEG frequencies—the phenothiazine compounds—are those with the greatest clinical efficacy in the therapy of psychoses. The compounds with lesser activity in this direction are less efficacious clinically.

(c) *Insulin Coma Therapy*

The effects of insulin coma therapy on the nervous system are well documented. 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 (43).

The relation between prolonged coma, altered brain function and behavioral response has been discussed at length. Revitch (31) reported eight cases of prolonged coma and concluded that improvement may be attributed to the induction of organic brain damage, similar to lobotomy. Yaeger, Simon, Margolis and Burch (43), describing twelve cases of prolonged insulin coma, noted a correlation between length of coma, degree of organic confusion, remission of mental symptoms and degree of EEG abnormality. Shagass and Rowsell (34), emphasizing EEG data, and Kwalwasser and Caplan (27) presented individual cases to support the same conclusion.

We reported a similar relationship between prolonged coma and behavioral response in a case study (22). A 34-year-old schizophrenic patient with paranoid ideation developed a left hemiplegia during insulin coma therapy. With the onset of neurologic signs of hemiparesis, hemianopsia, hemisensory syndrome and spatial inattention, there was a marked change in speech and behavior. He became lucid, loquacious and denied his illness. His former paranoid-withdrawal type pattern was replaced by a friendly cooperative attitude. These changes were accompanied by delta changes in the EEG, as well as language changes after amobarbital indicative of altered brain function. The neurologic symptoms resolved, but the behavioral changes persisted so that he was discharged two months later as "much improved."

(d) *Lobotomy*

While we have not had the 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 postoperatively (6) and persist for varying periods. Walter et al. (40) in a study of 150 patients, found an 80 per cent persistence of abnormal EEG activity after three years. These authors also noted a relation between clinical improvement and the degree and extent of postoperative slow wave activity.

Postoperative seizures are a frequent "complication," being variously reported as occurring in up to 20 per cent of subjects (25). Furthermore, there is a relationship between the extent of brain tissue cut and the therapeutic outcome. Circumscribed surgical lesions, regardless of locus, have an improvement rate lower than unilateral lobectomy; and these latter are frequently inadequate and are "improved" upon by a bilateral procedure (36).

Discussion

When the various physiodynamic therapies are essayed from the point of view of an alteration in brain function, a common mode of action becomes apparent. These therapies represent devices which induce appreciable changes in brain function, with resultant change in behavior. Convulsive therapy and lobotomy induce measurable diffuse changes in brain function directly; insulin coma primarily when complications ensue; and the phenothiazine and reserpine groups of tranquilizers when given in adequate dosage.

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 specific adaptive response is variable for each subject and is dependent on numerous historical and environmental factors. Premorbid personality (18), environmental situation and expectations (13), and the duration of the alteration in brain function (12) have recently been discussed as determinants of the behavioral response under these conditions.

The induced changes in behavior are evaluated by the psychiatrist, administrator or family 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 behavioral change which is secondarily 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 this context, the various physiodynamic therapies are not specific for a type of psychosis. The early enthusiasm that reserpine or chlorpromazine was specific for schizophrenia, or hypotheses that ascribe significance to an antagonism between these drugs and "psychosis" or "schizophrenia" are not tenable. Similar enthusiasm claiming a specificity of insulin coma for schizophrenia is also untenable, and support for this view is presented in a recent chlorpromazine-insulin coma control study (14).

EEG analysis of these therapies 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 slower range, with a concomitant increase in voltage and a periodicity described as "bursts" or "hypersynchrony" provide the change in milieu that is more effective in altering behavior. The significance of the delta shift has been clearly demonstrated in electroshock therapy; and can be inferred from the available data in lobotomy, insulin coma, and the tranquilizers.

That a delta shift has some specificity is seen in the analyses of the drug effects. Those drugs that induce the delta shift—the phenothiazines and reserpine—have been consistently reported as effective modifiers of psychotic behavior. Changes in brain function reflected by EEG desynchronization only, or a shift in frequency spectrum to the faster range, have a limited efficacy in altering psychotic behavior.[3] The significance of a delta shift is further seen in the limited efficacy of subconvulsive electroshock when compared to convulsive electroshock in the management of psychoses.

Another aspect of the alteration in brain function which may be defined is the change in seizure threshold. With the delta shift in

[3] These observations suggest the application of EEG screening of new chemotherapeutic compounds for therapeutic efficacy according to their ability to induce delta burst activity with a minimum of side effects.

the EEG, an increase in clinical seizures would be anticipated. This is indeed true. Seizures have been described following electroshock (4, 24); they are prominent after lobotomy (40) and a common "complication" during and occasionally following insulin coma therapy (23). With the tranquilizers, the parallel of clinical efficacy and seizure induction is most striking. Phenothiazine compounds induce seizures commonly; reserpine rarely; benactyzine not at all; and meprobamate is a potent anticonvulsant! The lowering of seizure threshold parallels the extent of the EEG delta shift induced by these compounds. Similar analyses can be made for the potentiation of sedative action and induction of parkinsonism—both potent indices of an alteration in cerebral function.

The neurologic basis for the delta shift and increase in seizure frequency is unclear. Whether this represents a persistent change in function of some specific brain stem nuclear system, as the centrencephalic, thalamic or hypothalamic, is conjectural. From the wide range of agents that can induce a delta shift, with or without hypersynchrony, it appears more likely that the EEG changes reflect an alteration in the diffuse biochemical activity of the nervous system rather than in a focal activity of specific cellular masses.

Summary

1. The neurophysiologic and clinical neurologic aspects of convulsive therapy, "tranquilizers," insulin coma and lobotomy, are reviewed.

2. The efficacy of each therapy in the treatment of psychoses is related to the ability to induce a persistent change in cerebral function, of which a delta shift in the EEG spectrum and an increase in incidence of seizures are two indices.

3. Alteration in cerebral function is an essential prerequisite of behavioral change with each of these therapies. Such alteration is neither a "complication," nor an "untoward effect," but is the *sine qua non* of the mode of action of these therapies.

4. No evidence has been educed in these studies that the physiodynamic therapies are specific agents for the relief of psychoses; nor do they affect a specific segment of the nervous system; nor do they induce specific behavioral changes.

5. The therapeutic process of convulsive therapy, 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.

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between the induced EEG effects and their potency in altering behavior. The drugs that most readily induce a delta shift in EEG frequencies - the phenothiazine compounds - are those with the greatest clinical efficacy in the therapy of psychoses. The compounds with lesser activity in this direction are less efficacious clinically.

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The effects of insulin coma therapy on the nervous system are well documented. 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 (43).

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DISCUSSION:

When the various physiodynamic therapies are essayed from the point of view of an alteration in brain function, a common mode of action becomes apparent. These therapies represent devices which induce appreciable changes in brain function, with resultant change in behavior. Electroshock and lobotomy induce measurable diffuse changes in brain function directly; insulin coma primarily when complications ensue; and the phenothiazine and reserpine groups of tranquillizers when given in adequate dosage.

How persistent changes in cerebral function affect behavior is not clear. Psychotic dehavior 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 specific adaptive response is variable for each subject and is dependent on numerous historical and environmental factors. Pre-morbid personality (18), environmental situation and expectations (11), and the duration of the alteration in brain function (10) have recently been discussed as determinants of the behavioral response under these conditions.

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EEG analysis of these therapies 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 slower range, with a concomitant increase in voltage and a periodicity described as "bursts" or "hypersynchrony" provide the change in milieu that is more effective in altering behavior. The significance of the delta shift has been clearly demonstrated in electroshock therapy; and can be inferred from the available data in lobotomy, insulin coma, and the tranquillizers.

That a delta shift has some specificity is seen in the analyses of the drug effects. Those drugs that induce the delta shift - the phenothiazines and reserpine - have been consistently reported as effective modifiers of psychotic

of psychotic behavior. Changes in brain function reflected by EEG desynchronization only, or a shift in frequency spectrum to the faster range, have a limited efficacy in altering psychotic behavior. * The significance of a delta shift is further seen in the limited efficacy of subconvulsive electroshock when compared to convulsive electroshock in the management of psychoses.

Another aspect of the alteration in brain function which may be defined is the change in seizure threshold. With the delta shift in the EEG, an increase in clinical seizures would be anticipated. This is indeed true. Seizures have been described following electroshock (4, 24), are prominent after lobotomy (40) and a common "complication" during and occasionally following insulin coma therapy (23). With the tranquillizers, the parallel of clinical efficacy and seizure induction is most striking. Phenothiazine compounds induce seizures commonly; reserpine rarely; benactyzine not at all; and meprobamate is a potent anticonvulsant! The lowering of seizure threshold parallels the extent of the EEG delta shift induced by these compounds. Similar analyses can be made for the potentiation of sedative action and induction of parkinsonism - both potent indices of an alteration in cerebral function.

The neurologic basis for the delta shift and increase in seizure frequency is unclear. Whether this represents a persistent change in function of some specific brain stem nuclear system, as the centrencephalic, thalamic or hypothalamic, is conjectural. From the wide range of agents that can induce a

* These observations suggest the application of EEG screening of new chemotherapeutic compounds for therapeutic efficacy according to their ability to induce delta burst activity with a minimum of side effects.

delta shift, with or without hypersynchrony, it appears more likely that the EEG changes reflect an alteration in the diffuse biochemical activity of the nervous system rather than in a focal activity of specific cellular masses.

SUMMARY:

1. The neurophysiologic and clinical neurologic aspects of electroshock, "tranquillizers," insulin coma and lobotomy, are reviewed.

2. The efficacy of each therapy in the treatment of psychoses is related to the ability to induce a persistent change in cerebral function, of which a delta shift in the EEG spectrum and an increase in incidence of seizures are two indices.

3. Alteration in cerebral function is an essential prerequisite of behavioral change with each of these therapies. Such alteration is neither a "complication," nor an "untoward effect," but is the sine qua non of the mode of action of these therapies.

4. No evidence has been educed in these studies that the physiodynamic therapies are specific agents for the relief of psychoses; nor do they affect a specific segment of the nervous system; nor do they induce specific behavioral changes.

5. The therapeutic process of electroshock, insulin coma, lobotomy and tranquillizers 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.

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A Unified Theory of the Action of Physiodynamic Therapies

Max Fink, M.D.

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

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A Unified Theory of the Action of Physiodynamic Therapies

The proper role of the physiodynamic therapies (electroshock, insulin coma and lobotomy) in psychiatry remains poorly defined. In part, this results 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 (41, 32, 38, 1). This view ascribes the therapeutic process in electroshock to a persistent alteration in cerebral function which provides the milieu for a change in adaptation of the subject to his environment. The type of adaptation evoked is dependent upon the personality of the subject, the environmental situation, and the duration of the induced alteration in cerebral function. Concurrently, an awareness of a similar mode of action in insulin coma (31) and lobotomy (40) has developed.

During the past four years we have studied the relation between alteration in various indices of brain function and the behavioral response of psychiatric patients to therapy. The neurophysiologic-adaptive view of electroshock has been supported and amplified (9, 10, 11, 20, 21); evidence for a similar view of insulin coma has been presented (19); and recently the concept has been extended to the newer "tranquillizers" (12). These studies provide the basis for a generalization concerning the efficacy of these therapies. It is our purpose in this report to examine the experimental evidence to determine whether or not the mode of action of each 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 a "complication" or "untoward effect."

The indices of brain function used in these studies have varied. These include memory scales (26), visual (22) and tactile (13) perceptual tasks, and changes in language patterns of orientation both clinically (21) and after intravenous amobarbital (20). In electroencephalographic studies of this problem, changes in the delta index, both in routine records (9, 10) and after activation by intravenous thiopentone (32, 33), and in the beta index (16) have been applied successfully. For this review, two indices will be stressed: changes in the delta index of the unactivated EEG, and clinical neurologic signs. These indices have been selected because of their successful application in the analysis of the electroshock process, and because data is available for each of the therapeutic modalities.

OBSERVATIONS:

(a) Electroshock:

The following notes summarize our experimental studies of the role of changes in EEG delta activity in the response of subjects to electroshock (9, 11). In these studies, electroencephalograms were obtained before treatment, and at weekly intervals on a day after a treatment in consecutive electroshock referrals. Grand mal treatments were administered three times a week, for 12-20 treatments. The EEG records were quantitatively analyzed for the amount of induced delta activity, and classified into categories of "high", "moderate" and "low" degrees of delta activity. At the end of treatment, the patients were independently rated for their short term clinical response into the categories of "much improved", "moderately improved" and "unimproved".

In the initial 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 percent of the records in the 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.

In a subsequent predictive study, the EEG records during the second and third weeks of treatment were analyzed. Of the patients who had high degree delta records on both occasions, 67% were rated as much improved, while of the patients without such records, 70% were in the unimproved and moderately improved categories.

Roth (32, 33) studying the EEG delta activity evoked by intravenous thiopentone after electroshock has related both the stability and the rate of remission of patients with endogenous depressions to the peak value of the induced slow activity. He concluded that patients not attaining a specified delta activity level, " ..... have not acquired an adequate physiological basis for recovery," and recommended measurement of delta activity levels after thiopentone as a guide to the clinical management of patients.

Further information is obtained from convulsive-subconvulsive control studies. While convulsive electroshock induces degrees of delta activity that vary from low to high, subconvulsive therapy rarely alters EEG patterns or induces low degrees of delta activity (11). In their comparative study of different convulsive and subconvulsive techniques, Ulett, Smith and Gleser (38) demonstrated a significantly greater recovery rate for the convulsive than the subconvulsive group.

In a similar study (11) recently completed here, twenty-seven patients received a course of subconvulsive therapy. Electroencephalograms, taken at weekly intervals, demonstrated minimal changes - none of the records were scored as middle or high delta activity. Of the 27 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 a high degree of delta activity in fourteen. All patients in this group showed significant changes in behavior, while of the five who did not show the delta response, only two showed a behavioral change.

(b) Tranquillizing Drugs:

When the newer drug therapies are studied from the viewpoint of

their electroencephalographic and clinical neurologic effects, a meaningful classification emerges. Furthermore, a relationship between the degree and type of induced change in cerebral function and therapeutic efficacy may be noted. The ability of these agents to induce such signs of central nervous system dysfunction as motor rigidity, depression, excitement and seizures are well known. Less well documented, however, are the clearly definable electroencephalographic patterns. Based on observations made in chronic administration of drugs in adult psychiatric patients, the EEG changes may be classified according to predominant changes in the frequency spectrum. There are three broad types:

I. Increased slow wave activity with hypersynchrony ("bursts") - "delta shift"

II. Desynchronization with voltage and frequency irregularity and irregular theta activity - "desynchronization"

III. Increased high voltage fast activity - "beta shift."

Of the group of drugs inducing a delta shift, the phenothiazine derivatives chlorpromazine, promazine, and perphenazine are clear examples. Each drug induces seizures in non-epileptics or exaggerates seizures in epileptic patients (7, 8, 15, 29, 37). Each drug induces clinical parkinsonian neurologic patterns when given in adequate dosage. In our laboratories, we have induced parkinsonism in all patients receiving chlorpromazine (14) and have observed seizures in 10% of a group of psychotic patients without previous history of seizures. Induced delta activity, including burst activity, was observed in more than half the patients in this series.

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Another aspect of the alteration in brain function which may be defined is the change in seizure threshold. With the delta shift in the EEG, an increase in clinical seizures would be anticipated. This is indeed true. Seizures have been described following electroshock (4, 24), are prominent after lobotomy (40) and a common "complication" during and occasionally following insulin coma therapy (23). With the tranquillizers, the parallel of clinical efficacy and seizure induction is most striking. Phenothiazine compounds induce seizures commonly; reserpine rarely; benactyzine not at all; and meprobamate is a potent anticonvulsant! The lowering of seizure threshold parallels the extent of the EEG delta shift induced by these compounds. Similar analyses can be made for the potentiation of sedative action and induction of parkinsonism - both potent indices of an alteration in cerebral function.

The neurologic basis for the delta shift and increase in seizure frequency is unclear. Whether this represents a persistent change in function of some specific brain stem nuclear system, as the centrencephalic, thalamic or hypothalamic, is conjectural. From the wide range of agents that can induce a

* These observations suggest the application of EEG screening of new chemotherapeutic compounds for therapeutic efficacy according to their ability to induce delta burst activity with a minimum of side effects.

SUMMARY:

1. The neurophysiologic and clinical neurologic aspects of electroshock, "tranquillizers," insulin coma and lobotomy, are reviewed.

2. The efficacy of each therapy in the treatment of psychoses is related to the ability to induce a persistent change in cerebral function, of which a delta shift in the EEG spectrum and an increase in incidence of seizures are two indices.

3. Alteration in cerebral function is an essential prerequisite of behavioral change with each of these therapies. Such alteration is neither a "complication," nor an "untoward effect," but is the sine qua non of the mode of action of these therapies.

4. No evidence has been educed in these studies that the physiodynamic therapies are specific agents for the relief of psychoses; nor do they affect a specific segment of the nervous system; nor do they induce specific behavioral changes.

5. The therapeutic process of electroshock, insulin coma, lobotomy and tranquillizers 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.

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delta shift, with or without hypersynchrony, it appears more likely that the EEG changes reflect an alteration in the diffuse biochemical activity of the nervous system rather than in a focal activity of specific cellular masses.

Differential Response to Drugs Useful in Treatment of Psychoses Revealed by Pentothal-Activated EEG.
D. Goldman MD.

Goldman'a göre Fr-h, Pentothal müessir psychozlarda hem de ayni [illegible] olduğu alındığında gayet güzel EEG, değişiklikleri tetkik ettiler. Chagass korku ile (Pentothal) sedation eşiği arasındaki münasebetlerini, Shneider + Thomalske ise EEG-Pentothal Aktivasyonunu neurochirurgie bakımından mütalaasını yapmışlardır.

Goldman 2000 psychotic psychotik olmayan hastada Pentothal Aktivasyonu değişimini tetkik etmiştir. Er spritzte nach 80–180 sec. Ableitung in 2–4 sec. 100 mg Pentothal Sodium. Pentothal Effekt wird in 10–25 sec. beobachtet. Bei nicht Schiz. Pat. lässt der Effekt in 40–60 sec. nach. Die 2–3 durchgeführte 2. Injektion von 100 mg. macht noch grössere Veränderungen, 1.5–3 min. später durchgeführte 3. Inj. löst meiste Veränderungen auf. Bei dieser Methode findet sich eine starke EEG-Veränd. bei Schizophr. "caracteristic Schizophrenic Trace" d. h. eine sehr ausgeprägte B-Aktiv. mit hoher Amplit. (bis über 1′), spezifische asymmetrische schnelle Burst aktivit. über den vorderen Hirnabschnitte betont u. gleich nach Ende der Inj. auftretende Theta Aktivität. Je die Pat. psychotischer sind desto zeigen stärkere EEG-Veränderungen. Diejenige die unter Perphenothi. od. Sch. 6894 Behandlung stehen, zeigen mit geringeren psychot. Symptome parallel geringere EEG-Veränderungen. Durch Medikament auftretende klinische Besserung der Schiz. Pat. zeigt mit den durch EEG-Veränderungen, die durch Med. Effekt resultieren klare Korrelation. Diese resultierende EEG-Veränderungen sind nicht auf einmalige Medikament Wirkung zurückführen, sondern sind sie eine Sättigung der monate lang dauernden Behandlung. Unter der Med. Auftretende EEG-Veränderungen zeigen eine Gemeinsamkeit mit den auftretenden psychopathologischen Manifestation. Wenn Symptome sich nicht verbessern, verbessert sich das EEG auch nicht. Bei einer Zahl von Pat. haben wir nach einer med. Behandlung

(B) | nach der Absetzung der Behandlung Wiederbeleb. die Ausprägung der Cyclus der EEG-Veränderungen (gleichzeitig) Rückfall der mit klinische Besserung beobachtet.

(Fig. 8–9) → zeigt sich dass die charak. EEG-Veränderungen vermindert werden, wenn der med. Effekt manifest war u. wenn die med. Behandlung mehrere Monate durchgeführt wird treten die EEG-Manifestation in verstärkte Masse wieder auf.

Die Studien der antidepressant Medikamente zeigt erstaunliche aber wahrscheinlich nicht überraschende Ergebnisse.

Turan M. Itil
Director, Dep. of Clinical
Neurophysiol. and EEG.

~~Die oralen An~~ Bei der oralen Gabe von antidepressiven Stoffe kann man nach längerer ~~Behandlung~~ Gabe die Aktivierung von Schiz. Exacerbationen od. bei Depressiven Pat. manische Tonen erzeugen. ~~Schiz. for~~ Bei der Behandlung von Schiz. mit antidepressiven Stoffe hat man fast immer diese Gefahr. Dieser klinische Effekt wird vom EEG meist reflektiert. Z.B. Pat WHA, ein depressiver Pat. nach einer Imipramin Behandlung mit der Aufklärung der ~~Depression~~ ~~g~~ keine parallelgehende EEG-Veränderunge gezeigt. Aber nachdem die Pat. manische Phase gekommen ist, zeigte ausgeprägte EEG-Veränderungen. Es ist die Tatsache dass in therap. Dosen ~~nicht~~ die antidepressiven Substanzen bei nicht aktive EEG- kennen keine Veränderunge erzeugen. Aber bei Schiz. u. Manische Zustände zeigt Pentothal Aktivierung spezifische EEG-Veränderungen wenn Pat. antidepressive Med. bekomme.

261. Depressive Pat. haben keine aktivierende Effekt auf Pentothal wie bei Schizophrene. Wenn die Depressive Pat. unter antidepressive Substanzen schizophrene od. manische Symptome zeigen, haben ganz andere Veränderunge wie die andere unter der Behandlung gebessert wurde.

FURTHER OBSERVATIONS MADE SINCE THE ARTICLE "Electro-encephalographic Evidence of Personality Changes by Ataraxic Drugs in Mentally Disturbed Patients." WAS WRITTEN.

1) A number of mistakes due to faulty or non-standardized technique in the assessment of alpha stability were made.

a) Duration of the recording:

It was found that some patients who had little alpha activity for the first five to ten minutes of the recording developed a more stable alpha activity, later on.

It is therefore suggested that samples of alpha activity should be taken at least ten minutes after the beginning of the E.E.G. recording.

b) Period of the day:

Slight differences of habitual alpha activity were observed in one and the same patient according to the time of the day when the E.E.G. recording was taken. The same applies also to the period of the last meal. It is therefore suggested that the E.E.G. tracings should be taken at the same time of the day and at the same intervals after the last mealhad been taken.

c) Waiting of the patient before the E.E.G. recording.

It was observed that if patients had to wait for long periods in the waiting room before his E.E.G. recordings were taken the alpha activity was poorer than on other occasions.

d) Noises.

The effect of any noises, particularly of any talk, during the E.E.G. recording changed the alpha E.E.G. pattern immediately.

It seems therefore that the total absence of any noise is necessary to produce a valid E.E.G. recording for the assessment of alpha stability.

c) A special alpha run, allowing the simultaneous tracing of temporal and parietal occipital alpha was found to be useful.

2) The alpha stabilizing effect of Largactil and Serpasil.

a) Single administration:

i. The intravenous and intramuscular administration of a single large dose of Largactil (100 mg.) or Serpasil (5 mg.) often had little or no effect on the alpha stability.

ii. The administration of the same drugs, over a period of 3 days to 2 weeks, did produce an alpha stabilization.

b) Age groups:

i. The effect of these two drugs, in sufficient quantities, was observed in all children whose habitual alpha activity was poor.

ii. In adults there were some exceptions to the rule, particularly elderly people suffering from depression.

c) Quantity:

The effect of alpha stabilization, even after a long period of administration, was sometimes only observed when large quantities of the drugs were given.

It is therefore suggested that in case of a negative E.E.G. effect the test should be repeated after increasing the dosage of the drug.

d) Temporal Alpha:

It is observed that in some cases the alpha stabilization occurred equally in the temporal and parietal occipital regions. Most often however, the alpha stabilization was more marked in the temporal regions, and not infrequently the alpha stabilization occurred in the temporal regions only.

e) An experiment was conducted on 30 schizophrenic patients, 10 patients received Serpasil 3 grs. daily, 10 patients received a new drug to be tested and 10 patients received a placebo. E.E.G. tracings were taken before the administration of the drugs and on one occasion after the course of drugs was started. Psychological tests were made to assess the clinical improvement.

It was found that the patients who had received Serpasil showed a statistically significant improvement of their alpha-stability. The ten patients who had received the new drug that was to be tested showed a significant diminution of alpha-stability in the temporal regions. The patients who received the placebo showed a random distribution of improvement or deterioration of their temporal alpha rhythm.

The correlation between improvement of alpha-stability in the temporal region and clinical improvement was about +0.45 only, in all 30 cases, whether this was due to the effect of drugs or not.

The Doctor who was conducting the experiment, the statistician of the Mental Hygiene Department and our own observations in our E.E.G. Department showed that many relevant factors during the psychological testing (in which unfortunately "socialisation" was not a part) suggesting improvement were not controlled.

f) It is a reasonable <u>hypothesis</u> to assume that alpha-stability may be correlated with relaxation and alpha-blocking with tension, though this is certainly not the full story, probably only an approximation. About 80% of true melancholics, who are certainly not relaxed, have an exceptionally high alpha index. Ostow's suggestion that alpha activity generally respons to a preparation for constructive thinking and the disappearance of the alpha activity when the constructive process was put into action, probably, is nearer to the truth. The more correct hypothesis would seem to be that relaxed patients generally ruminate less than tense subjects.

3) <u>Further references bearing on the subject of alpha stabilization</u>:

a) "By hypnotic suggestion to relax, Ford and Yeager reported the induction of "good" alpha patterns in several patients with anxiety states, whose previous E.E.G.'s showed little or no alpha-rhythm. Relaxation suggestions were not followed by EE.G. changes in subjects whose E.E.G.'s naturally showed "good" rhythm."

Ford, W.L. and Yeager, C.L. "changes in the electro-encephalogram in subjects under hypnosis. "Dis.nerv. Syst. 1948, 9, 190-192."

a) There are several references in the literature to the fact that short courses of electro-shock-treatment tend to increase the E.E.G. alpha activity.

4) Correction:

When quoting a reference of Ellingson a mistake occurred in my article which should be corrected.

Should read -

"The proposition by Saul and Davis that passive individuals tend to have regular persistent alpha rhythms of high index has been often cited in the literature and appears to have been accepted as fact. Sisson and Ellingson reviewed the evidence upon which that proposition was based and found it unconvincing."

DRUG: Chlorpromazine (Italian)

	Population	Pre-treatment EEG	EEG Changes	Pattern Changes	Route	Dosage	Rate
#36	6 pts. — 4 epileptics — shown on pre-Rx EEGs 2 manifest psychosis				IV	25 mg/50 cc solution	1 cc/5 min.