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

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In studies of convulsive, psychopharmacologic and insulin coma therapies, evidence for a neurophysiologic-adaptive hypothesis of the mode of action of these therapies has accumulated. This hypothesis ascribes the efficacy of each therapy in the treatment of psychoses to their ability to induce a persistent alteration in cerebral function, which provides the milieu for a change in adaptation of the subject to his environment. In these studies, analyses of changes in EEG have been used as indices of altered brain function.

In convulsive therapy, the shift in EEG frequencies to the delta range has been directly related to the behavioral change (A.M.A. Arch. Neurol. and Psychiat. 78: 516, 1957). A similar relationship has been observed to insulin coma (J. Hillside Hosp. 4: 134, 1955). Various psychopharmacologic agents can be classified according to their EEG effects: (J. Hillside Hosp. 6: 197, 1957): (a) induce a shift to delta frequencies (chlorpromazine, promazine, perphenazine, and high dose reserpine); (b) induce a shift to fast frequencies, with increased synchronization (meprobamate, barbiturates); and (c) desynchronize frequencies (diethazine, benactyzine and mepazine).

From these analyses, a shift in EEG frequencies to delta range and increased synchronization are suggested as the neurophysiologic concomitants of tranquilization and sedation. The neurophysiologic-adaptive hypothesis has application to the management of physiodynamic therapies, screening of psychopharmacologic agents and as a frame of reference for the study of behavior and neurophysiology.

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N.Y. Neurological Society, March 11, 1958.

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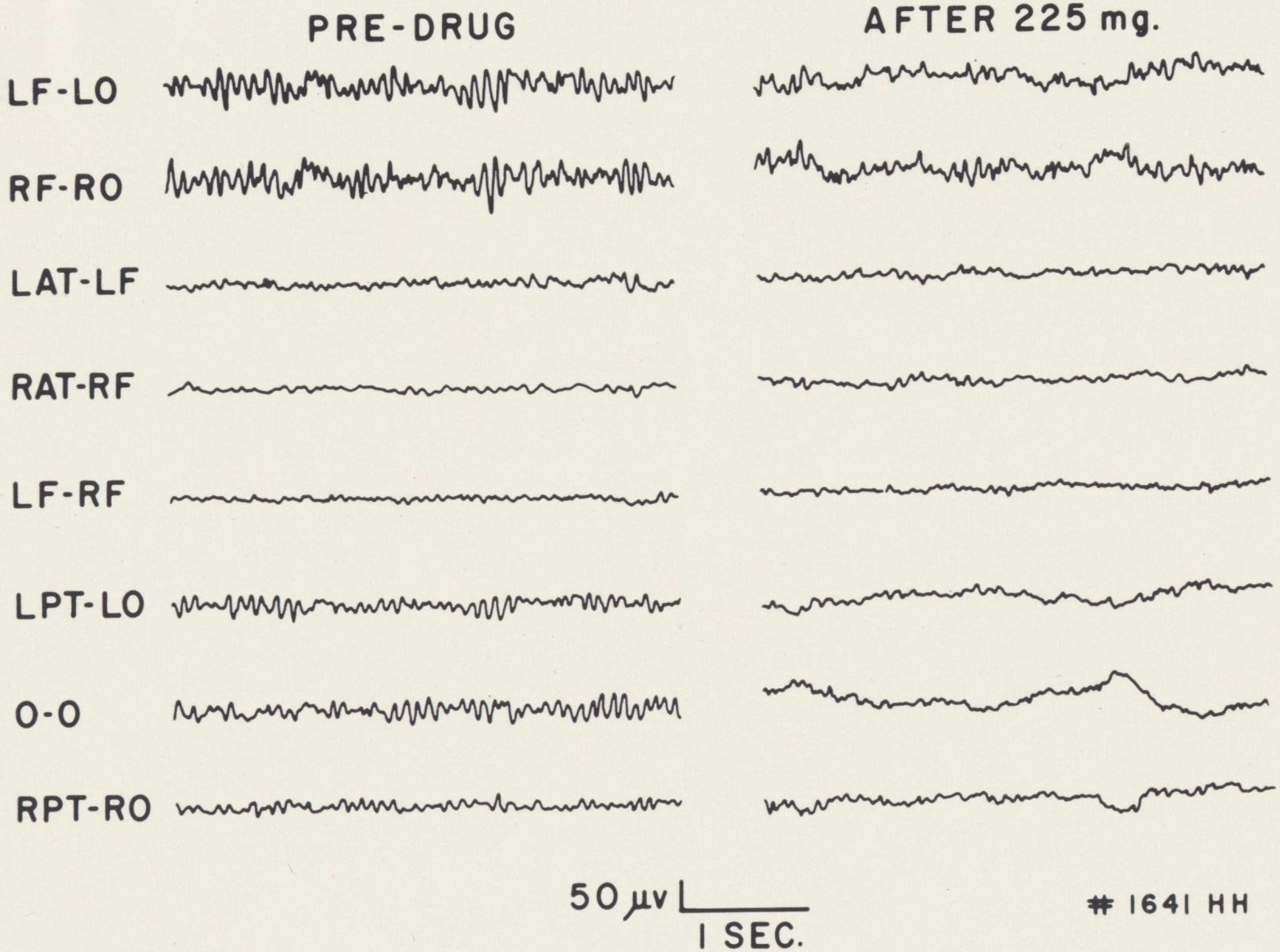
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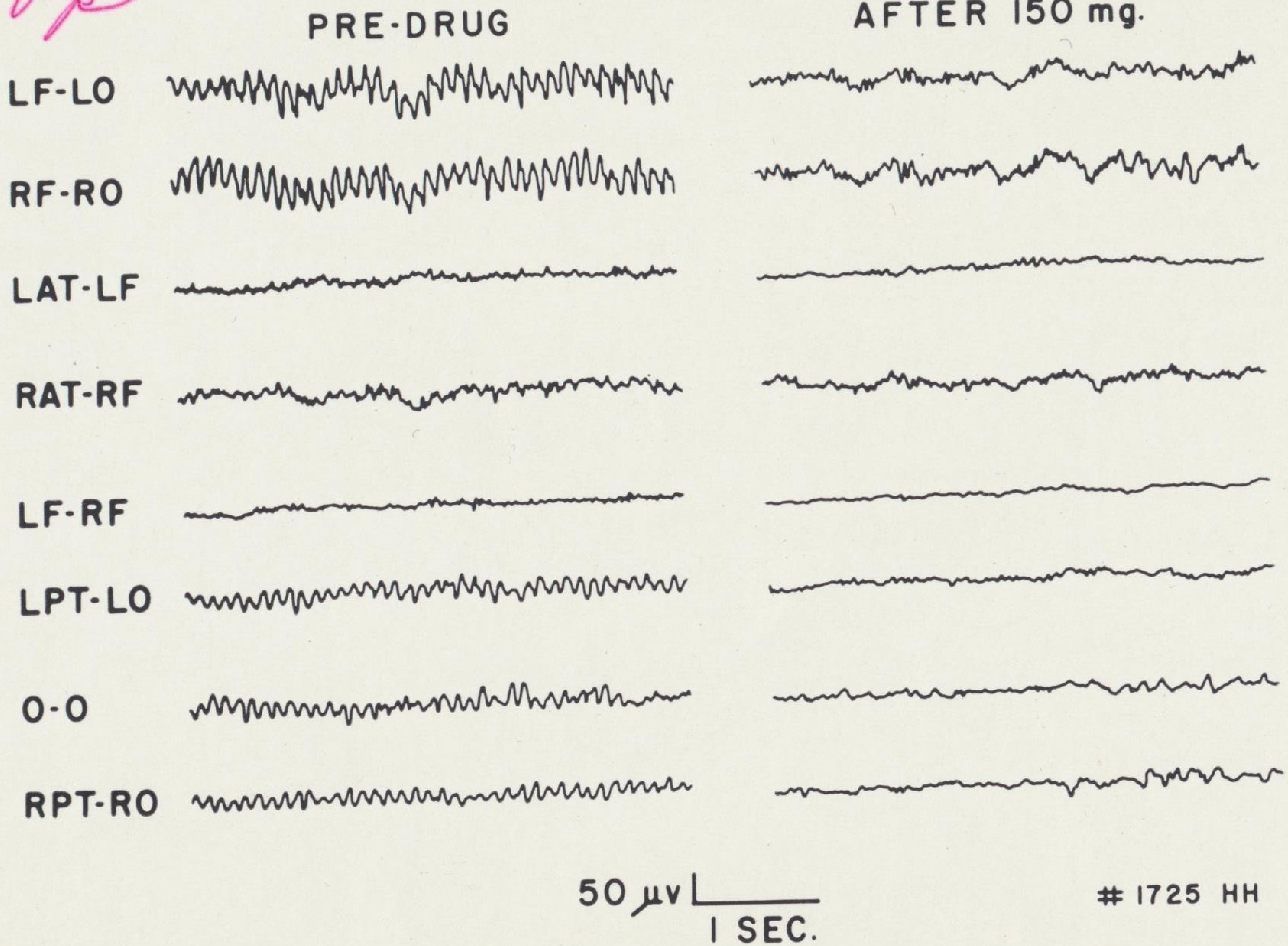
Chapter 14 Fig 2



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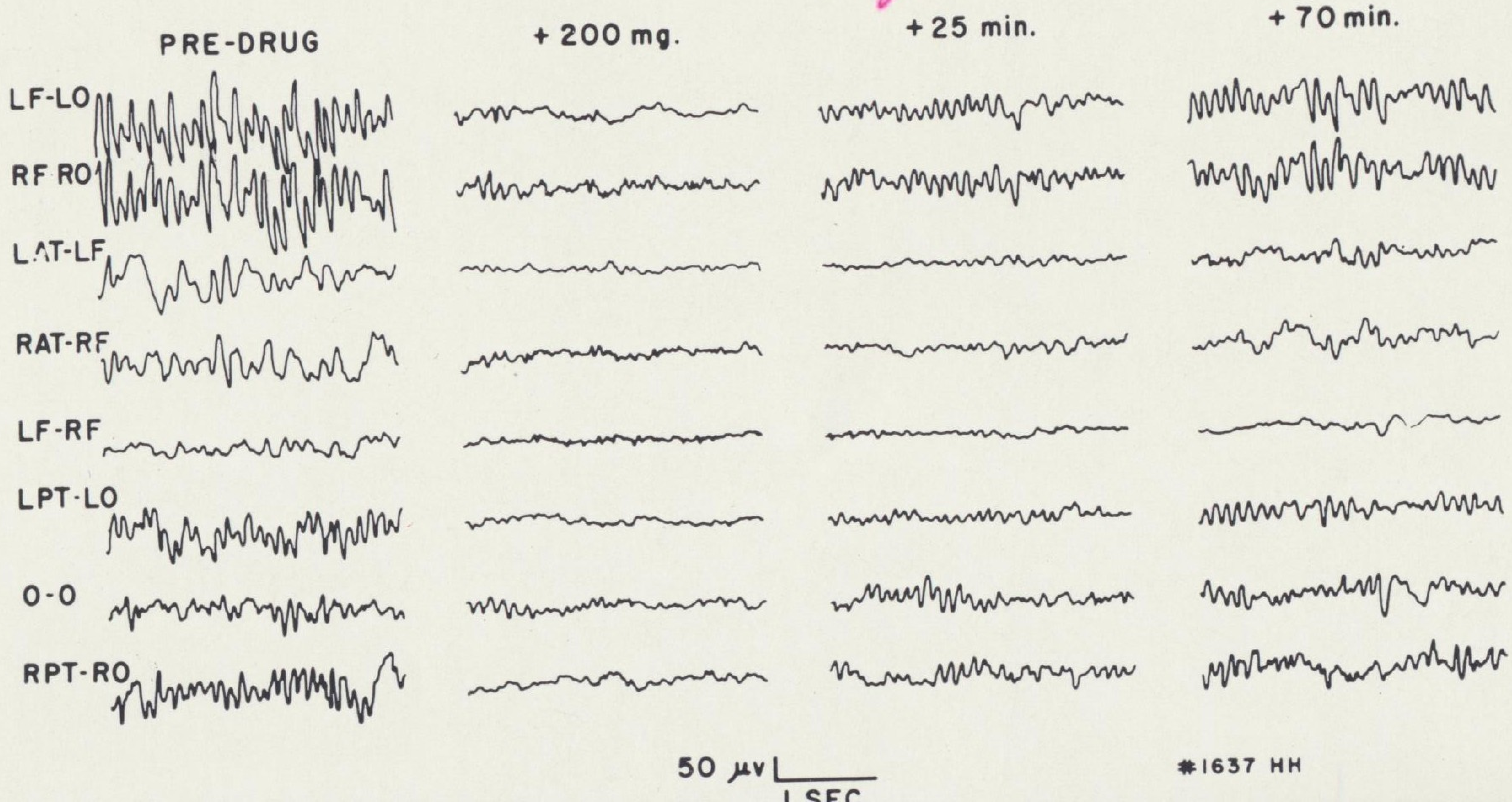

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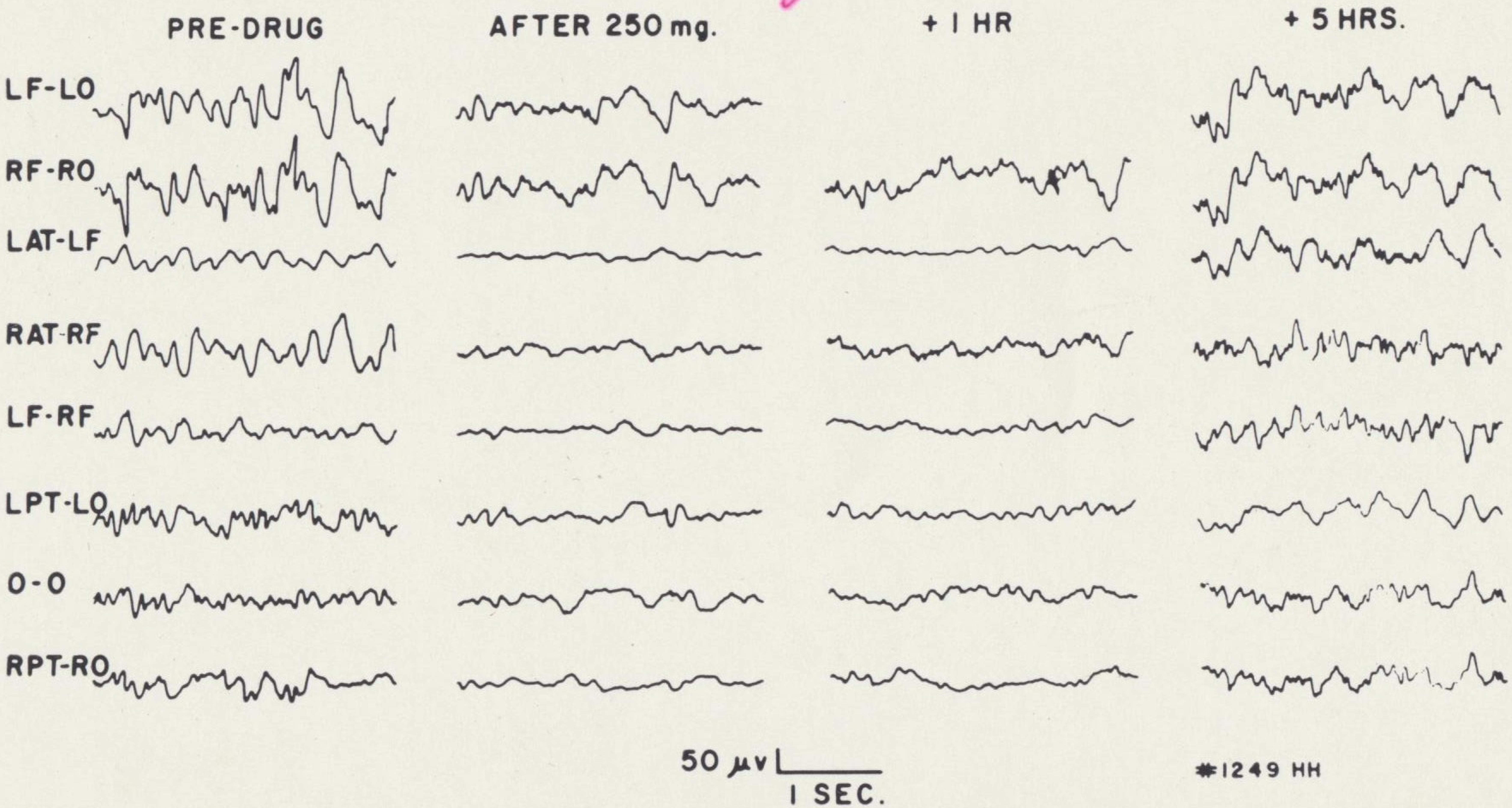

Effect of Anti-Cholinergic Agent, Diethazine, on EEG and Behavior: Significance for Theory of Convulsive Therapy

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Aided, in part, by grant M-927 of the National Institute of Mental Health, National Institutes of Health, U.S. Public Health Service.

Read (in part) at the meeting of the Eastern Association of Electroencephalographers, N.Y., December 1957; and at the Society of Biologic Psychiatry, San Francisco, May 1958

SBP: 3-58

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Effect of Anti-Cholinergic Agent, Diethazine, on EEG and Behavior: Significance for Theory of Convulsive Therapy

Recent investigations of convulsive therapy have emphasized EEG delta activity as the neurophysiologic basis for the induced behavioral change (1,2,3,4,5). Little study, however, has been given to the biochemical effects of this therapy, except in the course of investigations of head injuries.

In investigations of head trauma significance has been ascribed to changes in the acetylcholine-cholinesterase systems both for the behavioral and the electroencephalographic effects. An increase in free acetylcholine (6) and an alteration of the ratio of cholinesterases (7) in the spinal fluid have been positively correlated with the degree of EEG abnormality and degree of neurologic deficit. The EEG patterns were "blocked," and some improvement in clinical status was reported following the administration of atropine (7,8). In convulsive therapy, atropine and scopolamine were observed to block the appearance of delta activity, (9) although the systemic effects of the large doses of these agents were marked.

Recent reports (10) noted that EEG and behavioral effects similar to atropine were achieved in patients with head trauma by intravenous diethazine - a phenothiazine compound with anticholinergic properties - with minimal systemic effects. In our continuing studies of the role of delta activity in electroshock (3), the effect of diethazine was studied. It is the purpose of this report to describe the effects of diethazine on EEG patterns and on behavior of patients during electroconvulsive therapy; and to relate these observations to the present neurophysiologic-adaptive hypothesis of the mode of action of convulsive therapy.

SUBJECTS AND METHODS:

Forty psychiatric patients, at various stages of electroshock therapy in an open-ward, voluntary psychiatric hospital have been studied. All observations have been made in acute experiments in the EEG laboratory. Following a routine EEG recording, diethazine was administered intravenously at the rate of 25 mgm per minute, for a total of 175 to 250 mgm, depending upon the behavioral effect. Dosage varied from 2.8 to 4.0 mgm per kilogram body weight.

Diethazine is a soluble phenothiazine compound with pharmacologic properties similar to atropine. In experimental animals, diethazine blocks the bradycardia, bronchospasm, salivation, fasciculation and seizures induced by acetylcholine, di-isopropyl fluorophosphate and pilocarpine. It suppresses salivation, and induces mydriasis and hypotension (11).

EEG Analyses:

Recording was continuous for the duration of the observation period, except during interview periods. Needle electrodes, and an 8 channel Medcraft instrument were used. All records were analyzed for the degree of delta activity (3); the per cent time and principal alpha frequency; and the relative amount of fast activity. The alpha and delta activity were measured in anterior temporal-vertex, and parietal-ear lobe lead combinations.

Behavior Measures:

Prior to drug administration an unstructured psychiatric historical interview and a structured questionnaire period (12) were tape recorded. Following drug administration, periods of recorded interview were alternated with EEG recording periods, until the EEG had again manifested the pre-injection pattern on visual inspection.

Two estimates of behavioral effects were used: clinical descriptions by the participants - subject, interviewer and technician - of the changes occurring during the drug period, and language analyses of the recorded interviews. Changes in language were evaluated by a syntactic analysis (12) and an analysis of the variability in verbal interaction in the dyad (13,14).* Both measures have been shown to be sensitive to alterations in behavior induced by changes in the central nervous system.

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* Detailed analyses of these observations will be reported separately by Drs. J. Jaffe and R. L. Kahn.

OBSERVATIONS:

(a) Clinical:

Within two to five minutes of the start of the injection, subjects manifested spontaneous coughing followed by a dryness of the mouth and a thickness of speech. They reported a feeling of lassitude, and a heaviness and weakness of extremities which was soon succeeded by increased restlessness and difficulty in maintaining eyelid closure.

Reports of visual and haptic illusory sensations, feelings of unreality and distance, and delusional thoughts about their illness, the setting of the test procedures or our identity were voiced spontaneously in eighteen subjects in the period between 15 and 60 minutes after drug administration. In three instances, increasing agitation and panic led to a cessation of the recording. In two subjects withdrawal and negativism was the prominent behavioral response. Such patterns of behavior were transient and had disappeared in 1½ - 4 hours in all subjects.

(b) EEG Patterns:

Alteration in the EEG patterns was concurrent with the behavioral effects. In all records, changes occurred during drug administration and were sustained, with gradual diminution and restitution of the pre-injection patterns, in one to five hours. The initial response was a decrease in voltage and desynchronization of all frequencies. There was a decrease in prominence of prevailing rhythms. In patients without delta activity (pre-electroshock), desynchronization and voltage decrease was occasionally accompanied by low voltage 5-7 cps activity, symmetric and prominent in frontal and anterior temporal leads (Figure 1, 2). The alpha frequency was not altered.

The build-up in voltage and appearance of slower frequencies with hyperventilation was blocked.

In patients with varying degrees of high voltage delta activity there was a prominent decrease in voltage and desynchronization of the record. Both random and burst delta activity diminished or disappeared, and irregular low voltage alpha and beta frequencies became prominent (Fig. 3, 4). The hyperventilation response was no longer apparent.

(c) Language Patterns:

In previous studies, an intimate relationship between changes in syntactic language patterns and the behavioral response in electroshock had been reported (12). With alteration in brain function, increased use of third person, verbal denial, qualification, displacement and cliches became prominent. These effects could be enhanced by the administration of intravenous amobarbital (14).

In the subjects in the present study, syntactic analyses demonstrated a reversal of the patterns noted in electroshock. Use of third person, qualification and displacement decreased. Explicit verbal denial was modified and replaced by minimization and displacement, or by a reiteration of complaints of illness. In dyadic analyses, the verbal interaction was characterized by a greater diversity of vocabulary and less variability in the diversity scores for 25 word units.

The qualitative nature of these changes in the language patterns is opposite to that of amobarbital and electroshock. The duration of language changes was concurrent with the changes in the electroencephalogram.

DISCUSSION:

These observations confirm the report of Jenkner and Lechner of the effects of diethazine in "normal" subjects (10). Diethazine also alters electroshock induced delta activity in a fashion similar to atropine and scopolamine, as described by Ulett and Johnson (9), with minimal unpleasant symptoms. The effects of intravenous diethazine are immediate, both on the EEG and behavior, and thus provides a useful experimental agent with "anti-cholinergic" properties. Two aspects of these experimental observations warrant discussion: the role of acetylcholine-cholinesterase in the electro-convulsive therapy progress, and the significance of diethazine "alerting" for concepts of hallucinogenic activity.

1. Biochemical Basis of the Convulsive Therapy Process:

While there has been considerable study of the psychologic and neurophysiologic aspects of convulsive therapy, little information concerning biochemical processes is available. The studies of biochemical changes following head trauma and spontaneous seizures provide some analogic data. Bornstein (6), in a classical experimental study of head trauma in cats, demonstrated that within a few minutes after trauma, free acetylcholine appeared in the spinal fluid and persisted for periods up to 48 hours. He further demonstrated a positive relation between the severity of head trauma and the quantity of free acetylcholine, degree of electroencephalographic alteration and the severity of the behavioral changes. The electroencephalographic records initially showed short periods of high voltage fast activity, a transient period of flattening of electrical activity, followed by prolonged periods of high amplitude sharp waves in the delta frequencies. Concomitantly, alteration in consciousness, changes in reflexes and post-traumatic seizures were most prominent with highest concentrations of free acetylcholine and greatest degree of EEG change.

Tower and McEachern (7) confirmed these observations in clinical studies in man. In 112 neurologic patients, free acetylcholine was found in the cerebrospinal fluid only in patients following head trauma and recent grand mal seizures; and the level of free acetylcholine varied directly with the degree of cerebral damage. In addition, these authors assayed the cholinesterase activity of the spinal fluid, (7, 16). In patients following head trauma, they noted a sharp rise in non-specific cholinesterase (benzoylcholine-splitting) and a drop in the specific cholinesterase (mecholyl-splitting) activity of the spinal fluid. No such inversion was noted in fluids containing free acetylcholine following spontaneous seizures. Electroencephalograms were taken at varying intervals following trauma, and demonstrated a direct correlation of the extent of EEG abnormality and the appearance of free acetylcholine in the spinal fluid.

Tower and McEachern also reported observations in six patients receiving electroconvulsive therapy. In patients after 3-7 induced convulsions, they noted free acetylcholine in the spinal fluid in two, and an increase in non-specific cholinesterase with reversal of the cholinesterase ratio in five of the six. They concluded that the spinal fluid changes in electroshock are more like those of craniocerebral trauma than those found in epilepsy. *

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* Regarding the one patient of the six who failed to show either free acetylcholine or a reversal of the cholinesterase ratio, they noted: "It is interesting that this patient was the only one of the six to show no response to treatment."

More recently, Sachs (17) confirmed the reports of free acetylcholine in the spinal fluid after head trauma and after electroshock.

In his studies, Bornstein (6) administered 0.5-1.0 mg/kg atropine and demonstrated a reversal or a blocking of the EEG effects, and a modification of the behavioral and neurologic signs. Atropine also blocked the EEG and clinical signs induced by intracisternal acetylcholine.

Ward (8) applied these observations to the treatment of human subjects with varying degrees of head trauma. Subcutaneous doses of 0.1 mg/kg of atropine induced both clinical improvement and reversal of EEG effects. These observations were recently confirmed by Sachs (17), Ruge (18) and Hughes (19). Based on these observations, Ulett and Johnson (9) noted the effect of atropine and scopolamine in blocking the EEG changes of electroshock therapy, without noting the effect on clinical behavior. Concurrently, Jenkner and Lechner (10) reported effects similar to those of Ward, in studies of diethazine in cases of head injury.

Another group of investigations complete the available data. Studies of anticholinesterases, as DFP (di-isopropyl fluorophosphate) and TEPP (tetraethyl-pyrophosphate), which block the enzymatic breakdown of acetylcholine, demonstrate the development of high amplitude rapid frequency EEG patterns similar to status epilepticus as well as lesser degrees of abnormality as noted in post-traumatic states (20, 21, 22, 23). In these studies, atropine blocked both the electroencephalographic and the clinical toxic effects.

Thus, both from experimental and clinical studies of craniocerebral trauma we may assume that (a) the acetylcholine activity of the spinal fluid increases; (b) pseudo-cholinesterase activity increases with a reversal of the ratio of cholinesterases; (c) EEG hypersynchrony and slowing parallel these biochemical alterations; and (d) anticholinergic agents may block both the electroencephalographic and the clinical effects. From the data available it is probable that the biochemical basis of convulsive therapy is similar to that of craniocerebral trauma. Convulsive therapy results in free acetylcholine in the spinal fluid (7, 17) and a reversal of cholinesterase ratios (7, 16). The electroencephalographic effects of repeated induced convulsions is the development of high voltage, symmetric slow wave activity, occasionally with spike activity (3, 24, 25), which is similar to that observed in severe head trauma (26, 27). In previous studies we have reported the relationship between the degree of induced slow wave activity and behavioral response (3). The studies reported here and that of Ulett and Johnson (9) demonstrate a reversal of the EEG and the behavioral effects of convulsive therapy by anti-cholinergic compounds. In each characteristic, convulsive therapy is thus similar to cerebral trauma. While the acetylcholine-cholinesterase system is highlighted by these studies, other enzyme systems may also be altered (17). These studies also suggest that convulsive therapy provides an excellent experimental method for studies of craniocerebral trauma.

Studies of the brain stem activating system by Jasper and Drooglever-Fortuyn (28) and Lindsley _et al_. (29) had laid the foundation for the prevailing conclusion that symmetric EEG slow wave activity has its origin in mesencephalic structures, and that these structures intimately affect the states of "alerting" and "drowsiness." More recently, Rinaldi and

Himwich (30, 31) have related the site of action of atropine and cholinergic drugs to this mesodiencephalic activating system. It is also probable that these structures may be selectively affected by the convulsive therapy process, and that both the clinical and electrographic effects may be intimately related to changes in this system.

2. Diethazine "Alerting" and Hallucinogenic Activity:

The behavioral effects of diethazine provide information regarding another aspect of the convulsive therapy process. In patients without prior convulsive therapy, illusory phenomena and feelings of unreality were observed. These were similar to the hallucinogenic effects of LSD (32) and mescaline (33). Again analogic data about the clinical and EEG effects of these agents may provide some information about convulsive therapy.

In studies of mescaline, Wikler (34) noted that the EEG demonstrated either no change, intermittent or continuous low voltage fast activity or increase in alpha frequency. Denber and Merlis (35) noted a similar acceleration of alpha frequency, decrease in per cent time alpha including its disappearance, and non-specific random beta activity. Delta activity did not occur. In patients with delta activity induced by electroshock, Merlis and Hunter (38) noted that intravenous mescaline markedly diminished the amplitude and per cent time delta activity with an increase in per cent time alpha activity.

The effects of LSD on EEG are similar. Gastaut *et al.* (36) noted an acceleration of alpha frequency of 0.5 to 4.0 cps with an accentuation of beta rhythms. Rinkel *et al.* (37) confirmed this observation and noted, in addition, a reduced responsivity to hyperventilation.*

In summarizing his studies Wikler (34) concluded that " . . . 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." This generalization provides a meaningful construct in which these agents may be assessed. Agents that evoke EEG desynchronization tend to be hallucinogenic, and mescaline and LSD are clear examples. Agents that synchronize frequencies, such as barbiturate and meprobamate in the beta frequency range, and chlorpromazine, promazine and perphenazine in the delta frequency range (39) tend to be sedatives, euphoriants and relaxants.

The observations on diethazine reported here are consistent with this hypothesis. In patients without delta activity, the EEG demonstrated desynchronization of frequencies, and this was associated with clinical illusory phenomena. In patients with delta activity desynchronization occurred, and alerting and reversal of the speech patterns induced by electroshock were observed.

Electroconvulsive therapy may also be understood in this framework. We have previously noted a direct relationship between clinical evaluations

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* Studies are now in progress of the effects of LSD, Win-2299, benactyzine and other anticholinergic compounds on post-convulsive EEG delta activity. Initial experiments with intravenous LSD (50-100 gamma) demonstrated marked diminution in per cent time and amplitude of delta activity.

of improvement and the degree of EEG slowing induced by electroshock (3). Under these conditions, sedation and euphoria are most prominent and hallucinatory activity diminished. In patients in whom hypersynchrony is not induced, behavioral change is limited and 'improvement' does not occur (40).

Previously we have concluded that the mode of action of convulsive therapies is based on the induction of a state of altered cerebral function, in which changes in adaptive interpersonal behavior occur, and are interpreted as 'improvement' (3, 4, 39). The present studies amplify two aspects of this neurophysiologic-adaptive hypothesis. The biochemical substrate of the behavioral change is reflected by an alteration in the acetylcholine-cholinesterase relationships of the central nervous system. It is also probable that EEG hypersynchrony provides the neurophysiologic basis of the milieu change which is clinically manifest as sedation and euphoria and is evaluated as 'improvement.'

The neurophysiologic-adaptive hypothesis of convulsive therapy has provided a meaningful basis for studies of other physiodynamic therapies (39). In this study, it has been possible to amplify our understanding of neurophysiologic aspects of hallucinogens as well.

<u>SUMMARY:</u>

1. The effect of an anticholinergic agent, diethazine, on the EEG, behavior and language patterns was observed in 40 psychiatric patients, at various stages in the course of electroconvulsive treatment.

(a) <u>Behavior</u>: Increased restlessness and agitation, haptic and visual illusory sensations, and delusional thoughts about their illness or examiner's identity were observed.

(b) <u>EEG</u>: Alteration in EEG was concurrent with behavioral changes. There was a decrease in voltage and desynchronization of all frequencies. In patients with delta activity, the per cent time and voltage of delta activity decreased.

(c) <u>Language</u>: Syntactic patterns described for convulsive therapy were reversed. Use of third person, qualification and displacement decreased. In dyadic analyses, there was a decrease in the coefficient of variation.

2. These observations are discussed in the framework of the neuro-physiologic-adaptive hypothesis of the action of convulsive therapy; and it is concluded that:

(a) the biochemical basis for convulsive therapy is similar to that of craniocerebral trauma;

(b) changes in acetylcholine-cholinesterase metabolism are intimately related to the behavioral effects; and

(c) EEG desynchronization may be a physiologic concomitant of hallucinogenic activity; and EEG hypersynchrony associated with euphoria and sedation.

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Effect of Anti-Cholinergic Compound, Diethazine, on EEG and Behavior: Significance for Theory of Convulsive Therapy

Recent investigations of convulsive therapy have emphasized EEG delta activity as the neurophysiologic basis for the induced behavioral change (   ).

Previous investigations of animals and man subjected to head trauma had ascribed significance to change in the acetylcholine-cholinesterase systems for the behavioral and electroencephalographic changes. An increase in free acetylcholine (   ) and an alteration of the ratio of cholinesterase (   )in spinal fluid had been positively correlated with the degree of EEG abnormality and degree of neurologic deficit following head trauma. The EEG patterns were "blocked," and some improvement in clinical status was reported following the administration of atropine (B. Ward). Ulett and Johnson (   ) reported that atropine and scopolamine blocked the appearance of delta activity following convulsive therapy. From the limited number of cases, the relation between the degree of delta blocking and behavioral change was not assessed. Both in these studies, and those of Ward and Bornstein, the systemic effects of the large doses of atropine were marked.

In 1955, Jenkner and Lechner (   ) reported that EEG and behavioral effects similar to atropine were achieved by diethazine administered in patients with head trauma. From their report in these and in normal subjects, the systemic effects of diethazine appeared minimal.

Because of our interest in the role of delta activity in electroshock (   ), an investigation of the effect of diethazine, both in EEG and behavior, in patients undergoing convulsive therapy was undertaken. It is the purpose of this report to describe the effects of diethazine on the EEG and on behavior of patients during electroshock therapy; and to relate these observations to the present neurophysiologic adaptive hypothesis of the mode of action of convulsive therapy.

<u>Subjects and Methods:</u>

Psychiatric patients, at various stages of electroshock therapy in an open-ward, voluntary psychiatric hospital have been studied. All onservations have been made in the EEG laboratory. Following a routine EEG recording, diethazine was administered intravenously at the rate of 25 mgm per minute, for a total of 175 to 200 mgm, depending upon the behavioral effect. According to body weight, dosage varied from 2.8 mg/kg to 4.0 mg/kg.

Diethazine is a soluble phenothiazine compound with pharmacologic properties similar to atropine. In experimental animals, diethazine blocks the bradycardia, bronchospasm, salivation, fasuculation and seizures induced by acetylcholine, di-isopropylfluorophosphate (DFP and placarpine. It suppresses salivation, and induces mydriasis and hypotension (Heymans et al., 1949).

EEG analyses:

All records were analyzed for the degree of delta activity ( ); the per cent time and principal alpha frequency; and the relative amount of fast activity. Drug effects were classified as synchronizing (S) or desynchronizing (D) according to the methods described by Wikler ( ). In all recordings, both alpha and delta activity was measured in anterior-temporal vertex, and parietal ear lobe lead combinations.

Behavior Measures:

Prior to drug administration an unstructured psychiatric historical interview and a structured questionnaire period were tape recorded. Following drug administration, periods of tape recorded interview were alternated with EEG recording periods, until the EEG had again manifested the pre-injection pattern on visual inspection.

Two estimates of behavioral effects were used: clinical descriptions by the participants,-subject, interviewer and technician - of the changes occurring during drug period, and language analyses of the recorded interviews. Changes in language were evaluated by a syntactic analysis (K. & F) and a dyadic analysis of the coefficient of variability (Jaffe).*

<u>Observations:</u>

(a) <u>Clinical:</u>

Within two to five minutes of the start of the injection, subjects manifested spontaneous coughing followed by a dryness of the mouth and a thickness of speech. They reported a feeling of lassitude, and a heaviness and weakness of extremities which was soon succeeded by increased restlessness and difficulty in maintaining eyelid closure.

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* Detailed analyses of these observations will appear separately.

Reports of visual and haptic illusory sensations, feelings of unreality and distance, and delusional thoughts about their illness, the setting of the test procedures or our identity were voiced spontaneously in subjects in the rest period between 15 and 30 minutes after drug administration. In three instances, increasing agitation and panic led to a cessation of the recording. In one instance, withdrawal and negativism was the prominent behavioral response. Such patterns of behavior were transient and had disappeared in 1½ - 4 hours in all subjects.

(b) EEG Patterns:

Alteration in the EEG patterns was concurrent with the behavioral effects. In all records, changes occurred during drug administration and were sustained, with gradual diminution and restitution of the pre-injection patterns in one to five hours. The initial response was a decrease in voltage and desynchronization of all frequencies. There was a decrease in prominence of prevailing rhythms. In patients without delta activity (pre electroshock), desynchronization and voltage decrease was occasionally accompanied by low voltage 5-7 cps activity, symmetric and prominent in frontal and anterior temporal leads. (Figure 1, 2). The basic alpha frequency was not altered. The build-up in voltage and appearance of slower frequencies with hyperventilation was blocked.

In patients with varying degrees of high voltage delta activity there was a prominent decrease in voltage; and desynchronization of the record. Both random and burst delta activity disappeared and irregular, low voltage alpha and beta frequencies became prominent (Fig. 3, 4).

(c) Language Patterns:

In previous studies, an intimate relationship between changes in syntactic language patterns and the behavioral response in electroshock had been reported ( ). With alteration in brain function, increased use of third person, verbal denial, qualification, displacement and cliches became prominent. These effects could be enhanced by the administration of intravenous amobarbital ( ).

In the subjects in the present study, syntactic analyses demonstrated a reversal of the patterns noted in electroshock. Use of third person, qualification and displacement decreased. Verbal denial was modified and replaced by minimization and displacement, or by a reiteration of complaints of illness. The qualitative nature of the language changes was opposite to that of amobarbital. The period of change and language was concurrent with the changes in the electroencephalogram.

Discussion:

These observations confirm the report of Jenkner and Lechner of the effects of diethazine in "normal" subjects (   ). We have also noted that diethazine alters electroshock induced delta activity in a fashion similar to atropine and scopolamine, as described by Ulett and Johnson (   ) without the attendant unpleasant side effects. The effects of diethazine are immediate, both on the EEG and behavior, and thus provides a useful experimental agent with "anti-cholinergic" properties. Two aspects warrant discussion. The role of acetylcholine-cholinesterase in the electroconvulsive therapy process, and the significance of diethazine "alerting" for concepts of hallucinogenic activity.

1. Biochemical Bases of the Convulsive Therapy Process:

While there has been considerable study of the psychologic and neurophysiologic aspects of convulsive therapy, little information concerning biochemical processes is available. Studies of biochemical changes following head trauma and spontaneous seizures provide some analogic data. Bornstein (   ), in a classical experimental study of head trauma in cats, demonstrated that within a few minutes after trauma, there appeared in the spinal fluid, free acetylcholine which persisted for periods up to 48 hours. Bornstein further demonstrated positive relations between the severity of ~~the~~ head trauma and the quantity of free acetylcholine, degree of electroencephalographic changes and the severity of the behavioral changes. The electroencephalographic records initially showed short periods of high voltage fast activity, and a transient period of flattening of electrical activity followed by prolonged periods of high amplitude sharp waves in the delta frequencies. Concomitantly, alteration in consciousness, changes in reflexes and post-traumatic seizures were most prominent with highest concentration of free acetylcholine and greatest degrees of EEG change.

Tower and McEachern (   ) confirmed these observations in clinical studies in man. In 112 ~~122~~ neurologic patients, free acetylcholine was found in the cerebrospinal ~~cerebbrospinal~~ fluid only in patients following head trauma and recent grand mal seizures; and that the level of free acetylcholine varied directly with the degree of cerebral damage. In addition, these authors assayed the cholinesterase activity of the spinal fluid. In patients following head trauma, they noted a sharp rise in non-specific cholinesterase (bengaylcholine-splitting) and a drop in the specific cholinesterase (mecholyl-splitting) activity of the spinal fluid. No such inversion was noted in fluids containing free acetylcholine following spontaneous seizures. In most of these subjects, electroencephalograms were taken at varying intervals following trauma, and demonstrated a direct correlation of the extent of EEG abnormality and the appearance of free acetylcholine in the spinal fluid.

In their reports, Tower and McEachern report on six patients receiving electroconvulsive therapy. Studying the patients after 3-7 induced convulsions, they reported free acetylcholine in the spinal fluid in two, and an increase in non-specific cholinesterase with reversal of the cholinesterase ratio in five of the six patients. They concluded that the spinal fluid changes in electroshock ~~and~~ are more like those of cranocerebral trauma than those found in epilepsy.* More recently, Sachs ( ) confirmed the

*Regarding the one patient of the six who failed to show either free acetylcholine or a reversal of the cholinesterase ratio, they note: "It is interesting that this patient was the only one of the six to show no response to treatment."

reports of free acetylcholine in the spinal fluid after head trauma, but also after electroshock and brain tumor surgery.

In his studies, Bornstein ( ) administered 0.5-1.0 mg/kg atropine and demonstrated a reversal or a blocking of the EEG effects, and a modification of the behavioral and neurologic signs. Atropine also blocked the EEG and clinical signs induced by intracysternal acetylcholine.

Ward ( ) applied these observations to the treatment of human closed head injuries. In patients with varying degrees of trauma, subcutaneous doses of 0.1 mg;kg of atropine; both clinical improvement and reversal of EEG effects were reported. These observations were confirmed recently by Ruge ( ), Sachs ( ) and Hughes ( ). Based on these observations, Ulett and Johnson ( )noted the effect of both atropine and scopolamine in blocking the EEG changes of electroshock therapy, without noting the effect on clinical behavior. Concurrently, Jenkner and Lechner ( ) reported effects similar to those of Ward, in studies of diethazine in cases of head injury.

Another group of investigation complete the available data. Various studies of anticholinesterases, as DFP (di-isopropylfluorophosphate) and

TEPP (tetraethyl pyraphosphate). , which block the enzymatic breakdown of acetylcholine, demonstrate the development of high amplitude rapid frequency waves similar to status epilepticus as well as lesser degrees of abnormality noted in post-traumatic states (, ,). In these studies, atropine blocked both the electroencephalographic and clinical toxic affects.

Thus, both in experimental and clinical studies of cranocerebral we may assume that (a) the acetylcholine activity of the spinal fluid increases, (b) pseudo-cholinesterase activity increases with a reversal of the rates of cholinesterases; (c) EEG changes parallel these biochemical changes; and (d) that anticholinergic compounds may block both the electroencephalographic and the clinical effects. From the data available it is probble that the biochemical basis of the convulsive therapy process is similar to that of ~~crain~~ cranocerebral trauma. Convulsive therapy results in free acetylcholine in the spinal fluid (,) and a reversal of cholinesterase ratios ( ). The electroencephalographic effects of repeated induced convulsions is the development of high voltage, symmetric slow wave activity, occasionally with spike activity (, ,), which is similar to severe head trauma (, ,). In previous studies we have reported the relationship between the degree of induced slow wave activity and behavioral response (1). The studies reported here, now demonstrate a reversal of the EEG and the behavioral effects of convulsive therapy by anticholinergic compounds. In each characteristic, convulsive therapy is thus similar to craniocerebral trauma. While the acetylcholine-cholinesterase system is highlighted by these studies, other enzyme systems may also be altered ( ). These studies suggest that convulsive therapy provides an excellent experimental method for studies of craniocerebral trauma.

Recent studies of the brain stem activating system by Jasper and Drooglever-Fortwyn ( ) and Lindsley *et al.* ( ) had laid the foundation for the prevailing conclusion that symmetric EEG slow wave activity has its origin in the mesencephalic structures, and that these structures are central to states of "alerting" and "drowsiness." More recently, Rinaldi and Himwich (,) have related the site of action of atropine and cholinergic drugs to this mesodiencephalic activating system. It is also probable, therefore, that these structures may be selectively affected by the convulsive therapy process, and that both the clinical and electrographic effects may be intimately related to changes in this system.

The behavioral effects of diethazine provide information regarding another aspect of the convulsive therapy process. In the patients without prior convulsive therapy or head trauma, illusory phenomena and feelings of unreality were observed. These were similar to the hallucinogenic effects of LSD ( ), mescaline ( ), Win 2299 ( ), and harmine ( ). Again analogic data about the clinical and EEG effects of these agents may provide some information about convulsive therapy.

In studies of mescaline, Wikler ( ) noted that the EEG demonstrated either no change, intermittent or continuous low voltage fast activity or increase in alpha frequency. Denber and Merlis ( ) noted a similar acceleration of alpha frequency, decrease in percent time alpha including its disappearance, and non-specific random beta activity. Delta activity did not occur.

Reports of LSD effects are similar. Gastaut et al. ( ) noted an acceleration of alpha frequency of 0.5 to 4.0 cps with an accentuation of beta rhythms. Rinkel et al ( ) confirmed this report, and noted, in addition, a reduced responsivity to hyperventilation.

In patients with delta activity induced by electroshock, Merlis and Hunter ( ) noted that intravenous mescaline markedly diminished the amplitude and per-cent time delta activity with an increase in per-cent time alpha activity.

In summarizing his studies Wikler ( ) concluded that ". . . regardless 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." This generalization provides a meaningful construct in which these agents may be assessed. Agents that tend toward desyncronization are hallucinogenic- - and diethazine, mescaline and LSD are clear examples. Agents that tend to synchronize frequencies such as barbiturate and meprobamate in the beta ranges, and chlorpromazine, promazine and trilafon in the delta ranges are sedatives, euphoriants and relaxants.

The observations on diethazine reported here are also consistent with this hypothesis. In patients without delta activity, the EEG demonstrated desynchronization of frequencies, and this was associated with clinical illusory phenomena. In patients with delta activity desynchronization occurred and alerting and reversal of the speech patterns induced by electroshock ( ) were observed.

Electroconvulsive therapy may also be understood in this framework. We have previously noted a direct relationship between clinical evaluations of improvement and the degree of EEG slowing induced by electroshock ( ). Under these conditions, sedation and euphoria are most prominent. In patients in whom hypersynchrony is not induced, behavioral change is limited and 'improvement' does not occur.

Previously we have concluded that the mode of action of convulsive therapies is based on the induction of a state of altered cerebral function, in which changes in adaptive interpersonal behavior occur, which are interpreted as 'improvement' (, ,). The present studies amplify two aspects of this neurophysiologic hypothesis. The biochemical substrate of the behavioral change may be, or may be reflected by, an alteration in the acetylcholine-cholinesterase relationships of the central nervous system. It is also probable that EEG hypersynchrony provides the neurophysiologic basis of the milieu change which is clinically manifest as sedation and euphoria and is evaluated as 'improvement'.

The neurophysiologis-adaptive hypothesis of convulsive therapy has provided a meaningful basis for studies of other physiodynamic therapies (   ). In this study, it has been possible to amplify our understanding of neurophysiologic aspects of hallucinogens as well.

Effect of Anticholinergic Agent, Diethazine, on EEG and Behavior

Significance for Theory of Convulsive Therapy

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Reprinted from the A. M. A. Archives of Neurology & Psychiatry
September 1958, Vol. 80, pp. 380-387

Effect of Anticholinergic Agent, Diethazine, on EEG and Behavior

Significance for Theory of Convulsive Therapy

MAX FINK, M.D., Glen Oaks, N. Y.

Recent investigations of convulsive therapy have emphasized EEG delta activity as the neurophysiologic basis for the induced behavioral change.[1-5] Little study, however, has been given to the biochemical effects of this therapy, except in the course of investigations of head injuries.

In investigations of head trauma significance has been ascribed to changes in the acetylcholine-cholinesterase systems both for the behavioral and for the electroencephalographic effects. An increase in free acetylcholine[6] and an alteration of the ratio of cholinesterases[7] in the spinal fluid have been positively correlated with the degree of EEG abnormality and degree of neurologic deficit. The EEG patterns were "blocked," and some improvement in clinical status was reported following the administration of atropine.[7,8] In convulsive therapy, atropine and scopolamine were observed to block the appearance of delta activity,[9] although the systemic effects of the large doses of these agents were marked.

Recent reports[10] noted that EEG and behavioral effects similar to atropine were achieved in patients with head trauma by intravenous diethazine—a phenothiazine compound with anticholinergic properties—with minimal systemic effects. In our continuing studies of the role of delta activity in electroshock,[3] the effect of diethazine was studied. It is the purpose of this report to describe the effects of diethazine on EEG patterns and on behavior of patients during electroconvulsive therapy, and to relate these observations to the present neurophysiologic-adaptive hypothesis of the mode of action of convulsive therapy.

Submitted for publication March 24, 1958.

From the Department of Experimental Psychiatry, Hillside Hospital.

Aided, in part, by Grant M-927 of the National Institute of Mental Health, National Institutes of Health, U. S. Public Health Service.

Read (in part) at the meeting of the Eastern Association of Electroencephalographers, New York, December, 1957. Awarded A. E. Bennett Psychiatric Research Award of the Society of Biologic Psychiatry, May, 1958.

Subjects and Methods

Forty psychiatric patients, at various stages of electroshock therapy in an open-ward, voluntary psychiatric hospital were studied. All observations were made in acute experiments in the EEG laboratory. After a routine EEG recording, diethazine was administered intravenously at the rate of 25 mg. per minute, for a total of 175 to 250 mg., depending upon the behavioral effect. The dosage varied from 2.8 to 4.0 mg. per kilogram of body weight.

Diethazine is a soluble phenothiazine compound with pharmacologic properties similar to those of atropine. In experimental animals, diethazine blocks the bradycardia, bronchospasm, salivation, fasciculation, and seizures induced by acetylcholine, fluorophosphate, and pilocarpine. It suppresses salivation and induces mydriasis and hypotension.[11]

EEG Analyses.—Recording was continuous for the duration of the observation period, except during interview periods. Needle electrodes, and an eight-channel Medcraft instrument were used. All records were analyzed for the degree of delta activity,[3] the per cent time and principal alpha frequency, and the relative amount of fast activity. The alpha and delta activities were measured in anterior temporal-vertex, parietal-ear lobe, and frontal-occipital lead combinations.

Behavior Measures.—Prior to drug administration an unstructured psychiatric historical interview and a structured questionnaire period[12] were tape-recorded. Following drug administration, periods of recorded interview were alternated with EEG recording periods, until the EEG had again manifested the preinjection pattern on visual inspection.

Two estimates of behavioral effects were used: clinical descriptions by the participants—subject, interviewer, and technician—of the changes occurring during the drug period, and language analyses of the recorded interviews. Changes in language were evaluated by a syntactic analysis [12] and an analysis of the variability in verbal interaction in the dyad.[13,14] * Both measures have been shown to be sensitive to alterations in behavior induced by changes in the central nervous system.

Observations

(*a*) *Clinical.*—Within two to five minutes of the start of the injection, subjects manifested spontaneous coughing followed by a dryness of the mouth and a thickness of speech. They reported a feeling of lassitude and a heaviness and weakness of the extremities, soon succeeded by increased restlessness and difficulty in maintaining eyelid closure.

Reports of visual and haptic illusory sensations, feelings of unreality and distance, and delusional thoughts about their illness, the setting of the test procedures, or our identity were voiced spontaneously by 18 subjects in the period between 15 and 60 minutes after drug administration. In three instances increasing agitation and panic led to a cessation of the recording. In two subjects withdrawal and negativism were the prominent behavioral response. Such patterns of behavior were transient and had disappeared in one and one-half to four hours in all subjects.

* Detailed analyses of these observations will be reported separately by Dr. J. Jaffe and Dr. R. L. Kahn.

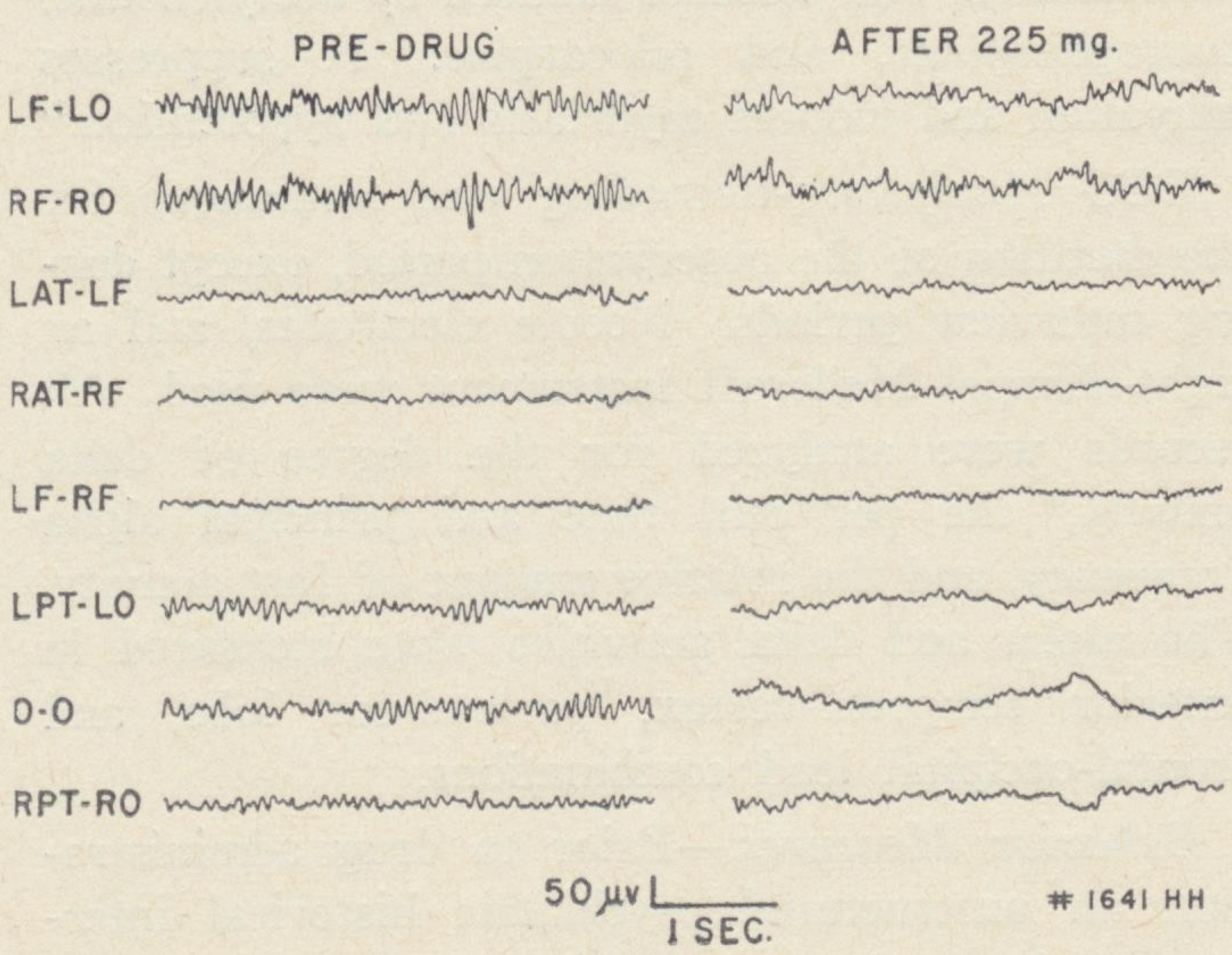

Fig. 1.—Effect of intravenous diethazine prior to electroshock in a man aged 27.

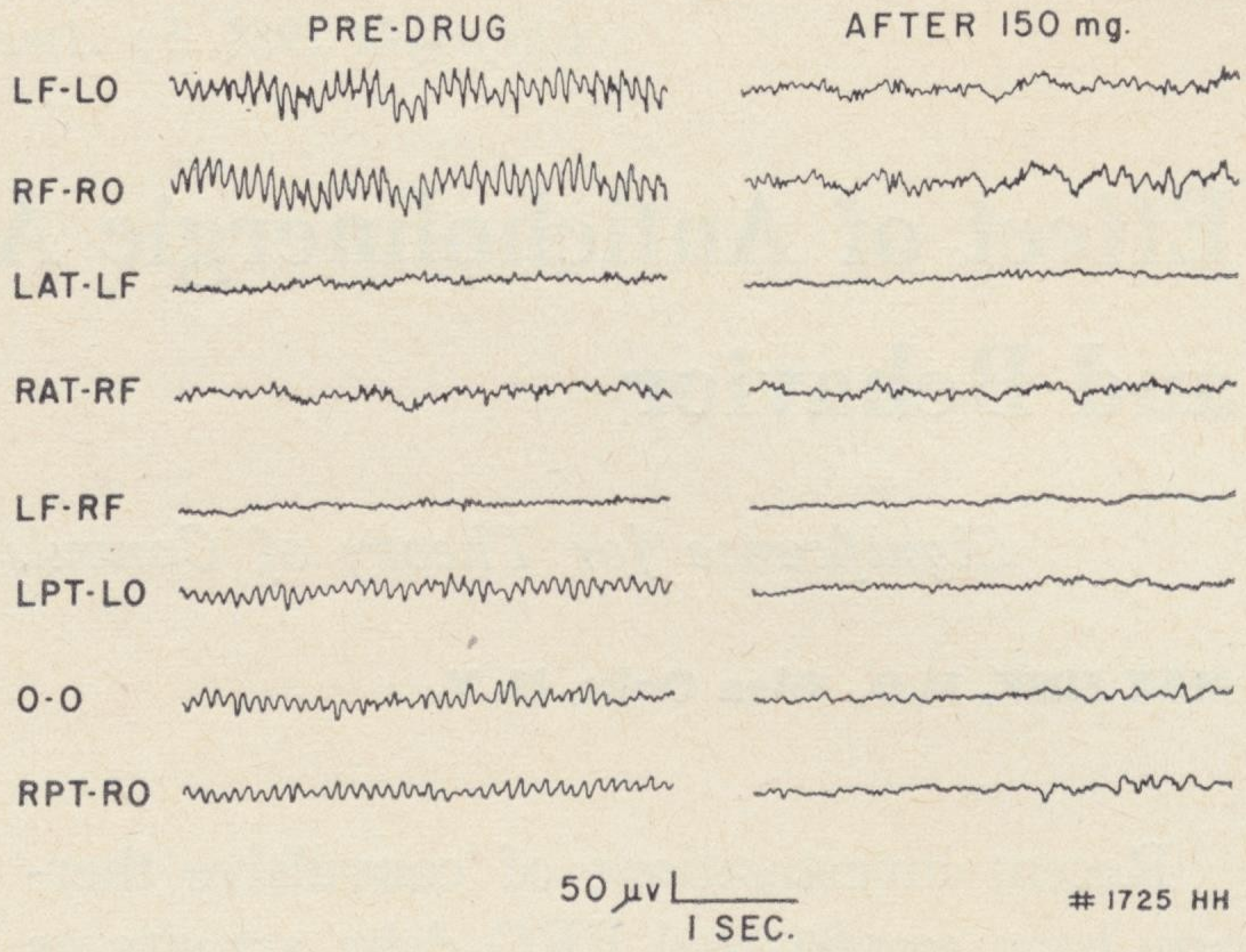

Fig. 2.—Effect of intravenous diethazine prior to electroshock in a woman aged 57.

(*b*) *EEG Patterns.*—Alteration in the EEG patterns was concurrent with the behavioral effects. In all records, changes occurred during drug administration and were sustained, with gradual diminution and restitution of the preinjection patterns, in one to five hours. The initial response was a decrease in voltage and desynchronization of all frequencies. There was a decrease in prominence of prevailing rhythms. In patients without delta activity (preelectroshock), desynchronization and voltage decrease were occasionally accompanied by low-voltage 5-7 cps activity, symmetric and prominent in frontal and anterior temporal leads (Figs. 1 and 2). The alpha frequency was not altered. The build-up in voltage and appearance of slower frequencies with hyperventilation were blocked.

In patients with varying degrees of high-voltage delta activity, desynchronization of the records became prominent, with a significant decrease both in voltage and in per cent time of slow wave activity. From an average per cent time delta of 45% in frontal-occipital leads, there was a reduction to a mean of 20%. Both random and burst delta activity diminished or disap-

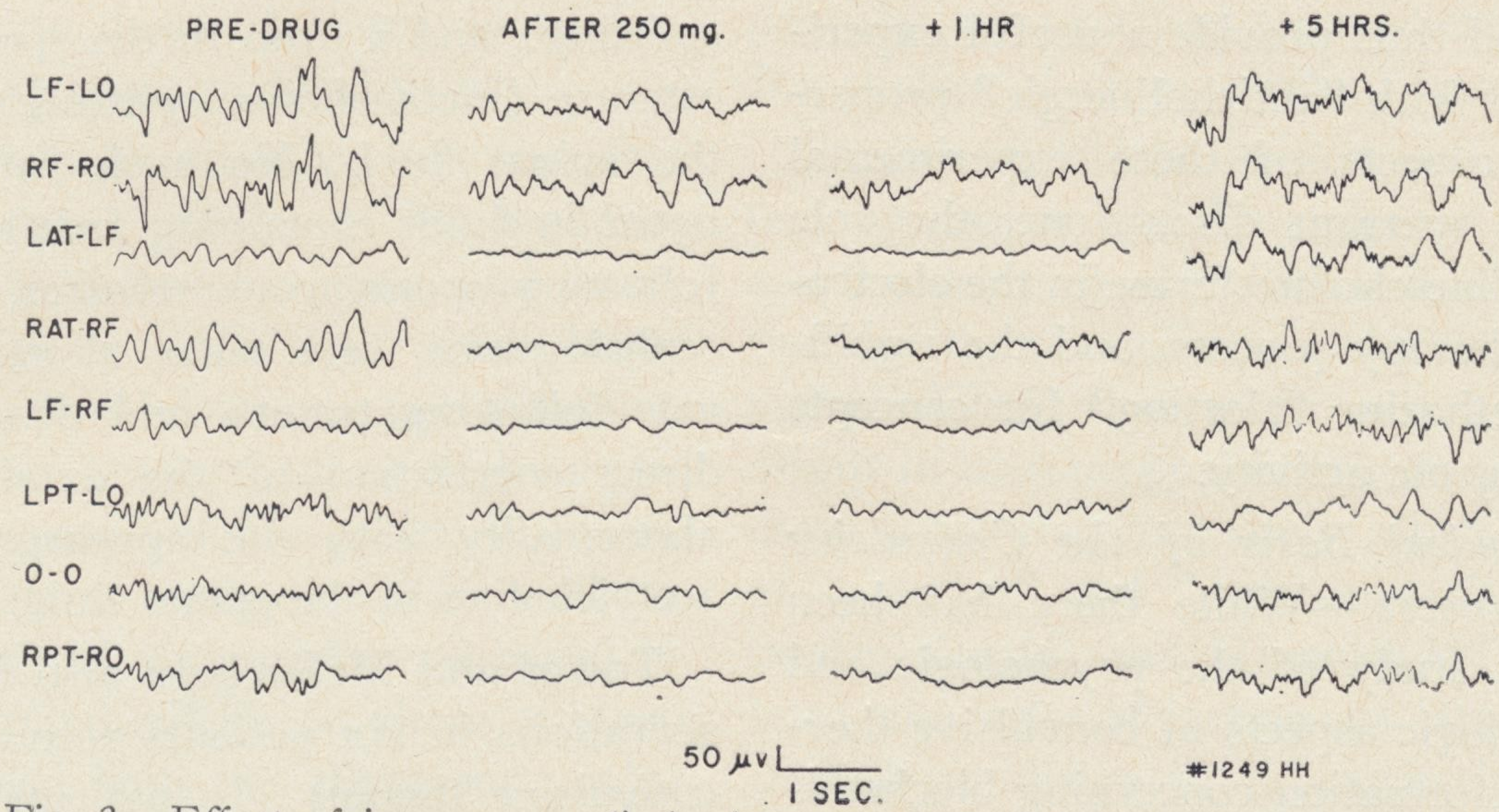

Fig. 3.—Effect of intravenous diethazine on delta activity after electroshock.

peared, and irregular low-voltage alpha and beta frequencies became prominent (Figs. 3 and 4). The hyperventilation response was no longer apparent.

(*c*) *Language Patterns.*—In previous studies, an intimate relationship between changes in syntactic language patterns and the behavioral response in electroshock had been reported.[12] With alteration in brain function, increased use of the third person, verbal denial, qualification, displacement, and clichés became prominent. These effects could be enhanced by the administration of intravenous amobarbital.[15]

In the subjects in the present study, syntactic analyses demonstrated a reversal of the patterns noted in electroshock. Use of the third person, qualification, and displacement decreased. Explicit verbal denial was modified and replaced by minimization and displacement, or by a reiteration of complaints of illness. In dyadic analyses, the verbal interaction was characterized by a greater diversity of vocabulary and less variability in the diversity scores for 25 word units.

The qualitative nature of these changes in the language patterns is opposite that of amobarbital and electroshock. The duration of language changes was concurrent with the changes in the electroencephalogram.

Comment

These observations confirm the report of Jenkner and Lechner of the effects of diethazine in "normal" subjects.[10] Diethazine also alters electroshock-induced delta activity in a fashion similar to atropine and scopolamine, as described by Ulett and Johnson,[9] with minimal unpleasant symptoms. The effects of intravenous diethazine are immediate, both on the EEG and on

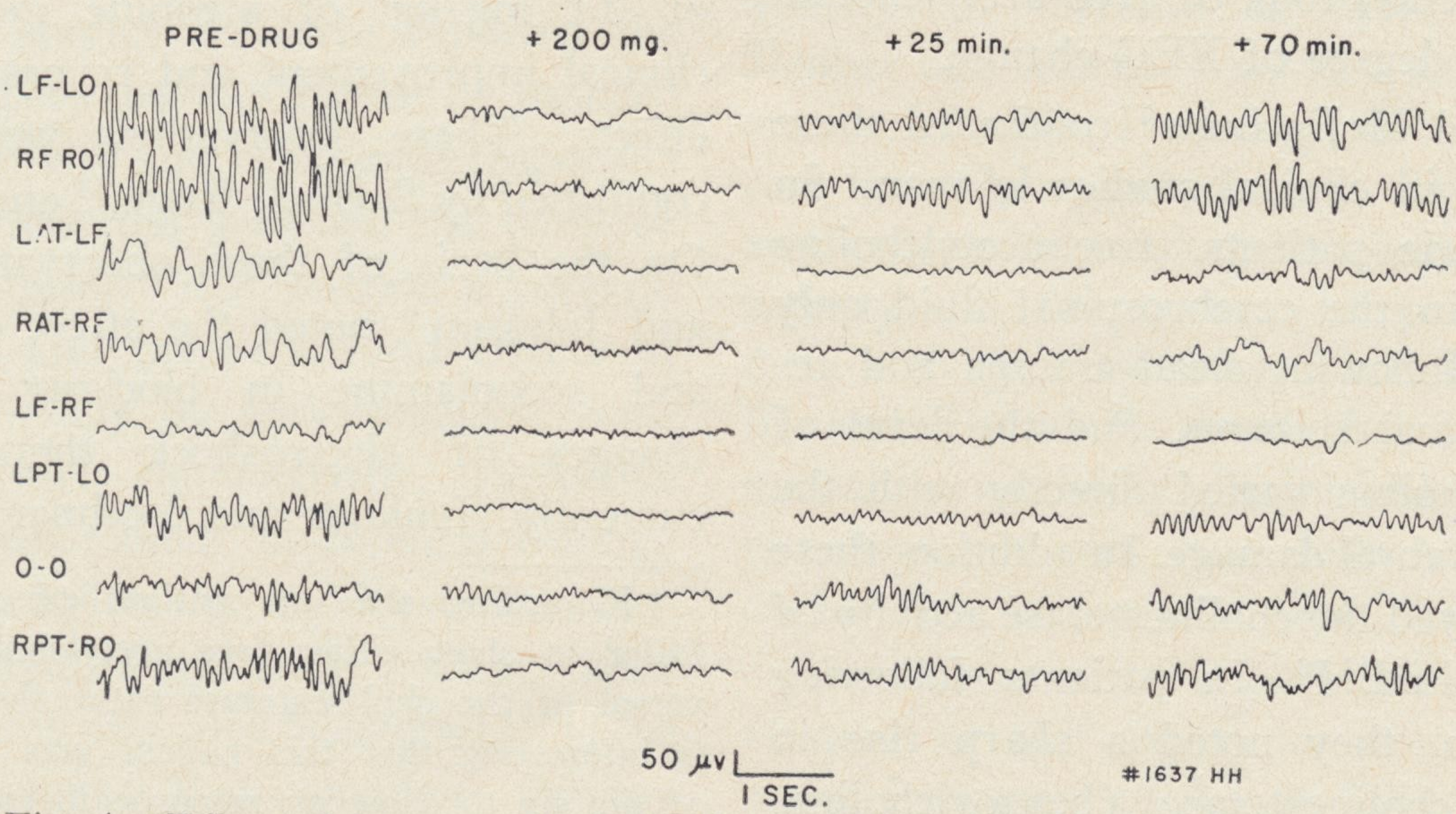

Fig. 4.—Effect of intravenous diethazine on delta activity after electroshock.

behavior, and thus provide a useful experimental agent with "anticholinergic" properties. Two aspects of these experimental observations warrant discussion: the role of acetylcholine-cholinesterase in the electroconvulsive therapy process, and the significance of diethazine "alerting" for concepts of hallucinogenic activity.

1. *Biochemical Basis of the Convulsive Therapy Process.*—While there has been considerable study of the psychologic and neurophysiologic aspects of convulsive therapy, little information concerning biochemical processes is available. The studies of biochemical changes following head trauma and spontaneous seizures provide some analogic data. Bornstein,[6] in a classical experimental study of head trauma in cats, demonstrated that within a few minutes after trauma free acetylcholine appeared in the spinal fluid and persisted for periods up to 48 hours. He further demonstrated a positive relation between the severity of head trauma and the quantity of free acetylcholine, the degree of electroencephalographic alteration, and the severity of the behavioral changes. The electroencephalographic records initially showed short periods of high-voltage fast activity, and a transient period of flattening of electrical activity, followed by prolonged periods of high-amplitude sharp waves in the delta frequencies. Concomitantly, alteration in consciousness, changes in reflexes, and post-traumatic seizures were most prominent with highest concentrations of free acetylcholine and greatest degree of EEG change.

Tower and McEachern [7] confirmed these observations in clinical studies in man. In 112 neurologic patients, free acetylcholine was found in the cerebrospinal fluid only in patients following head trauma and recent grand mal seizures, and the level of free acetylcholine varied directly with the degree of cerebral damage. In addition, these authors assayed the cholinesterase activity of the spinal fluid.[7,16] In patients following head trauma, they noted a sharp rise in nonspecific cholinesterase (benzoylcholine-splitting) and a drop in the specific cholinesterase (methacholine-splitting) activity of the spinal fluid. No such inversion was noted in fluids containing free acetylcholine following spontaneous seizures. Electroencephalograms were taken at varying intervals following trauma and demonstrated a direct correlation of the extent of EEG abnormality with the appearance of free acetylcholine in the spinal fluid.

Tower and McEachern also reported observations in six patients receiving electroconvulsive therapy. In patients after three to seven induced convulsions, they noted free acetylcholine in the spinal fluid in two patients and an increase in nonspecific cholinesterase with reversal of the cholinesterase ratio in five of the six. They concluded that the spinal fluid changes in electroshock are more like those of craniocerebral trauma than those found in epilepsy.† More recently, Sachs [17] confirmed the reports of free acetylcholine in the spinal fluid after head trauma and after electroshock.

In his studies, Bornstein [6] administered 0.5-1.0 mg/kg. of atropine and demonstrated a reversal or a blocking of the EEG effects and a modification of the behavioral and neurologic signs. Atropine also blocked the EEG and clinical signs induced by intracisternal acetylcholine.

Ward [8] applied these observations to the treatment of human subjects with varying degrees of head trauma. Subcutaneous doses of 0.1 mg/kg. of atropine induced both clinical improvement and reversal of EEG effects. These observations were recently confirmed by Sachs,[17] Ruge,[18] and Hughes.[19] On the basis of these observations, Ulett and Johnson [9] noted the effect of atropine and scopolamine in blocking the EEG changes of electroshock therapy. Concurrently, Jenkner and Lechner [10] reported

† Regarding the one patient of the six who failed to show either free acetylcholine or a reversal of the cholinesterase ratio, they noted: "It is interesting that this patient was the only one of the six to show no response to treatment."

effects similar to those of Ward, in studies of diethazine in cases of head injury.

Another group of investigations complete the available data. Studies of anticholinesterases, such as fluorophosphate, and tetraethylpyrophosphate (TEPP), which block the enzymatic breakdown of acetylcholine, demonstrate the development of high-amplitude rapid-frequency EEG patterns similar to those of status epilepticus, as well as slighter degrees of abnormality, as noted in post-traumatic states.[20-23] In these studies, atropine blocked both the electroencephalographic and the clinical toxic effects.

Thus, from both experimental and clinical studies of craniocerebral trauma we may assume that (*a*) the acetylcholine activity of the spinal fluid increases, (*b*) pseudocholinesterase activity increases, with a reversal of the ratio of cholinesterases, (*c*) EEG hypersynchrony and slowing parallel these biochemical alterations, and (*d*) anticholinergic agents may block both the electroencephalographic and the clinical effects. From the data available, it is probable that the biochemical basis of convulsive therapy is similar to that of craniocerebral trauma. Convulsive therapy results in free acetylcholine in the spinal fluid [7,17] and a reversal of cholinesterase ratios.[7,16] The electroencephalographic effects of repeated induced convulsions is the development of high-voltage, symmetric, slow-wave activity, occasionally with spike activity,[3,24,25] which is similar to that observed in severe head trauma.[26,27] In previous studies we have reported the relationship between the degree of induced slow-wave activity and behavioral response.[3] The studies reported here and the work of Ulett and Johnson [9] demonstrate a reversal of the EEG and the behavioral effects of convulsive therapy by anticholinergic compounds. In each characteristic, convulsive therapy is thus similar to cerebral trauma. While the acetylcholine-cholinesterase system is highlighted by these studies, other enzyme systems may also be altered.[17] These studies also suggest that convulsive therapy provides an excellent experimental method for studies of craniocerebral trauma.

Studies of the brain-stem-activating system by Jasper and Droogleever-Fortuyn [28] and Lindsley et al.[29] had laid the foundation for the prevailing conclusion that symmetric EEG slow-wave activity has its origin in mesencephalic structures, and that these structures intimately affect the states of "alerting" and "drowsiness." More recently, Rinaldi and Himwich [30,31] have related the site of action of atropine and cholinergic drugs to this mesodiencephalic activating system. It is also probable that these structures may be selectively affected by the convulsive therapy process, and that both the clinical and the electrographic effects may be intimately related to changes in this system.

2. *Diethazine "Alerting" and Hallucinogenic Activity.*—The behavioral effects of diethazine provide information regarding another aspect of the convulsive therapy process. In patients without prior convulsive therapy, illusory phenomena and feelings of unreality were observed. These were similar to the hallucinogenic effects of lysergic acid diethylamide (LSD[32]) and mescaline.[33] Again, analogic data about the clinical and EEG effects of these agents may provide some information about convulsive therapy.

In studies of mescaline, Wikler [34] noted that the EEG demonstrated no change, or intermittent or continuous low-voltage fast activity, or increase in alpha frequency. Denber and Merlis [35] noted a similar acceleration of alpha frequency, decrease in per cent time alpha, including its disappearance, and nonspecific random beta activity. Delta activity did not occur. In patients with delta activity induced by electroshock, Merlis and Hunter [38] noted that intravenous mescaline markedly diminished the amplitude and per cent time delta activity with an increase in per cent time alpha activity.

The effects of LSD on EEG are similar. Gastaut et al.[36] noted an acceleration of alpha frequency of 0.5 to 4.0 cps, with an accentuation of beta rhythms. Rinkel et al.[37] confirmed this observation and noted, in addition, a reduced responsivity to hyperventilation.‡

In summarizing his studies, Wikler[34] concluded that "regardless of the . . . drug administered, shifts on 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." This generalization provides a meaningful construct in which these agents may be assessed. Agents that evoke EEG desynchronization tend to be hallucinogenic, and mescaline and LSD are clear examples. Agents that synchronize frequencies, such as barbiturate and meprobamate in the beta frequency range, and chlorpromazine, promazine, and perphenazine in the delta frequency range[39] tend to be sedatives, euphoriants, and relaxants.

The observations on diethazine reported here are consistent with this hypothesis. In patients without delta activity, the EEG demonstrated desynchronization of frequencies, and this was associated with clinical illusory phenomena. In patients with delta activity desynchronization occurred, and alerting and reversal of the speech patterns induced by electroshock were observed.

Electroconvulsive therapy may also be understood in this framework. We have previously noted a direct relationship between clinical evaluations of improvement and the degree of EEG slowing induced by electroshock.[3] Under these conditions, sedation and euphoria are most prominent, and hallucinatory activity diminished. In patients in whom hypersynchrony is not induced, behavioral change is limited, and "improvement" does not occur.[4]

Previously we have concluded that the mode of action of convulsive therapies is based on the induction of a state of altered cerebral function, in which changes in adaptive interpersonal behavior occur, and are interpreted as "improvement."[3,4,39] The present studies amplify two aspects of this neurophysiologic-adaptive hypothesis. The biochemical substrate of the behavioral change is reflected by an alteration in the acetylcholine-cholinesterase relationships of the central nervous system. It is also probable that EEG hypersynchrony provides the neurophysiologic basis of the milieu change, which is clinically manifest as sedation and euphoria and is evaluated as "improvement."

The neurophysiologic-adaptive hypothesis of convulsive therapy has provided a meaningful basis for studies of other physiodynamic therapies.[39] In this study, it has been possible to amplify our understanding of neurophysiologic aspects of hallucinogens as well.

Summary and Conclusions

The effect of an anticholinergic agent, diethazine, on the EEG, behavior, and language patterns was observed in 40 psychiatric patients, at various stages in the course of electroconvulsive treatment.

(*a*) Behavior: Increased restlessness and agitation, haptic and visual illusory sensations, and delusional thoughts about their illness or the examiner's identity were observed.

(*b*) EEG: Alteration in EEG were concurrent with behavioral changes. There were a decrease in voltage and desynchronization of all frequencies. In patients with delta activity, the per cent time and voltage of delta activity decreased.

(c) Language: Syntactic patterns described for convulsive therapy were reversed. Use of third person, qualification, and displacement decreased. In dyadic analyses there was a decrease in the coefficient of variation.

‡ Studies are now in progress on the effects of LSD, Win-2299 (2-diethylaminoethyl-cyclopentylhydroxy-2-thienylacetate), benactyzine, and other anticholinergic compounds on postconvulsive EEG delta activity. Initial experiments with these compounds have demonstrated marked diminution in per cent time and amplitude of delta activity associated with behavioral changes similar to those seen with diethazine.

These observations are discussed in the framework of the neurophysiologic-adaptive hypothesis of the action of convulsive therapy, and it is concluded that (*a*) the biochemical basis for convulsive therapy is similar to that of craniocerebral trauma; (*b*) changes in acetylcholine-cholinesterase metabolism are intimately related to the behavioral effects, and (*c*) EEG desynchronization may be a physiologic concomitant of hallucinogenic activity, and EEG hypersynchrony, associated with euphoria and sedation.

Mrs. Hannah Mosquera gave technical assistance in the EEG recordings, and Dr. Joseph Jaffe and Dr. Robert L. Kahn made the analyses of the tape recordings.

Diethazine was made available through the courtesy of Smith, Kline & French Laboratories, Philadelphia.

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 Printed and Published in the United States of America

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Effect of Anti-Cholinergic Agent, Diethazine, on EEG and Behavior: Significance for Theory of Convulsive Therapy

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Aided, in part, by grant M-927 of the National Institute of Mental Health, National Institutes of Health, U.S. Public Health Service.

Effect of Anti-Cholinergic Agent, Diethazine, on EEG and Behavior: Significance for Theory of Convulsive Therapy

Recent investigations of convulsive therapy have emphasized EEG delta activity as the neurophysiologic basis for the induced behavioral change (1,2,3,4,5). Little study, however, has been given to the biochemical effects of this therapy, except in the course of investigations of head injuries.

In investigations of head trauma significance has been ascribed to changes in the acetylcholine-cholinesterase systems both for the behavioral and the electroencephalographic effects. An increase in free acetylcholine (6) and an alteration of the ratio of cholinesterases (7) in the spinal fluid have been positively correlated with the degree of EEG abnormality and degree of neurologic deficit. The EEG patterns were "blocked," and some improvement in clinical status was reported following the administration of atropine (7,8). In convulsive therapy, atropine and scopolamine were observed to block the appearance of delta activity, (9) although the systemic effects of the large doses of these agents were marked.

Recent reports (10) noted that EEG and behavioral effects similar to atropine were achieved in patients with head trauma by intravenous diethazine - a phenothiazine compound with anticholinergic properties - with minimal systemic effects. In our continuing studies of the role of delta activity in electroshock (3), the effect of diethazine was studied. It is the purpose of this report to describe the effects of diethazine on EEG patterns and on behavior of patients during electroconvulsive therapy; and to relate these observations to the present neurophysiologic-adaptive hypothesis of the mode of action of convulsive therapy.

SUBJECTS AND METHODS:

Forty psychiatric patients, at various stages of electroshock therapy in an open-ward, voluntary psychiatric hospital have been studied. All observations have been made in acute experiments in the EEG laboratory. Following a routine EEG recording, diethazine was administered intravenously at the rate of 25 mgm per minute, for a total of 175 to 250 mgm, depending upon the behavioral effect. Dosage varied from 2.8 to 4.0 mgm per kilogram body weight.

Diethazine is a soluble phenothiazine compound with pharmacologic properties similar to atropine. In experimental animals, diethazine blocks the bradycardia, bronchospasm, salivation, fasciculation and seizures induced by acetylcholine, di-isopropyl fluorophosphate and pilocarpine. It suppresses salivation, and induces mydriasis and hypotension (11).

EEG Analyses:

Recording was continuous for the duration of the observation period, except during interview periods. Needle electrodes, and an 8 channel Medcraft instrument were used. All records were analyzed for the degree of delta activity (3); the per cent time and principal alpha frequency; and the relative amount of fast activity. The alpha and delta activity were measured in anterior temporal-vertex, and parietal- ear lobe lead combinations.

Behavior Measures:

Prior to drug administration an unstructured psychiatric historical interview and a structured questionnaire period (12) were tape recorded. Following drug administration, periods of recorded interview were alternated with EEG recording periods, until the EEG had again manifested the pre-injection pattern on visual inspection.

Two estimates of behavioral effects were used: clinical descriptions by the participants - subject, interviewer and technician - of the changes occurring during the drug period, and language analyses of the recorded interviews. Changes in language were evaluated by a syntactic analysis (12) and an analysis of the variability in verbal interaction in the dyad (13, 14)*. Both measures have been shown to be sensitive to alterations in behavior induced by changes in the central nervous system.

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* Detailed analyses of these observations will be reported separately by Drs. J. Jaffe and Robert L. Kahn.

OBSERVATIONS:

(a) Clinical:

Within two to five minutes of the start of the injection, subjects manifested spontaneous coughing followed by a dryness of the mouth and a thickness of speech. They reported a feeling of lassitude, and a heaviness and weakness of extremities which was soon succeeded by increased restlessness and difficulty in maintaining eyelid closure.

Reports of visual and haptic illusory sensations, feelings of unreality and distance, and delusional thoughts about their illness, the setting of the test procedures or our identity were voiced spontaneously in eighteen subjects in the period between 15 and 60 minutes, after drug administration. In three instances, increasing agitation and panic led to a cessation of the recording. In two subjects withdrawal and negativism was the prominent behavioral response. Such patterns of behavior were transient and had disappeared in 1½ - 4 hours in all subjects.

(b) EEG Patterns:

Alteration in the EEG patterns was concurrent with the behavioral effects. In all records, changes occurred during drug administration and were sustained, with gradual diminution and restituion of the pre-injection patterns, in one to five hours. The initial response was a decrease in voltage and desynchronization of all frequencies. There was a decrease in prominence of prevailing rhythms. In patients without delta activity (pre-electroshock), desynchronization and voltage decrease was occasionally accompanied by low voltage 5-7 cps activity, symmetric and prominent in frontal and anterior temporal leads (Figure 1, 2). The alpha frequency was not altered. The build-up in voltage and appearance of slower frequencies with hyperventilation was blocked.

In patients with varying degrees of high voltage delta activity there was a prominent decrease in voltage and desynchronization of the record. Both random and burst delta activity diminished or disappeared, and irregular low voltage alpha and beta frequencies became prominent (Fig. 3, 4). The hyperventilation response was no longer apparent.

(c) Language Patterns:

In previous studies, an intimate relationship between changes in syntactic language patterns and the behavioral response in electroshock had been reported (12). With alteration in brain function, increased use of third person, verbal denial, qualification, displacement and cliches became prominent. These effects could be enhanced by the administration of intravenous amobarbital (14).

In the subjects in the present study, syntactic analyses demonstrated a reversal of the patterns noted in electroshock. Use of third person, qualification and displacement decreased. Explicit verbal denial was modified and replaced by minimization and displacement, or by a reiteration of complaints of illness. In dyadic analyses, the verbal interaction was characterized by a greater diversity of vocabulary and less variability in the diversity scores for 25 word units.

The qualitative nature of these changes in the language patterns is opposite to that of amobarbital and electroshock. The duration of language changes was concurrent with the changes in the electroencephalogram.

DISCUSSION:

These observations confirm the report of Jenkner and Lechner of the effects of diethazine in "normal" subjects (10). Diethazine also alters electroshock induced delta activity in a fashion similar to atropine and scopolamine, as described by Ulett and Johnson (9), with minimal unpleasant symptoms. The effects of intravenous diethazine are immediate, both on the EEG and behavior, and thus provides a useful experimental agent with "anti-cholinergic" properties. Two aspects of these experimental observations warrant discussion: the role of acetylcholine-cholinesterase in the electro-convulsive therapy process, and the significance of diethazine "alerting" for concepts of hallucinogenic activity.

1. Biochemical Basis of the Convulsive Therapy Process:

While there has been considerable study of the psychologic and neurophysiologic aspects of convulsive therapy, little information concerning biochemical processes is available. The studies of biochemical changes following head trauma and spontaneous seizures provide some analogic data. Bornstein (6), in a classical experimental study of head trauma in cats, demonstrated that within a few minutes after trauma, free acetylcholine appeared in the spinal fluid and persisted for periods up to 48 hours. He further demonstrated a positive relation between the severity of head trauma and the quantity of free acetylcholine, degree of electroencephalographic alteration and the severity of the behavioral changes. The electroencephalographic records initially showed short periods of high voltage fast activity, a transient period of flattening of electrical activity, followed by prolonged periods of high amplitude sharp waves in the delta frequencies. Concomitantly, alteration in consciousness, changes in reflexes and post-traumatic seizures were most prominent with highest concentration of free acetylcholine and greatest degree of EEG change.

Tower and McEachern (7) confirmed these observations in clinical studies in man. In 112 neurologic patients, free acetylcholine was found in the cerebrospinal fluid only in patients following head trauma and recent grand mal seizures; and the level of free acetylcholine varied directly with the degree of cerebral damage. In addition, these authors assayed the cholinesterase activity of the spinal fluid, (7, 16). In patients following head trauma, they noted a sharp rise in non-specific cholinesterase (benoylcholine-splitting) and a drop in the specific cholinesterase (mecholyl-splitting activity of the spinal fluid. No such inversion was noted in fluids containing free acetylcholine following spontaneous seizures. Electro-encephalograms were taken at varying intervals following trauma, and demonstrated a direct correlation of the extent of EEG abnormality and the appearance of free acetylcholine in the spinal fluid.

Tower and McEachern also reported observations in six patients receiving electroconvulsive therapy. In patients after 3-7 induced convulsions, they noted free acetylcholine in the spinal fluid in two, and an increase in non-specific cholinesterase with reversal of the cholinesterase ratio in five of the six. They concluded that the spinal fluid changes in electroshock are more like those of craniocerebral trauma than those found in epilepsy.*
More recently, Sachs (17) confirmed the reports of free acetylcholine in the spinal fluid after head trauma and after electroshock.

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* Regarding the one patient of the six who failed to show either free acetylcholine or a reversal of the cholinesterase ratio, they note: "It is interesting that this patient was the only one of the six to show no response to treatment."

In his studies, Bornstein (6) administered 0.5-1.0 mg/kg atropine and demonstrated a reversal or a blocking of the EEG effects, and a modification of the behavioral and neurologic signs. Atropine also blocked the EEG and clinical signs induced by intracisternal acetylcholine.

Ward (8) applied these observations to the treatment of human subjects with varying degrees of head trauma. Subcutaneous doses of 0.1 mg/kg of atropine induced both clinical improvement and reversal of EEG effects. These observations were recently confirmed by Sachs (17), Ruge (18) and Hughes (19). Based on these observations, Ulett and Johnson (9) noted the effect of atropine and scopolamine in blocking the EEG changes of electroshock therapy, without noting the effect on clinical behavior. Concurrently, Jenkner and Lechner (10) reported effects similar to those of Ward, in studies of diethazine in cases of head injury.

Another group of investigations complete the available data. Studies of anticholinesterases, as DFP (di-isopropyl fluorophosphate) and TEPP (tetraethyl-pyrophosphate), which block the enzymatic breakdown of acetylcholine, demonstrate the development of high amplitude rapid frequency EEG patterns similar to status epilepticus as well as lesser degrees of abnormality as noted in post-traumatic states (20, 21, 22, 23). In these studies, atropine blocked both the electroencephalographic and the clinical toxic effects.

Thus, both from experimental and clinical studies of craniocerebral trauma we may assume that (a) the acetylcholine activity of the spinal fluid increases; (b) pseudo-cholinesterase activity increases with a reversal of the ratio of cholinesterases; (c) EEG hypersynchrony and slowing parallel these biochemical alterations; and (d) anticholinergic agents may block both the electroencephalographic and the clinical effects. From the data available it is probable that the biochemical basis of convulsive therapy is similar to that of craniocerebral trauma. Convulsive therapy results in free acetylcholine in the spinal fluid (7, 17) and a reversal of cholinesterase ratios (7, 16). The electroencephalographic effects of repeated induced convulsions is the development of high voltage, symmetric slow wave activity, occasionally with spike activity (3, 24, 25), which is similar to that observed in severe head trauma (26, 27). In previous studies we have reported the relationship between the degree of induced slow wave activity and behavioral response (3). The studies reported here and that of Ulett and Johnson (9) demonstrate a reversal of the EEG and the behavioral effects of convulsive therapy by anticholinergic compounds. In each characteristic, convulsive therapy is thus similar to cerebral trauma. While the acetylcholine-cholinesterase system is highlighted by these studies, other enzyme systems may also be altered (17). These studies also suggest that convulsive therapy provides an excellent experimental method for studies of craniocerebral trauma.

Studies of the brain stem activating system by Jasper and Droogleever-Fortuyn (28) and Lindsley _et al._ (29) had laid the foundation for the prevailing conclusion that symmetric EEG slow wave activity has its origin in mesencephalic structures, and these these structures intimately affect the states of "alerting" and "drowsiness." More recently, Rinaldi and Himwich (30, 31) have related the site of action of atropine and cholinergic drugs to this mesodiencephalic activating system. It is also probable that these structures may be selectively affected by the convulsive therapy process, and that both the clinical and electrographic effects may be intimately related to changes in this system.

2. Diethazine "Alerting" and Hallucinogenic Activity:

The behavioral effects of diethazine provide information regarding another aspect of the convulsive therapy process. In patients without prior convulsive therapy, illusory phenomena and feelings of unreality were observed. These were similar to the hallucinogenic effects of LSD (32) and mescaline (33). Again analogic data about the clinical and EEG effects of these agents may provide some information about convulsive therapy.

In studies of mescaline, Wikler (34) noted that the EEG demonstrated either no change, intermittent or continuous low voltage fast activity or increase in alpha frequency. Denber and Merlis (35) noted a similar acceleration of alpha frequency, decrease in per cent time alpha including its disappearance, and non-specific random beta activity. Delta activity did not occur. In patients with delta activity induced by electroshock, Merlis and Hunter (38) noted that intravenous mescaline markedly diminished the amplitude and per cent time delta activity with an increase in per cent time alpha activity.

The effects of LSD on EEG are similar. Gastaut et al. (36) noted an acceleration of alpha frequency of 0.5 to 4.0 cps with an accentuation of beta rhythms. Rinkel et al. (37) confirmed this observation and noted, in addition, a reduced responsivity to hyperventilation.*

In summarizing his studies Wikler (34) concluded that "... regardless of the drug administered, shifts in the pattern of electroencephalogram in the

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* Studies are now in progress of the effects of LSD, Win-2299, benactyzine and other anticholinergic compounds on post-convulsive EEG delta activity. Initial experiment with intravenous LSD (50-100 gamma) demonstrated marked diminution in per cent time and amplitude of delta activity.

direction of desynchronization occurred in association with anxiety, hallucinations, fantasies, illusions or tremors, and in the direction of synchronization with euphoria, relaxation or drowsiness." This generalization provides a meaningful construct in which these agents may be assessed. Agents that evoke EEG desynchronization tend to be hallucinogenic and mescaline and LSD are clear examples. Agents that synchronize frequencies, such as barbiturate and meprobamate in the beta frequency range, and chlorpromazine, promazine and trilafon in the delta frequency range (39) tend to be sedatives, euphoriants and relaxants.

The observations on diethazine reported here are consistent with this hypothesis. In patients without delta activity, the EEG demonstrated desynchronization of frequencies, and this was associated with clinical illusory phenomena. In patients with delta activity desynchronization occurred, and alerting and reversal of the speech patterns induced by electroshock were observed.

Electroconvulsive therapy may also be understood in this framework. We have previously noted a direct relationship between clinical evaluations of improvement and the degree of EEG slowing induced by electroshock (3). Under these conditions, sedation and euphoria are most prominent and hallucinatory activity diminished. In patients in whom hypersynchrony is not induced, behavioral change is limited and 'improvement' does not occur (40).

Previously we have concluded that the mode of action of convulsive therapies is based on the induction of a state of altered cerebral function, in which changes in adaptive interpersonal behavior occur, and are interpreted as 'improvement' (3, 4, 39). The present studies amplify two aspects of this neurophysiologic-adaptive hypothesis. The biochemical substrate of the behavioral change is reflected by an alteration in the acetylcholine-cholinesterase relationships of the cerebrospinal fluid. It is also probable that EEG hypersynchrony provides the neurophysiologic basis of the milieu change which is clinically manifest as sedation and euphoria and is evaluated as 'improvement.'

The neurophysiologic-adaptive hypothesis of convulsive therapy has provided a meaningful basis for studies of other physiodynamic therapies (39). In this study, it has been possible to amplify our understanding of neurophysiologic aspects of hallucinogens as well.

SUMMARY:

1. The effect of an anticholinergic agent, diethazine, on the EEG, behavior and language patterns was observed in 40 psychiatric patients, at various stages in the course of electroconvulsive treatment.

(a) Behavior: Increased restlessness and agitation, haptic and visual illusory sensations, and delusional thoughts about their illness or examiner's identity were observed.

(b) EEG: Alteration in EEG was concurrent with behavioral changes. There was a decrease in voltage and desynchronization of all frequencies. In patients with delta activity, the per cent time and voltage of delta activity decreased.

(c) Language: Syntactic patterns described for convulsive therapy were reversed. Use of third person, qualification and displacement decreased. In dyadic analyses, there was a decrease in the coefficient of variability.

2. These observations are discussed in the framework of the neuro-physiologic-adaptive hypothesis of the action of convulsive therapy; and it is concluded that:

(a) the biochemical basis for convulsive therapy is similar to that of craniocerebral trauma;

(b) changes in acetylcholine-cholinesterase metabolism are intimately related to the behavioral effects; and

(c) EEG desynchronization may be a physiologic concomitant of hallucinogenic activity; and EEG hypersynchrony associated with euphoria and sedation.

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Effect of Intravenous Diethazine pre-Electroshock

Fig. 1

Effect of Intravenous Diethazine pre-Electroshock

Fig. 2

Effect of Intravenous Diethazine After Electroshock

Fig. 3.

Effect of Intravenous Diethazine After Electroshock

Fig. 4

Acknowledgement

I am indebted to Mrs. Hannah Mosquera for her technical assistance in the EEG recordings; and to Drs. Joseph Jaffe and Robert L. Kahn for their analyses of the tape recordings. ~~D.~~ ~~[illegible]~~ Diethazine was made available through courtesy of Smith, Kline and French Labs., Philadelphia.

JUN 9 '58

Drug	No. c̄ Δ	No. s̄ Δ	Av. Δ Pre Drug	Av. Δ post Drug
Diethazine	17	15	45.3 %	20.5 %
WIN 2299	11	5	49.5 %	22.8 %
Benactyzine	8	3	38.6 %	16.6 %
LSD	4	1	46.8 %	15.5 %
Atropine	6	5		

EEG - Mescaline - Drugs

(1) Stockings J.n.m.d. 86 : 29, 1940

(2) Gibbs et al Arch Int Med 60 : 154, 1937

Effect of Anticholinergic Compounds on Post Convulsive EEG and Behavior

In 1956 Ulett and Johnson (1) reported to this society that large doses of atropine or scopolamine blocked the appearance of the high voltage delta activity usually induced by convulsive therapy. They also noted that the dose of atropine necessary to affect the EEG was such as to be associated with unpleasant systemic effects. The reports by Jenkner and Lechner (2) describing diethazine as an anticholinergic compound with potent neurologic but minimal systemic effects led us to undertake studies similar to those of Ulett and Johnson; and these observations, in turn led to an investigation of other similar agents. It is the purpose of this report to describe the clinical and EEG correlations on the intravenous administration of various hallucinogens and anticholinergic agents in psychiatric patients at various stages of convulsive therapy; and to relate these observations to the recently expressed neurophysiologic-adaptive hypothesis of the mode of action of convulsive therapy and of hallucinogens.

Subject and Method:

Our subjects were consecutive referrals for convulsive therapy in an open ward voluntary psychiatric hospital. Patients have been studied at various stages of therapy, with observations being made in acute experiments in the EEG laboratory. Following a standard 8 channel EEG recording from 17 leads using needle electrodes, the compound under study was administered intravenously at a set rate per minute, until clinical behavioral or electrographic changes were observed. The compounds studied have been diethazine, Win 2299*, LSD-25, benactyzine, JB-318* and JB-336.* Diethazine was administered at 25 mgm. per minute, for a total of 175-250 mgm; Win-2299 and benactyzine at 0.5 mgm per minute for 2-5 mgm; LSD-25 at 10 gamma per minute for 50-150 gamma; and JB-318 and JB-336 at 0.4 mgm per minute for 1.2-3.6 mgm.

Observations:

On the administration of diethazine, in 15 patients prior to convulsive therapy, there was a decrease in voltage and a desynchronization of all frequencies. Prevailing rhythmic patterns became less prominent. In some instances, symmetric low voltage 6-7 cps activity appeared, most prominent in the frontal and anterior temporal leads. The alpha frequency was not altered, but the build-up in voltage and slower frequencies induced by hyperventilation was blocked (Fig. 1, 2).

In 17 patients during convulsive therapy, with varying degrees of induced high voltage delta activity, there was a significant decrease both in voltage and in per cent time of slow wave activity. From an average per cent time delta of 45% in the fronto-occipital leads, there was a reduction to a mean of 20%. Both random and burst delta activity diminished and low voltage alpha and beta frequencies became prominent. The hyperventilation response was no longer apparent. These electrographic effects persisted for

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* Win-2299 is 2-diethylaminoethyl cyclopentyl (2-thienyl) glycolate; JB-318 is n-ethyl-3-piperidylbenzilate; JB-336 is m-methyl-3-piperidylbenzilate.

one to five hours (Fig. 3, 4).

Concurrent with these EEG effects, we observed distinctive behavioral changes. Patients became more irritable and restless and complained of sensations of unreality with dysesthesias of the extremities. Visual illusory phenomena and delusional thoughts about their illness, the setting of the test procedure or the examiner's identity were described. Their language patterns were characteristically altered in a fashion opposite to that previously described for amobarbital (3), so that verbal denial, minimization, cliches, third person mode and past tense became less prominent. These changes were concurrent with maximum electrographic change.

The behavioral observations with diethazine led to a review of the effects of hallucinogens on EEG activity. In 1955 Denber and Merlis (4) had reported that mescaline altered EEG delta activity induced by electroshock, in a fashion similar to diethazine. They described a marked reduction in amplitude and per cent time of high voltage symmetric slow wave bursts with an increase in alpha per cent time and in low voltage, random slow wave activity.

Reports by Pennes (5) that an experimental compound, Win-2299 manifested both potent anticholinergic activity and induced hallucinations in man led to our study of this compound. The effects were similar to that observed in the diethazine group. In patients pre-convulsive therapy, EEG desynchronization and decrease in voltages of all frequencies were induced (Fig. 5). In eleven patients with high voltage delta activity there was a decrease in amplitude and per cent time of slow wave activity with an increase in alpha and beta frequencies. The mean per cent time delta activity dropped from 50% to 23% in these subjects. Associated with these electrographic effects were clinical patterns of restlessness, excitement, and hallucinatory and illusory activity (Fig. 6). As the hallucinogenic activity of LSD-25 was well established, these studies were next repeated with this compound. Here, too, the behavioral and electroencephalographic effects, on intravenous administration, were similar to diethazine. There was a difference in the time constant in that the behavioral effects occurred 1½ to 2 hours after drug administration, but the electrographic changes were concurrent with the behavioral change. While there was less desynchronization with LSD, the delta activity was significantly repressed. Mean per cent time delta activity fell from 47% to 16% in five subjects (Fig. 7, 8, 9).

Recalling reports that benactyzine, a potent anticholinergic compound, induced EEG desynchronization we next administered this compound intravenously in eleven subjects, and again observed similar clinical and electrographic patterns. Both in the well modulated alpha record and in the record with high voltage delta activity, desynchronization was prompt. Delta activity decreased from a mean per cent time of 39% to 17% in 8 subjects (Fig. 10, 11). These electrographic patterns were accompanied by clinical restlessness and excitement. While we did not observe illusory or hallucinatory activity, we did note that the language patterns were altered in the same fashion as with the other agents tested.

Lately, following reports by Abood (6) that various piperidylbenzilates had potent anticholinergic properties and induced clinical hallucinogenic activity, we tested two of these, JB-318 and JB-336. The electrographic patterns were identical to those of Win-2299 and in each instance in which desynchronization was observed, clinical restlessness and hallucinatory activity was noted (Fig. 12, 13). The hallucinatory activity persisted for 1 to 3 hours, and during this period, electrographic alteration was prominent.

Thus, six compounds have been shown to have similar electrographic and behavioral effects. Each has definitive anticholinergic activity. Each induces hallucinogenic or excitatory activity; and these behavioral changes are accompanied by EEG desynchronization. Furthermore, these compounds have a similar chemical structure (Fig. 14). The tertiary amine in a substituted diethylaminethanol is prominent, corroborating the recent reports by Denber (7) on the hallucinogenic activity of tertiary amines, and amplifying his studies by the common concurrent electrographic patterns.

These observations amplify our understanding of the convulsive therapy process. In earlier studies we indicated that the development of high voltage slow wave activity was the neurophysiologic correlate of behavioral change in convulsive therapy, and a necessary, though not sufficient, condition for clinical improvement (8). During the past ten years, studies by Bernstein, Tower and McEachern, Ward, Sachs, Ruge and others have noted similarities in the biochemical changes in convulsive therapy to craniocerebral trauma (9). They reported an elevation of free acetylcholine and pseudocholinesterase in the spinal fluid during convulsive therapy. In addition, topical administration of acetylcholine induces high voltage bursts and spike activity. Ulett and Johnson emphasized the blocking of these cholinergic effects by the anticholinergic activity of atropine and scopolamine. The observations on this report on diethazine, Win-2299, LSD-25, benactyzine and the piperidylbenzilates support their observations. Each of these compounds has potent anticholinergic activity and the clinical behavioral and language effects are opposite to those described for convulsive therapy. We may thus amplify the earlier conclusion that the neurophysiologic basis for behavioral change in convulsive therapy is the development of high voltage slow wave activity by noting that this EEG change reflects an alteration in the acetylcholine-cholinesterase relations of the nervous system, probably in the direction of increased cholinergic activity.

These observations lend themselves to application in studies of craniocerebral trauma. Ward's (10) reports of the efficacy of high doses of atropine in altering the clinical manifestations of head trauma also indicated that effective doses brought with them severe systemic effects. It would be advisable to repeat these studies, utilizing such more potent, more neurologically specific anticholinergic compounds as used in these experiments.

Finally, these observations, and our earlier reports on the significance of EEG delta activity in convulsive therapy, support the observation of Wikler (11) who concluded his report on mescaline, n-allylnormorphine and morphine with the comment that: "... regardless 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." This conclusion, supported by our observations, permit a more meaningful generalization of the recently expressed neurophysiologic-adaptive hypothesis of the mode of action of somatic therapies in psychiatry. We may infer that agents that synchronize EEG frequencies, like barbiturate and meprobamate in the beta frequency range and chlorpromazine, promazine and perphenazine in the delta frequency range, tend to be sedative, euphoriant and relaxant; while agents that evoke EEG desynchronization tend to be excitant and hallucinogenic, as was noted for diethazine, LSD-25, Win-2299, benactyzine, mescaline, and the piperidylbenzilates.

In summary, we have observed the effects of various hallucinogenic and anticholinergic compounds on the electroencephalogram and behavior in psychiatric patients at various stages of convulsive therapy.

Behaviorally, these compounds induced increased restlessness, haptic and visual illusory sensations and delusional thoughts about the subject's illness or the examiner's identity. The syntactic language patterns described for convulsive therapy and barbiturate were reversed. Concurrent with these changes were a decrease in voltage and a desynchronization of all frequencies in the EEG. In patients with high voltage delta activity, the per cent time and voltage of the delta activity were markedly decreased.

These observations have been discussed in the framework of the common biochemical structure and anticholinergic properties of these agents with the conclusion that:

(a) The biochemical basis for convulsive therapy and for high voltage EEG delta activity may be an alteration in the acetylcholine-cholinesterase relation of the nervous system, probably in the direction of increased cholinergic activity.

(b) The recently expressed neurophysiologic-adaptive hypothesis of the mode of action of somatic therapies in psychiatry is amplified to encompass the action of hallucinogens.

It is recommended that further studies of the effects of anti-cholinergic compounds in craniocerebral trauma to be undertaken, utilizing more neurologically specific compounds as diethazine, benactyzine and Win-2299.

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Effect of Anti-Cholinergic Agent, Diethazine, on EEG and Behavior: Significance for Theory of Convulsive Therapy

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Aided, in part, by grant M-927 of the National Institute of Mental Health, National Institutes of Health, U.S. Public Health Service.

Read (in part) at the meeting of the Eastern Association of Electroencephalographers, N.Y., December 1957.

SBP: 3-58

Effect of Anti-Cholinergic Agent, Diethazine, on EEG and Behavior: Significance for Theory of Convulsive Therapy

Recent investigations of convulsive therapy have emphasized EEG delta activity as the neurophysiologic basis for the induced behavioral change (1,2,3,4,5). Little study, however, has been given to the biochemical effects of this therapy, except in the course of investigations of head injuries.

In investigations of head trauma significance has been ascribed to changes in the acetylcholine-cholinesterase systems both for the behavioral and the electroencephalographic effects. An increase in free acetylcholine (6) and an alteration of the ratio of cholinesterases (7) in the spinal fluid have been positively correlated with the degree of EEG abnormality and degree of neurologic deficit. The EEG patterns were "blocked," and some improvement in clinical status was reported following the administration of atropine (7,8). In convulsive therapy, atropine and scopolamine were observed to block the appearance of delta activity, (9) although the systemic effects of the large doses of these agents were marked.

Recent reports (10) noted that EEG and behavioral effects similar to atropine were achieved in patients with head trauma by intravenous diethazine - a phenothiazine compound with anticholinergic properties - with minimal systemic effects. In our continuing studies of the role of delta activity in electroshock (3), the effect of diethazine was studied. It is the purpose of this report to describe the effects of diethazine on EEG patterns and on behavior of patients during electroconvulsive therapy; and to relate these observations to the present neurophysiologic-adaptive hypothesis of the mode of action of convulsive therapy.

SUBJECTS AND METHODS:

Forty psychiatric patients, at various stages of electroshock therapy in an open-ward, voluntary psychiatric hospital have been studied. All observations have been made in acute experiments in the EEG laboratory. Following a routine EEG recording, diethazine was administered intravenously at the rate of 25 mgm per minute, for a total of 175 to 250 mgm, depending upon the behavioral effect. Dosage varied from 2.8 to 4.0 mgm per kilogram body weight.

Diethazine is a soluble phenothiazine compound with pharmacologic properties similar to atropine. In experimental animals, diethazine blocks the bradycardia, bronchospasm, salivation, fasciculation and seizures induced by acetylcholine, di-isopropyl fluorophosphate and pilocarpine. It suppresses salivation, and induces mydriasis and hypotension (11).

EEG Analyses:

Recording was continuous for the duration of the observation period, except during interview periods. Needle electrodes, and an 8 channel Medcraft instrument were used. All records were analyzed for the degree of delta activity (3); the per cent time and principal alpha frequency; and the relative amount of fast activity. The alpha and delta activity were measured in anterior temporal-vertex, and parietal-ear lobe lead combinations.

Behavior Measures:

Prior to drug administration an unstructured psychiatric historical interview and a structured questionnaire period (12) were tape recorded. Following drug administration, periods of recorded interview were alternated with EEG recording periods, until the EEG had again manifested the pre-injection pattern on visual inspection.

Two estimates of behavioral effects were used: clinical descriptions by the participants - subject, interviewer and technician - of the changes occurring during the drug period, and language analyses of the recorded interviews. Changes in language were evaluated by a syntactic analysis (12) and an analysis of the variability in verbal interaction in the dyad (13,14).* Both measures have been shown to be sensitive to alterations in behavior induced by changes in the central nervous system.

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* Detailed analyses of these observations will be reported separately by Drs. J. Jaffe and R. L. Kahn.

OBSERVATIONS:

(a) Clinical:

Within two to five minutes of the start of the injection, subjects manifested spontaneous coughing followed by a dryness of the mouth and a thickness of speech. They reported a feeling of lassitude, and a heaviness and weakness of extremities which was soon succeeded by increased restlessness and difficulty in maintaining eyelid closure.

Reports of visual and haptic illusory sensations, feelings of unreality and distance, and delusional thoughts about their illness, the setting of the test procedures or our identity were voiced spontaneously in eighteen subjects in the period between 15 and 60 minutes after drug administration. In three instances, increasing agitation and panic led to a cessation of the recording. In two subjects withdrawal and negativism was the prominent behavioral response. Such patterns of behavior were transient and had disappeared in 1½ - 4 hours in all subjects.

(b) EEG Patterns:

Alteration in the EEG patterns was concurrent with the behavioral effects. In all records, changes occurred during drug administration and were sustained, with gradual diminution and restitution of the pre-injection patterns, in one to five hours. The initial response was a decrease in voltage and desynchronization of all frequencies. There was a decrease in prominence of prevailing rhythms. In patients without delta activity (pre-electroshock), desynchronization and voltage decrease was occasionally accompanied by low voltage 5-7 cps activity, symmetric and prominent in frontal and anterior temporal leads (Figure 1, 2). The alpha frequency was not altered.

The build-up in voltage and appearance of slower frequencies with hyperventilation was blocked.

In patients with varying degrees of high voltage delta activity there was a prominent decrease in voltage and desynchronization of the record. Both random and burst delta activity diminished or disappeared, and irregular low voltage alpha and beta frequencies became prominent (Fig. 3, 4). The hyperventilation response was no longer apparent.

(c) Language Patterns:

In previous studies, an intimate relationship between changes in syntactic language patterns and the behavioral response in electroshock had been reported (12). With alteration in brain function, increased use of third person, verbal denial, qualification, displacement and cliches became prominent. These effects could be enhanced by the administration of intravenous amobarbital (14).

In the subjects in the present study, syntactic analyses demonstrated a reversal of the patterns noted in electroshock. Use of third person, qualification and displacement decreased. Explicit verbal denial was modified and replaced by minimization and displacement, or by a reiteration of complaints of illness. In dyadic analyses, the verbal interaction was characterized by a greater diversity of vocabulary and less variability in the diversity scores for 25 word units.

The qualitative nature of these changes in the language patterns is opposite to that of amobarbital and electroshock. The duration of language changes was concurrent with the changes in the electroencephalogram.

DISCUSSION:

These observations confirm the report of Jenkner and Lechner of the effects of diethazine in "normal" subjects (10). Diethazine also alters electroshock induced delta activity in a fashion similar to atropine and scopolamine, as described by Ulett and Johnson (9), with minimal unpleasant symptoms. The effects of intravenous diethazine are immediate, both on the EEG and behavior, and thus provides a useful experimental agent with "anti-cholinergic" properties. Two aspects of these experimental observations warrant discussion: the role of acetylcholine-cholinesterase in the electro-convulsive therapy progress, and the significance of diethazine "alerting" for concepts of hallucinogenic activity.

1. Biochemical Basis of the Convulsive Therapy Process:

While there has been considerable study of the psychologic and neurophysiologic aspects of convulsive therapy, little information concerning biochemical processes is available. The studies of biochemical changes following head trauma and spontaneous seizures provide some analogic data. Bornstein (6), in a classical experimental study of head trauma in cats, demonstrated that within a few minutes after trauma, free acetylcholine appeared in the spinal fluid and persisted for periods up to 48 hours. He further demonstrated a positive relation between the severity of head trauma and the quantity of free acetylcholine, degree of electroencephalographic alteration and the severity of the behavioral changes. The electroencephalographic records initially showed short periods of high voltage fast activity, a transient period of flattening of electrical activity, followed by prolonged periods of high amplitude sharp waves in the delta frequencies. Concomitantly, alteration in consciousness, changes in reflexes and post-traumatic seizures were most prominent with highest concentrations of free acetylcholine and greatest degree of EEG change.

Tower and McEachern (7) confirmed these observations in clinical studies in man. In 112 neurologic patients, free acetylcholine was found in the cerebrospinal fluid only in patients following head trauma and recent grand mal seizures; and the level of free acetylcholine varied directly with the degree of cerebral damage. In addition, these authors assayed the cholinesterase activity of the spinal fluid, (7, 16). In patients following head trauma, they noted a sharp rise in non-specific cholinesterase (benzoylcholine-splitting) and a drop in the specific cholinesterase (mecholyl-splitting) activity of the spinal fluid. No such inversion was noted in fluids containing free acetylcholine following spontaneous seizures. Electroencephalograms were taken at varying intervals following trauma, and demonstrated a direct correlation of the extent of EEG abnormality and the appearance of free acetylcholine in the spinal fluid.

Tower and McEachern also reported observations in six patients receiving electroconvulsive therapy. In patients after 3-7 induced convulsions, they noted free acetylcholine in the spinal fluid in two, and an increase in non-specific cholinesterase with reversal of the cholinesterase ratio in five of the six. They concluded that the spinal fluid changes in electroshock are more like those of craniocerebral trauma than those found in epilepsy. *

* Regarding the one patient of the six who failed to show either free acetylcholine or a reversal of the cholinesterase ratio, they noted: "It is interesting that this patient was the only one of the six to show no response to treatment."

More recently, Sachs (17) confirmed the reports of free acetylcholine in the spinal fluid after head trauma and after electroshock.

In his studies, Bornstein (6) administered 0.5-1.0 mg/kg atropine and demonstrated a reversal or a blocking of the EEG effects, and a modification of the behavioral and neurologic signs. Atropine also blocked the EEG and clinical signs induced by intracisternal acetylcholine.

Ward (8) applied these observations to the treatment of human subjects with varying degrees of head trauma. Subcutaneous doses of 0.1 mg/kg of atropine induced both clinical improvement and reversal of EEG effects. These observations were recently confirmed by Sachs (17), Ruge (18) and Hughes (19). Based on these observations, Ulett and Johnson (9) noted the effect of atropine and scopolamine in blocking the EEG changes of electroshock therapy, without noting the effect on clinical behavior. Concurrently, Jenkner and Lechner (10) reported effects similar to those of Ward, in studies of diethazine in cases of head injury.

Another group of investigations complete the available data. Studies of anticholinesterases, as DFP (di-isopropyl fluorophosphate) and TEPP (tetraethyl-pyrophosphate), which block the enzymatic breakdown of acetylcholine, demonstrate the development of high amplitude rapid frequency EEG patterns similar to status epilepticus as well as lesser degrees of abnormality as noted in post-traumatic states (20, 21, 22, 23). In these studies, atropine blocked both the electroencephalographic and the clinical toxic effects.

Thus, both from experimental and clinical studies of craniocerebral trauma we may assume that (a) the acetylcholine activity of the spinal fluid increases; (b) pseudo-cholinesterase activity increases with a reversal of the ratio of cholinesterases; (c) EEG hypersynchrony and slowing parallel these biochemical alterations; and (d) anticholinergic agents may block both the electroencephalographic and the clinical effects. From the data available it is probable that the biochemical basis of convulsive therapy is similar to that of craniocerebral trauma. Convulsive therapy results in free acetylcholine in the spinal fluid (7, 17) and a reversal of cholinesterase ratios (7, 16). The electroencephalographic effects of repeated induced convulsions is the development of high voltage, symmetric slow wave activity, occasionally with spike activity (3, 24, 25), which is similar to that observed in severe head trauma (26, 27). In previous studies we have reported the relationship between the degree of induced slow wave activity and behavioral response (3). The studies reported here and that of Ulett and Johnson (9) demonstrate a reversal of the EEG and the behavioral effects of convulsive therapy by anti-cholinergic compounds. In each characteristic, convulsive therapy is thus similar to cerebral trauma. While the acetylcholine-cholinesterase system is highlighted by these studies, other enzyme systems may also be altered (17). These studies also suggest that convulsive therapy provides an excellent experimental method for studies of craniocerebral trauma.

Studies of the brain stem activating system by Jasper and Droogleever-Fortuyn (28) and Lindsley _et al_. (29) had laid the foundation for the prevailing conclusion that symmetric EEG slow wave activity has its origin in mesencephalic structures, and that these structures intimately affect the states of "alerting" and "drowsiness." More recently, Rinaldi and

Himwich (30, 31) have related the site of action of atropine and cholinergic drugs to this mesodiencephalic activating system. It is also probable that these structures may be selectively affected by the convulsive therapy process, and that both the clinical and electrographic effects may be intimately related to changes in this system.

2. Diethazine "Alerting" and Hallucinogenic Activity:

The behavioral effects of diethazine provide information regarding another aspect of the convulsive therapy process. In patients without prior convulsive therapy, illusory phenomena and feelings of unreality were observed. These were similar to the hallucinogenic effects of LSD (32) and mescaline (33). Again analogic data about the clinical and EEG effects of these agents may provide some information about convulsive therapy.

In studies of mescaline, Wikler (34) noted that the EEG demonstrated either no change, intermittent or continuous low voltage fast activity or increase in alpha frequency. Denber and Merlis (35) noted a similar acceleration of alpha frequency, decrease in per cent time alpha including its disappearance, and non-specific random beta activity. Delta activity did not occur. In patients with delta activity induced by electroshock, Merlis and Hunter (38) noted that intravenous mescaline markedly diminished the amplitude and per cent time delta activity with an increase in per cent time alpha activity.

The effects of LSD on EEG are similar. Gastaut et al. (36) noted an acceleration of alpha frequency of 0.5 to 4.0 cps with an accentuation of beta rhythms. Rinkel et al. (37) confirmed this observation and noted, in addition, a reduced responsivity to hyperventilation.*

In summarizing his studies Wikler (34) concluded that " . . . 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." This generalization provides a meaningful construct in which these agents may be assessed. Agents that evoke EEG desynchronization tend to be hallucinogenic, and mescaline and LSD are clear examples. Agents that synchronize frequencies, such as barbiturate and meprobamate in the beta frequency range, and chlorpromazine, promazine and perphenazine in the delta frequency range (39) tend to be sedatives, euphoriants and relaxants.

The observations on diethazine reported here are consistent with this hypothesis. In patients without delta activity, the EEG demonstrated desynchronization of frequencies, and this was associated with clinical illusory phenomena. In patients with delta activity desynchronization occurred, and alerting and reversal of the speech patterns induced by electroshock were observed.

Electroconvulsive therapy may also be understood in this framework. We have previously noted a direct relationship between clinical evaluations

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* Studies are now in progress of the effects of LSD, Win-2299, benactyzine and other anticholinergic compounds on post-convulsive EEG delta activity. Initial experiments with intravenous LSD (50-100 gamma) demonstrated marked diminution in per cent time and amplitude of delta activity.

of improvement and the degree of EEG slowing induced by electroshock (3). Under these conditions, sedation and euphoria are most prominent and hallucinatory activity diminished. In patients in whom hypersynchrony is not induced, behavioral change is limited and 'improvement' does not occur (40).

Previously we have concluded that the mode of action of convulsive therapies is based on the induction of a state of altered cerebral function, in which changes in adaptive interpersonal behavior occur, and are interpreted as 'improvement' (3, 4, 39). The present studies amplify two aspects of this neurophysiologic-adaptive hypothesis. The biochemical substrate of the behavioral change is reflected by an alteration in the acetylcholine-cholinesterase relationships of the central nervous system. It is also probable that EEG hypersynchrony provides the neurophysiologic basis of the milieu change which is clinically manifest as sedation and euphoria and is evaluated as 'improvement.'

The neurophysiologic-adaptive hypothesis of convulsive therapy has provided a meaningful basis for studies of other physiodynamic therapies (39). In this study, it has been possible to amplify our understanding of neurophysiologic aspects of hallucinogens as well.

SUMMARY:

1. The effect of an anticholinergic agent, diethazine, on the EEG, behavior and language patterns was observed in 40 psychiatric patients, at various stages in the course of electroconvulsive treatment.

(a) Behavior: Increased restlessness and agitation, haptic and visual illusory sensations, and delusional thoughts about their illness or examiner's identity were observed.

(b) EEG: Alteration in EEG was concurrent with behavioral changes. There was a decrease in voltage and desynchronization of all frequencies. In patients with delta activity, the per cent time and voltage of delta activity decreased.

(c) Language: Syntactic patterns described for convulsive therapy were reversed. Use of third person, qualification and displacement decreased. In dyadic analyses, there was a decrease in the coefficient of variation.

2. These observations are discussed in the framework of the neurophysiologic-adaptive hypothesis of the action of convulsive therapy; and it is concluded that:

(a) the biochemical basis for convulsive therapy is similar to that of craniocerebral trauma;

(b) changes in acetylcholine-cholinesterase metabolism are intimately related to the behavioral effects; and

(c) EEG desynchronization may be a physiologic concomitant of hallucinogenic activity; and EEG hypersynchrony associated with euphoria and sedation.

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Effect of Anticholinergic Compounds on Post-Convulsive EEG and Behavior *

Max Fink M.D.

Following the observations of Ulett and Johnson (EEG Clin. Neurophysiol. 9: 217, 1957) that atropine and scopolamine blocked the delta activity induced by convulsive therapy, similar studies were undertaken with an anticholinergic compound, diethazine. Pre-electroshock, diethazine induced desynchronization of EEG frequencies and a decrease in voltages. In patients with delta activity, voltage and per-cent time of delta activity decreased, dominant alpha and beta frequencies increased and burst activity disappeared. Concurrent behavioral changes included illusory sensations, paranoid ideation and withdrawal, increased restlessness, difficulty in maintaining eyelid closure, and reversal of the language patterns associated with altered cerebral function after convulsive therapy.

The apparent psychotomimetic activity of diethazine led to the study of lysergic acid diethylamide, Win 2299 and benactyzine in voluntary psychiatric patients at various stages of convulsive therapy. These anticholinergic compounds were administered intravenously in amounts of 50-150 gamma, 2-5 mgm and 1-5 mgm respectively, under continuous EEG recording. For each compound the behavioral changes and language measures paralleled those of diethazine. In EEG recordings pre-treatment, each compound induced EEG desynchronization with an increase in beta activity and in the alpha frequency. In records with slow wave activity, both the voltage and per-cent time of this activity decreased, per-cent time fast frequencies increased, and the alpha frequency increased. Behavioral changes were concurrent with these electrographic changes, and both were inhibited by intravenous chlorpromazine.

Similar observations for mescaline have been reported by Denber, Merlis and Hunter (Psychiat. Quart. 29: 421, 1955).

Previous reports noted that the clinical response to induced convulsions was dependent upon the development of extensive high voltage slow wave activity (A.M.A. Arch. Neurol. Psychiat. 78: 516, 1957). The reversal of postconvulsive EEG and behavior patterns by these potent anticholinergic compounds suggest that an increase in cholinergic activity may be the basis for EEG hypersynchrony and clinical sedation and euphoria. Conversely, a decrease in cholinergic activity may be associated with EEG desynchronization and clinical psychotomimetic activity.

The relation of these observations to studies of head trauma, and to the neurophysiologic-adaptive hypothesis of the mode of action of convulsive therapy will be discussed.

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AEEG: 4/3/58.

II: 4-2-58

Effect of Anticholinergic Hallucinogens on Post-Convulsive EEG and Behavior *

Max Fink M.D.

Following the observation of Ulett and Johnson that atropine and scopolamine blocked the delta activity induced by convulsive therapy, similar studies were undertaken with another anticholinergic compound, diethazine. Pre-electroshock, diethazine induced desynchronization of EEG frequencies and a decrease in voltages. In patients with delta activity, voltage and per-cent time of delta activity ~~in~~decreased, dominant alpha and beta frequencies increased and burst activity disappeared. Concurrent behavioral changes included illusory sensations, paranoid ideation and withdrawal, increased restlessness, difficulty in maintaining eyelid closure, and reversal of the language patterns indicative of altered cerebral function.

The apparent psychotomimetic activity of diethazine led to study of LSD, Win 2299, and benactyzine in patients at various stages of convulsive therapy. The behavioral changes for each of these compounds in the doses employed, paralleled those of diethazine. In EEG recordings pre-treatment, each agent induced desynchronization of the record with increases in beta activity, and in frequency and per-cent time of alpha activity. In records with slow wave activity, both the voltage and percent time of this activity decreased, per-cent time fast frequencies increased, and the alpha frequency increased. Behavioral changes were concurrent with these electrographic changes, and both were inhibited by intravenous chlorpromazine.

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AEEG: 4/58

These observations are similar to those of Denber *et al.* for mescaline.

Each of those compounds have potent anticholinergic properties, and structurally, each contains a tertiary nitrogen linkage. The significance of these observations for the theory of the mode of action of convulsive therapy in psychoses, as well as for the neurophysiology and pharmacology of hallucinogens will be discussed.

Effect of Anticholinergic Compounds on Post-Convulsive EEG and Behavior *

Max Fink M.D.

Following the observations of Ulett and Johnson (EEG Clin. Neurophysiol. 9: 217, 1957) that atropine and scopolamine blocked the delta activity induced by convulsive therapy, similar studies were undertaken with another anticholinergic compound, diethazine. Pre-electroshock, diethazine induced desynchronization of EEG frequencies and a decrease in voltages. In patients with delta activity, voltage and per-cent time of delta activity decreased, dominant alpha and beta frequencies increased and burst activity disappeared. Concurrent behavioral changes included illusory sensations, paranoid ideation and withdrawal, increased restlessness, difficulty in maintaining eyelid closure, and reversal of the language patterns associated with altered cerebral function after convulsive therapy (Psychopathology of Communication, Grune & Stratton, pg. 126, 1958)

The apparent psychotomimetic activity of diethazine led to the study of lysergic and diethylamide, Win 2299 and benactyzine in voluntary psychiatric patients at various stages of convulsive therapy. These anticholinergic compounds were administered intravenously in amounts of 50-150 gamma, 2 to 5 mgm and 1-5 mgm respectively, under continuous EEG recording. For each compound the behavioral changes and language measures paralleled those of diethazine. In EEG recordings pre-treatment, each compound induced EEG desynchronization with an increase in beta activity and in the alpha frequency. In records with slow wave activity, both the voltage and per-cent time of this activity decreased, per-cent time fast frequencies increased, and the alpha frequency increased. Behavioral changes were concurrent with these electrographic changes, and both were inhibited by intravenous chlorpromazine.

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AEEG: 4/3/58

Similar observations for mescaline have been reported by Denber, Merlis and Hunter (Psychiat. Quart. 29: 421, 1955).

The reversal of postconvulsive EEG and behavior patterns by these potent anticholinergic compounds suggests a neurophysiologic basis for convulsive therapy. Previous reports noted that the clinical reponse to induced convulsions was dependent upon the development of extensive high voltage slow wave activity (A.M.A. Neurol. Psychiat. 78: 516, 1957). An increase in cholinergic activity may thus be associated with EEG hypersynchrony and clinical sedation and euphoria. Similarly, a decrease in cholinergic activity may be associated with EEG desynchronization and clinical psychotomimetic activity.

The therapy of the mode of action of convulsive therapy and the neurophysiologic effects of anticholinergic compounds will be discussed.

Effects of Antichplinergic Hallucinogens on Post-Convulsive EEG and Behavior

Following the observations of Ulett and Johnson that atropine and scopolamine blocked the delta activity induced by convulsive therapy, studies were undertaken with another anticholinergic compound, diethazine. Pre-electroshock diethazine induced desynchronization of frequencies and decrease in voltages. In patients with delta activity, voltage and per-cent time of delta activity decreases, frequency increases and burst activity disappears.

Concurrent behavioral changes included illusory sensations, paranoid ideation and withdrawal, increased restlessness, difficulty in maintaining eyelid closure, and reversal of the language patterns indicative of altered central function. The apparent hallucinogenic activity led to assay of various compounds including LSD, Win 2299, benactyzine and mescaline.

The behavioral changes in the doses employed were parallel to those of diethazine. In EEG recording pre-treatment, each agent induced desynchronization of the record with an increase in fast frequencies, increase in alpha frequency, and alpha voltage and per-cent time. In records with delta activity, both the voltage and per-cent time of delta activity decreased, per-cent time fast frequencies increased, and alpha frequency increased.

Behavioral changes were concurrent with these electrographic changes, and both were inhibited by intravenous chlorpromazine.

Each of these compounds have potent anticholinergic properties as well as a common tertiary amine linkage. The significance of these observations for the theory of the mode of action of convulsive therapy in psychoses, as well as for the neurophysiology and pharmacology of hallucinogens will be discussed.

0+4
SS.

Effect of Anticholinergic Compounds on Post-Convulsive EEG and Behavior *

Max Fink M.D.

Following the observations of Ulett and Johnson (EEG Clin. Neurophysiol. 9: 217, 1957) that atropine and scopolamine blocked the delta activity induced by convulsive therapy, similar studies were undertaken with an~~other~~ anticholinergic compound, diethazine. Pre-electroshock, diethazine induced desynchronization of EEG frequencies and a decrease in voltages. In patients with delta activity, voltage and per-cent time of delta activity decreased, dominant alpha and beta frequencies increased and burst activity disappeared. Concurrent behavioral changes included illusory sensations, paranoid ideation and withdrawal, increased restlessness, difficulty in maintaining eyelid closure, and reversal of the language patterns associated with altered cerebral function after convulsive therapy. ~~(Psychopathology of Communication, Grune & Stratton, pg. 126, 1958)~~

The apparent psychotomimetic activity of diethazine led to the study of lysergic ~~and~~ ACID diethylamide, Win 2299 and benactyzine in voluntary psychiatric patients at various stages of convulsive therapy. These anticholinergic compounds were administered intravenously in amounts of 50-150 gamma, 2 ~~to~~ 5 mgm and 1-5 mgm respectively, under continuous EEG recording. For each compound the behavioral changes and language measures paralleled those of diethazine. In EEG recordings pre-treatment, each compound induced EEG desynchronization with an increase in beta activity and in the alpha frequency. In records with slow wave activity, both the voltage and per-cent time of this activity decreased, per-cent time fast frequencies increased, and the alpha frequency increased. Behavioral changes were concurrent with these electrographic changes, and both were inhibited by intravenous chlorpromazine.

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AEEG: 4/3/58

Similar observations for mescaline have been reported by Denber, Merlis and Hunter, ~~(Psychiat. Quart. 29: 421, 1955).~~

In ~~P~~previous reports we noted that the clinical response to induced convulsions was dependent upon the development of extensive high voltage slow wave activity. ~~(A.M.A. Arch. Neurol. Psychiat. 78: 516, 1957).~~ The reversal of postconvulsive EEG and behavior patterns by these potent anticholinergic compounds suggests that an increase in cholinergic activity may be the basis for EEG hypersynchrony and clinical sedation and euphoria ~~are associated with~~. Conversely, ~~Also~~, EEG desynchronization and clinical psychotomimetic activity ~~are associated with~~ may be associated with a decrease in cholinergic activity.

The relation of these observations to studies of head trauma, and to the neurophysiologic-adaptive hypothesis of the mode of action of convulsive therapy will be discussed.

0+2
T.S.

~~I:6-5-68~~ II: 6:10:58

Effect of Anticholingeric Compounds on Post Convulsive EEG

and Behavior

In 1956 Ulett and Johnston reported to this society that large doses of atropine ~~or~~ scopolamine blocked the appearance of the high voltage delta activity usually induced by convulsive therapy. ~~In their study~~ They also noted that the dose~~s~~ of atropine necessary to affect the EEG ~~were~~ was such as to be ~~those that also~~ ~~carried~~ associated with ~~them~~ unpleasant ~~septimie~~ systemic effects. ~~Following~~ The reports by Jenkner and Lechner ~~on the effects of~~ describing diethazine ~~was~~ ~~, a potent neurologic~~ as an anticholinergic compound ~~with~~ with potent neurologic ~~nervous system~~ but minimal systemic effects ~~-~~ led us to undertake studies similar to those of Ulett and Johnson. ~~were undertaken~~. Our initial observations with ~~this~~ diethazine ~~compound~~ led to an investigation of other anticholinergic and hallucinogenic ~~hallucinogens.~~ agents. It is the purpose of this report to describe the clinical and EEG correlations on the intravenous administration of LSD-25, Win-2299, benactyzine and diethazine in psychiatric patients at various stages of convulsive therapy~~,~~ and to relate these observations to the recently expressed neurophysiologic-adapative hypothesis of the mode of action of convulsive therapy and of hallucinogens.

Subject and Method:

Our subjects ~~are~~ were consecutive referrals for convulsive therapy in an open ward voluntary psychiatric hospital. Patients have been studied at various stages of therapy, with ~~All~~ all observations being ~~have been~~ made in acute experiments in the EEG laboratory. Following a standard EEG recording from 17 leads, the compound under study was ~~is~~ administered intravenously at a set ~~fixed~~ rate per minute, until clinical behavioral or electrographic changes were ~~are~~ observed. The compounds studied have been diethazine, Win-2299, LSD-25 and benactyzine.

Fig. I - Chemistry structure

Diethazine was administered at 25 mgm. per minute, for a total of 175-250 mgm; Win-2299 and benactyzine at 0.5 mgm per minute for 2-5 mgm; and LSD-25 at 10 gamma per minute for 50-150 gamma.

<u>Observations:</u>

~~(a) Diethazine:~~ On the administration of diethazine;

in 15 ~~In~~ patients (prior to convulsive therapy) ~~pretreatment, without EEG delta activity,~~ there was a decrease in voltage and a desynchronization of all frequencies. Prevailing rhythmic patterns became less prominent. In some instances, symmetric low voltage 6-7 cps activity appeared, most prominent in the frontal and anterior temporal leads. The alpha frequency was not altered, but ~~and~~ the build-up <u>in voltage and slower frequencies induced</u> by hyperventilation was blocked.

Fig. 2, 3

Diethazine - EEG - Pre-Convulsive Treatment

In patients during convulsive therapy, with varying degrees of high voltage delta activity, there is a significant decrease in voltage and in per-cent time of delta activity. Both random and burst delta activity diminished and low voltage alpha and beta frequencies became prominent. The hyperventilation response was no longer apparent.

Fig. 4, 5

Diethazine - EEG - Convulsive Treatment

The electrographic effects persisted for one to five hours.

Concurrent with these EEG effects, we observed destructive behavioral changes. Patients became more irritable and restless and complained of sensations of unreality and dysesthesias of the extremities. Visual illusory phenomena and delusional thoughts about their illness, the setting of the test procedures or the examiner's identity were expressed by some. Their language patterns were altered, opposite to that previously described for amobarbital, NB: per cent - two words

so that [verbal] denial, minimization, cliches, third person mode and past tense ~~were~~ [become] less prominent. These behavioral changes were ~~present~~ [prominent] during the period of maximum ~~EEG~~ [Electrographic] change.

~~The ability of~~ [these behavioral observations with] diethazine ~~to induce illusory and hallucinatory activity~~ led to ~~an evaluation~~ [a review] of [the effects of] ~~other known~~ hallucinogens [on EEG activity]. ~~In checking the literature, we noted that~~ [In 1955] Denber and Merlis had ~~previously described that~~ [reported that] mescaline altered ~~the~~ EEG ~~changes~~ [delta activity] induced by electroshock, in a fashion similar to diethazine. They ~~reported that the~~ [described a marked reduction in amplitude and per cent time of] high voltage symmetric slow wave bursts ~~were diminished markedly in amplitude and per-cent time,~~ with an increase in alpha per cent time and in low voltage, random slow wave activity.

~~Earlier~~ Reports by Pennes ~~and~~ ~~on~~ [that an experimental compound, Win-2299] ~~the hallucinogenic activity of Win 2299~~ - ~~a~~ [manifested both] potent anticholinergic ~~compound~~ [activity and induced hallucinations in man] - led to ~~a similar~~ [our] study ~~with~~ [of] this compound. The effects were similar to ~~that~~ [that observed] in the diethazine group. In patients pre-convulsive therapy, EEG desynchronization [and decrease in voltages of all frequencies] was induced.

Fig. 6

Win 2299 - Pre-Convulsive Treatment

In [eleven] patients with high voltage slow wave activity induced by convulsive therapy, there was a decrease in amplitude and per-cent time of slow wave activity with an increase in alpha and beta frequencies. Associated with these electrographic effects were clinical patterns of restlessness, excitement,

The mean per cent time delta activity dropped from 50% to 23% in seven subjects.

Fig. 7

Win 2299 - Post Convulsive Treatment

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and hallucinatory and illusory activity.

Previous experience with lysergic acid diethylamide had indicated this to be a most potent hallucinogen.

The ~~same~~ studies ~~were~~ repeated with intravenous LSD ~~and again the patterns~~ ~~were repeated~~. There is a difference in the time constant ~~but with the~~ behavioral effects, ~~there were concurrent~~ electrographic changes. ~~With~~ ~~LSD~~ there was less desynchronization, ~~but~~ the delta activity ~~appears to be~~ ~~selectively~~ repressed.

Here, too, there has been concurrent behavioral and electroencephalographic effects, similar to diethazine ... in that the behavioral effects occur in 1½ to 2 hours after the drug administration, but the electrographic changes are concurrent with the behavioral change. While there is less desynchronization, the delta activity was significantly repressed with LSD. Mean per cent time delta activity fell from 47% to 16% in five subjects.

Fig. 8, 9, 10

LSD - EEG

Recalling ~~the~~ reports that benactyzine, a potent anticholinergic compound, induced EEG desynchronization, we administered ~~the~~ this compound intravenously, in 11 subjects, and again, observed similar clinical and electrographic patterns. In the well modulated alpha record, desynchronization is prompt. In the record with high voltage delta activity, desynchronization is prominent and the

~~and decrease in~~ delta activity ~~is equally prompt.~~ decreased from a mean per-cent time of 39% to 17%.

Fig. 11, 12

Benactyżine - EEG

These Electrographic patterns were accompanied by clinical restlessness and excitement.

While we did not observe illusory or hallucinatory activity, we did note that the

~~same kinds of~~ language ~~changes in these patients as was observed with~~ patterns were altered in the same fashion as with

diethazine, Win-2299 and LSD.

New Pg →

Thus, four compounds ~~with definitive anticholinergic properties~~ have been

shown to have similar electrographic, and behavioral effects. ~~In addition~~ Each has definitive anticholinergic action

Each ~~has~~ induced hallucinogenic or excitatory activity, and these behavioral

changes were accompanied by ~~to their~~ EEG desynchroniz~~ing activity and clinical hallucinogenic activity~~ation,

Furthermore, these compounds have ~~some common~~ a similar chemical structure, as may be seen in ~~Each is a tertiary~~

the next figure. Prominent is a tertiary amine in

~~ammineamine with~~ a ~~similar~~ diethyl-amino-ethyl organization. These

---

Repeat Fig 1

---

observations corroborate the recent report by Deuber on the hallucinogenic action of tertiary amines

~~Further corroboration of the activity of this organization in the recent~~

and amplify his studies by the concurrent common Electrographic

~~report of Pfeiffer that such antiparkinson, anticholinergic compounds as~~

patterns.

~~kemadrin, panparnit, artane, parsidol and benadryl, which contain such an~~

~~amine structure, have hallucinogenic properties.~~

These observations ~~also~~ amplify our understanding of the convulsive therapy process. In earlier studies we indicated that the development of high voltage slow wave activity was the neurophysiologic correlate of behavioral change in convulsive therapy, and a necessary, though not sufficient, condition for clinical improvement. During the past ten years, studies by Bornstein, Tower and McEachern, Ward, Sachs, Ruge and others have noted similarities in the biochemical changes in ~~correlates of~~ convulsive therapy to craniocerebral trauma. They reported that an elevation of free acetylcholine and pseudocholinesterase ~~are elevated~~ in the spinal fluid during convulsive therapy. In addition, topical administration of acetylcholine induces high voltage burst and spike activity. Ulett and Johnson emphasized the blocking of these cholinergic effects by the anticholinergic activity of ~~compounds,~~ atropine and scopolamine. The observations in this report on diethazine, Win-2299, LSD-25 and benactyzine support their observations. Each of these compounds has potent anticholinergic activity and the clinical behavioral and language effects are opposite to those described for convulsive therapy. We may thus amplify the earlier conclusion that the neurophysiologic basis for ~~correlate of~~ behavioral changes in convulsive therapy is the development of high voltage slow wave activity, by ~~the addition~~ noting that this EEG change reflects an alteration in the acetylcholine-cholinesterase relations of the ~~brain~~ nervous system, probably in the direction of increased cholinergic activity. ~~These observations do not preclude, however, concomitant alteration of other enzyme systems of the brain as indicated by the observations of Sachs on the serotonin changes in head trauma.~~

These observations lend themselves to application in studies of cranio-cerebral trauma. ~~The report of~~ Ward's reports of ~~on~~ the clinical efficacy of high doses of atropine ~~in~~ altering the clinical manifestations of head trauma, also noted that effective doses brought with them severe peripheral effects. It would be advisable to repeat these studies, utilizing such more potent, more neurologically specific anticholinergic compounds as Win-2299, diethazine or benactyzine.

Finally, these observations, and our earlier reports on the significance of EEG delta activity in convulsive therapy, support the observation of Wikler (1954) who concluded his report on mescaline, n-allylnormorphine and morphine with the comment that: ".... regardless 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." This conclusion, supported by ~~these~~ our observations, permit a more ~~neur~~ meaningful generalization of the recently expressed neurophysiologic - adaptive hypothesis of the mode of action of somatic therapies in psychiatry. We may infer that agents that synchronize EEG frequencies, like barbiturate and meprobamate in the beta frequency range and chlorpromazine, promazine and perphenazine in the delta frequency range, tend to be sedative, euphoriant and relaxant; while agents that evoke EEG desynchronization tend to be excitant and hallucinogenic, as was noted for diethazine, LSD-25, Win-2299, benactyzine and mescaline.

New Pg:

In summary, we have observed the effects of various compounds as diethazine, Win-2299, LSD-25, benactyzine and mescaline on the electroencephalogram and behavior in psychiatric patients at various stages of convulsive therapy.

Behaviorally, these compounds induced increased restlessness, haptic and visual illusory sensations and delusional thoughts about the subject's illness or the examiner's identity. The syntactic language patterns described for convulsive therapy and barbiturate were reversed. Concurrent with these changes were a decrease in voltage and a desynchronization of all frequencies in the EEG. In patients with high voltage delta activity, the per-cent time and voltage of the delta activity were markedly decreased.

These observations have been discussed in the framework of the common biochemical structure - that of a substituted diethylanimoethanol - and their anticholinergic properties with the conclusion that:

(a) The biochemical basis for convulsive therapy and for high voltage delta activity may be an alteration in the acetylcholine-cholinesterase relation of the nervous system, probably in the direction of increased cholinergic activity.

(b) The recently expressed neurophysiologic adaptive hypothesis of the mode of action of somatic therapies in psychiatry is amplified to encompass the action of hallucinogens. It is recommended that further studies of the effects of anticholinergic compounds in craniocerebral trauma be undertaken, utilizing more neurologically specific compounds as diethazine, benactyzine and Win-2299.

Effect of Anticholinergic Hallucinogens on Post Convulsive EEG and Behavior *

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Aided, in part, by grant M-927 and MY-2092 of the National Institute of Mental Health, National Institutes of Health, U.S. Public Health Service.

Read at the American EEG Society meeting, Atlantic City, June, 1958,

VI: 1/59 - EEG.

Effect of Anticholinergic Hallucinogens on Post Convulsive EEG and Behavior

In 1956 Ulett and Johnson ( ) reported that atropine and scopolamine blocked the appearance of the high voltage delta activity usually induced by convulsive therapy. They also noted that the dose of atropine necessary to affect the EEG was such as to be associated with unpleasant systemic effects. Reports by Jenkner & Lechner ( ) describing diethazine as an anticholinergic compound with potent neurologic but minimal systemic effects led us to undertake studies similar to those of Ulett and Johnson using this compound ( ); and these observations, in turn, led to an investigation of other experimental anticholinergic agents. It is the purpose of this report to describe clinical and electro-encephalographic observatinns on the intravenous administration of various anticholinergic agents in psychiatric patients at various stages of convulsive therapy and to relate these observations to hypotheses concerning the mode of action of convulsive therapy ( ) and the physiology of hallucinogens ( ).

SUBJECTS AND METHOD:

Our subjects were consecutive referrals for convulsive therapy in an open ward voluntary psychiatric hospital. While varying numbers of subjects have been studied for each compound, 86 subjects in 104 experiments have been essayed. Ages ranged from 18 to 67 years, and diagnoses include schizophrenic reactions, manic-depressive and involutional depressive psychoses.

Patients have been studied at various stages of the treatment process. The observations were made in acute experiments in the EEG laboratory. A standard 8 channel EEG recorder and needle electrodes applied in 17 lead placements following Strauss *et al* (   ) were used. In each experiment, the compound under study was administered intravenously at a set rate per minute, until clinical behavioral or electrographic changes were observed. The compounds studied have been diethazine, Win-2299, benactyzine, JB-318, JB-336, and atropine. Each is a potent anticholinergic agent *in vitro*. Diethazine (diethylaminoethyl-N-dibenzoparathiazine), for example, induces mydriasis and hypotension, suppresses salivation and blocks the bradycardia, salivation and seizures of acetylcholine and fluero-phosphate ( ). Win-2299 (2-dietylaminoethyl cyclopentyl-2-thienyl-glycolate) and benactyzine (2-diethylaminoethyl benzilate) are synthetic anticholinergic agents similar to atropine but with potent central effects and minimal peripheral effects (,). JB-318 and JB-336 (N-ethyl-3-piperidylbenzilate, N-methyl-3-piperidylbenzilate) are two of a recent series of synthetic anticholinergic ~~agent~~ compounds of high central potency and high hallucinogenic activity ( ). Diethazine was administered at 25 mgm. per minute for a total of 175-250 mgm; Win-2299 and benactyzine at 0.5 mgm. per minute for 2 to 5 mgm.; and JB-318, JB-336, and atropine at 0.4 mgm. per minute for 1.2 to 4.0 mgm.

OBSERVATIONS:

(a) Diethazine: As previously reported ( ), the administration of diethazine in 15 patients prior to convulsive
ron
therapy resulted in a decrease ib voltages and a desychonnization of all frequencies. Prevailing rhythmic patterns became less prominent. In some instances, symmetric low voltage 6-7 cps activity appeared, most prominent in the frontal and anterior temporal leads. The alpha frequency was not altered, but the build-up in voltage and the slower frequencies induced by hyper-ventilation were blocked (Fig. 1).

Fig. 1

In 25 patients during convulsive therapy, with varying degrees of induced high voltage delta activity ( ) there was a significant decrease both in voltage and in per cent time of slow wave activity. From an average per cent time delta of 45% in the fronte-occipital leads, there was a reduction to a mean per cent time of 20%. Both random and burst delta activity diminished and low voltage alpha and beta frequencies became prominent. The increase in degree of slow wave activity on hyperventilation was no longer apparent. These electrographic effects persisted for one to five hours (Fig. 2).

Fig. 2

Concurrent with these electrographic effects, we observed distinctive behavioral changes. Patients became more irritable and restless and complained of sensations of unreality and of dysthesias of the extremities. Visual illusory phenomena and delusional thoughts about their illness, the setting of the test procedure or the examiner;s identity were reported. Their syntactic language patterns were characteristically altered in a fashion opposite to that previously described for amobarbital ( ), so that verbal denial, minimization, cliches, third person mode and past tense ~~bxxxxx/fxxx~~ became less prominent. These changes were concurrent with maximum electrographic change.

(b) Win-2299: Reports by Pennes ( ) that an experimental compound, Win 2299, manifested both potent anticholinergic activity and induced excitatory states in man led to our study of this compound. The observations were similar to those observed with diethazine. In five patients without slow wave activity, desynchronization of frequencies and decrease in voltages of all frequencies were noted in four (Fig. 3).

Fig. 3

In 11 patients with high voltage delta activity there was a decrease in amplitude and per cent time of slow wave activity with an increase in alpha and beta frequencies. The mean per cent time delta activity dropped from 50% to 23% (Fig. 4).

Fig. 4

Associated with these electrographic effects were clinical patterns of restlessness and excitement. Patients became fearful and tense. Visual sensations were reported and in three subjects, delusional elaborations about their hospital experience were prominent. These behavioral changes appeared during drug administration or within ten minutes, and disappeared, at these dosage levels, within two to three hours.

(c) Benactyzine: Reports that benactyzine induced EEG desynchronization ( ) and its structural similarity both to diethazine and Win-2299 led to our testing of this compound. Intravenous administration in 12 subjects elicited similar clinical and electrographic patterns. Both in the well modulated alpha record and in the record with high voltage delta activity, desynchronization was prompt. Delta activity decreased from a mean per cent time of 39% to 17% in 8 subjects (Figs. 5, 6).

Figs. 5, 6

These electrographic patterns were accompanied by clinical restlessness, irritability and excitement. Artifact-free recording was more difficult. The illusory sensations and delusional thoughts seen with the initial compounds were mot noted at these dosage levels. In patients with manifest disorientation and language changes associated with convulsive therapy ( ), however, there was an alerting and a reversal of the language patterns.

(d) Piperidylbenzilates: Following recent reports by Abood ( ) that various piperidylbenzilates both manifested anticholinergic activity and induced hallucinations in psychiatric subjects, we tested two of these, JB-318 and JB-336 in 24 subjects. The electrographic patterns were identical to those other experimental compounds. Onset of desynchronization was during injection or within 15 minutes and persisted for one to four hours (Fig. 7, 8).

Figs. 7, 8

In each instance in which desynchronization was observed, clinical restlessness and excitement, illusory and hallucinatory activity were noted, and were concurrent with the electrographic changes. In two instances the behavioral changes were halted by the subsequent intravenous administration of chlorpromazine.

(e) <u>Atropine</u>: Continuing our study of anticholinergic compounds, we administered atropine intravenously in 12 subjects, in dosages of 0.8 to 4.0mgm. Systemic effects were prominent during the injection with increased respiratory rate, pallor, dry skin and dry mouth, precordial complaints and marked tachycardia (Figs. 9, 10).

Figs. 9, 10

Subjects became restless and fearful (as did the observer's) and ~~Suchxsymptomsxwerexprominentxasxin~~ recording became difficult. Within ten minutes these symptoms subsided and the subjects became drowsy and relaxed.

In subjects without delta activity little change was seen in the initial record, to be followed during the period of lassitude by decreased voltages, desychronization and increased slowing (Fig. 9).

Fig. 9

In subjects with delta activity, there was an initial decrease in voltage and per cent time of such activity during the period of restlessness, following by an increase during the period of quietude (Fig. 10).

Fig. 10

DISCUSSION:

Various compounds with measurable anticholinergic activity have thus been shown to have similar electrographic and behavioral effects. These experimental compounds exhibiting the greater facility in altering electrographic patterns have a common structure each containing a tertiary nitrogen with a diethyl linkage to varying roots (Fig. 11); while atropine, relatively impotent in altering electrographic patterns contains a quaternary nitrogen. Behaviorally each compound induces stimulating, excitatory and illusory and hallucinatory activity. Electrographically each induces desynchronization of frequencies, and decrease in voltages, most prominent in subjects with delta activity following therapeutically induced convulsions.

(a) Convulsive therapy process:

These observations amplify our understanding of the convulsive therapy process and of the induced EEG slow wave activity. In earlier studies we indicated that the development of high voltage slow wave activity was the neurophysiologic correlate of behavioral change in convulsive therapy, and a necessary, though not sufficient, condition for clinical improvement ( ). During the past ten years, numerous authors including Bornstein, Tower and McEachern, Ward, Sachs, Ruge have reported similarities in the biochemical changes of the central nervous system in convulsive therapy to that seen in craniocerebral trauma ( ). They observed an increase in cholmergic activity as manifest by an elevation of free acetylcholine and pseudocholinesterases in the spinal fluid. In addition, the direct increase in central nervous system acetylcholine activity by topical administration of acetylcholine induced high voltage bursts and spike activity. Ulett and Johnson ( ) emphasized the blocking of the behavioral and electrographic effects by the anticholinergic activity of atropine and scopolamine.

The observations in this report on diethazine, Win-2299, benactyzine and the piperidylbenzilates support their observations. The potent anticholinergic activity of each of these compounds (with apparent predominant locus of activity in the central nervous system) amplifies the suggestion that the biochemical basis for the induced slow wave activity of convulsive therapy results from an increased level of central acetylcholine-cholinesterase activity. Support for such a hypothesis is also seen in the considerable degrees of slow wave activity observed after the administration of DFP (di-isopropylfluorophosphate) - a potent cholinesterase blocking agent.

While these observations demonstrate that anticholinergic compounds are effective in reducing slow wave activity, reports of other compounds with similar effects have also appeared. Amphetamine (Benzedrine) ( ), mescaline ( ), lysergic acid diethylamide ( ) and diphenhydramine (Benadryl) ( ) have been reported as reducing post-convulsive slow wave activity. These compounds are primarily described as sympathomimetic and antihistaminic in pharmacologic activity, yet each has excitatory and stimulating effects on behavior (, , ,). The relations of these observations to those seen in this report are possibly best assessed in relation to synaptic activity.

In a study of the effects of various agents on the EEG and behavior of unanesthetized cats with chronic implanted electrodes, Bradley and Elkes (   ) postulated the existence of two, or possibly three, types of interacting chemoresponsive receptors within the central nervous system: cholinergic, non-cholinergic susceptible to amphetamine, and non-cholinergic susceptible to LSD and tryptaminic derivatives. Marazzi and Hart (   ) exploring intercortical (transcollosal) partways in the cat, described the effects of various compounds on the evoked potentials on direct electrical stimulation. They postulated the presence of two chemoreceptive potentialities of the synapse - cholinergic and adrenergic - with opposing stimulatory and inhibitory action. In both constructs, the administration of anticholinergic agents, or of sympathomimetic agents, results in equivalent synaptic electrical effects. Thus adrenaline, amphetamine, mescaline and LSD inhibit the electrical activity recorded across a synapse. An identical effect is achieved with atropine.

In the light of these suggestions, the present experiments permit a more specific hypothesis regarding the pharmacologic basis of the convulsive therapy process. Repeated induced convulsions leads to an increase in synaptic cholinergic activity with an increase in the level of electrical activity of the central nervous system, which is recorded by surface electrodes as augmented high voltage slow wave activity. Administration of anticholinergic agents reduces the level of synaptic activity, resulting in a decrease in the manifest cortical electrical activity to pre-convulsive levels. The administration of sympathomimetic agents, however, also achieves the same electrical effects, not by altering the level of cholinergic activity but by increasing the level of adrenergic activity. The manifest slow wave activity, so prominent and so persistent in the waking EEG of the post-seizure state (   ) may thus be related to a persistent alteration in synaptic transmission activity of large numbers of cells of the central nervous system. The delicate nature of this balance is seen in the ready reversibility with ~~ax~~ alerting (   ), time (   ) and the wide variety of pharmacologic agents noted here. Repeated induced convulsions may thus be described as a device to create biochemical changes in the brain for their resulting behavioral effects. Such a formulation is consistent with the view that convulsive therapy is a non-specific therapeutic process ( ).

The initial suggestion ( ) that the pharmacologic basis for the convulsive therapy process may lie in an alteration in acetylcholine-cholinesterase relationships, can, thus be focused on the alteration in the level of synaptic activity. In this regard, the observation that diphenhydramine , primarily an anti-hystaminic agent, also reduces slow wave activity of induced convulsions ( ), and the observations by Sachs ( ) that increased amounts of serotinin appear in the spinal fluid after convulsions suggest that this image of synaptic activity in convulsive therapy is oversimplified. Nevertheless, further animal studies of the effects of various drugs on the post-seizure electrical activity are warranted.

(b) Neurophysiology of hallucinogenic activity:

These observations of anticholinergic compounds on EEG delta activity also may be related to concepts of hallucinogenic activity. Each of the compounds studied induced excitatory behavior including illusory and hallucinatory phenomena.* Here, too, synaptic models may be useful. Sympathomimetic agents, as mescaline, LSD, and amphetamine, and anticholinergic agents as those described here, are equally potent hallucinogens, The neuropharmacologic basis for such behavior may be characterized as an alteration in synaptic balance in the direction of increased inhibition (decreased transmission) of stimuli.

The clinical efficacy of convulsive therapy in modifying hallucinatory activity may thus lie in an alteration at this biochemical level. Equally significant are the effects of other known anti-hallucinogens, as chlorpromazine and reserpine, on electrical activity. Both compounds induce EEG hypersynchrony in man ( ), block the EEG desynchronizing effects of LSC and medcaline ( ), and in animal studies, block LSD and mescaline behavioral and electrographic effects (,). The non-specific nature of the neurophysiologic basis of experimental hallucinatory activity is thus emphasized.

* In the doses used, hallucinatory phenomena were not observed for benactyzine. A report of such activity was reported at higher dosage ( ).