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CHAPTER 14

Effect of An Anticholinergic Agent, Diethazine, on EEG and Behavior: Significance for Theory of Convulsive Therapy

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RECENT INVESTIGATIONS of convulsive therapy have emphasized EEG delta activity as the neurophysiologic basis for the induced behavioral change.[1-5] 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 those produced by atropine were achieved in patients with head trauma by intravenous diethazine—a phenothiazine compound with anticholinergic properties—with minimal systemic effects. The effect of diethazine was studied in the course of our continuing studies of the role of delta activity in electroshock.[3] It is the purpose of this report to describe the effects of diethazine on EEG patterns and on the 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.

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

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 mg. per minute, for a total of 175 to 250 mg., depending upon the behavioral effect. Dosage varied from 2.8 to 4.0 mg. per Kg. body weight.

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 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 analyses of the language 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

Clinical: Within two to five minutes after the start of the injection, subjects manifested spontaneous coughing followed by dryness of the mouth and thickness of speech. They reported feelings of lassitude and heaviness and weakness of extremities, soon succeeded by increased restlessness and difficulty in maintaing 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 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 responses. Such patterns of behavior were transient and had disappeared in one and one-half to four hours in all subjects.

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*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, di-isopropyl fluorophosphate and pilocarpine. It suppresses salivation, and induces mydriasis and hypotension.[11]

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

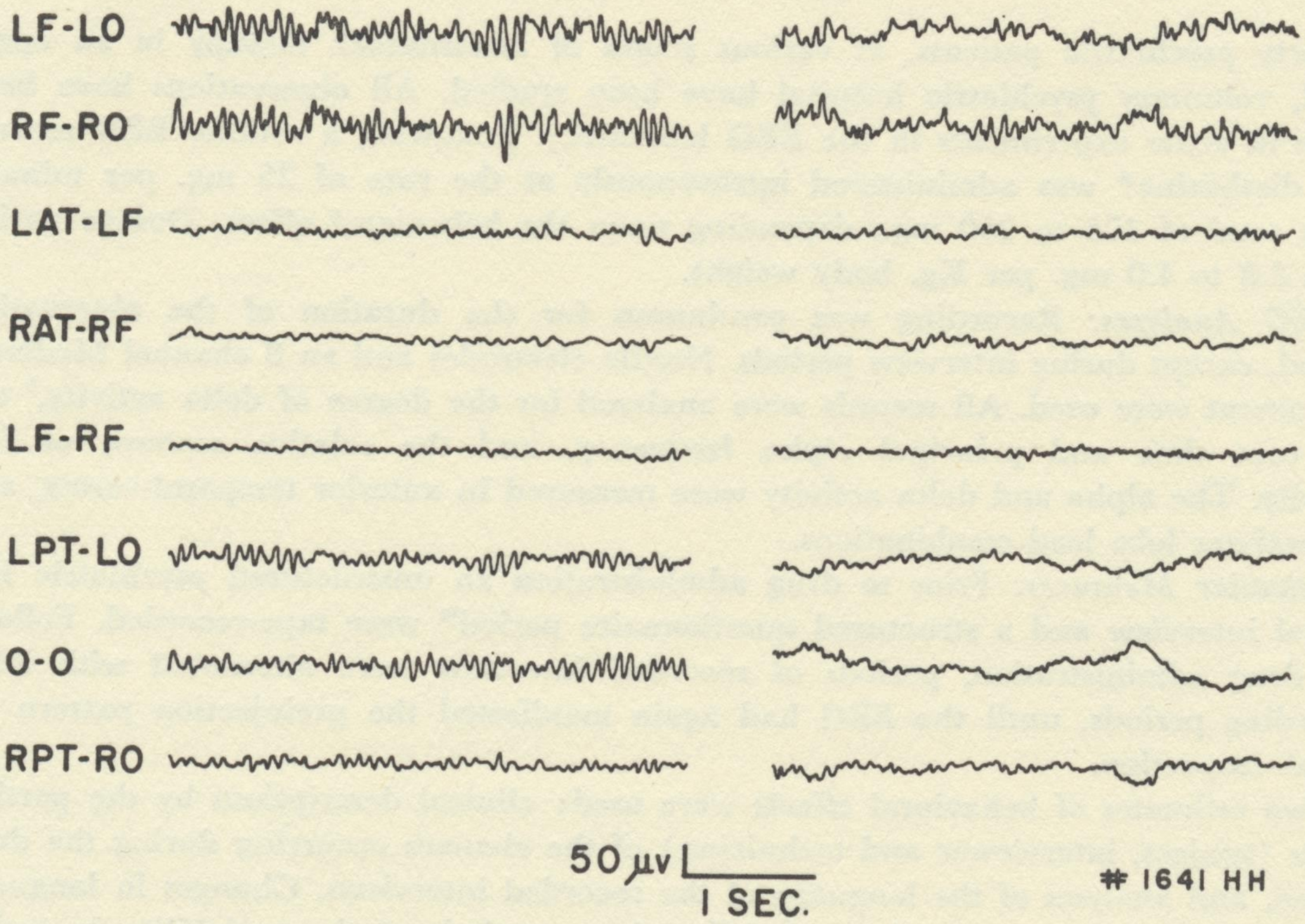

FIG. 1.—Effect of intravenous diethazine, pre-electroshock (male, age 27).

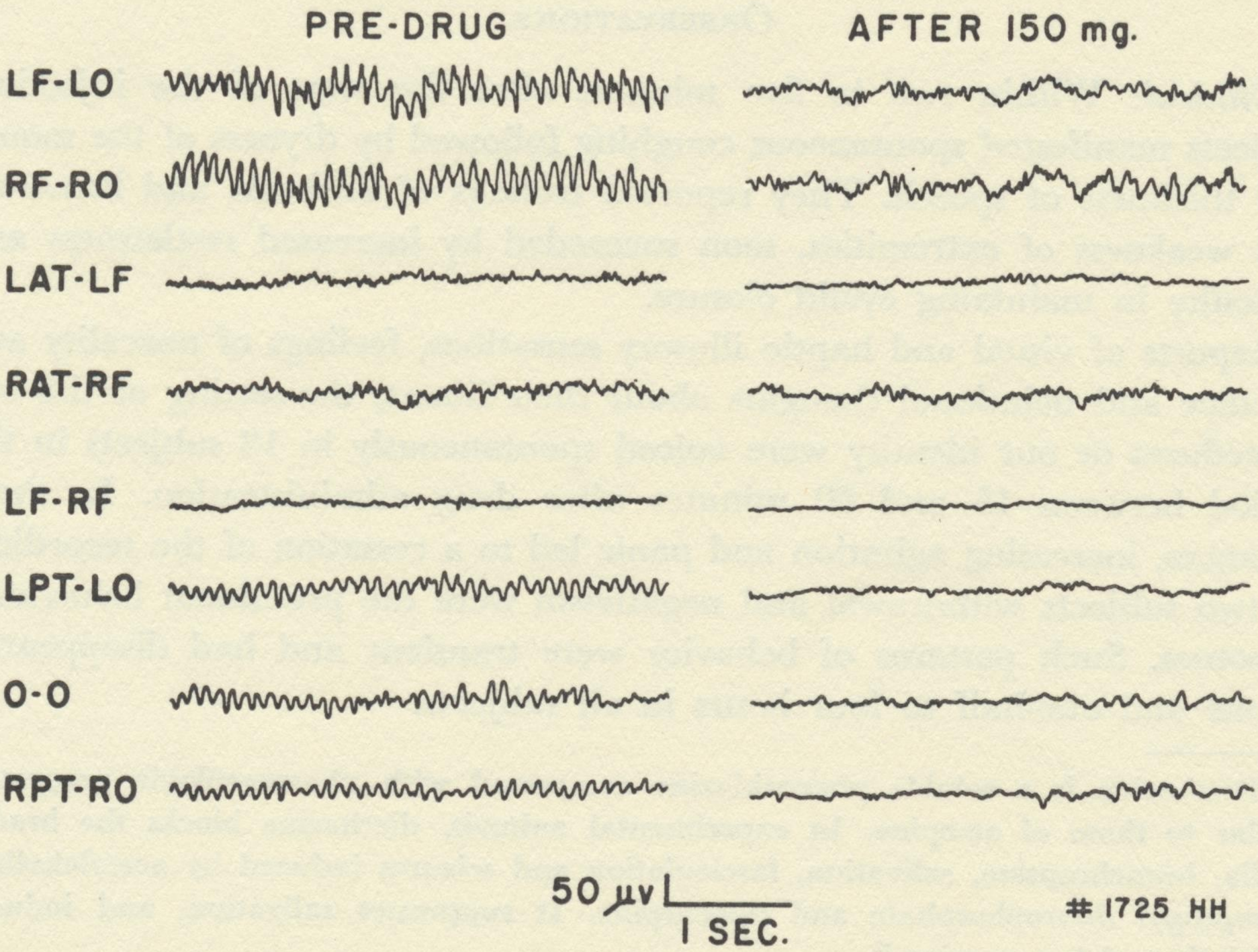

FIG. 2.—Effect of intravenous diethazine, pre-electroshock (female, age 57).

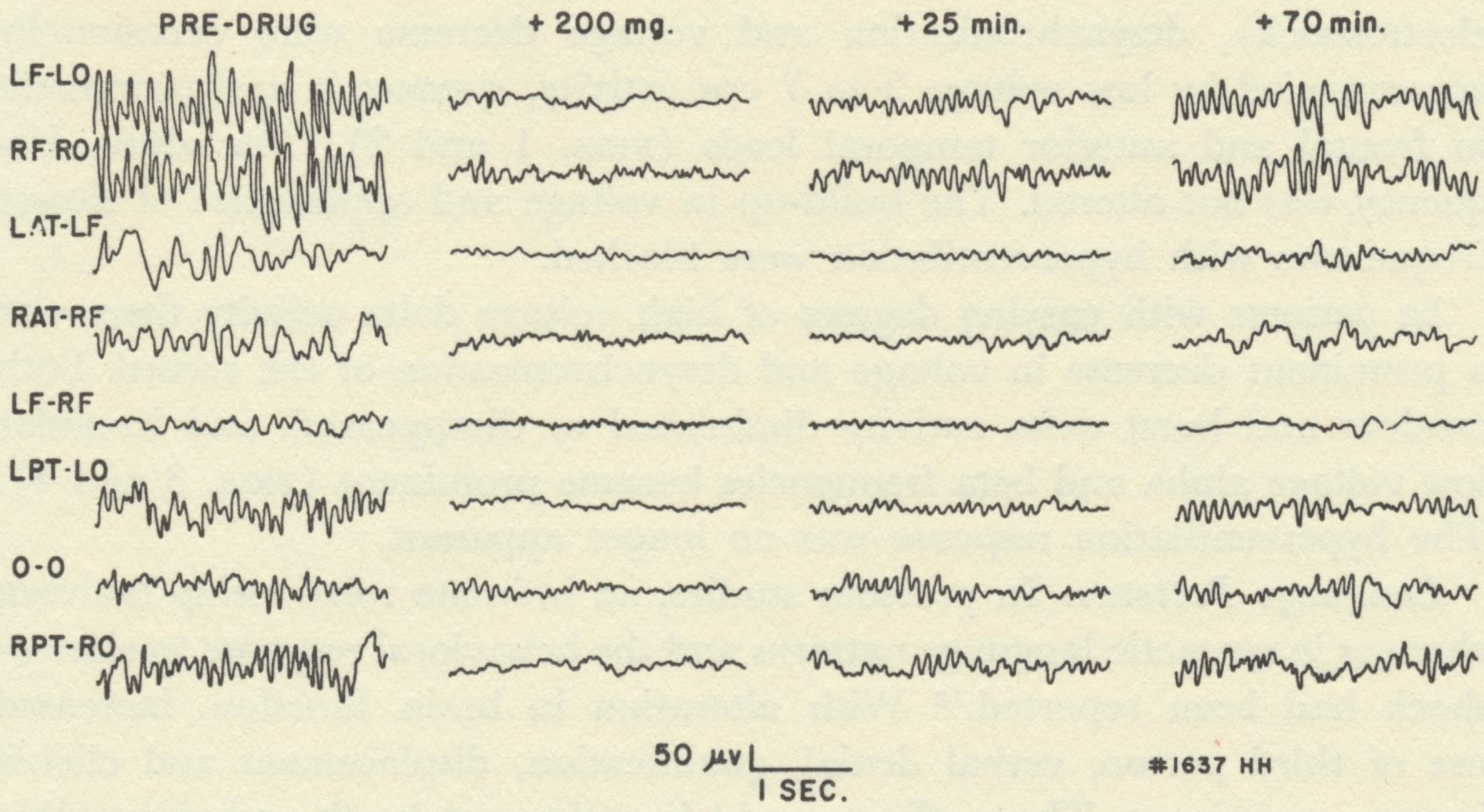

FIG. 3.—Effect of intravenous diethazine after electroshock (note especially effect on delta).

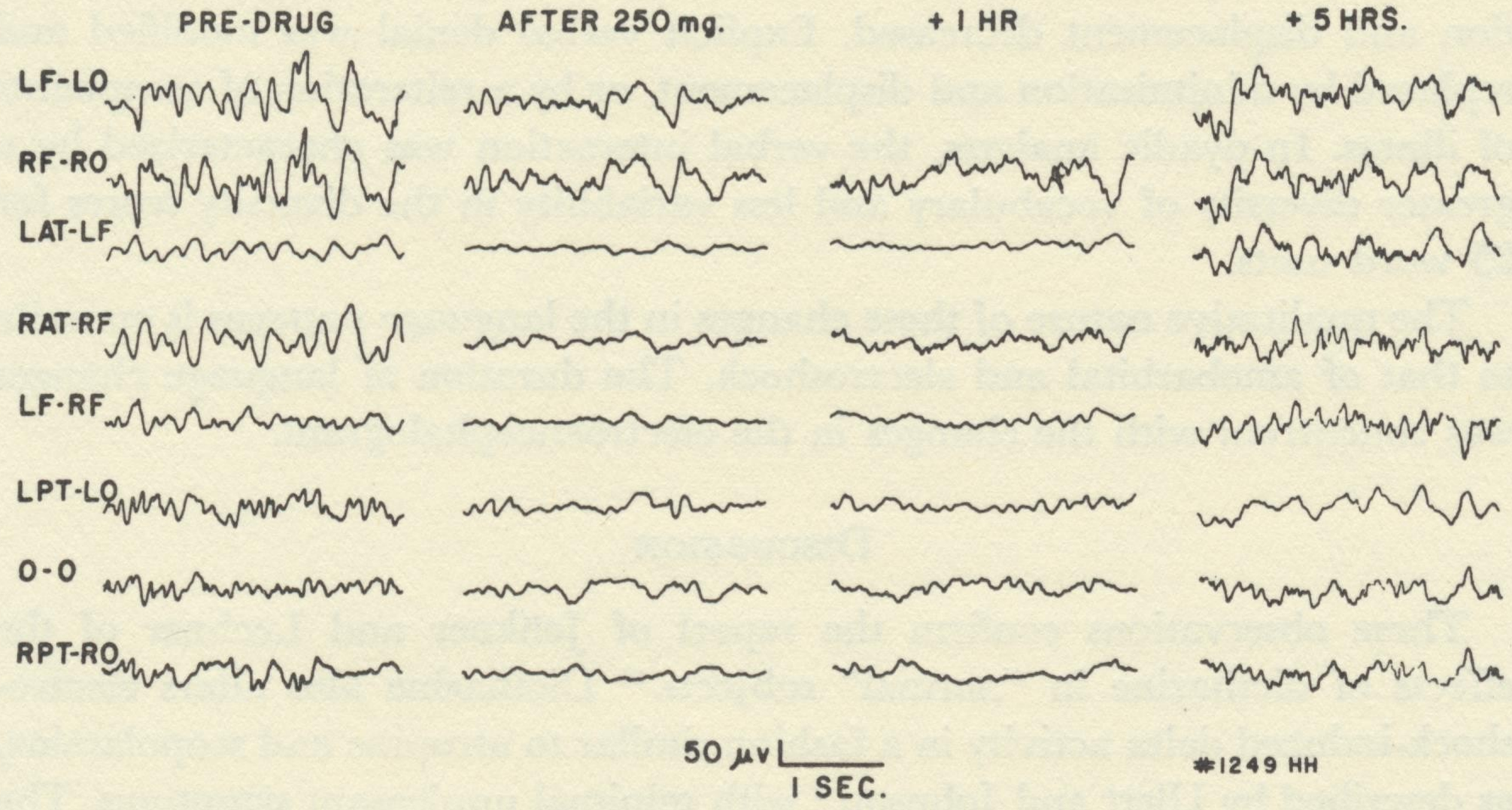

FIG. 4.—Effect of intravenous diethazine after electroshock (note especially effect on delta).

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 (pre-

electroshock), desynchronization and voltage decrease were occasionally accompanied by low voltage 5 to 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 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 (FIGS. 3 and 4). The hyperventilation response was no longer apparent.

Language Patterns: In previous studies, an intimate relationship between changes in syntactic language patterns and the behavioral response to electroshock had been reported.[12] With alteration in brain function, increased use of third person, verbal denial, qualification, displacement and clichés 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 it is thus a useful experimental agent with "anticholinergic" properties. Two aspects of these experimental observations warrant discussion: the role of acetylcholine-cholinesterase in the process of electroconvulsive therapy, and the significance of diethazine "alerting" for concepts of hallucinogenic activity.

Biochemical Basis of the Convulsive Therapy Process: Bornstein,[6] in a classic 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 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 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] They noted a sharp rise in nonspecific cholinesterase (benzoylcholine-splitting) and a drop in the specific cholinesterase (mecholyl-splitting) activity of the spinal fluid in patients following head trauma. 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 three to seven induced convulsions, they noted free acetylcholine in the spinal fluid in two, 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 to 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

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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."

Hughes.[19] Basing their study on 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 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 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.[20-23] 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) that pseudo-cholinesterase activity increases with a reversal of the ratio of cholinesterases; (c) that EEG hypersynchrony and slowing parallel these biochemical alterations; and (d) that 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 Drooglever-Fortuyn[28] and Lindsley et al.[29] had laid the foundation for 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 process of convulsive therapy, and that

both the clinical and electrographic effects may be intimately related to changes in this system.

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 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 the 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 responsiveness 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.

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*Studies on the effects of LSD and such anticholinergic compounds as Win-2299, benactyzine, and hallucinogenic piperidyl benzilates (JB-318, 336) demonstrated marked diminution in per cent time and amplitudes of delta activity, associated with behavioral changes similar to those seen with diethazine.[40]

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 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. *Behavior:* Increased restlessness and agitation, haptic and visual illusory sensations, and delusional thoughts about their illness or examiner's identity were observed. *EEG:* Alteration in the 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. *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; 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 may be associated with euphoria and sedation.

REFERENCES

1. Weinstein, E. A., and Kahn, R. L.: Denial of Illness, Illness: Symbolic and Physiologic Aspects, Springfield, Ill., C. C. Thomas, 1955.
2. Roth, M., Kay, D. W. K., Shaw, J. and Green, J.: Prognosis and pentothal-induced electroencephalographic changes in electroconvulsive treatment. EEG & Clin. Neurophysiol. *9:* 225-237, 1957.
3. Fink, M. and Kahn, R. L.: Relation of electroenecephalographic delta activity to behavioral response in electroshock. A.M.A. Arch. Neurol. & Psychiat. *78:* 516-525, 1957.
4. ——, Green, M. A. and Kahn, R. L.: Experimental studies of the electro-shock, process. Dis. Nerv. Sys. *19:* 113-118, 1958.
5. Ulett, G. A., Smith, K. and Gleser, G. C.: Evaluation of convulsive and sub-convulsive shock therapies utilizing a control group. Am. J. Psychiat. *112:* 795-802, 1956.
6. Bornstein, M.: Presence and action of acetylcholine in experimental brain trauma. J. Neurophysiol. *9:* 349-366, 1946.
7. Tower, D. B. and McEachern, D.: Acetylcholine and neuronal activity. Canad. J. Research. *27:* 105-131, 1949.
8. Ward, A.: Atropine in the treatment of closed head injury. J. Neurosurg. *7:* 398-402, 1950.
9. Ulett, G. A. and Johnson, M. W.: Effect of atropine and scopolamine upon electroencephalographic changes induced by electroconvulsive therapy. EEG & Clin. Neurophysiol. *9:* 217-224, 1957.
10. Jenkner, F. L. and Lechner, H.: The effect of Diparcol on the electroencephalogram in the normal subject and in those with cerebral trauma. EEG & Clin. Neurophysiol. *7:* 303-305, 1955.
11. Heymans, C., Estable, J. J. and de Bonneveaux, S. C.: Sur la pharmacologie de la phenothiazinyl-ethyldiethylamine (2987 R. P.). Arch Int. Pharmacodyn. *79:* 123-138, 1949.
12. Kahn, R. L. and Fink, M.: Changes in language during electroshock therapy. *In* Hoch, P. and Zubin, J. Eds: Psychopathology of Communication. New York, Grune & Stratton, 1958, pp. 126–139.
13. Jaffe, J.: An objective study of communication in psychiatric interviews. J. Hillside Hospital. *6:* 207-215, 1957.
14. ——: Language of the dyad: A method of interaction analyses in psychiatric interview. Psychiatry. *21:* 249-258, 1958.
15. Weinstein, E. A., Kahn, R. L., Sugarman, L. A. and Linn, L.: Diagnostic use of amobarbital sodium in organic brain disease. Am. J. Psychiat. *112:* 889-894, 1953.
16. Tower, D. B. and McEachern, D.: The content and characterization of Cholinesterases in human cerebrospinal fluids. Canad. J. Research. *27:* 132-145, 1949.
17. Sachs, E.: Acetylcholine and serotonin in the spinal fluid. J. Neurosurg. *14:* 22-27, 1957.
18. Ruge, D.: The use of cholinergic blocking agents in the treatment of cranio-cerebral injuries. J. Neurosurg. *11:* 77-83, 1954.
19. Hughes, B.: The role of acetylcholine in head injury. J. Neurol. Neurosurg. and Psychiat. *20:* p. 70, 1957.
20. Freedman, A. M., Bales, P. D., Willis, A. and Himwich, H. E.: Experimental production of electrical major convulsive patterns. Am. J. Physiol. *146:* 117-124, 1949.

21. Grob. D., Harvey, A. M., Langworthy, O. R. and Lilienthal, J. L.: The administration of di-isopropyl fluorophosphate (DFP) to man. Bull. the Johns Hopkins Hosp. *81:* 257-266, 1947.
22. Hampson, J. L., Essig, C. F., McCauley, A. and Himwich, H. E.: Effects of di-isopropyl fluorophosphate (DFP) on electroencephalogram and cholinesterase activity. EEG & Clin. Neurophysiol. *2:* 41-48, 1950.
23. Himwich, H. E., Essig, C. F., Hampson, J. L., Bales, P. D. and Friedman, A. M.: Effect of trimethadione (tridone) and other drugs on convulsions caused by di-isopropyl fluorophosphate (DFP). Am. J. Psychiat. *106:* 816-820, 1950.
24. Callaway, E.: Slow wave phenomena in intensive electroshock. EEG. & Clin. Neurophysiol. *2:* 157-162, 1950.
25. Green, M.: Significance of individual variability in EEG response to electroshock. J. Hillside Hosp. *6:* 229-240, 1957.
26. Jasper, H. H., Kershman, J. and Elvidge, A.: Electroencephalographic studies of injury to the head. Arch. Neurol. & Psychiat. *44:* 328-348, 1940.
27. Strauss, H., Ostow, M. and Greenstein, L.: Diagnostic Electroencephalography. New York, Grune & Stratton, 1952.
28. Jasper, H. H. and Drooglever-Fortuyn, J.: Experimental studies on the functional anatomy of petit mal epilepsy. Res. Publ. A. Nerv. Ment. Dis. *26:* 272-298, 1947.
29. Lindsley, D., Schreiner, L. H., Knowles, W. B., and Magoun, H. W.: Behavioral and EEG changes following chronic brain stem lesion in the cat. EEG & Clin. Neurophysiol. *2:* 483-498, 1950.
30. Rinaldi, F. and Himwich, H. E.: Alerting responses and actions of atropine and cholinergic drugs. A.M.A. Arch. Neurol. & Psychiat. *73:* 387-395, 1953.
31. Himwich, H. and Rinaldi, F.: The effect of drugs on reticular system. *In* Brain Mechanism and Drug Action. Springfield, Ill., C. C Thomas, 1957.
32. Stoll, W.: Lysergsaure—diethylamid, ein Phantastikum aus der Mutterkorngruppe. Schweiz Arch. Neurol. Psychiat. *60:* 1-47, 1947.
33. Beringer, K.: Der Meskalinrausch, Monog. Neurol. Psychiat. Berlin, Springer, 1927.
34. Wikler, A.: Clinical and electroencephalographic studies on the effects of mescaline, N-allylnormorphine and morphine in man. J. Nerv. Ment. Dis. *120:* 157-175, 1954.
35. Denber, H. and Merlis, S.: Studies on mescaline. I: Action in schizophrenic patients. Psychiat. Quart. *29:* 421-429, 1955.
36. Gastaut, H., Ferrer, S. and Castello, C.: Action de la diethylamide de l'acide d-lysergique (LSD 25) sur les fonctions psychiques at l'electroencephalogramme. Conf. Neurol. *13:* 102-120, 1953.
37. Rinkel, M., DeShon, H. J., Hyde, R. W. and Solomon, H. C.: Experimental schizophrenia-like symptoms. Am. J. Psychiat. *108:* 572-578, 1953.
38. Merlis, S. and Hunter, W.: Studies on mescaline. II: Electroencephalogram in schizophrenics. Psychiat. Quart. *29:* 430-432, 1955.
39. Fink, M.: A unified theory of the action of physiodynamic therapies. J. Hillside Hosp. *6:* 197-206, 1957.
40. ——: Effect of Anticholinergic Compounds on Post-convulsive EEG and Behavior, *EEG and Clin. Neurophysiol. 10:* 776 (Abst.) 1958.