4/26/57

To: Dr. Max Fink
From: Dr. H. Goldenberg

We are contemplating a change in our cholinesterase incubation system which would cause significant differences (5-15% increase) in the reported values for true and pseudocholinesterase. This is the primary reason we haven't forwarded your spinal fluid values as well as the more recent serum analyses.

Our cholinesterase method (like all methods) comprises 2 steps:
(1) incubation of enzyme with substrate under fixed conditions, and
(2) analysis of the reaction products, from which enzyme activity is calculated. The second step employs our new and efficient color procedure. Step 1 is essentially that of earlier workers. On reinvestigating step 1 we find objections to the large amount of salt used by others in their system and may eliminate this ingredient. As salt is inhibitory, this would cause an apparent increase in enzyme concentration.

All our past analyses can be corrected for this change by using appropriate factors, but the ultimate decision whether we are to shift our medium will be about 10 days in the making.

However, as you are naturally anxious to get some idea of the relative changes in spinal fluid values following EST, I will forward figures based on the original salt system on Tuesday.

Next Friday we will start running benzoylcholine as well as the butyryl susbstrate to determine whether there are 2 pseudocholinesterases in spinal fluid. This should resolve our uncertainties on this point and just might possibly lead to new findings.

February 4, 1966

Dr. Harvey Robinson
The Psychiatric Institute
University of Maryland
Baltimore, Maryland 21201

Dear Dr. Robinson:

In mid-October, I submitted the manuscript "Cholinergic Mechanisms in Convulsive Therapy" for your consideration for publication in the *Journal of Nervous and Mental Disease*. I would be grateful for your advice as to the present status of this manuscript.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

MF:jmh

THE JOURNAL OF
Nervous and Mental Disease

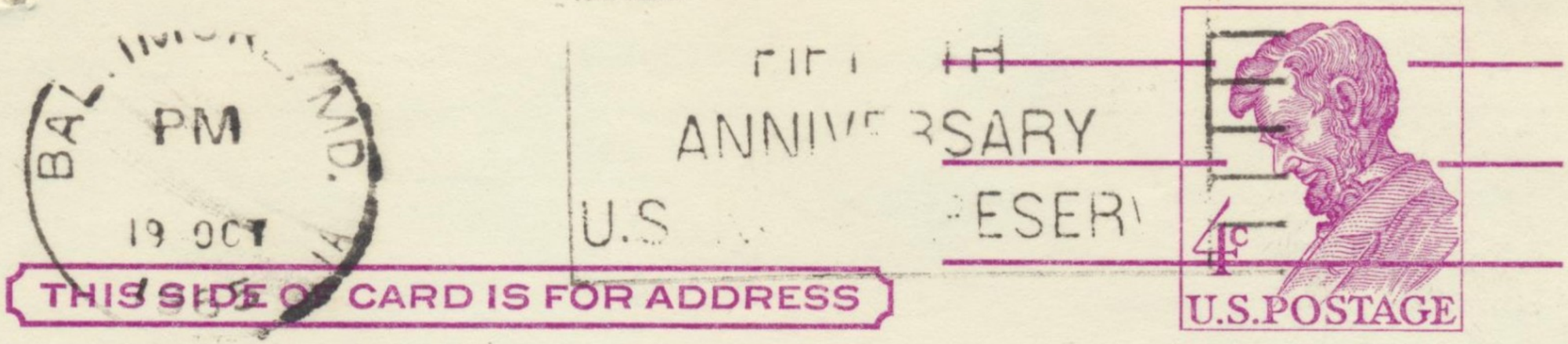
The Psychiatric Institute
University of Maryland
Baltimore 1, Maryland

Harvey A. Robinson, Managing Editor

October 19, 1965

This is to acknowledge receipt of your manuscript entitled "Cholinergic Mechanisms in Convulsive Therapy."

JNMD/ss



Max Fink, M. D.
Department of Psychiatry
Missouri Institute of Psychiatry
5400 Arsenal Street
St. Louis, Missouri 63139

October 15, 1965

Dr. Harvey Robinson
The Psychiatric Institute
University of Maryland
Baltimore, Maryland 21201

Dear Dr. Robinson:

Enclosed are two copies of the manuscript "Cholinergic Mechanisms in Convulsive Therapy" for your consideration for publication in the *Journal of Nervous and Mental Disease*.

While the style of the citations follow those of this institution, we will submit corrected copies following your style if the article meets your approval.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

MF:jmh

THE JOURNAL OF

Nervous and Mental Disease

FOUNDED IN 1874

Lawrence S. Kubie, Editor-in-Chief
Harvey A. Robinson, Managing Editor
Eugene B. Brody, Consulting Editor

The Psychiatric Institute
University of Maryland
Baltimore, Md. 21201

February 10, 1966

Dr. Max Fink
Department of Psychiatry
Missouri Institute of Psychiatry
University of Missouri
5400 Arsenal Street
St. Louis, Missouri 63139

Dear Doctor Fink:

I am very sorry to have to tell you that your manuscript is still under editorial consideration. I do hope to be able to be able to write to you about it very soon.

Sincerely yours,

H. A. Robinson

HAR/sa

THE JOURNAL OF

Nervous and Mental Disease

FOUNDED IN 1874

Lawrence S. Kubie, Editor-in-Chief
Harvey A. Robinson, Managing Editor
Eugene B. Brody, Consulting Editor

The Psychiatric Institute
University of Maryland
Baltimore, Md. 21201

February 11, 1966

Dr. Max Fink
Missouri Institute of Psychiatry
5400 Arsenal Street
St. Louis, Missouri 63139

Dear Doctor Fink:

The Editorial Board has carefully considered your manuscript entitled "Cholinergic Mechanisms in Convulsive Therapy." Subject to your willingness to meet a number of minor criticisms and to make some changes that have been suggested by our readers, we should be very pleased to publish this article. This, then, is in the nature of a provisional acceptance.

This consideration of brain cholinergic mechanisms and their significance in convulsive therapy represents an interesting and valuable point of view. Of course, other chemical changes have been demonstrated after seizures and have been assigned equally as important roles as acetylcholine. However, this position is clearly stated, developed forcefully, and the argument is pertinently documented. We feel that the manuscript makes a definite contribution.

Nonetheless the Editors are of the opinion that the report embodies some weaknesses which if dealt with would significantly improve the quality of the paper. No one doubts that acetylcholine is important in neural function and that changes in acetylcholine and cholinesterase occur with induced seizures. The assumption that the handling of acetylcholine is fundamentally related to the amount p13. of hypersynchrony of the EEG is, we feel, an oversimplification. The thesis that the results of treatment by induced convulsions is related to the sensitivity to changes in acetylcholine levels (pp. 18-19) has no information to substantiate it. Although you describe a "rational biochemical theory" for the mode of action of induced con- (1)

vulsions, you state only what is already known, that acetylcholine decreases in the tissues and increases in the spinal fluid with induced seizure and that the slow waves can be modified by anti-cholinergic drugs. Although you cite your own work for the effects of atropine in counteracting the acetylcholine effects of induced seizures, you do not give evidence that the use of atropine changes the therapeutic results in any confirmed study. There is no convincing evidence for differences in reactivity or sensitivity of the central nervous system between psychotics and normals to acetylcholine or cholinesterase. (2) (3)

We recommend that you consider the following ideas for inclusion in the summary:

1) There is as yet no consistent evidence for differences in anticholinesterase or acetylcholine senstivity or levels between the psychotic and the normal brain. ✓

2) There is as yet no reproducible evidence that anticholinesterases given before, during or after electro-convulsive therapy change the results of the treatment. ✓

3) Cholinesterase and acetylcholine levels changes in response to electroconvulsive treatment and in response to trauma may be a result of other biochemical changes resulting in vasodilation and increased cellular permeability which affect the level of consciousness, EEG, and behavior as well as acetylcholine distribution. ✓

At a more superficial level, we should also recommend that the manuscript be carefully scrutinized so as to ensure consistency in drug terminology. We would recommend that the generic names be used throughout the manuscript and that the capitalized trade name be included in parentheses, e. g., methacholine (Mecholyl). We have indicated a few of these changes on p. 7, p. 9, and p. 10.

I regret to note that the references do not follow the style we prefer to use. I am enclosing an information sheet, which may be of some help. Please note that the references should be alphabetized, then numbered, and cited by number in parentheses in the

text. Please note, too, that the references should be typed double-spaced. This enormously facilitates preparing copy for the printer.

On the hopeful assumption that you will be of a mind to undertake the recommended changes, I am returning one copy of the manuscript, and will retain the other for purposes of reference. Please let me know how you feel about all of this.

Very sincerely,

H. A. Robinson

HAR/sa
Enclosures

February 16, 1966

Dr. Harvey Robinson
Journal of Nervous and Mental Disease
Psychiatric Institute
University of Maryland
Baltimore, Maryland 21201

Dear Dr. Robinson:

Thank you very much for your comments regarding the manuscript "Cholinergic Mechanisms in Convulsive Therapy."

The various comments included in your letter appear relevant and cogent. I will make every effort to respond to each one and then have the manuscript retyped, including the citations following the style which you have requested. The completed draft should be returned to you within two weeks.

Thank you for your consideration.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

MF:kp

March 4, 1966

Mr. Harvey A. Robinson, Managing Editor
The Journal of Nervous and Mental Disease
The Psychiatric Institute
University of Maryland
Baltimore, Maryland 21201

Dear Mr. Robinson:

Following your suggestions, I have redrafted portions of the report "Cholinergic Mechanisms in Convulsive Therapy," corrected the use of generic names, and modified the citations to fit the style of the journal. The suggested changes in the summary have been included, using my own language.

I have altered the title and deleted some sections which were contradictory.

I hope that this draft, which I like much better, meets with your approval.

Thank you for your comments.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

MF:kp

THE JOURNAL OF

Nervous and Mental Disease

FOUNDED IN 1874

F: Abnl ECT

Lawrence S. Kubie, Editor-in-Chief
Harvey A. Robinson, Managing Editor
Eugene B. Brody, Consulting Editor

The Psychiatric Institute
University of Maryland
Baltimore, Md. 21201

March 9, 1966

Dr. Max Fink
Missouri Institute of Psychiatry
5400 Arsenal Street
St. Louis, Missouri 63139

Dear Doctor Fink:

We have the revision of your manuscript, for which many thanks. This now looks perfectly fine in all respects, and we shall be pleased to schedule it for publication.

My best guess is that this material should get to the printer in five weeks' time or so. Galley proof, then, should come to you some time late in April.

When you receive the galley proof, I hope you will be able to correct it and to return it to me promptly.

Very sincerely,

H. A. Robinson

HAR/sa

THE JOURNAL OF NERVOUS AND MENTAL DISEASE
Vol. 140, No. 2
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Printed in U.S.A.

Information for Authors

Manuscripts and correspondence pertaining thereto should be addressed to the Managing Editor: DR. H. A. ROBINSON, The Psychiatric Institute, University of Maryland, Baltimore, Maryland 21201.

Manuscripts should be typed double spaced on one side only of 8½ x 11 paper. The original and one clearly legible carbon copy should be submitted.

It is helpful if the author supplies a short title for use as a running head. This should be typed on a separate sheet and be the first page of manuscript. Type the complete title of the article on a second sheet, and the authors' names and affiliations on a third sheet. Type double-spaced on separate sheets: tabular matter, case histories, quotations, formulas, and other subsidiary matter in the text, footnotes, bibliographies, and legends for illustrations. Legends must not be attached to or written on the illustration copy. Positions for tables and figures in the text should be indicated in the margin of the text page.

Manuscripts should be accompanied by two copies of an abstract of 300 words or less.

Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be glossy prints. The title of the article, name of author, and number of the figure should be written with a soft pencil on the back of each illustration, and the top designated.

References should be designated in the text by number in parentheses, e.g., (7). The list headed REFERENCES at the end of the paper should be arranged in alphabetical order and numbered. Abbreviations should follow the style of the Index Medicus. Examples:

Book reference:

3. Critchley, M. *The Parietal Lobes*, pp. 171–181. Arnold, London, 1953.

Journal reference:

11. Rosvold, H. E., Mirsky, A. F. and Pribram, K. H. Influence of amygdalectomy on social behavior in monkeys. J. Comp. Physiol. Psychol., *47:* 173–178, 1954.

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The editorial office should be notified promptly of any change of address.

Galley proofs are sent to the author, and should be returned with manuscript to the editorial office. A table of cost of reprints with an order slip. is sent with galley proof.

(7)

CHOLINERGIC ASPECTS OF CONVULSIVE THERAPY

Max Fink, M.D.

From the Department of Psychiatry, Washington University School
of Medicine and the Department of Psychiatry at the
Missouri Institute of Psychiatry, University of Missouri
School of Medicine, 5400 Arsenal St., St. Louis, Missouri 63139.

Aided, in part, by USPHS grants MH-927, MH-2715, MH-07249, and
MH-11380; and the Psychiatric Research Foundation of Missouri.

IX: 2-25-66 Revised for the *Journal of Nervous and Mental Disease.*

65-8

CHOLINERGIC ASPECTS OF CONVULSIVE THERAPY

While the mode of action of convulsive therapies remains enigmatic, one theory holds that the early development and persistence of changes in brain function are requisite to change in behavior (17, 20, 22). A useful index of neurophysiological changes is the appearance of high voltage electroencephalographic slow wave activity (22, 23). While the biochemistry of this activity is poorly understood, demonstrations that it may be inhibited by atropine premedication (34,66) or blocked by anti-cholinergic compounds (18, 19) suggest that cholinergic systems may play an active part.

The EEG patterns and the response to anticholinergic drugs is similar in experimental and clinical head trauma and to a lesser extent, in spontaneous seizures to that seen with convulsive therapy. The activity and changes in concentration of cholinesterases in brain and spinal fluid in head trauma, spontaneous seizures and convulsive therapy also show many similarities. This review discusses these observations to provide the basis for a hypothesis of the role of cholinergic changes in the convulsive therapy process.

Acetylcholine has been extensively studied as an agent in the transmission of nervous impulses since its early identification by Dale (12) and Loewi (38). A constituent of nervous tissue in a bound form, acetylcholine is liberated during the excitation process. It is rapidly hydrolyzed through the mediation of acetylcholinesterase and is rapidly reconstituted by the choline-acetylase system(45). Free acetylcholine has not been measurable

in normal cerebrospinal fluid despite the rapid breakdown of bound acetylcholine during periods of activity and excitement(63). But the normal cerebrospinal fluid does have measurable cholinesterase activity, principally of the "true" of mecholyl hydrolyzing type (41).

Cholinergic Aspects of Craniocerebral Trauma. Free acetylcholine was found in the cerebrospinal fluid of cats within a few minutes after experimental head trauma and persisted for varying periods up to 48 hours. The quantity of free acetylcholine varied between 2.7 and 9.0 gamma percent, and the amount was related to the degree of induced trauma (6).

Concurrent electroencephalograms first demonstrated high voltage fast activity, interpreted as evidence of an intense neuronal discharge, which was soon succeeded by a short period of flattening of all recorded electrical activity. These phases were followed by prolonged periods of high amplitude sharp waves in the delta frequencies.

The behavioral changes related to the degree of induced trauma and to the amount of measured free acetylcholine. With higher levels of acetylcholine, Bornstein reported greater degrees of EEG abnormality and greater changes in consciousness. Spontaneous post-traumatic seizures were also related to the amount of free acetylcholine appearing in the cerebrosponal fluid.

Bornstein applied acetylcholine to exposed cat cerebral cortex. When the concentration of acetylcholine was 1 gamma percent or less, high amplitude sharp waves of low frequency appeared in the electroencephalogram. When the concentration was increased to 2 gamma percent, the electroencephalogram flattened in a fashion parallel to the post-traumatic records.

Investigations in neurological patients by Tower and McEachern demonstrated free acetylcholine in the cerebrospinal fluid only in patients with recent head trauma, recent grand-mal seizures or after electroconvulsive therapy (63). Free acetylcholine varied from 0.2 to 100 gamma percent. In assaying spinal fluid cholinesterase activity, they noted a sharp rise in the nonspecific cholinesterase fraction (benzoylcholine-splitting) and a drop in the specific cholinesterase fraction (methacholine-splitting) in patients with head trauma and following convulsive therapy. After spontaneous seizures, however, the cerebrospinal fluid did not exhibit such inversion although it contained free acetylcholine. They concluded that the level of free acetylcholine varied directly with the degree of cerebral damage and that reversal of the cholinesterase fractions was a more sensitive indicator of cerebral damage. Electroencephalograms, taken at varying intervals following trauma, also indicated a relation between the degree of EEG abnormality and the appearance of free acetylcholine in the cerebrospinal fluid.

Increased acetylcholine in rat brain after traumatic shock was also reported by Kovach, et al. (36). This acetylcholine activity was inhibited in vitro by the administration of atropine to the muscle preparation.

The electrographic, behavioral and neurologic signs of head trauma were blocked by the parenteral administration of 0.5-1.0 mg/kg atropine, as were similar clinical changes occurring after the intracisternal addition of acetylcholine (6). Ward applied these observations to the treatment of closed head injuries (67). In 20 patients with varying degrees of trauma, he administered atropine subcutaneously in doses of 0.1 mg/kg, noting clinical improvement in some and a reversal of the electrographic effects in others. The same changes in the post-traumatic electroencephalogram were reported by Jenkner and Lechner in a study of diethazine, another anticholinergic drug (33). A single intravenous dose in forty patients resulted in normalizing the abnormal electroencephalogram in twenty-two and marke dimprovementin six others.

Similarly, in experiments of post-traumatic shock and cerebral edema in animals, Denisenko reported a blocking of the clinical changes by such anticholinergic compounds as methylbenactyzine and trasentin (13).

Thus, the amount of free acetylcholine may increase in the spinal fluid following craniocerebral trauma and the amount of free acetylcholine, the degree and type of electroencephalographic abnormality, and changes in clinical behavior appear as interrelated phenomena, which may be reduced by the administration of anticholinergic drugs.

Brain acetylcholine and anticholinergic drugs. The effects of the direct application of acetylcholine to the central nervous system may also be blocked by anticholinergic drugs. The administration of the cholinesterase inhibitor di-isopropyl fluorophosphate (DFP) elicited high amplitude rapid frequency EEG patterns similar to status epilepticus and some post-traumatic states (24, 31, 32, 68). These EEG effects were blocked by small doses of parenteral atropine and scopolamine. The great increase in acetylcholine after tetraethyl pyrophosphate (TEPP) was measured and related to the toxic effects and the induced convulsions (29, 59).

Chatfield and Dempsey prepared exposed animal cortex with prostigmine and evoked electroencephalographic spike activity. The prior administration of atropine blocked the appearance of spiking, or if present, this electrical activity could be eliminated by atropine (9).

In contrast to these findings, Brenner and Merritt applied topical acetylcholine in concentrations of 2-1/3 to 10% to the exposed cortex of cats, and noted no effect on the electro-encephalographic changes after intravenous atropine (1 mg/kg) (7). The concentrations of acetylcholine in these experiments, however, were higher than the topical applications (1-4 gamma percent) and the intracisternal (0.2-10 gamma percent) injections of Bornstein (6). Brenner and Merritt also noted electroencephalographic effects similar to acetylcholine after methacholine (Mecholyl) and carbamylcholine (Doryl) in concentrations much lower than the acetylcholine concentrations. They ascribed the increased

effectiveness of these cholinergic drugs to their lack of sensitivity to cerebral cholinesterases.

These data are conflicting and further study is necessary to qualify this issue.

Cerebrospinal Fluid Acetylcholine and Seizures. One view of acetylcholine metabolism finds it in nervous tissues in an inactive and bound form. During periods of activity, acetylcholine is liberated at the cell membrane where it is rapidly deactivated by cholinesterases. The amount of bound acetylcholine is the resultant of the continuous processes of synthesis, liberation and breakdown. It has been postulated that the level rises during sleep and falls during waking activity (15, 29, 45, 60). Tobias et al. reported increased free and total acetylcholine after chloroform and nembutal (ck) anesthesia in rat and frog brain, but no changes after strychnine or picrotoxic convulsions (60). Richter and Crossland measured the level of acetylcholine (micro-gamma per mg. brain tissue) during anesthesia and sleep in rat brain to be 300 % higher than post-seizure levels. The difference in tissue levels in transient, however, as the resynthesis rate for acetylcholine in rat brain is high (7 gamma/gm/minute) (45). These observations were confirmed by Elliot et al. (15) and Crossland and Merrick (11). Giarman and Pepeu found the increase in acetylcholine following various depressants to be roughly proportional to the degree of depression of the central nervous system and the reduction in motor activity (29). Maynert and Buck, however, studying brain acetylcholine levels

during sedation concluded that some sedatives were associated with elevated brain acetylcholine, but that no rigorous relationships existed (39). In part, this may be related to the earlier observations of McLennan and Elliot that acetylcholine synthesis measured in rat brain slices is accelerated by low dosages of narcotic drugs, but inhibited by high dosages (40).

Free acetylcholine was reported in the spinal fluid in patients with epilepsy (10, 63). Of 56 epileptic patients, 44 demonstrated free acetylcholine in quantities of 0.02 to 5.0 gamma percent with an average of 1.0 gamma percent. Acetylcholine levels were related to the frequency of seizures, the extent of electroencephalographic abnormality, and to the time since the last seizure, but bore no relation to medication, type of epilepsy or level of cholinesterase activity. Elliot et al. also noted free acetylcholine in the spinal fluid in concentrations up to 3 gamma percent after pentylene tetrazol (Metrazol) convulsions (15).

Tower and McEachern viewed the increased acetylcholine as a by-product of the seizure, and not causal (63). Studying the hypothesis that seizures were induced by the accumulation of acetylcholine, Torda measured the level of acetylcholine in brain tissue after pentylenetetrazol convulsions. She noted a

rise in the acetylcholine content of brain before and a fall during the convulsion. Below certain levels of acetylcholine, convulsions failed to occur. She suggested that the fall in tissue acetylcholine during a convulsion was due to the inhibition of acetylcholine synthesis by increased concentrations of metabolites such as ammonium ions (61, 62).

Giarman and Pepeu also measured changes in central nervous system acetylcholine following various stimulants (29). Only after methacholine and 3, 5-dimethylbutylethyl-barbiturate was there a significant changein the acetylcholine level. They noted a decrease in association with induced convulsions. With other drugs which they classified as stimulants (LSD, iproniazid, iproniazid + hydroxytryptophan, and iproniazid + DOPA) there were no changes in acetylcholine level. They concluded that despite intense excitation produced by these compounds, there were no changes in acetylcholine levels unless these were accompanied by convulsions. (The differences in observations between these observers and Cone et al. and Tower and McEachern may be related to the differences in methods of biochemical measurements, for the latter measured changes reflecting free acetylcholine only, while Giarman and Pepeu measured the total acetylcholine, including bound and free forms of acetylcholine.[40]).

These studies suggest that spontaneous or induced seizures are accompanied by an increase in intercellular free acetylcholine liberated from its bound form which may be reflected in the spinal fluid. Cerebral activity and seizures enhance acetylcholine destruction, lowering tissue levels of acetylcholine, while sleep and anesthesia augment acetylcholine produdtion increasing tissue levels.

Central Nervous System Cholinesterases. Tower and McEachern also measured spinal fluid cholinesterase activity (63, 64, 65). Two types of cholinesterases which hydrolyze acetylcholine are normally found in the spinal fluid: cholinesterase-I ("true," "specific," or methacholine-hydrolyzing) which has a high specificity for acetylcholine; and cholinesterase-II ("pseudo," "non-specific," or benzoylcholine-hydrolyzing). The different rates of hydrolysis for methacholine and benzoylcholine permits qualitative distinctions. By reporting the cholinesterase activity as a ratio of the activity with methacholine and benzoylcholine substrates compared to an acetylcholine substrate cholinesterase-I/acetylcholine and cholinesterase-II/ acetylcholine ratios are derived. Normal cerebrospinal fluid contains esterases in the ratio of 33:17 for cholinesterase-I to cholinesterase-II.

In patients with head trauma, Tower and McEachern reported an inversion of the cholinesterases with an increase in the cholinesterase-II fraction of the spinal fluid and a decrease in cholinesterase-I activity. The extent of the cholinesterase reversal was related to the severity of trauma and to the degree of the electroencephalographic abnormality.

In patients with elevated spinal fluid acetylcholine after spontaneous seizures, however, no change in the ratio of cholinesterases or total cholinesterase activity was found.

Following the recent demonstrations that neurol stimulation produces changes in brain weight and acetylcholinesterase activity (37, 49,), Pryor and Otis studied the effects of repeated induced swizures in Wistar rats (43). After as little as 4 weeks, they observed increases in brain weight and in acetylcholinesterase activity, which was related to decrements in behavioral performance.

Changes in cholinesterase activity may be related to changes in cell membrane permeability. Cholinesterase-I is found in highest concentration in the central nervous system while cholinesterase-II predominates in other tissues, especially blood serum. With increased cerebral acetylcholine, vasodilation and increased cellular permeability may be predicted, with a degree of vascular fluid transudation varying with the extent and duration of the vasodilation (35). Spiegel, Spiegel-Adolf, and their co-workers demonstrated such permeability changes and increased conductivity of the tissues associated with the appearance of various ions (as potassium and phosphate) in the spinal fluid following electrically induced convulsions (54-58). Such non-electrolytes as nucleic-acid splitting enzymes also increased. Changes in cellular permeability may be the basis for the high concentrations of acetylcholine and increased concentrations of cholinesterase-II after induced seizures or head trauma (65).

The persistance of acetylcholine in spinal fluid after head trauma and after seizures despite increased cholinesterase activity may be related to the sensitivity of the acetylcholine-cholinesterase-I system to concentration relationships (8, 41, 65).

At "physiologic" concentrations, hydrolysis of acetylcholine is rapid (3-4 microseconds) but at higher and lower concentrations, the activity falls off quickly. In contrast, the cholinesterase-II acetylcholine relationship is non-specific and the rate of hydrolysis increases with increased concentration.

These relationships are related to the induction of seizures. While the usual concentrations of acetylcholine at cell membranes are destroyed by the specific activity of cholinesterase-I in a few microseconds, an excessive concentration following excitation may exceed the rate of hydrolysis by cholinesterase-I. The seizure threshold is reached and a seizure induced, with the seizure itself adding to the amount of free acetylcholine. The increased acetylcholine affects vascular and cellular permeability, altering the concentrations of various ions, including cholinesterase-II, in tissues and in the derebrospinal fluid. The activity of cholinesterase-II, though the low efficiency and depending on concentration kinetics, reduces the acetylcholine in the tissues in hours to days to levels for the physiologic action of cholinesterase-I.

Cholinesterase appears in the spinal fluid as a reflection of their increase in intercellular fluids, resulting from changes in cell membrane permeability occasioned by increased acetylcholine. The increased cholinesterases are part of the homeostatic mechanisms controlling the levels of acetylcholine at cell membranes necessary for nervous system activity.

EEG Hypersynchrony and Induced Convulsions. The significance of the development of high voltage slow wave activity for the convulsive therapy process has been repeatedly stated (22, 23, 50, 51). The early appearance of high degree hypersynchrony and its persistence throughout a treatment course has been described as prerequisite to improvement. Both the electrographic and the behavioral changes of induced convulsions were transiently reversed by the acute administration of experimental anticholinergic compounds (18, 19). The intravenous injection of diethazine, benactyzine, the piperidylbenzilates JB-318, JB-336 and JB-329 (Ditran), and WIN-2299 induced EEG desynchronization in psychiatric subjects. These EEG changes were associated with behavioral ~~alter~~ alerting, anxiety, tremors, illusions, and hallucinations. In patients who had recently received electroconvulsive therapy, there was a reduction in slow wave activity and a reversal of euphoria, denial and confusion. Atropine in low doses was associated with EEG desynchronization accompanied by tachycardia, nervousness and tension. At higher dosages, hypersynchronous slow waves, followed by lower voltage, poorly organized delta activity with superimposed beta activity was associated with progressive confusion and disorientation.

The effect of anticholinergic drugs on slow wave activity was also assessed in convulsive therapy by the chronic administration of atropine (5 mgm per day) and scopalomine (1 - 3 mg) ~~of treatment during the~~ during the weeks of treatment. The

amount of EEG slowing was significantly less than in a control group who had not received the atropine administration (66). The samples were too small for clinical correlation, but the data is consistent with a definite blocking of the clinical effect. Marked improvement was seen in 2 of 7 atropine treated, none of 5 scapolamine treated and in four of the six controls receiving unmodified ECT. This study was not replicated by the authors who suggest that dosage factors or population changes may have contributed to the different results (34).

As in cerebral trauma, the electrographic changes of induced convulsions may be modified by the administration of anticholinergic drugs, suggesting that increased amounts of acetylcholine or increased cholinergic receptivity is associated with the high voltage slow wave activity.

Acetylcholine and Induced Convulsions. Despite a constant application of treatments, however, there is a great variability in the time of appearance, the duration and the exgent of the electrographic slow wave activity as well as the sensitivity of to modification by alerting, hyperventilation and barbiturates in psychiatric populations(30).

The differences in the degree of induced EEG hypersynchrony may be related to differences in central cholinergic activity. The failure of certain patients to develop hypersynchrony may be associated with the absence of free acetylcholine and with minimal changes in cerebral function, thus precluding a clinical response to induced convulsions. Tower and McEachern,

in their study of craniocerebral trauma, included observations of six psychiatric patients undergoing convulsive therapy (63). Studying the patients after 3-7 treatments they reported free spinal fluid acetylcholine in two patients; and an increase in cholinesterase-II and a decrease in cholinesterase-I with a reversal of the ratio of cholinesterases in five of the six patients. The one patient in the series who failed to show either free acetylcholine or a cholinesterase ratio reversal in the spinal fluid was described as: "It is interesting that this patient was the only one of the six to show no response to treatment." From these observations they concluded that the spinal fluid changes in induced convulsions were more like those of craniocerebral trauma than those of spontaneous epilepsy.

Other evidence of alterations in the permeability barrier may be seen in the demonstrations of an increased concentration of cocaine in brain tissues three days after a series of 12 induced convulsions (1). The change in concentration of this large molecule, ordinarily absent in brain tissue, was associated with the appearance of hypersynchrony (delta bursts) in the electroencephalogram.

From these observations we would conclude that induced convulsions, like craniocerebral trauma and spontaneous seizures, are associated with an increase in free acetylcholine in intercellular fluids, altering cerebral permeability and enhancing the appearance of cholinesterases. The level of free

acetylcholine is maintained by repeated induced seizures. EEG hypersynchrony is one reflaction of altered levels of acetylcholine and the altered permeability of electrolytes, and other substances, including cholinesterases. The changes in intercellular electrolytes, including acetylcholine (that ?) provide the biochemical substrate for the persistent behavioral changes and EEG hypersynchrony following induced convulsions.

An application of these conclusions is seen in the studies of the prediction of the convulsive therapy response and the classification of psychoses (22).

Cholinesterases and the Classification of Psychoses. Funkenstein et al. demonstrated a relationship between the blood pressure response to methacholine, an active cholinergic agent, ~~the~~ and the clinical response to convulsive therapy (25-27). Immediately after the injection of methacholine, blood pressure falls, usually returning to the baseline within 5-20 minutes. A return within 5 minutes places in the patients in Groups I, II or III; while a return after 20 minutes places the patient in Groups VI and VII. Group I and Group II-III have a 9 and a 35% recovery rate, respectively, while Group VI and Group VII reactors 89% and 97% recovery rates to induced convulsions (27). Group I to III reactors may be looked upon as patients in whom methacholine is rapidly hydrolyzed; while Groups VI and VII have a slow hydrolysis rate. (The response to injected epinephrine was suggested as a second criteria in the

classification, but is of limited discriminating value (48). While we have no biochemical explanation of the differences in the metabolism of methacholine in these psychiatric groups, it is possible that the blood and tissue cholinesterase activity levels of Groups I-III is high, while that of Groups VI-VII is low compared to general psychiatric populations.

The differences in blood cholinesterase levels in normal and mentally ill subjects have been extensively ~~titled~~ studied. Despite differences in methods (4, 5), elevated cholinesterase levels compared to normal populations have been reported for depressive subjects (44, 46, 47, 52), schizophrenic subjects (14, 28, 53) and a mixed psychiatric population (42). Alpern reported lowered cholinesterase levels in schizophrenic subjects (2). While these studies appear inconclusive, they provide data that the variations in blood cholinesterase levels are generally greater and frequently elevated in the mentally ill. Negative reports include the failure by Ellman and Callaway (16) to confirm Rubin's study; and Altschule's review of the data suggesting no abnormality of cholinesterase levels in the mentally ill (3).

Conclusion. This review summarizes some of the available data suggesting that cholinergic mechanisms may be central to the convulsive therapy process. Induced convulsions are associated with vasodilation and increased cellular permeability, followed by the appearance of increased amounts of enzymes and electrolytes in

intercellular and cerebrospinal fluids. Among the changes are an increase in intercellular acetylcholine to levels greater than can be destroyed by acetylcholinesterase activity, and enhanced amounts of butyrylcholinesterase. The increase in acetylcholine, vasodilation, and increased cellular permeability appear as interrelated phenomena associated with trauma, seizures and induced convulsions.

These biochemical changes are associated with increased electrical hypersynchrony which is recorded as EEG slow wave activity in scalp electrodes, and which can be modified by acute and chronic administrations of many anticholinergic drugs, including atropine, benactyzine, diethazine, procyclidine and various piperidylbenzilates.

In these regards, induced convulsions are more similar to cerebral trauma than to spontaneous seizures.

The changes in cerebral biochemistry alter cellular activity sufficiently to affect consciousness and the behavior of subjects. Failure to induce persistent biochemical changes, including the concentration of acetylcholine, results in failure to produce behavioral change.

There is, as yet, no consistent evidence for differences in the sensitivity or dependence of populations on cholinergic mechanisms; the differences in the rate of development of cerebral changes to the same number and frequency of induced convulsions and the classification based on the blood pressure response to methacholine suggest, however, that such differences may be important in the pathogenesis of different psychoses.

To Dr Fink: Paper #156.

Delta.

The slow wave high voltage activity referred to as providing the "most reliable index of brain function" in fact is an index of what type of brain function and is the desired alteration accompanying altered brain function necessary to allow improvement with convulsive therapy?

Does the similar DFP induced high voltage activity without convulsion correlate similarly with altered brain function and desired behavoral change?

~~How much slow wave activity is produced by 1.0 mgm of atropine 1/2 hr before EST? How much behavioral change results?~~ Does barbiturate plus succinyl modify slow wave activity & to what degree and does it effect CST acetylcholine

Were not Frambertis results
with acetylcholine ^ Shock therapy inferior to EST
today?

How strongly ^ Is amnesia correlated with the
slow high voltage ^ Delta waves seen
after a series of EST convulsions?

Must the % of Delta wave activity
increase reach a critical level
to be positively correlated with
sustained improvement in
behavior and/or mood? How
long must this level persist
to render early relapse unlikely?

How much Atropine is required
to ~~modify~~ decrease the Delta wave
activity induced by a convulsion?
Does 1 mgm have such effect.

Does the anti-cholinergic drug
effect that reverses the Delta wave
increase reverse amnesia as
well as mood?

Drugs + Dreaming

? Chol phase in dreaming

40 records - 8 volunteers - Students
78 " 9 PTS. - Person. Disorders

Saline
Scop ——→ dec Stage I inc Stage II
M) Methylscop ——→ inc " "
P) Physostigmine ——→ inc " "
M+P
Atropine ——→ no chan
CP2 ——→ inc Stage I
Meprobamate

Correlated T

Pts more stage one than volunteers who
~~Subjs~~ spend more time in Stages 3, 4

CP2 see { Fisher + Feinberg "9 | dec Stage I
" Zung
" Freeman et al

Feinberg

Imp 1 difference in subjects!

Baseline!
duration of any stage short

122nd ANNUAL MEETING

AMERICAN PSYCHIATRIC ASSOCIATION

ATLANTIC CITY, N. J.—MAY 9-13, 1966

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CHOLINERGIC ASPECTS OF CONVULSIVE THERAPY

Max Fink, M.D.

Read at the 122nd meeting of the American Psychiatric Association,
May 12, 1966, Atlantic City.

Now, Professor of Psychiatry, New York Medical College, New York City.

5-9-66.

The mode of action of induced convulsions is still puzzling. Various theories have been proposed, including those best described as wholly psychological in scope, and those wholly biological or organic - structural. Neither extreme point of view is consistent with the available facts, and the neurophysiological - adaptive models - combining, as they do, both the biological data and the personality historical facts - are the most satisfactory today.

One of the neurophysiological - adaptive theories suggests that persistent alterations in brain function are a necessary condition for behavioral change and improvement in the convulsive therapies. While many measures of altered brain function have been studied, and each has shown a similar relationship of change in measure to behavioral change, the appearance of high voltage slow wave activity in the scalp recorded electroencephalogram has been the most useful index in these studies. The induced delta activity is readily observed, easily quantified and the amount, distribution over the scalp, amplitude and persistence are each directly related to the number and the frequency of the induced seizures and are independent of the mode of induction of the seizure.

While the biochemical basis for these EEG changes ~~were~~ are poorly understood, observations that the induced slow wave activity was inhibited by the intravenous administration of anticholinergic compounds, suggested that cholinergic mechanisms may play an active part not only in the EEG activity but in the therapeutic process as well.

The EEG patterns and the response to anticholinergic drugs in convulsive therapy ~~were seen~~ appear to be similar to the EEG and behavioral changes in experimental and clinical head trauma and to a lesser extent, in spontaneous seizures. This was clearly reflected in measures of the cholinesterases in brain and spinal fluid in these conditions. These observations led to a review of the neurological and biochemical data in induced convulsions, head trauma and spontaneous seizures, to attempt to relate the available observations to the neurophysiological and therapeutic changes observed in the convulsive therapy process.

The activity of acetylcholine in the transmission of nervous impulses has been extensively sutdied since the early descriptions by Dale and Loewi in 1914 and 1921. A constituent of nervous tissue in a bound form, acetylcholine is liberated during the excitation process. It is rapidly hydrolyzed through the mediation of acetylcholinesterase and is rapidly reconstituted by choline-acetylase. Free acetylcholine has not been measurable in normal cerebrospinal fluid despite the rapid breakdown of bound acetylcholine during periods of activity and excitement. But the normal cerebrospinal fluid does have measurable cholinesterase activity.

~~In experimental trauma in cats,~~ free acetylcholine was found in the cerebrospinal fluid within a few minutes after head trauma IN CATS and persisted for varying periods up to 48 hours. The quantity of free acetylcholine varied between 2.7 and 9.0 gamma percent and the amount was directly related to the degree of induced trauma - the greater the induced head trauma, the higher the amount of measured acetylcholine.

Concurrent electroencephalograms first demonstrated high voltage fast activity, interpreted as evidence of an intense neuronal discharge, which was soon succeeded by short periods of flattening of all recorded electrical activity. These phases were followed by prolonged and persistent periods of high amplitude sharp waves in the delta frequencies.

The degree to which the animal's behavior was disorganized was related both to the degree of induced trauma and to the amount of measured free acetylcholine. The higher the observed levels of acetylcholine, the greater the degree of EEG abnormality and the greater the changes in consciousness. The development and the persistence of spontaneous post-traumatic seizures were also related to the amount of free acetylcholine measured in the cerebrospinal fluid.

In a parallel study, acetylcholine was applied directly to the exposed cat cerebral cortex. When the concentration of acetylcholine was 1 gamma percent or less, high amplitude sharp

waves of low frequency appeared in the electroencephalogram. When the concentration was increased to 2 gamma percent, the electro-encephalogram flattened in a fashion parallel to the post-traumatic records, thus again showing a relationship between the EEG changes and the concentration of free acetylcholine.

Investigations in neurological patients by Tower and McEachern in 1948 demonstrated free acetylcholine in the cerebrospinal fluid only in patients with recent head trauma and recent grand-mal seizures, but also after electroconvulsive therapy. Free acetylcholine varied from 0.2 to 100 gamma percent.

In parallel studies they measured the spinal fluid cholinesterase activity. They noted a sharp rise in the butyrylcholinesterase (non-specific) fraction and a fall in the acetylcholinesterase (specific) fraction both in the patients with head trauma and in those following convulsive therapy. After spontaneous seizures, however, the cerebrospinal fluid did not exhibit such an inversion of cholinesterases although it did contain free acetylcholine. They concluded that the level of free acetylcholine varied directly with the degree of cerebral damage and that the reversal of cholinesterase fractions was a more sensitive indicator of cerebral damage. Electroencephalograms taken at varying intervals following trauma also indicated a relation between the degree of EEG abnormality and the appearance of free acetylcholine in the cerebrospinal fluid.

Continuing a review of head trauma, we note that the EEG, behavioral and neurologic signs of head trauma may be blocked by the parenteral administration of atropine. Ward applied these observations to the treatment of closed head injuries. In 20 patients with varying degrees of trauma, the subcutaneous administration of atropine was associated with clinical improvement in some and a reversal of the EEG effects in others. The same changes in the post-traumatic electroencephalogram were reported by Jenkner and Lechner in a study of diethazine, another anti-cholinergic drug. A single intravenous dose in forty patients resulted in normalizing the abnormal electroencephalogram in twenty-two and marked improvement in six others.

Thus, the amount of free acetylcholine may increase in the spinal fluid following crainocerebral trauma and the amount of free acetylcholine, the degree and type of electroencephalographic abnormality, and changes in clinical behavior appear as interrelated phenomena, which may be reduced by the administration of anti-cholinergic drugs.

Brain acetylcholine and anticholinergic drugs. While the data is not as clear, the effects of the direct application of acetylcholine to the central nervous system may also be blocked by anticholinergic drugs. The administration of cholinesterase inhibitor di-isopropyl fluorophysphate (DFP) elicits high amplitude

rapid frequency EEG patterns similar to status epilepticus and post-traumatic states. These EEG effects have been blocked by small doses of parenteral atropine and scopolamine.

Chatfield and Dempsey prepared exposed animal cortex with prostigmine and evoked electroencephalographic spike activity. The prior administration of atropine blocked the appearance of spiking, or if present, thes electrical activity could be eliminated by atropine.

Bornstein also reported that the parenteral administration of atropine seemed to modify the behavioral and neurological signs observed after the intracisternal addition of acetylcholine.

In contrast to these findings, Brenner and Merritt applied topical acetylcholine in concentrations of 2-1/2 to 10% to the exposed cortex of cats and noted no effect on the electro-encephalographic changes after intravenous atropine.

While not definite, the observations suggest that atropine may block the behavioral and EEG effects of free introduced acetylcholine in the spinal fluid.

Cerebrospinal Fluid Acetylcholine and Seizures. Turning to free acetylcholine and spontaneous seizures we again note a relationship. One view of acetylcholine metabolism finds it in nervous tissues in an inactive and bound form. During periods of activity,

acetylcholine is said to be liberated at cell membranes where it is rapidly hydrolyzed and deactivated by cholinesterases. The amount of bound acetylcholine is thus the resultant of the continuous processes of synthesis, liberation and breakdown. It has been postulated that the level rises during sleep and falls during waking activity.

Free acetylcholine was reported in the spinal fluid in patients with epilepsy. Of 56 epileptic patients, 44 demonstrated free acetylcholine in quantities of 0.02 to 5.0 gamma percent with an average of 1.0 gamma percent. Acetylcholine levels were related to the frequency of siezures, the extent of electroencephalographic abnormality, and to the time since the last seizure but bore no relation to medication, type of epilepsy or level of cholinesterase activity. Elliott *et al.* also noted free acetylcholine in the spinal fluid in concentrations up to 3 gamma percent after pentylenetetrazol (Metrazol) convulsions.

Tower and McEachern viewed the increased acetylcholine as a by-product of the seizure and not causal. Studying the hypothesis that seizures were induced by the accumulation of acetylcholine, Torda noted a rise in the acetylcholine content of brain before and a fall during pentylenetetrazol convulsions. Below certain levels of acetylcholine, convulsions failed to occur. She suggested that the fall in tissue acetylcholine during a convulsion was due to the inhibition of acetylcholine synthesis by increased concentrations of metabolites such as ammonium ions.

These studies suggest that spontaneous or induced seizures are accompanied by an increase in intericellular free acetylcholine liberated from its bound form which may be reflected in the spinal fluid. Cerebral activity and seizures enhance acetylcholine destruction, lowering tissue levels of acetylcholine, while sleep and anesthesia augment acetylcholine production increasing tissue levels.

EEG Hypersynchrony and Induced Convulsions. The significance of high voltage EEG slow wave activity for the convulsive therapy process has been repeatedly described, with numerous observers indicating that increased slowing is associated with behavioral improvement. In the usual course of convulsive therapy, inter-treatment electroencephalograms record progressive increases in amplitude and in theta activity and a reduction in beta activity. As treatment continues, delta activity appears in bursts and eventually is the dominant activity in all leads. These changes are directly related to the number and rate of induced convulsions, and is not specific for a method of induction. While some relation-ships to type of electrical current has been observed, all seizure inducing methods — electrical, intravenous chemical or inhalant — exhibit the same type of EEG pattern changes.

The early appearance of high degree hypersynchrony and its persistence throughout a treatment course ~~has been found to be~~ appears to be prerequisite to improvement. Both the electrographic and the behavioral changes of induced convulsions are transiently reversed by the acute administration of experimental anticholinergic compounds. The intravenous injection of diethazine, benactyzine, the piperidylbenzilates JB-318, JB-336 and JB-329 (Ditran), and WIN-2299 induced EEG desynchronization in psychiatric subjects. These EEG changes were associated with behavioral alerting, anxiety, tremors, illusions and hallucinations. In patients who had recently received electroconvulsive therapy there was a reduction in slow wave activity and a reversal of euphoria, denial and confusion. Atropine, in low doses, was also associated with EEG desynchronization accompanied by tachycardia, nervousness and tension. At higher dosages, hypersynchronous slow waves followed by lower voltage, poorly organized delta activity with superimposed beta activity was accompanied by progressive confusion and disorientation.

The effect of anticholinergic drugs on the slow wave activity of convulsive therapy was also assessed by the chronic administration of atropine (5 mgm per day) and scopolamine (1-3 mg) during the weeks of treatment. The amount of EEG slowing was significantly less than in a control group. The samples were too small for a clinical correlation but the data is consistent

with blocking of the clinical effects of electroconvulsive therapy. Marked improvement was reported in 2 of 7 atropine-treated, none of 5 scopolamine-treated and in 4 of the 6 controls receiving unmodified ECT. This study was not replicated by the authors who suggest that dosage factors or population changes may have contributed to the different results in a second study.

As in cerebral trauma, the electrographic changes of induced convulsions may be modified by the administration of anticholinergic drugs suggesting that increased amounts of acetylcholine or increased cholinergic receptivity is associated with the high voltage slow wave activity.

Acetylcholine and INduced Convulsions. Despite a constant application of treatments, however, there is great variability in the time of appearance, the duration, amount, and sensitivity to modification by alerting, hyperventilation and barbiturates of the electrographic slow wave activity in psychiatric populations. We would suggest that these differences may relate to differences in central cholinergic activity. The failure of certain patients to develop hypersynchrony may be associated with the failure to liberate excessive amounts of free acetylcholine, and with the minimal changes in cerebral function

Does DFP reduced Hyl vol → decreased bl

Comb of succ & bot → slow wave act

CSF

Alexander - (1) ~~Auditory~~ - ECT + antidepr ?

(2) antichol - antidep

(3) Zulueta + bleth atrop

a clinical response to induced convulsions is precluded.

Tower and McEachern in their study of patients with head trauma, included observations of six psychiatric patients undergoing convulsive therapy. Studying the patients after 3 to 7 treatments they reported free spinal fluid acetylcholine in two patients; and a reversal of the ratio of cholinesterase ratio reversal in the spinal fluid, the authors stated: "It is interesting that this patient was the only one of the six to show no response to treatment." From these observations they concluded that the spinal fluid changes in induced convulsions were more like those of craniocerebral trauma than those of spontaneous epilepsy.

From these observations we would conclude that induced convulsions, like craniocerebral trauma and spontaneous seizures, are associated with an increase in free acetylcholine in intercellular fluids, altering cerebral permeability and enhancing the appearance of cholinesterases. The level of free acetylcholine is maintained by repeated induced seizures. EEG hypersynchrony is one reflection of altered levels of acetylcholine and the altered permeability of electrolytes and other substances, including cholinesterases. The changes in intercellular electrolytes, including acetylcholine, provide the biochemical substrate for the persistent behavioral changes and EEG hypersynchrony following induced convulsions.

Dr Ellicott:

1947 Feldberg + Vogt

Localized fx of ach -
areas devoid of Ach esterase

Feldberg & Skenwood - difference in behavior varied i local of acetylcholine

Localized effects: | hypothalamus / amygdala

Interactin betwn acetylcholine & serotonin

~~secret effect~~

change in intracellular permeability

receptor of ach
↓
effect begins

Holt Frambesia Ach Shock Rx enhances & ECT

? amnesia rel. & Hyperbolize slow wave

% Δ reach a critical level for
improvement
& how long persist for early elapse

? atropine reg. & reduce
1 mg - ped. Δ.

anticholinergic reflect amnesia?

Is Δ ? Kind of Rx - the type of brain fx we desire or a side effect?

CONCLUSIONS

This review summarizes some of the available data suggesting that cholinergic mechanisms may be central to the convulsive therapy process. We have observed that induced convulsions are associated with cerebral vasodilation and increased cellular permeability, followed by the appearance of increased amounts of enzymes and electrolytes in intercellular and cerebrospinal fluids. The increase in acetylcholine, vasodilation and increased permeability appear as interrelated phenomena associated with trauma, seizures and induced convulsions.

These biochemical changes accompany increased electrical hypersynchrony which is recorded as EEG slow wave activity in scalp electrodes and which can be modified by the acute and chronic administration of anticholinergic drugs as atropine, benactyzine, diethazine, procyclidine and various piperidyl-benzilates.

In these regards, induced convulsions are more similar to cerebral trauma than to spontaneous seizures.

The changes in cerebral biochemistry alter cellular activity sufficiently to affect consciousness and the behavior of subjects. Failure to induce persistent biochemical changes, including the concentration of acetylcholine, results in failure to produce behavioral change.

There is, as yet, no consistent evidence for differences in the sensitivity or dependence of the cerebral mechanisms underlying interpersonal behavior of populations on cholinergic mechanisms. Differences in the rate of development of cerebral changes to the same number and frequency of induced convulsions and classifications of the mentally ill based on the blodo pressure response to methacholine suggest, however, that such differences may exist and may be related to the pathogenesis of different types of psychoses, as well as the success or failure of our present varieties of biological treatments.

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One of the neurophysiological - adaptive theories suggests that persistent alterations in brain function are a necessary condition for behavioral change and improvement in the convulsive therapies. While many measures of altered brain function have been studied, and each has shown a similar relationship of change in measure to behavioral change, the appearance of high voltage slow wave activity in the scalp recorded electroencephalogram has been the most useful index in these studies. The induced delta activity is readily observed, easily quantified and the amount, distribution over the scalp, amplitude and persistence are each directly related to the number and the frequency of the induced seizures and are independent of the mode of induction of the seizure.

While the biochemical basis for these EEG changes were poorly understood, observations that the induced slow wave activity was inhibited by the intravenous administration of anticholinergic compounds, suggested that cholinergic mechanisms may play an active part not only in the EEG activity but in the therapeutic process as well.

The EEG patterns and the response to anticholinergic drugs in convulsive therapy were seen to be similar to the EEG and behavioral changes in experimental and clinical head trauma and to a lesser extent, in spontaneous seizures. This was clearly reflected in measures of the cholinesterases in brain and spinal fluid in these conditions. These observations led to a review of the neurological and biochemical data in induced convulsions, head trauma and spontaneous seizures, to attempt to relate the available observations to the neurophysiological and therapeutic changes observed in the convulsive therapy process.

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From these observations we would conclude that induced convulsions, like craniocerebral trauma and spontaneous seizures, are associated with an increase in free acetylcholine in intercellular fluids, altering cerebral permeability and enhancing the appearance of cholinesterases. The level of free acetylcholine is maintained by repeated induced seizures. EEG hypersynchrony is one reflection of altered levels of acetylcholine and the altered permeability of electrolytes and other substances, including cholinesterases. The changes in intercellular electrolytes, including acetylcholine, provide the biochemical substrate for the persistent behavioral changes and EEG hypersynchrony following induced convulsions.

CONCLUSIONS

This review summarizes some of the available data suggesting that cholinergic mechanisms may be central to the convulsive therapy process. We have observed that induced convulsions are associated with cerebral vasodilation and increased cellular permeability, followed by the appearance of increased amounts of enzymes and electrolytes in intercellular and cerebrospinal fluids. The increase in acetylcholine, vasodilation and increased permeability appear as interrelated phenomena associated with trauma, seizures and induced convulsions.

These biochemical changes accompany increased electrical hypersynchrony which is recorded as EEG slow wave activity in scalp electrodes and which can be modified by the acute and chronic administration of anticholinergic drugs as atropine, benactyzine, diethazine, procyclidine and various piperidyl-benzilates.

In these regards, induced convulsions are more similar to cerebral trauma than to spontaneous seizures.

The changes in cerebral biochemistry alter cellular activity sufficiently to affect consciousness and the behavior of subjects. Failure to induce persistent biochemical changes, including the concentration of acetylcholine, results in failure to produce behavioral change.

There is, as yet, no consistent evidence for differences in the sensitivity or dependence of the cerebral mechanisms underlying interpersonal behavior of populations on cholinergic mechanisms. Differences in the rate of development of cerebral changes to the same number and frequency of induced convulsions and classifications of the mentally ill based on the blodo pressure response to methacholine suggest, however, that such differences may exist and may be related to the pathogenesis of different types of psychoses, as well as the success or failure of our present varieties of biological treatments.

CHOLINERGIC MECHANISMS IN

CONVULSIVE THERAPY

MAX FINK, M.D.

DEPARTMENT OF PSYCHIATRY AT THE MISSOURI INSTITUTE OF PSYCHIATRY

UNIVERSITY OF MISSOURI SCHOOL OF MEDICINE

5400 Arsenal Street St. Louis, Missouri 63139

PSYCHIATRIC RESEARCH FOUNDATION OF MISSOURI

Publication No. 65-8

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Max Fink, M.D.

Psychiatric Research Foundation
Publication 65-8
September, 1965

From the Department of Psychiatry, Washington University School of Medicine and the Department of Psychiatry at the Missouri Institute of Psychiatry, University of Missouri School of Medicine, 5400 Arsenal Street, St. Louis, Missouri 63139

Aided, in part, by USPHS grants MH-927, MH-2715, MH-07249, and MH-11380; and the Psychiatric Research Foundation of Missouri.

VIII: 8/21/65

65-8

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Despite extensive use, the mode of action of the convulsive therapy process remains enigmatic. The neurophysiological-adaptive theory attempts an assimalation of neurophysiological, psychological, clinical, and social aspects of the process (Fink, 1957, 1962). In this view, the early development and persistence of signs of altered cerebral function are requisite to changes in behavior (Fink and Kahn, 1956), with electroencephalographic slow wave activity as the most significant index of altered brain function. Demonstrations that premedication with atropine inhibited this slow wave activity (Ulett and Johnson, 1957) and that anticholinergic compounds reversed clinical as well as electrographic changes (Fink, 1958) suggests that the biochemical basis for the convulsive therapy process may be in the cholinergic mechanisms of the central nervous system. The role of acetylcholine and the cholinesterases in the convulsive therapy process is discussed in this review.

Acetylcholine has been extensively studied as an active agent in the transmission of nervous impulses since the first descriptions by Dale (1914) and Loewi (1921). It is a constituent of nervous tissue, existing in a bound form which is liberated during the excitation process. It is rapidly hydrolyzed through the specific action of cholinesterase and is rapidly reconstituted by the choline-acetylase system(Richter and Crossland, 1949). In normal

cerebrospinal fluid, free acetylcholine is not present despite the rapid breakdown of bound acetylcholine during periods of activity and excitement (Tower and McEachern, 1949a). The cerebrospinal fluid does have measurable cholinesterase activity, principally of the "true" or mecholyl hydrolyzing type (Nachmanson and Rothenberg, 1945). In the absence of free acetylcholine and under resting conditions, electroencephalograms fail to show abnormality.

(a) Cholinergic Aspects of Craniocerebral Trauma: Free acetylcholine was found in the cerebrospinal fluid within a few minutes after experimental head trauma in cats and persisted for varying periods up to 48 hours (Bornstein, 1946). The quantity of free acetylcholine varied between 2.7 and 9.0 gamma percent, and the amount was related to the degree of induced trauma.

Concurrent electroencephalograms demonstrated records first filled with high voltage fast activity, interpreted as evidence of an intense neuronal discharge, which was soon succeeded by a short period of flattening of all recorded electrical activity. These phases were then followed by prolonged periods of high amplitude sharp waves in the delta frequencies.

The behavioral changes were related both to the degree of trauma and to the amount of measured free acetylcholine. With higher levels of acetylcholine, Bornstein reported greater degrees of EEG abnormality and greater changes in consciousness. Spontaneous post-traumatic seizures were also related to the amount of free acetylcholine

appearing in the spinal fluid.

Bornstein applied acetylcholine to exposed cat cerebral cortex. When the concentration of acetylcholine was 1 gamma percent or less, high amplitude sharp waves of low frequency appeared in the electroencephalogram. When the concentration was increased to 2 gamma percent, the electroencephalogram flattened in a fashion parallel to the post-traumatic records.

Investigations in neurological patients by Tower and McEachern (1949a) demonstrated free acetylcholine in the cerebrospinal fluid only in patients with recent head trauma, recent grand-mal seizures or after electroconvulsive therapy. Free acetylcholine varied from 0.2 to 100 gamma percent. In assaying spinal fluid cholinesterase activity, they noted a sharp rise in the nonspecific cholinesterase fraction (benzoylcholine-splitting) and a drop in the specific cholinesterase fraction (mecholyl-splitting) in patients with head trauma and following convulsive therapy. After spontaneous seizures, however, the cerebrospinal fluid did not exhibit such inversion although it contained free acetylcholine. They concluded that the level of free acetylcholine varied directly with the degree of cerebral damage and that reversal of the cholinesterase fractions was a more sensitive indicator of cerebral damage. Electroencephalograms, taken at varying intervals following trauma, also indicated a relation between the degree of EEG abnormality and the appearance of free acetylcholine in the cerebrospinal fluid.

These observations were recently confirmed by Kovach, et al. (1957) who recorded increased acetylcholine in rat brain after traumatic shock and an inhibition of this activity by the administration of atropine to the muscle preparation.

Thus the amount of free acetylcholine may increase in the spinal fluid following craniocerebral trauma and the amount of free acetylcholine, the degree and type of electroencephalographic abnormality, and changes in clinical behavior appear as interrelated phenomena.

(b) Anticholinergic drugs and trauma: The electrographic, behavioral and neurologic signs of head trauma were blocked by the parenteral administration of 0.5-1.0 mg/kg atropine (Bornstein, 1946), as were similar clinical changes occurring after the intracisternal addition of acetylcholine. Ward (1950) applied these observations to the treatment of closed head injuries. In 20 patients with varying degrees of trauma, he administered atropine subcutaneously in doses of 0.1 mg/kg, noting clinical improvement in some and a reversal of the electrographic effects in others. Similar alterations in the post-traumatic electroencephalogram were reported by Jenkner and Lechner (1955) in a study of diethazine, another anticholinergic drug. A single intravenous dose in forty patients resulted in normalizing the abnormal electroencephalogram in twenty-two and marked improvement in six others.

Similar observations have been reported with methylbenactyzine and trasentin in animal experiments of post-traumatic shock and cerebral edema (Denisenko, 1965).

The effect of atropine was assessed in the convulsive therapy process by Ulett and Johnson (1957). With the administration of atropine up to 5 mgm per day during the weeks the patients received electroshock therapy, the amount of slow wave activity was significantly less than in a control group who had not received the atropine administration. (These authors failed to replicate this study, suggesting that dosage factors or population changes may have contributed to different results [Johnson et al., 1960]).

Both the electrographic and the behavioral changes of induced convulsions were also reversed by the administration of experimental anticholinergic compounds (Fink, 1958, 1960). The intravenous injection of diethazine, benactyzine, the piperidylbenzilates JB-318, JB-336 and JB-329 (Ditran), and WIN-2299 induced EEG desynchronization in psychiatric subjects. These EEG changes were associated with behavioral alerting, anxiety, tremors, illusions, and hallucinations. In patients who had recently received electroconvulsive therapy, there was a reduction in slow wave activity and a reversal of euphoria, denial and confusion. Atropine in low doses, was associated with EEG desynchronization accompanied by tachycardia, nervousness and tension.

At higher dosages, hypersynchronous slow waves, followed by lower voltage, poorly organized delta activity with superimposed beta activity was associated with progressive confusion and disorientation.

Both in cerebral trauma and induced convulsions, the electrographic changes may be modified by the administration of anticholinergic drugs, suggesting that increased amounts of acetylcholine or increased cholinergic receptivity is associated with the high voltage slow wave activity.

(c) Brain acetylcholine and anticholinergic drugs:

Similar EEG changes and similar blocking by anticholinergic drugs has been observed following the direct application of acetylcholine to the central nervous system. The administration of a cholinesterase inhibitor DFP (di-isopropyl fluorophosphate) elicited high amplitude rapid frequency EEG patterns similar to status epilepticus, as well as changes similar to those of post-traumatic states (Freedman et al., 1949; Hampson et al., 1950; Himwich et al., 1950; and Wescoe et al., 1948). These EEG effects were blocked by small doses of parenteral atropine and scopolamine. The great increase in acetylcholine after tetraethyl pyrophosphate (TEPP) was measured and related to the toxic and convulsions induced (Giarman and Pepeu, 1952; Stone, 1957).

Chatfield and Dempsey (1942) prepared exposed animal cortex with prostigmine and evoked electroencephalographic spike activity. The prior administration of atropine blocked this spiking, or if present, the abnormality could be eliminated by atropine.

In contrast to these findings, Brenner and Merritt (1942) applied topical acetylcholine in concentrations of 2-1/2 to 10% to the exposed cortex of cats, and noted no effect on the electroencephalographic changes after intravenous atropine (1 mg/kg). The concentrations of acetylcholine in these experiments, however, were higher than the topical applications (1-4 gamma percent) and the intracisternal (0.2-10 gamma percent) injections of Bornstein (1946). Brenner and Merritt also made note of electroencephalographic effects similar to acetylcholine from mecholyl (acetylbetamethylcholine) and doryl (carbamylcholine) in concentrations much lower than the acetylcholine concentrations. They ascribed the increased effectiveness of these cholinergic drugs to their lack of sensitivity to cerebral cholinesterases.

These data are conflicting and further study is necessary to qualify this issue.

(d) Cerebrospinal Fluid Acetylcholine and Seizures: One view of acetylcholine metabolism indicates that it is found in nervous tissues in an inactive bound form. During periods of activity, acetylcholine is liberated at the cell membrane where it is rapidly deactivated by cholinesterase. The amount of bound acetylcholine is the resultant of the continuous processes of synthesis, liberation and breakdown. It has been postulated that the level rises during sleep and falls during activity. (Tobias et al., 1946; Richter and Crossland, 1949; Elliot, Swank and Henderson, 1950; Giarman and Pepeu, 1962). Tobias et al. found

increased free and total acetylcholine after chloroform and nembutal anesthesia in rat and frog brain, but no significant changes after strychnine or picrotoxin convulsions. Richter and Crossland measured the level of acetylcholine (micro-gamma per mg. brain tissue) during anesthesia and sleep in rat brain to be 300% higher than post-seizure levels. The difference in tissue levels is transient, however, as the resynthesis rate for acetylcholine in rat brain is high (7 gamma/gm/minute). These observations were confirmed by Elliot et al. (1950) and Crossland and Merrick (1954). Giarman and Pepeu (1962) found the increase in acetylcholine following various depressants to be roughly proportional to the degree of depression of the central nervous system and the reduction in motor activity. Maynert and Buck (1964), however, studying brain acetylcholine levels and sedation concluded that some sedating agents are associated with elevated brain acetylcholine, but that no rigorous relationships existed. In part, this may be related to the earlier observations of McLennan and Elliot (1951) that acetylcholine synthesis measured in rat brain slices is accelerated by low dosages of narcotic drugs, but inhibited by high dosages.

Free acetylcholine was reported in the spinal fluid in patients with epilepsy (Cone, Tower and McEachern, 1948; Tower and McEachern, 1949b). Of 56 epileptic patinets, 44 demonstrated free acetylcholine in quantities of 0.02 to 5.0 gamma percent with an average of 1.0 gamma percent. Acetylcholine levels were related

to the frequency of seizures, the extent of electroencephalographic abnormality, and to the time since the last seizure, but bore no relation to medication, type of epilepsy or level of cholinesterase activity. Elliot et al. (1950) also noted free acetylcholine in the spinal fluid in concentrations up to 3 gamma percent after metrazole convulsions.

Tower and McEachern (1949b) viewed the increased acetylcholine as a by-produce of the seizure, and not causal. Studying the hypothesis that seizures were induced by the accumulation of acetylcholine, Torda (1953) measured the level of acetylcholine in brain tissue after metrazole convulsions. She noted a rise in the acetylcholine content of brain before a seizure and a fall during the convulsion. Below certain levels of acetylcholine, convulsions failed to occur. She suggested that the fall in tissue acetylcholine during a convulsion was due to inhibition of acetylcholine synthesis by increased concentrations of metabolites such as ammonium ions.

Giarman and Pepeu also measured changes in central nervous system acetylcholine following various stimulants. Only after mecholyl and 3, 5-dimethylbutylethyl-barbiturate was there a significant change in the acetylcholine level. They noted a decrease in association with induced convulsions. With other drugs which they classified as stimulants (LSD, iproniazid, iproniazid + hydroxytryptophan, and iproniazid + DOPA) there were no changes in acetylcholine level. They concluded that

despite intense excitation produced by these compounds, there were no changes in acetylcholine levels unless these were accompanied by convulsions. (The differences in observations between these workers and Cone et al. and Tower and McEachern may be related to the differences in methods of biochemical measurements, for the latter measured changes reflecting free acetylcholine only, while Giarman and Pepeu measured the total acetylcholine reflecting bound and free forms of acetylcholine. [McLennan and Elliot, 1951]).

These studies suggest that spontaneous or induced seizures are accompanied by an increase in intercellular free acetylcholine liberated from its bound form which may be reflected in the spinal fluid. Cerebral activity and seizures enhance acetylcholine destruction, lowering tissue levels of acetylcholine, while sleep and anesthesia may augment acetylcholine production increasing tissue levels.

(e) Central Nervous System Cholinesterases: Tower and McEachern (1949) also measured spinal fluid cholinesterase activity. Two types of cholinesterases are normally found in the spinal fluid: cholinesterase-I ("true," "specific," or mecholyl-hydrolyzing), which has a high specificity for acetylcholine; and cholinesterase-II ("pseudo," "non-specific," or benzoylcholine-hydrolyzing). Both compounds hydrolyze acetylcholine but have different rates of hydrolysis for mecholyl and benzoylcholine. This differential rate permits qualitative distinctions. By reporting the cholinesterase

activity as a ratio of the activity with a mecholyl substrate and with a benzoylcholine substrate compared to a substrate of acetylcholine, two ratios are found: cholinesterase-I/acetylcholine and cholinesterase-II/acetylcholine. In such ratios normal cerebrospinal fluid contains esterases in the ratio of 33:17 for cholinesterase-I to cholinesterase-II.

In patients with head trauma, Tower and McEachern reported an inversion of the cholinesterases with a increase in the cholinesterase-II fraction of the spinal fluid and a decrease in cholinesterase-I activity. The extent of the cholinesterase reversal was related to the severity of trauma and to the degree of the electroencephalographic abnormality.

In patients with elevated spinal fluid acetylcholine after spontaneous seizures, however, no change in the ratio of cholinesterases or total cholinesterase activity was found.

The change in cholinesterase activity may be related to changes in cell membrane permeability. Cholinesterase-I is found in highest concentration in the central nervous system while cholinesterase-II predominates in other tissues, especially blood serum. With an increase in acetylcholine levels in cerebral intercellular fluids, vasodilation and increased cellular permeability may be predicted, with a degree of transudation of vascular fluids into the intercellular spaces varying with the extent and duration of the vasodilation (Kabat et al., 1948). Spiegel, Spiegel-Adolf,

and their co-workers (1941, 1942, 1944, 1948, 1953) demonstrated such permeability changes and increased conductivity of the tissues associated with the appearance of various ions (as potassium and phosphate) in the spinal fluid following electrically induced convulsions. Such non-electrolytes as nucleic-acid splitting enzymes also increased. Changes in cellular permeability may thus provide the basis for the high concentrations of acetylcholine and the increased concentrations of cholinesterase-II in induced seizures or head trauma (Tower and McEachern, 1949c).

The persistance of acetylcholine in spinal fluid after head trauma and after seizures despite increased cholinesterase activity may be related to the sensitivity of the acetylcholine-cholinesterase-I system to concentration relationships (Nachmanson and Rothenberg, 1945; Tower and McEachern, 1949c; Burgen and MacIntosh, 1955). At "physiologic" concentrations, hydrolysis of acetylcholine is rapid (3-4 microseconds) but at higher and lower concentrations, the activity falls off quickly. In contrast, the cholinesterase-II acetylcholine relationship is non-specific and the rate of hydrolysis increases with increased concentration.

These relationships are related to the induction of seizures. While the usual concentrations of acetylcholine at cell membranes are destroyed by the specific activity of cholinesterase-I in a few microseconds, an excessive concentration following excitation may exceed the rate of hydrolysis by cholinesterase-I. The seizure

threshold is reached and a seizure induced, with the seizure itself adding to the amount of free acetylcholine. The increased acetylcholine diffuses rapidly, affecting vascular and cellular permeability and increasing the concentrations of various ions, including cholinesterase-II, in tissues and in the cerebrospinal fluid. The activity of cholinesterase-II, though of low efficiency and depending on concentration kinetics, reduces the acetylcholine in the tissues in hours to days to levels for the physiologic action of cholinesterase-I.

Cholinesterases appear in the spinal fluid as a reflection of their increase in intercellular fluids, resulting from changes in cell membrane permeability occasioned by increased acetylcholine. The increased cholinesterases are part of the homeostatic mechanisms controlling the levels of acetylcholine at cell membranes necessary for nervous system activity.

(f) Acetylcholine, EEG Hypersynchrony and Induced Convulsions:

Alteration in the blood-brain permeability barrier by the continuing action of acetylcholine may be a biochemical substrate for the post-electroshock hypersynchrony of the electroencephalogram. Such a possibility is evident in the demonstration of an increase in the concentration of cocaine in brain tissues three days after a series of 12 induced convulsions (Aird et al., 1956). The change in concentration of this large molecule, ordinarily absent in brain tissue, was associated with the appearance of hypersynchrony (delta bursts) in the electroencephalogram.

We have confirmed the many previous reports that convulsive thrapy induces electrographic hypersynchrony (Fink and Kahn, 1956; Fink et al., 1961). Despite a constant application of treatments there is a great variability in the time of appearance, the duration and the extent of the electrographic slow wave activity as well as the sensitivity to modification by alerting, hyperventilation and barbiturates in psychiatric populations (Green, 1957). The early appearance of high degree hypersynchrony and its persistence throughout a treatment course has been described as prerequisite to improvement following electroshock (Roth, 1951; Roth et al., 1957; Fink and Kahn, 1956). The differences in the degree of induced EEG hypersynchrony may be related to differences in central cholinergic activity. The failure of certain patients to develop hypersynchrony may be associated with the absence of free acetylcholine and with minimal changes in cerebral function, thus precluding a clinical response to induced convulsions. Tower and McEachern (1949a), in their study of craniocerebral trauma, included observations of six psychiatric patients undergoing convulsive therapy. Studying the patients after 3-7 treatments they reported free spinal fluid acetylcholine in two patients; and an increase in cholinesterase-II and a decrease in cholinesterase-I with a reversal of the ratio of cholinesterases in five of the six patients. The one patient in the series who failed to show either free acetylcholine or a cholinesterase ratio reversal in the spinal fluid was described as: "It is interesting that this patient was the only one of the six to show no response to treatment."

From these observations they concluded that the spinal fluid changes in induced convulsions were more like those of craniocerebral trauma than those of spontaneous epilepsy.

If electrographic hypersynchrony is a reflection of increased free acetylcholine, subjects who maintain hypersynchrony and those in whom it disappears rapidly may be exhibiting differences in the kinetics of the cholinesterase-acetylcholine hydrolysis systems. Persistent hypersynchrony may result from a decreased rate of hydrolysis of acetylcholine, associated with low concentrations of either cholinesterase-I or cholinesterase-II. (Conversely, in patients with short-lived hypersynchrony, cholinesterase-I and -II in tissue and spinal fluid may be unusually high.)

From these observations we would conclude that induced convulsions are associated with an increase in free acetylcholine in intercellular fluids, altering cerebral permeability and enhancing the appearance of cholinesterases. The level of free acetylcholine is maintained by repeated induced seizures. EEG hypersynchrony is one reflection of altered levels of acetylcholine and altered permeability of other electrolytes. It is probable that these changes in intercellular electrolytes provide the biochemical substrate for the persistent behavioral changes following induced convulsions.

(g) Cholinesterases and the Classification of Psychoses:

These studies have application to the problem of autonomic reactivity and the classification of the psychoses. Funkenstein et al. (1948, 1951, 1952) have demonstrated a relationship between the blood pressure response to injected methacholine (Mecholyl) and the clinical response of psychiatric patients to convulsive therapy. Methacholine is a potent cholinergic agent which induces vasodilation, tachycardia, sweating, and increased peristalsis. It is rapidly hydrolyzed by cholinesterase-I and slowly by cholinesterase-II. The blood pressure of subjects falls after injected mecholyl and returns to the baseline within five to 20 minutes. Patients whose blood pressure returns to the baseline within 5 minutes have been classified as Group I, II, or III reactors; those whose blood pressure takes 20 or more minutes to return to baseline, as Group VI and VII reactors. Group I and Group II-III reactors have a 9 and a 35% recovery rate, respectively, while Group VI and Group VII reactors 89% and 97% recovery rates (Funkenstein et al., 1952). Group I to III reactors may be looked upon as patients in whom the injected mecholyl is rapidly hydrolyzed; while Groups VI and VII have a slow hydrolysis rate. [For a recent review, see Rose, 1962.] It is possible that the blood and tissue cholinesterase activity levels of Groups I-III is high, while that of Groups VI-VII is low compared to general psychiatric populations.

The differences in blood cholinesterase levels in normal and mentally ill subjects have been extensively studied. Despite differences

in methods (Augustinsson, 1955, 1957) elevated cholinesterase levels compared to normal populations have been reported for depressive subjects (Richter and Lee, 1942; Rowntree et al., 1950; Ravin and Altshule, 1952), schizophrenic subjects (Early et al., 1949; Rubin, 1958; Gal, 1963) and a mixed psychiatric population (Plum, 1960). Alpern (1956) reported lowered cholinesterase levels in schizophrenic subjects. While these studies appear inconclusive, they provide data that the variations in blood cholinesterase levels are generally greater and frequently elevated in the mentally ill. Negative reports include the failure by Ellman and Callaway (1961) to confirm Rubin's study; and Altschule's (1953) review of the data suggesting no abnormality of cholinesterase levels in the mentally ill.

A similar analysis may be made regarding the relation of central nervous system levels of cholinesterase in the development of EEG hypersynchrony and spinal fluid levels of acetylcholine, thus providing a congruent hypothesis regarding central nervous system reactivity to induced convulsions and to peripheral cholinergic agents.

CONCLUSION:

This review indicates that central cholinergic mechanisms are significant in the convulsive therapy process. Induced convulsions are associated with an increase in intercellular acetylcholine to levels greater than can be destroyed by acetylcholinesterase activity. Vasodilation and increased cellular permeability are followed by the appearance of increased amounts of butyrylcholinesterase and other enzymes and electrolytes in intercellular fluids.

These biochemical changes are associated with increased electrical hypersynchrony which is recorded as EEG slow wave activity in scalp electrodes, and which can be modified by many anticholinergic drugs, including atropine, benactyzine, diethazine, procyclidine and piperidylbenzilates.

In these regards, induced convulsions are more similar to cerebral trauma than to spontaneous seizures.

These changes in cerebral biochemistry alter cellular recovery and firing rates sufficiently to alter the behavior of subjects. Failure to induce high and persistent concentrations of acetylcholine or failure to induce concomitant electrolyte changes does not alter cerebral cellular activities and results in a failure to produce behavioral change.

Differences in the rate of development of cerebral changes to the same number and frequency of induced convulsions may reflect differences in the dependence of subjects on cholinergic mechanisms or

in their sensitivity to changes in acetylcholine levels. These differences provide the basis for the classifications of the mentally ill based on neurophysiological responsitivity by Funkenstein and by Fink and Kahn.

These data on cholinergic mechanisms provide a rational biochemical theory for the mode of action of induced convulsions in altering the behavior of psychotic subjects, and are consistent with the more general neurophysiologic-adaptive theory of the convulsive therapy process expressed earlier.

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[1] Department of Psychiatry, Washington University School of Medicine; Missouri Institute of Psychiatry, University of Missouri School of Medicine, 5400 Arsenal Street, St. Louis, Missouri.

New York Medical College

This study was aided, in part, by USPHS grants MH-927, MH-2715, MH-07249 and MH-11380; and by the Psychiatric Research Foundation of Missouri.

While the mode of action of convulsive therapies remains enigmatic, one theory holds that the early development and persistence of changes in brain function are requisite to changes in behavior (18, 21, 22). A useful index of neurophysiological change is the appearance of high voltage electroencephalographic slow wave activity (22, 23). While the biochemistry of this activity is poorly understood, demonstrations that it is inhibited by anticholinergic compounds (19, 20, 34, 66) suggest that cholinergic systems may play an active part.

The EEG patterns and the response to anticholinergic drugs in convulsive therapy are similar to experimental and clinical head trauma and, to a lesser extent, spontaneous seizures. Changes in concentration of cholinesterases in brain and spinal fluid also show many similarities in these conditions. This review discusses these observations to provide a hypothesis for the role of cholinergic changes in convulsive therapy.

The activity of acetylcholine in the transmission of nervous impulses has been extensively studied since the early descriptions by Dale (12) and Loewi (38). A constituent of nervous tissue in a bound form, acetylcholine, is liberated during the excitation process. It is rapidly hydrolyzed through the mediation of acetylcholinesterase and is rapidly reconstituted by the choline-acetylase system (45). Free acetylcholine has not been measurable in normal cerebrospinal fluid despite the rapid breakdown of bound acetylcholine during periods of activity and excitement (63).

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CHOLINERGIC ASPECTS OF CRANIOCEREBRAL TRAUMA

Free acetylcholine was found in the cerebrospinal fluid of cats within a few minutes after experimental head trauma and persisted for varying periods up to 48 hours. The quantity of free acetylcholine varied between 2.7 and 9.0 gama/100 cc, and the amount was related to the degree of induced trauma (6).

Concurrent electroencephalograms first demonstrated high voltage fast activity, interpreted as evidence of an intense neuronal discharge, which was succeeded by a short period of flattening of all recorded electrical activity. These phases were followed by prolonged periods of

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high amplitude sharp waves in the delta frequencies.

The behavioral changes related to the degree of induced trauma and to the amount of measured free acetylcholine. With higher levels of acetylcholine, Bornstein (6) reported greater degrees of EEG abnormality and greater changes in consciousness. Spontaneous post-traumatic seizures were also related to the amount of free acetylcholine measured in the cerebrospinal fluid.

Bornstein applied acetylcholine to exposed cat cerebral cortex. When the concentration of acetylcholine was one gamma/100 cc or less, high amplitude sharp waves of low frequency appeared in the electroencephalogram. When the concentration was increased to two gamma/100 cc, the electroencephalogram flattened in a fashion parallel to the post-traumatic records.

Investigations in neurological patients by Tower and McEachern (63) demonstrated free acetylcholine in the cerebrospinal fluid only in patients with recent head trauma, recent grand-mal seizures or after electroconvulsive therapy. Free acetylcholine varied from 0.2 to 100 gamma/100 cc. In assaying spinal fluid cholinesterase activity, they noted a sharp rise in the butyrylcholinesterase fraction and a fall in the acetylcholinesterase fraction in patients with head trauma and following convulsive therapy. After spontaneous seizures, however, the cerebrospinal fluid did not exhibit such inversion although it contained free acetylcholine. They concluded that the level of free acetylcholine varied directly with

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Increased acetylcholine in rat brain after traumatic shock was also reported by Kovach *et al.* (36). This acetylcholine activity was inhibited by the administration of atropine *in vitro*.

The electrographic, behavioral and neurologic signs of head trauma were blocked by the parenteral administration of 0.5–1.0 mg/kg atropine, as were similar clinical changes occurring after the intracisternal addition of acetylcholine (6). Ward applied these observations to the treatment of closed head injuries. In 20 patients with varying degrees of trauma, he administered atropine subcutaneously in doses of 0.1 mg/kg, noting clinical improvement in some and a reversal of the electrographic effects in others (67). The same changes in the post-traumatic electroencephalogram were reported by Jenkner and Lechner in a study of diethazine, another anticholinergic drug. A single intravenous dose in 40 patients resulted in normalizing the abnormal electroencephalogram in 22 and marked improvement in six others (33).

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Similarly, in experiments of post-traumatic shock and cerebral edema in animals, Denisenko (13) reported a blocking of the clinical changes by such anticholinergic compounds as methylbenactyzine and adiphenine (Trasentin).

Thus, the amount of free acetylcholine may increase in the spinal fluid following craniocerebral trauma and the amount of free acetylcholine, the degree and type of electroencephalographic abnormality, and changes in clinical behavior appear as interrelated phenomena, which may be reduced by the administration of anticholinergic drugs.

BRAIN ACETYLCHOLINE AND ANTICHOLINERGIC DRUGS

The effects of the direct application of acetylcholine to the central nervous system may also be blocked by anticholinergic drugs. The administration of the cholinesterase inhibitor di-isopropyl fluorophysphate (DFP) elicited high amplitude rapid frequency EEG patterns similar to status epilepticus and some post-traumatic states (24, 31, 32, 68). These EEG effects were blocked by small doses of parenteral atropine and scopolamine. The great increase in acetylcholine after tetraethyl pyrophosphate (TEPP) was measured and related to the toxic effects and the induced convulsions (29, 59).

Chatfield and Dempsey (9) prepared exposed animal cortex with prostigmine and evoked electroencephalographic spike activity. The prior administration of atropine blocked the appearance of spiking, or if present, this electrical activity could be eliminated by atropine.

In contrast to these findings, Brenner and Merritt (7) applied topical acetylcholine in concentrations of two and one-half to ten per cent to the exposed cortex of cats and noted no effect on the electroencephalographic changes after intravenous atropine (one mg/kg). The concentrations of acetylcholine in these experiments, however, were higher than the topical applications (one to four gamma/100 cc) and the intracisternal (0.2–10 gamma/100 cc) injections of Bornstein (6). Brenner and Merritt (7) also noted electroencephalographic effects similar to acetylcholine after methacholine (Mecholyl) and carbamylcholine (Doryl) in concentrations much lower than the acetylcholine concentrations. They ascribed the increased effectiveness of these cholinergic drugs to their lack of sensitivity to cerebral cholinesterases.

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CEREBROSPINAL FLUID ACETYLCHOLINE AND SEIZURES

One view of acetylcholine metabolism finds it in nervous tissues in an inactive and bound form. During periods of activity, acetylcholine is liberated at the cell membrane where it is rapidly deactivated by cholinesterases. The amount of bound acetylcholine is the resultant of the continuous processes of synthesis, liberation and breakdown (15). It has been postulated that the level rises during sleep and falls during waking activity (16, 29, 45, 60).

Tobias *et al.* (60) reported increased free and total acetylcholine after chloroform and pentobarbital anesthesia in rat and frog brain but no changes after strychnine or pictrotoxin convulsions. Richter and Crossland (45) measured the level of acetylcholine (microgamma per mg brain tissue) during anesthesia and sleep in rat brain to be 300 per cent higher than post-seizure levels. The difference in tissue levels is transient, however, as the resynthesis rate for acetylcholine in rat brain is high (seven gamma/gm/minute). These observations were confirmed by Elliott *et al.* (16) and Crossland and Merrick (11). Giarman and Pepeu reported the increase in acetylcholine following various depressants to be roughly proportional to the degree of depression of the central nervous system and the reduction in motor activity (29). Maynert and Buck, however, studying brain acetylcholine levels during sedation concluded that some sedatives were associated with elevated brain acetylcholine but that no rigorous relationships existed (39). In part, this may be related to the earlier observations of McLennan and Elliott (40) that acetylcholine synthesis measured in rat brain slices is accelerated by low dosages of narcotic drugs, but inhibited by high dosages.

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Free acetylcholine was reported in the spinal fluid in patients with epilepsy (10, 63). Of 56 epileptic patients, 44 demonstrated free acetylcholine in quantities of 0.02 to 5.0 gamma/100 cc with an average of 1.0 gamma/100 cc. Acetylcholine levels were related to the frequency of seizures, the extent of electoencephalographic abnormality, and to the time since the last seizure, but bore no relation to medication, type of epilepsy or level of cholinesterase activity. Elliott *et al.* (16) also noted free acetylcholine in the spinal fluid in concentrations up to three gamma/100 cc after pentylenetetrazol (Metrazol) convulsions.

Tower and McEachern (63) viewed the increased acetylcholine as a by-product of the seizure and not causal. Studying the hypothesis that seizures were induced by the accumulation of acetylcholine, Torda (61, 62) measured the level of acetylcholine in brain tissue after pentylenetetrazol convulsions. She noted a rise in the acetylcholine content of brain before and a fall during the convulsion. Below certain levels of acetylcholine, convulsions failed to occur. She suggested that the fall in tissue acetylcholine during a convulsion was due to the inhibition of acetylcholine synthesis by increased concentrations of metabolites such as ammonium ions.

Giarman and Pepeu also measured changes in central nervous system acetylcholine following various stimulants (29). Only after methacholine and 3,5-dimethylbutylethyl-barbiturate was there a significant change in the acetylcholine level. They noted a decrease in association with induced convulsions. With other drugs which they classified as stimulants (LSD, iproniazid, iproniazid plus hydroxytryptophan, and iproniazid plus DOPA) there were no changes in the acetylcholine level. They concluded that despite intense excitation produced by these compounds, there were no changes in acetylcholine levels unless these were accompanied by convulsions. (The differences in observations between these observers and Cone *et al.* (10) and Tower and McEachern ( ) may be related to the differences in methods of biochemical measurements, for the latter measured changes reflecting free acetylcholine only, while Giarman and Pepeu ( ) measured total acetylcholine including bound and free forms of acetylcholine (40).

These studies suggest that spontaneous or induced seizures are accompanied by an increase in intercellular free acetyl choline liberated from its bound form which may be reflected in the spinal fluid. Cerebral activity and seizures enhance acetylcholine destruction, lowering tissue levels of acetylcholine, while sleep and anesthesia augment acetylcholine production increasing tissue levels.

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CENTRAL NERVOUS SYSTEM CHOLINESTERASES

Tower and McEachern (63, 64, 65) also measured spinal fluid cholinesterase activity. By reporting cholinesterase activity as a ratio of the rate of hydrolysis with two substrates compared to an acetylcholine substrate, acetylcholinesterase/acetylcholine and butyrylcholinesterase/acetylcholine ratios are derived. Normal cerebrospinal fluid contains these esterases in the ratio of 33:17.

In patients with head trauma, Tower and McEachern reported an inversion of the cholinesterases with an increase in the butyrylcholinesterase of the spinal fluid and a decrease in acetylcholinesterase activity. The extent of the cholinesterase reversal was related to the severity of trauma and to the degree of EEG abnormality. A similar reversal was observed in patients undergoing convulsive therapy.

In patients with elevated spinal fluid acetylcholine after spontaneous seizures, however, no change in the ratio of cholinesterases or total cholinesterase activity was found.

Changes in cholinesterase activity may be related to changes in cell membrane permeability. Acetylcholinesterase is found in highest concentration in the central nervous system while butyrylcholinesterase predominates in other tissues, especially blood serum. With increased cerebral acetylcholine, vasodilation and increased cellular permeability may be predicted, with vascular fluid transudation varying with the extent and duration of the vasodilation (35). Spiegel, Spiegel-Adolf and their coworkers (54–58) demonstrated such permeability changes and increased conductivity of the tissues associated with the appearance of various ions (as potassium and phosphate) in the spinal fluid following electrically induced convulsions. Such non-electrolytes as nucleic-acid splitting enzymes also increased. Changes in cellular permeability may be the basis for the high

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concentrations of acetylcholine and increased concentrations of butyrylcholinesterase after induced seizures or head trauma (65).

That changes in cholinesterases may be large and measurable is suggested by the recent demonstrations that neural stimulation and learning produces changes in brain weight and acetylcholinesterase activity (37, 49). Following these reports, Pryor and Otis (43) studied the effects of repeated induced seizures in Wistar rats. After as little as four weeks, they observed increases in brain weight and in acetylcholinesterase activity which was related to decrements in behavioral performance.

The persistance of acetylcholine in spinal fluid after head trauma and after seizures despite increased cholinesterase activity may be related to the sensitivity of the acetylcholine-acetylcholinesterase system to concentration relationships (8, 41, 65). At "physiologic" concentrations, hydrolysis of acetylcholine is rapid (three to four microseconds) but at higher and lower concentrations, the activity falls off quickly. In contrast, the butyrylcholinesterase-acetylcholine relationship is non-specific, and the rate of hydrolysis increases with increased concentration.

These relationships relate to theories of the induction of seizures. While the usual concentrations of acetylcholine at cell membranes are destroyed by the specific activity of acetylcholinesterase in a few microseconds, an excessive concentration following excitation may exceed its rate of hydrolysis. The seizure threshold may be reached and a seizure induced, with the seizure itself adding to the amount of free acetylcholine. Increased acetylcholine affects vascular and cellular permeability altering the concentrations of various ions, including butyrylcholinesterase in tissues and in the cerebrospinal fluid. Through the activity of this esterase, though of low efficiency and depending on concentration kinetics, acetylcholine is reduced in tissues to levels for the more direct action of acetylcholinesterase.

Cholinesterases appears in the spinal fluid as a reflection of their increase in intercellular fluids resulting from changes in cell membrane permeability accompanying increased acetylcholine.

EEG HYPERSYNCHRONY AND INDUCED CONVULSIONS

The significance of high voltage EEG slow wave activity for the convulsive therapy process has been repeatedly described (22, 23, 50, 51). In the usual course of convulsive therapy, inter-treatment electroencephalograms record progressive increases in amplitude and in theta activity and a reduction in beta activity. As treatment continues, delta activity

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The early appearance of high degree hypersynchrony and its persistence throughout a treatment course has been found to be prerequisite to improvement. Both the electrographic and the behavioral changes of induced convulsions are transiently reversed by the acute administration of experimental anticholinergic compounds (19, 20). The intravenous injection of diethazine, benactyzine, the piperidylbenzilates JB–318, JB–336 and JB–329 (Ditran), and WIN–2299 induced EEG desynchronization in psychiatric subjects. These EEG changes were associated with behavioral alerting, anxiety, tremors, illusions and hallucinations. In patients who had recently received electroconvulsive therapy there was a reduction in slow wave activity and a reversal of euphoria, denial and confusion. Atropine, in low doses, was also associated with EEG desynchronization accompanied by tachycardia, nervousness and tension. At higher dosages, hypersynchronous slow waves followed by lower voltage, poorly organized delta activity with superimposed beta activity was accompanied by progressive confusion and disorientation.

The effect of anticholinergic drugs on the slow wave activity of convulsive therapy was also assessed by the chronic administration of atropine (five mgm per day) and scopolamine (one to three mg) during the weeks of treatment. The amount of EEG slowing was significantly less than in a control group (66). The samples were too small for a clinical correlation but the data is consistent with blocking of the clinical effects of electroconvulsive therapy.

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Marked improvement was reported in two of seven atropine-treated, none of five scopolamine-treated and in four of the six controls receiving unmodified ECT. This study was not replicated by the authors who suggest that dosage factors or population changes may have contributed to the different results in a second study (34).

As in cerebral trauma, the electrographic changes of induced convulsions may be modified by the administration of anticholinergic drugs suggesting that increased amounts of acetylcholine or increased cholinergic receptivity is associated with the high voltage slow wave activity.

ACETYLCHOLINE AND INDUCED CONVULSIONS

Despite a constant application of treatments, however, there is great variability in the time of appearance, the duration, amount, and sensitivity to modification by alerting, hyperventilation and barbiturates of the electrographic slow wave activity in psychiatric populations (30). These differences relate to differences in central cholinergic activity. The failure of certain patients to develop hypersynchrony may be associated with the absence of free acetylcholine and with minimal changes in cerebral function, thus precluding a clinical response to induced convulsions. Tower and McEachern (63), in their study of craniocerebral trauma, included observations of six psychiatric patients undergoing convulsive therapy. Studying the patients after three to seven treatments they reported free spinal fluid acetylcholine in two patients, and an increase in butyrylcholinesterase and a decrease in acetylcholinesterase with a reversal of the ratio of cholinesterases in five of the six patients. Only one patient in the series failed to show either free acetylcholine or a cholinesterase ratio reversal in the spinal fluid. They concluded that the spinal fluid changes in induced convulsions were more like those of craniocerebral trauma than those of spontaneous epilepsy.

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Other evidence of alterations in the permeability barrier may be seen in the demonstrations of an increased concentration of cocaine in brain tissues three days after a series of 12 induced convulsions (1). The change in concentration of this large molecule, ordinarily absent in brain tissue, was associated with the appearance of hypersynchrony (delta bursts) in the electroencephalogram.

From these observations we would conclude that induced convulsions, like craniocerebral trauma and spontaneous seizures, are associated with an increase in free acetylcholine in intercellular fluids, altering cerebral permeability and enhancing the

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From these observations we would conclude that induced convulsions, like craniocerebral trauma and spontaneous seizures, are associated with an increase in free acetylcholine in intercellular fluids, altering cerebral permeability and enhancing the appearance of cholinesterases. The level of free acetylcholine is maintained by repeated induced seizures. EEG hypersynchrony is one reflection of altered levels of acetylcholine and the altered permeability of electrolytes and other substances, including cholinesterases. The changes in intercellular electrolytes, including acetylcholine, provide the biochemical substrate for the persistent behavioral changes and EEG hypersynchrony following induced convulsions.

An application of these conclusions is seen in the studies of the prediction of the convulsive therapy response and the classification of psychoses.

CHOLINESTERASES AND THE CLASSIFICATION OF PSYCHOSES

Funkenstein *et al.* (25–27) reported a relationship between the blood pressure response to methacholine and the clinical response to convulsive therapy. Immediately after the injection of methacholine the blood pressure falls, usually returning to the baseline within five to 20 minutes. A return within five minutes places the patients in Groups I, II or III; while a return after 20 minutes place the patients in Groups VI and VII. Group I and Group I–III have a nine per cent and a 35 per cent recovery rate, respectively, while Group VI and Group VII subjects have 89 per cent and 97 per cent recovery rates to induced convulsions (27). Group I, II and III reactors may be looked upon as patients in whom methacholine is rapidly hydrolyzed; while Groups VI and VII have a slow hydrolysis rate. (The response to injected epinephrine was suggested as a second criteria in the classification, but is of limited discriminating value [48].) While we have no biochemical explanation for the differences in the metabolism of methacholine in these psychiatric groups, it is possible that the blood and tissue cholinesterase activity levels of Groups I–III is high while that of Groups VI–VII is low compared to general psychiatric populations.

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The differences in blood cholinesterase levels in normal and mentally ill subjects have been extensively studied. Despite differences in methods (4, 5), elevated cholinesterase levels compared to normal populations have been reported for depressive subjects (44, 46, 47, 52), schizophrenic subjects (14, 28, 53) and a mixed psychiatric populations (42). Alpern reported lowered cholinesterase levels in schizophrenic subjects (2). While these studies appear inconclusive, they provide data that the variations in blood cholinesterase levels are generally greater and frequently elevated in the mentally ill. Negative reports include the failure by Ellman and Callaway (17) to confirm Rubin's study; and Altchule's review of the data suggesting no abnormality of cholinesterase levels in the mentally ill (3).

These studies suggest that cholinergic measures may play a significant role in the therapeutic response to convulsive therapy and in the pathogenesis of psychoses.

CONCLUSION

This review summarizes some of the available data suggesting that cholinergic mechanisms may be central to the convulsive therapy process. Induced convulsions are associated with cerebral vasodilation and increased cellular permeability, followed by the appearance of increased amounts of enzymes and electrolytes in intercellular and cerebrospinal fluids. The increase in acetylcholine, vasodilation and increased permeability appear as interrelated phenomena associated with trauma, seizures and induced convulsions.

These biochemical changes accompany increased electrical hypersynchrony which is recorded as EEG slow wave activity in scalp electrodes and which can be modified by the acute and chronic administration of anticholinergic drugs as atropine, benactyzine, diethazine, procyclidine and various piperidyl-benzilates.

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In these regards, induced convulsions are more similar to cerebral trauma than to spontaneous seizures.

The changes in cerebral biochemistry alter cellular activity sufficiently to affect consciousness and the behavior of subjects. Failure to induce persistent biochemical changes, including the concentration of acetylcholine, results in failure to produce behavioral change.

There is, as yet, no consistent evidence for differences in the sensitivity or dependence of populations on cholinergic mechanisms. Differences in the rate of development of cerebral changes to the same number and frequency of induced convulsions and classifications of the mentally ill based on the blood pressure response to methacholine suggest, however, that such differences may be significant in the pathogenesis of different psychoses.

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