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# Inhalant-Induced Convulsions

## *Significance for the Theory of the Convulsive Therapy Process*

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Despite many years of investigation of the convulsive therapy process, there is still much controversy concerning the importance of the seizure itself. Most studies have concluded that the convulsion is a necessary index of cerebral change essential to clinical behavioral change.[9,10,15,33,39] Some investigators, nevertheless, have assigned significance not to the seizure but to such factors as the psychological meaning of the treatment to the patient, feelings of fear, and the repeated loss of consciousness.[3,4,28]

The early studies of Kalinowsky et al.[24] and Pacella et al.,[30] demonstrating both clinical and electrographic differences between grand mal and petit mal treatments indicated the significant role of the seizure. The various studies comparing convulsive with subconvulsive treatment demonstrated that techniques culminating in a convulsion were uniformly associated with measurable degrees of neurophysiologic and behavioral change, while subconvulsive techniques were not.[15,27,38-40] In recent studies from this laboratory, similar differences in the 2 treatment types were observed for such aspects of behavior as EEG slow-wave activity,[8,10] language changes after amobarbital,[19-21] and perceptual tasks.[13,22,25]

A second aspect to the problem of understanding convulsive therapy concerns the relation of the method of inducing the seizure to the therapeutic outcome. Seizure duration, type of current, and electrode placement are among the variables that have

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been studied. While the investigations indicate that changes in behavioral and neurophysiologic indices are related to these parameters, the differences reported for the various seizure-producing methods are small and statistically insignificant. Major differences, however, are observed between seizure and nonseizure groups. For example, in a recent monograph, Ottosson reported an increase in the duration of unmodified electrically induced seizures compared with those modified by premedication with lidocaine.[29] Although the lidocaine-treated patients showed less change in indices of anxiety, retardation, and global behavior than patients treated with unmodified seizures, the differences were not significant. In our studies, while seizure duration [17] and type of current [11] have been related to the degree of behavioral and neurophysiologic change, there were no differences with relation to therapeutic outcome. Thus, while parameters of the seizure method may bear some relation to therapeutic efficacy, the differences are slight among the techniques, provided that grand mal seizures have been induced.

Further exploration of the importance of the seizure was made possible by recent experimental interest in seizures induced by inhalant (hexafluorodiethyl ether, Indoklon,[7]), and intravenous (PM-1090 [6]) agents. This study was undertaken to compare the electrical and inhalant seizure-producing methods with regard to effects on clinical behavior, interseizure electroencephalogram, and psychologic test performance in order to clarify the role of the mode of seizure induction in the convulsive therapy process.

In a voluntary psychiatric hospital 27 consecutive unselected patients referred for convulsive therapy were randomly divided into 2 groups using a Gellerman order.[16] In 12 patients, convulsions were induced by a Medcraft alternating current instrument using suprathreshold currents, and in 15 others by inhalation of hexafluorodiethyl ether, following the method of Esquibel et al.[7] Premedication in all cases was limited to sublingual atropine (1.0 mg.). Treatments were administered 3 times per week for 10 to 24 applications, the total number being determined by the clinical judgment of the staff psychiatrist.

Ages ranged from 19 to 58, with a mean age of 38.5 years in the electric convulsive therapy (ECT) group; and 19 to 49, with a mean age of 35.5 years in the hexafluorodiethyl ether group. The mean years of education were 11.5 years (ECT) and 12.6 years (hexafluorodiethyl ether). Of the 27 subjects, 12 were classified as depressive psychoses, 8 as schizophrenia, mixed type, and 7 as schizophrenia, paranoid type. The distribution of diagnoses, age range and years of education within the 2 samples, did not differ significantly.

Behavioral change was evaluated weekly in interviews by the patient's therapist and by the staff psychiatrist. Such aspects as mood, ideation, memory, sleep, appetite, speech patterns, participation in group activities, and relation to staff and to other patients were recorded and changes assessed qualitatively.

Electroencephalograms were done prior to treatment, weekly during the treatment course on a day after a convulsion, and 2 weeks after the last treatment. Records were measured for the amount of induced slowing (6 cps and slower) in anterior temporal-vertex leads, in 66 second samples.[8]

Various psychologic procedures were administered prior to treatment, during the fourth week (10-12 treatment period), and 2 weeks after the last treatment. The measures included Wechsler-Bellevue subtests (information, digit span, object assembly, and digit symbol); Gottschaldt type embedded geometric figures [22]; perceptions of pseudoisochromatic embedded colored figures at high-speed tachistoscopic exposure,[31] and a modified California F Scale.[23]

In addition, spine x-ray studies were done prior to and at the end of the treatment course.

## Observations

1. *Clinical Behavior.*—The inhalation of hexafluorodiethyl ether regularly resulted in a grand mal convulsion, similar to that induced electrically. For the hexafluorodiethyl ether group, induction was slower and the initial cry and opisthotonic posturing were often omitted. In clonic and tonic manifestations, postseizure apnea, and postseizure behavior, the groups resembled each other closely.

In short term evaluations of clinical behavioral change, the types of behavior manifested were similar in the two groups. Patterns of denial, hypomania, withdrawal, somatization, paranoid excitement, and confusional-memory loss were observed in both

TABLE 1.—*Behavioral Patterns*

| | No. of Subjects | |
|---|---|---|
| | Indoklon * | ETC |
| Euphoria, denial, hypomania | 6 | 7 |
| Somatization, withdrawal | 6 | 2 |
| Severe confusion, memory loss | 3 | 3 |

* Hexafluorodiethyl ether.

TABLE 2.—*Discharge Evaluations*

| | Recovered Much Improved | Improved | Unimproved |
|---|---|---|---|
| Indoklon | 7 | 5 | 3 |
| ECT | 6 | 5 | 1 |

$\chi^2 < 1.0$, not significant.

populations with approximately equal frequency (Table 1).

Complication rates were similar. While patients tolerated the inhalation procedure, there were frequent episodes of breath holding and leakage about the mask, making this induction less reliable. Fractures were observed radiographically in 3 patients treated with hexafluorodiethyl ether and in 3 during ECT.

Administrative evaluations of clinical improvement at the time of discharge from the hospital were equivalent (Table 2). Ratings of recovered and much improved were recorded for approximately half of each group.

2. *Electroencephalography.*—Interseizure serial electroencephalograms, both qualitatively and quantitatively were similar in the 2 groups. Progressive symmetric slowing of dominant frequencies and an increase in voltages were apparent in all leads, with frontal and anterior-temporal preponderance. Burst and occasional spike formations were noted in both. Quantitative measures of induced slow-wave activity during each week of treatment were not significantly different (Table 3), although the maximum EEG change appeared earlier in the hexafluorodiethyl ether group than in the ECT group.

3. *Psychologic Measures.*—Intergroup analyses (Mann Whitney U Test) of the observations for each of the psychological tasks revealed no difference prior to treatment, during the fourth week, and 2 weeks after treatment for the 2 treatment groups. Intragroup analyses, however, showed consistent changes in various measures from pretreatment to the fourth week; and from the fourth week to 2 weeks after treatment (Table 4), both in the hexafluorodiethyl ether and in the ECT groups.

In the Wechsler-Bellevue subtests, group means showed a significant decrease in scores (poorer performance) for each subtest during treatment, and a return to pretreatment levels in the post-treatment period. One subtest, object assembly, demonstrated significantly increased scores after treatment.

Similar patterns were observed for the tachistoscopic measures and the F scores. While increased errors on the embedded figure tests were observed during treatment, the difference was not significant. After treatment, the errors in this test decreased significantly from pretreatment scores. On the F scale there was an increase in scores with treatment, and a decrease following treatment. For each of these measures, both treatment groups reflected a similar pattern of change.

TABLE 3.—*Postconvulsive EEG Slow-Wave Activity (Average % Time)*

| | No. | Pretreatment | 4-6 Rx | 7-9 Rx | 10-12 Rx | 2 Wk. After Last Treatment |
|---|---|---|---|---|---|---|
| Indoklon | 15 | 6.0 | 29.4 | 50.3 | 51.2 | 16.8 |
| ECT | 12 | 4.0 | 29.8 | 39.2 | 47.5 | 18.0 |

TABLE 4.—*Effect of Hexafluorodiethyl Ether and Electrically Induced Seizures on Psychologic Test Performances*
(Scores Expressed as Mean Differences)

| | | Pretreatment and Fourth Week | Pretreatment and Post-Treatment | Fourth Week and Post-Treatment |
|---|---|---|---|---|
| 1. Wechsler-Bellevue (weighted subtest score) | | | | |
| (*a*) Information | Ind | −1.3 * | +0.2 | +1.5 † |
| | ECT | −2.4 † | −0.7 | +1.7 † |
| (*b*) Digit span | Ind | −1.9 * | +0.8 | +2.7 † |
| | ECT | −2.7 * | −0.4 | +2.3 ‡ |
| (*c*) Object assembly | Ind | −1.4 | +2.7 * | +4.1 * |
| | ECT | −1.3 | +3.5 † | +4.8 ‡ |
| (*d*) Digit symbol | Ind | −2.5 † | +0.8 | +3.3 ‡ |
| | ECT | −2.4 ‡ | −0.1 | +2.3 ‡ |
| 2. Tachistoscopy (errors) | Ind | +9.7 * | −6.5 | −16.2 ‡ |
| | ECT | +8.2 * | −4.9 | −13.1 ‡ |
| 3. Embedded figures (errors) | Ind | +2.0 | −2.1 | −4.1 ‡ |
| | ECT | +3.3 | −2.6 * | −5.9 ‡ |
| 4. F scale | Ind | +7.7 † | −3.9 | −11.6 ‡ |
| | ECT | +5.2 † | +1.2 | −4.0 † |

Ind = Indoklon (hexafluorodiethyl ether).
Using Wilcoxon's T for paired replicates: * $p < 0.02$ † $p < 0.05$. ‡ $p < 0.01$.

4. *Test Performance: EEG Correlations.* The changes in performance on the psychologic tasks from the pretreatment to the fourth week testing period were significantly related to the degree of induced EEG slow-wave activity for both groups (Table 5). Rank order correlations demonstrated that decrements in performance on the Wechsler-Bellevue digit span and object assembly subtests, tachistoscopy, and embedded figures tasks were significantly related to the amount of electrographic change. Similarly, an increase in F score was associated with increased EEG slowing.

When the observations in the hexafluorodiethyl ether and ECT groups were individually analyzed, significant correlations were noted for various tasks. In the hexafluorodiethyl ether group, the decrement in the Wechsler-Bellevue information and digit span subtests and in tachistoscopy was related to the degree of EEG slowing. In the ECT group, similar relations were noted for tachistoscopy, Wechsler-Bellevue digit span, and object assembly subtests and the F score.

## Comment

1. *Mode of Induction.*—The inhalant and the electrically induced seizure groups were indistinguishable on the various measures of behavior at each stage of the treatment process. Since the factor common to both treatments was the induction of seizures and not the method of induction, we may conclude that the method of induction is not a significant variable in the therapy process. Specifically, changes in the be-

TABLE 5.—*Change in Task Performance and Degree of EEG Slow-Wave Activity*
(Pretreatment *vs.* Fourth Week; Rank Order Correlations)

| | Wechsler-Bellevue Form 1 | | | | | | |
|---|---|---|---|---|---|---|---|
| | Information | Digit Span | Object Assembly | Digit Symbol | Tachistoscopy | Embedded Figures | F Scale |
| Indoklon | 0.73 * | 0.54 † | 0.31 | 0.38 | 0.62 † | 0.13 | 0.12 |
| ECT | 0.28 | 0.72 † | 0.60 † | 0.34 | 0.80 * | 0.37 | 0.66 † |
| Indoklon and ECT | 0.25 | 0.61 * | 0.46 † | 0.31 | 0.67 * | 0.43 † | 0.38 † |

* $p < 0.01$
† $p < 0.05$

havioral and neurophysiologic indices are dependent upon the induction of seizures, and not dependent on any single property of the electrical or the inhalant mode of induction.

Kurland et al.[26] and Chatrian and Petersen[5] have also compared electrical and inhalant seizures. Kurland and his co-workers assigned convulsive therapy referrals alternately to hexafluorodiethyl ether and ECT groups. They reported that behavioral ratings, complication rates, psychologic test performances, and cardiovascular reactions were similar in the 2 samples. Chatrian and Petersen, studying schizophrenic subjects with implanted intracerebral electrodes, reported identical electrographic patterns during seizures and at various postseizure periods for hexafluorodiethyl ether, pentylenetetrazol (Metrazol), and electrical techniques.

In studies of seizures induced by various electrical means, equivalent behavioral, psychologic, and electrographic effects have been reported.[3,11,29,39] While these studies equate the effects of different convulsive techniques, various nonconvulsive methods such as subconvulsive, brief stimulus, unidirectional stimulating, monopolar stimulating, and focal "convulsive" techniques have been described, and each in turn discarded in routine therapy as ineffective.[10,27,39,40] For example, Bergman,[2] in describing the electrographic effects of the "focal-seizure" technique noted that 75% of patients had normal records after 15 such applications, while 70% had "abnormal" records after grand mal seizures. Ulett et al.[39] have reported differences in the improvement rates of patients receiving convulsive treatments (60%-80%) and those receiving subconvulsive (33%), or controls (38%). Our own studies[10] also demonstrate significantly greater degrees of behavioral and physiologic change for convulsive than for subconvulsive treatments.

A number of investigators, however, have failed to observe differences in improvement rates for patients treated by convulsive and subconvulsive means.[3,4,28] We would consider these results as reflecting differences both in population samples and in methods of scoring behavioral change. While acute illness and affective-depressive reactions are described for the majority of subjects in the positive studies,[10,27,38] 70% of the subjects in one negative[4] and 100% in another[28] were classed as having schizophrenic reactions. The facilities in these investigations serve chronically ill populations, and prior courses of convulsive therapy were recorded for nearly half the subjects in one group[4] and 90% in the other.[28] The failure to obtain significant differences may also lie in the small samples used to test the null hypothesis.

Changes in behavior are observed in all subjects receiving a course of convulsive therapy,[10,29,30,33,38] but those changes evaluated as clinical improvement occur only in some. While induced convulsions are a sufficient condition for behavioral change, they are only a necessary condition for improvement. Thus, measures of behavioral change, such as memory,[25] language,[19,21] and perception[13,22] readily demonstrate significant differences between convulsive and subconvulsive techniques within the individual differences in personality organization of the subjects. Ratings of "improvement," however, vary with the personality organization of the subject as expressed in adaptive patterns and flexibility for change; with such environmental variables as therapist, staff, and family expectations and tolerance for the elicited adaptive behavior, and with the duration and degree of induced neurophysiologic changes. In global estimates of "improvement" the environmental variables become prepotent. The failure to observe significant differences in improvement ratings in convulsive and nonconvulsive groups may be related as much to these environmental variables and the personality characteristics of the subjects as to the induced physiologic changes.

2. *Significance of the Convulsion.*—The evidence indicates that convulsions are, or reflect, the significant physiologic events which are basic for the therapeutic efficacy

of convulsive therapies. The specific role of the seizure is, however, not clear. That neither the motor aspects of the seizure nor the accompanying psychologic factors are determining variables is demonstrated by the efficacy of treatments under conditions of muscle paralysis and anesthesia.[32] That the loss of consciousness, itself, is not the significant variable is seen in the relative inefficacy of repeated administrations of thiopental (Pentothal) or nonconvulsive techniques under thiopental.[10,27,39] Although the means by which various agents achieve such changes are not specified, it is probable that the seizure is but one expression of a diffuse alteration in cerebral functioning.[9,12] It is this alteration in brain function which provides the necessary conditions for the behavioral changes of convulsive therapy.[14,20,40] Among the behavioral changes we would include the immediate alteration in consciousness, recall, motor patterns, and breathing; and the more persistent psychologic, perceptual, vegetative, physiologic, and hormonal patterns, characteristically described in convulsive therapy.

Alterations in brain function are reflected in neurochemical changes as the acetylcholine and cholinesterase,[37] transaminase,[36] and serotonin[34] content of the spinal fluid. They are also observed in such neurophysiologic measures as increased delta and theta activity[8] and decreased beta activity[18] in electroencephalograms, and in altered electrographic[33,35] and behavioral[20,21,40] responsivity to intravenous barbiturates and to anticholinergic and sympathomimetic agents.[9,12] The correlations between the degree of neurophysiologic change and changes in perceptual test performance reported here are a reflection of these central changes, as are the perceptual,[10,13,22] linguistic,[19,21] and clinical behavioral[10,20] changes described in earlier studies.

In a recent review[9] the significance of the acetylcholine-cholinesterase system in these neurochemical alterations was discussed. Observations with various anticholinergic agents and reports of similar patterns with antihistaminic and sympathomimetic agents indicate the necessity for a broadly based view of biochemical and brain function relations, with emphasis on synaptic models.[12] A suggestive mechanism for the prolonged alterations in brain function is seen in the blood-brain barrier studies of Aird,[1] who noted persistent changes in cerebrovascular permeability following induced convulsions. He related these to the seizure and not to the passage of electric currents, and suggested that these changes may be the enduring physiologic basis for the induced behavioral change.

Thus, we would conclude that the convulsion, per se, is not a necessary condition for behavioral change, but neurochemical change, of which the convulsion is the immediate reflection, is prerequisite. Indeed, were persistent neurochemical and neurophysiologic effects induced as readily by other means, "convulsive" methods would no longer be necessary. In this regard, the nonspecific nature of the convulsive therapy process has been repeatedly emphasized.[14,40]

## Summary and Conclusions

Consecutive patients referred for convulsive therapy were randomly assigned to treatment courses by an inhalant (hexafluorodiethyl ether, Indoklon) or electrical inducing agent.

There were no differences in the two groups on behavioral, electrographic, or psychological measures prior to, during, or 2 weeks after treatment. Hospital discharge ratings were equivalent. Intragroup test differences were noted on all measures in both groups during treatment. These differences were related to the degree of induced neurophysiologic change and the pattern of such changes were similar in both treatment methods.

It is concluded that the observed alterations in brain function are equivalent to seizures induced by inhalant or electrical means. The nonspecificity of convulsions induced by hexafluorodiethyl ether and the greater difficulty of administration are con-

sidered as deterrents to the continued clinical use of this treatment.

The mode of induction of seizures is an insignificant factor in the convulsive therapy process. Seizures are viewed as one index of the persistent neurochemical alterations which are requisite to the behavioral changes of convulsive therapy.

These observations are discussed within the framework of the neurophysiologic-adaptive model of the mode of action of somatic therapies in psychiatry.

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The significance of the method of inducing the seizure in electroconvulsive therapy was investigated by comparing an inhalant, hexafluorodiethylether (Indoklon), with the more conventional electrical inducing technique. Twenty-seven consecutive hospitalized psychiatric patients were divided into two randomly assigned treatment groups. Treatment was administered three times per week for 10 to 24 applications.

There was no difference in the two groups in behavioral, electroencephalographic or psychological measures prior to, during, or two weeks after treatment. Hospital discharge ratings of improvement were equivalent.

The mode of induction of seizure is an insignificant factor in the convulsive therapy process. The non-specificity of Indoklon-convulsions and the greater difficulty of administration are deterrents to the clinical use of this treatment.

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Despite many years of investigation of the convulsive therapy process, there is still much controversy concerning the importance of the seizure itself. Most studies have concluded that the convulsion is a necessary index of the cerebral change essential to clinical behavioral change (9,10,15,33,39). Some investigators, nevertheless, have assigned significance not to the seizure but to such factors as the psychological meaning of the treatment to the patient, feelings of fear, and the repeated loss of consciousness (3,4,28).

The early studies of Kalinowsky et al., (24) and Pacella et al. (30), demonstrating both clinical and electrographic differences between grand mal and petit mal treatments, indicated the significant role of the seizure. The various studies comparing convulsive with subconvulsive treatment demonstrated that techniques culminating in a convulsion were uniformly associated with measurable degrees of neurophysiologic and behavioral change, while subconvulsive techniques were not (15,27,28,39,40). In recent studies from this laboratory, similar differences in the two treatment types were observed for such aspects of behavior as EEG slow wave activity (8,10), language changes after amobarbital (19,20,21) and perceptual tasks (13,22,25).

A second aspect to the problem of understanding convulsive therapy concerns the relation of the method of inducing the seizure to the therapeutic outcome. Seizure duration, type of current and electrode placement are among the variables that have been studied. While the investigations indicate that changes in behavioral and neurophysiologic indices are related to these parameters, the differences reported for the various seizure producing methods are small, and statistically insignificant. Major differences, however, are observed between seizure and non-seizure groups. For example, in a recent monograph, Ottosson reported an increase in the duration of unmodified electrical induced seizures compared with those modified by premedication with lidocaine (29). Although the lidocaine treated patients showed less change in indices of anxiety, retardation and global behavior than patients treated with unmodified seizures, the differences were not significant. In our studies, while seizure duration (17) and type of current (11) have been related to the degree of behavioral and neurophysiologic change, there were no differences with relation to therapeutic outcome. Thus, while parameters of the seizure method may bear some relation to therapeutic efficacy, the differences are slight among the techniques, provided that grand mal seizures have been induced.

Further exploration of the importance of the seizure was made possible by recent experimental interest in seizures induced by inhalant (Indoklon, (7) ), and intravenous (PM-1090, (6) )

agents. This study was undertaken to compare the electrical and inhalant seizure producing methods with regard to effects on clinical behavior, inter-seizure electroencephalogram and psychologic test performance in order to clarify the role of the mode of seizure induction in the convulsive therapy process.

METHOD:

Twenty-seven consecutive unselected patients in a voluntary psychiatric hospital referred for convulsive therapy were randomly divided into two groups using a Gillerman order (16). In twleve patients, convulsions were induced by a Medcraft alternating current instrument using suprathreshold currents; and in fifteen others, by inhalation of hexafluoro-diethylether (Indoklon), following the method of Esquibel et al. (7). Premedication in all cases was limited to sublingual atropine (1.0 mg). Treatments were administered three times per week for 10 to 24 applications with the total number determined by the clinical judgement of the staff psychiatrist.

Ages ranged from 19 to 58, with a mean age of 38.5 years in the ECT group; and 19 to 49, with a mean age of 35.5 years in the Indoklon group. The mean years of education were 11.5 years (ECT) and 12.6 (Indoklon). Of the twenty-seven subjects, twelve were classified as depressive psychoses, eight as schizophrenia, mixed type, and seven as schizophrenia, paranoid type. The distribution of diagnoses, age range and years of education within the two samples, did not differ significantly.

Behavioral change was evaluated weekly in interviews by the patient's therapist and by the staff psychiatrist. Such aspects as mood, ideation, memory, sleep, appetite, speech patterns, participation in group activities, and relation to staff and to other patients were recorded and changes assessed qualitatively.

Electroencephalograms were done prior to treatment, weekly during the treatment course on a day after a convulsion, and two weeks after the last treatment. Records were measured for the amount of induced slowing ( 6 cps and slower) in anterior temporal-vertex leads, in 66 second samples (8).

Various psychologic procedures were adminstered prior to treatment, during the fourth week (10-12 treatment period), and two weeks after the last treatment. The measures included Wechsler-Bellevue subtests (information, digit span, object assembly and digit symbol); Gottschaldt type embedded geometric figures (22); perceptions of pseudoisochromatic embedded colored figures at high speed tachistoscopic exposure (31); and a modified California F Scale (23).

In addition, spine X-ray studies were done prior to and at the end of the treatment course.

OBSERVATIONS:

1. Clinical Behavior.

The inhalation of Indoklon regularly resulted in a grand mal convulsion, similar to that induced electrically. For the Indoklon group, induction was slower and the initial cry and opisthotonic posturing were often omitted. In clonic and tonic manifestations, post seizure apnea, and post seizure behavior, the groups resembled each other closely.

In short term evaluations of clinical behavioral change, the types of behavior manifested were similar in the two groups. Patterns of denial, hypomania, withdrawal, somatization, paranoid excitement and confusional-memory loss were observed in both populations with approximately equal frequency (Table I).

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TABLE I

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Complication rates were similar. While patients tolerated the inhalation procedure, there were frequent episodes of breath-holding and leakage about the mask, making this induction less reliable. Fractures were observed radiographically in three Indoklon treated patients and in three during ECT.

Administrative evaluations of clinical improvement at the time of discharge from the hospital were equivalent (Table 2). Ratings of recovered and much improved were recorded for approximately half of each group.

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TABLE 2

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2. Electroencephalography.

Interseizure serial electroencephalograms, both qualitatively and quantitatively, were similar in the two groups. Progressive symmetric slowing of dominant frequencies and an increase in voltages was apparent in all leads, with frontal and anterior-temporal preponderance. Burst and occasional spike formations were noted in both. Quantitative measures of induced slow wave activity during each week of treatment were not significantly different (Table 3), although the maximum EEG change appeared earlier in the Indoklon group than in the ECT group.

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TABLE 3

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3. Psychologic Measures.

Inter-group analyses (Mann Whitney U Test) of the observations for each of the psychological tasks revealed no difference prior to treatment, during the fourth week, and two weeks post-treatment for the two treatment groups. Intra-group analyses, however, showed consistent changes in various measures fron pre-treatment to the fourth week; and from the fourth week to two weeks after treatment (Table 4), both in the Indoklon and in the ECT groups.

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TABLE 4

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In the Wechsler-Bellevue subtests, group means showed a significant decrease in scores (poorer performance) for each subtest during treatment; and a return to pre-treatment levels in the post-treatment period. One subtest, object assembly, demonstrated significantly increased scores post-treatment.

Similar patterns were observed for the tachistoscopic measures and the F scores. While increased errors on the embedded figure tests were observed during treatment, the difference was not significant. Post-treatment, the errors in this test decreased significantly from pre-treatment scores. On the F scale there was an increase in scores with treatment, and a decrease following treatment. For each of these measures, both treatment groups reflected a similar pattern of change.

4. Test Performance - EEG Correlations.

The changes in performance on the psychologic tasks from the pre-treatment to the fourth week testing period were significantly related to the degree of induced EEG slow wave activity for both groups (Table 5). Rank order correlations demonstrated that decrements in performance on the Wechsler-Bellevue digit span and object assembly subtests, tachistoscopy and embedded figures tasks were significantly related to the amount of electrographic change. Similarly, an increase in F score was associated with increased EEG slowing.

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TABLE 5

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When the observations in the Indoklon and ECT groups were individually analyzed, significant correlations were noted for various tasks. In the Indoklon group, the decrement in the Wechsler-Bellevue information and digit span subtests and in tachistoscopy was related to the degree of EEG slowing. In the ECT group, similar relations were noted for tachistoscopy, Wechsler-Bellevue digit span and object assembly subtests and the *F* score.

DISCUSSION:

1. Mode of Induction.

The inhalant and the electrical induced seizure groups were indistinguishable on the various measures of behavior at each stage of the treatment process. Since the factor common to both treatments was the induction of seizures and not the method of induction, we may conclude that the method of induction is not a significant variable in the therapy process. Specifically, changes in the behavioral and neurophysiologic indices are dependent upon the induction of seizures, and not dependent on any single property of the electrical or the inhalant mode of induction.

Kurland et al. (26) and Chatrian and Petersen (5) have also compared electrical and inhalant seizures. Kurland and his co-workers assigned convulsive therapy referrals alternately to Indoklon and ECT treatment groups. They reported that behavioral ratings, complication rates, psychologic test performances and cardiovascular reactions were similar in the two samples. Chatrian and Petersen, studying schizophrenic subjects with implanted intracerebral electrodes, reported identical electrographic patterns during seizures and at various post-seizure periods for Indoklon, Metrazol and electrical techniques.

In studies of seizures induced by various electrical means, equivalent behavioral, psychologic and

electrographic effects have been reported (3,11,29,39). While these studies equate the effects of different convulsive techniques, various non-convulsive methods such as subconvulsive, brief stimulus, unidirectional stimulating, monopolar stimulating, and focal "convulsive" techniques have been described, and each in turn, discarded in routine therapy as ineffective (10,27,39,40). For example, Bergman (2), in describing the electrographic effects of the "focal-seizure" technique noted that 75% of patients had normal records after fifteen such applications, while 70% had "abnormal" records after grand mal seizures. Ulett et al. (39) have reported differences in the improvement rates of patients receiving convulsive treatments (60-80%) and those receiving subconvulsive (33%), or controls (38%). Our own studies (10) also demonstrate significantly greater degrees of behavioral and physiologic change for convulsive than subconvulsive treatments.

A number of investigators, however, have failed to observe differences in improvement rates for patients treated by convulsive and subconvulsive means (3,4,28). We would consider these results as reflecting differences both in population samples and in methods of scoring behavioral change. While acute illness and affective-depressive reactions are described for the majority of subjects in the positive studies (10,27,38) 70% of the subjects in one negative study (4) and 100% in another (28) were classed as schizophrenic reactions. The facilities in these investigations serve chronically ill

populations, and prior courses of convulsive therapy were recorded for nearly half the subjects in one group (4) and 90% in the other (28). The failure to obtain significant differences may also lie in the small samples used to test the null hypothesis.

Changes in behavior are observed in all subjects receiving a course of convulsive therapy (10,29,30,33,38), but those changes evaluated as clinical improvement, occur only in some. While induced convulsions are a sufficient condition for behavioral change, they are only a necessary condition for improvement. Thus, measures of behavioral change, such as memory (25), language (19,21) and perception (13,22) readily demonstrate significant differences between convulsive and subconvulsive techniques within the individual differences in personality organization of the subjects. Ratings of "improvement", however, vary with the personality organization of the subject as expressed in adaptive patterns and flexibility for change; with such environmental variables as therapist, staff and family expectations and tolerance for the elicited adaptive behavior; and the duration and degree of induced neurophysiologic changes. In global estimates of "improvement" the environmental variables become prepotent. The failure to observe significant differences in improvement ratings in convulsive and non-convulsive groups may be related as much to these environmental variables and the personality characteristics of the subjects, as to the induced physiologic changes.

2. Significance of the Convulsion.

The evidence indicates that convulsions are, or reflect, the significant physiologic events which are basic for the therapeutic efficacy of convulsive therapies. The specific role of the seizure is, however, not clear. That neither the motor aspects of the seizure nor the accompanying psychologic factors are determining variables is demonstrated by the efficacy of treatments under conditions of muscle paralysis and anesthesia (32). That the loss of consciousness, itself, is not the significant variable is seen in the relative inefficacy of repeated administrations of pentothal or non-convulsive techniques under pentothal (10,27,39). Without specifying the means by which various agents achieve such changes, it is probable that the seizure is but one expression of a diffuse alteration in cerebral functioning (9,12). It is this alteration in brain function which provides the necessary conditions for the behavioral changes of convulsive therapy (14,20,40). Among the behavioral changes we would include the immediate alteration in consciousness, recall, motor patterns, and breathing; and the more persistent psychologic, perceptual, vegetative, physiologic and hormonal patterns, characteristically described in convulsive therapy.

Alterations in brain function are reflected in neuro-chemical changes as the acetylcholine and cholinesterase (37), transaminase (36), and serotonin (34) content of the spinal fluid. They are also observed in such neurophysiologic measures as increased delta and theta activity (8) and

decreased beta activity (18) in electroencephalograms; and altered electrographic (33,35) and behavioral (20,21,40) responsivity to intravenous barbiturates and to anticholinergic and sympathomimetic agents (9,12). The correlations between the degree of neurophysiologic change and changes in perceptual test performance reported here are a reflection of these central changes, as are the perceptual (10,13,22) linguistic (19,21) and clinical behavioral (10,20) changes described in earlier studies.

In a recent review (9), the significance of the acetylcholine~~s~~cholinesterase system in these neurochemical alterations was discussed. Observations with various anticholinergic agents and reports of similar patterns with antihistaminic and sympathomimetic agents, indicates the necessity for a broadly based view of biochemical and brain function relations, with emphasis on synaptic models (12). A suggestive mechanism for the prolonged alterations in brain function is seen in the blood-brain barrier studies of Aird (1) who noted persistent changes in cerebrovascular permeability following induced convulsions. He related these to the seizure and not to the passage of electric currents, and suggested that these changes may be the enduring physiologic basis for the induced behavioral change.

Thus, we would conclude that the convulsion, <u>per se</u>, is not a necessary condition for behavioral change, but neurochemical change, of which the convulsion is the immediate reflection, is prerequisite. Indeed, were persistent neuro-

chemical and neurophysiologic effects induced as readily by other means, "convulsive" methods would no longer be necessary. In this regard, the non-specific nature of the convulsive therapy process has been repeatedly emphasized (14,40).

## SUMMARY AND CONCLUSIONS

Consecutive patients referred for convulsive therapy were randomly assigned to treatment courses by an inhalant (Indoklon) or electrical inducing agent.

There were no differences in the two groups on behavioral, electrographic or psychological measures prior to, during, or two weeks after treatment. Hospital discharge ratings were equivalent. Intra-group test differences were noted on all measures in both groups during treatment. These differences were related to the degree of induced neurophysiologic change and the pattern of such changes were similar in both treatment methods.

It is concluded that the observed alterations in brain function are equivalent with seizures induced by inhalant or electrical means. The non-specificity of Indoklon-convulsions and the greater difficulty of administration are considered as deterrants to the continued clinical use of this treatment.

The mode of induction of seizures is an insignificant factor in the convulsive therapy process. Seizures are viewed as one index of the persistent neurochemical alterations which are requisite to the behavioral changes of convulsive therapy.

These observations are discussed within the framework of the neurophysiologic-adaptive model of the mode of action of somatic therapies in psychiatry.

The cooperation of Smith Kline & French Laboratories in providing the hexafluorodiethylether (Indoklon) used in these studies is gratefully acknowledged.

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## TABLE I

### Behavioral Patterns

| | Number of Subjects | |
|---|---|---|
| | Indoklon | Electrical |
| Euphoria, denial, hypomania | 6 | 7 |
| Somatization, withdrawal | 6 | 2 |
| Severe confusion, memory loss | 3 | 3 |

## TABLE 2

## Discharge Evaluations

| | Recovered<br>Much Improved | Improved | Unimproved |
|---|---|---|---|
| Indoklon | 7 | 5 | 3 |
| Electrical | 6 | 5 | 1 |

$x^2 < 1.0$, not significant

## TABLE 3

**Post-Convulsive EEG Slow Wave Activity**

**(Average Per-cent Time)**

| | No. | Pre-Treatment | 4-6 Rx | 7-9 Rx | 10-12 Rx | Two Weeks After Last Treatment |
|---|---|---|---|---|---|---|
| Indoklon | 15 | 6.0 | 29.4 | 50.3 | 51.2 | 16.8 |
| Electrical | 12 | 4.0 | 29.8 | 39.2 | 47.5 | 18.0 |

## TABLE 4

### Effect of Indoklon and Electrically Induced Seizures on Psychologic Test Performances

### (Scores Expressed as Mean Differences)

| | | Pre-treatment and Fourth Week | Pre-treatment and Post-treatment | Fourth Week and Post-treatment |
|---|---|---|---|---|
| 1. Wechsler-Bellevue (Weighted Subtest Score) | | | | |
| a. Information | Ind | -1.3** | +0.2 | + 1.5* |
| | ECT | -2.4* | -0.7 | + 1.7* |
| b. Digit Span | Ind | -1.9** | +0.8 | + 2.7* |
| | ECT | -2.7** | -0.4 | + 2.3*** |
| c. Object Assembly | Ind | -1.4 | +2.7** | + 4.1** |
| | ECT | -1.3 | +3.5* | + 4.8*** |
| d. Digit Symbol | Ind | -2.5* | +0.8 | + 3.3*** |
| | ECT | -2.4*** | -0.1 | + 2.3*** |
| 2. Tachistoscopy (Errors) | Ind | +9.7** | -6.5 | -16.2*** |
| | ECT | +8.2** | -4.9 | -13.1*** |
| 3. Embedded Figures (Erroks) | Ind | +2.0 | -2.1 | - 4.1*** |
| | ECT | +3.3 | -2.6** | - 5.9*** |
| 4. F Scale | Ind | +7.7* | -3.9 | -11.6*** |
| | ECT | +5.2* | +1.2 | - 4.0* |

Using Wilcoxon's T for paired replicates

* $p < .05$
** $p < .02$
*** $p < .01$

TABLE 5

Change in Task Performance and Degree of EEG Slow Wave Activity

(Pre-Treatment vs. Fourth Week)

(Rank Order Correlations)

| | Wechsler-Bellevue Form 1 | | | | Tachistoscopy | Embedded Figures | F-Scale |
|---|---|---|---|---|---|---|---|
| | Information | Digit Span | Object Assembly | Digit Symbol | | | |
| Indoklon | .73** | .54* | .31 | .38 | .62* | .13 | .12 |
| Electrical | .28 | .72* | .60* | .34 | .80** | .37 | .66* |
| Indoklon and Electrical | .25 | .61** | .46* | .31 | .67** | .43* | .38* |

* $p < .05$

** $p < .01$