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ALTERATION OF BRAIN FUNCTION IN THERAPY

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The following summary of observations made at a 200-bed voluntary, nonprofit, open-ward psychiatric hospital during the past three years is presented as the basis for discussion. The major interest of our Research Service is an investigation of the mode of action of various somatic therapies, especially electroshock and drugs. The disciplines represented in the research unit are clinical and psychodynamic psychiatry, neuropsychology, and experimental and clinical psychology. The following data summarize various studies that have previously been reported only in part:

(1) High-dose reserpine for relief of anxiety: double-blind placebo study.

(2) Chlorpromazine-insulin coma study.

(3) Electroencephalographic effects of various drugs.

(4) Electroshock process: concurrent psychiatric, psychologic, and neurophysiologic observations.

Observations

Reserpine

In a placebo-controlled, double-blind study of oral and intramuscular reserpine, consecutive patients referred for drug therapy were rated for degree of manifest anxiety.[1] The patients with high degrees of anxiety received randomized three-week periods of reserpine therapy, divided into the following daily dosage periods: 10 mg. of reserpine (5 mg. oral, 5 mg. intramuscular), 5 mg. of reserpine (oral or intramuscular), or

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placebo. Drugs were administered daily. None of the observing therapists knew which sequence was being followed or the dosages administered.

Relief of anxiety symptoms related to drug dosage was seen in 20 per cent of the group. In 80 per cent no relief was noted, and of these, one-third exhibited severe depressive reactions which eventually responded to electroshock therapy. The high doses of reserpine administered resulted in significant clinical manifestations in every patient. The behavioral changes induced were directly related to the degree of concomitant physiologic disturbance.

It was the conclusion of this study that high-dosage reserpine therapy has limited usefulness in the relief of anxiety symptoms. The dangers of induced depressions were clearly manifest, and the uncomfortable nature of the side effects of drug administration has resulted in a limited application of this drug in this environment.

Chlorpromazine-insulin coma

During a fifteen-month period, all patients referred by the supervising psychiatrists at this hospital for insulin coma therapy were divided by random sampling into an experimental group and a control group.[2] The control group received classical insulin coma treatment, following the basic technique of Sakel. All patients received fifty comas, each of a duration of one hour or longer, at the physiologic level of Babinski reflex or absent lid reflex or deeper. The experimental group received chlorpromazine therapy in rapidly increasing dosages until toxicity had been induced. When toxic signs of rigidity, drooling, fixed facies, seizures, dermatitis, or marked weakness appeared, the dosage was gradually reduced until a maintenance level was obtained. Patients were sustained on this regime for a period of three to four months. In both groups, behavioral observations were made by investigators none of whom was the patient's therapist. Sixty patients were referred for treatment, resulting in two groups of 30 each.

The maintenance dosage of chlorpromazine was 300 to 2000 mg. daily. Initial dosages ranged from 1400 to 3600 mg. daily.

Chlorpromazine induced motor retardation in all subjects. Overactive, destructive behavior rapidly disappeared, and the patients were more tractable, less negativistic, and less violent. One-third of the patients were more sociable and less seclusive, and were noted to care for themselves in a more presentable fashion. In the instances where severe parkinsonism supervened, however, the patients were less able to care for themselves, became sloppy, and failed to dress.

Affective changes during chlorpromazine were varied. Four patients became increasingly agitated, tense, and tremulous, and either refused to continue on the drug regime or were induced to do so only with

difficulty. Such an affective storm appeared early in the therapy and persisted.

In 4 other cases, depressive symptoms were significantly relieved, with an increase in affective lability and responsivity. In 2 patients, depressive ideation increased and was associated with complaints of insomnia. The medication was continued, however, with eventual alleviation. In most patients mood changes were small.

Ideation was altered during the period of chlorpromazine therapy in 12 of the patients. Eight patients had a loss or a significant diminution of psychotic ideation. In 5, the hallucinatory and referential experiences were no longer reported even on inquiry, and in 3 others, delusional ideation was less prominent. In 1 patient, however, paranoid ideation became more prominent. This was associated with increasing anxiety and panic during drug administration, with resultant discontinuation of the drug regime.

The clinical effects of insulin coma therapy have been exhaustively reported, and the findings in this series are comparable to those previously published.

With regard to the evaluation of improvement, all 60 patients of this study have been discharged from the hospital. Table I lists patients according to the four-fold classification in use in the hospital at the discharge conference.

TABLE I

DISCHARGE RATINGS

	Chlorpromazine	*Insulin Coma*
Recovered	2	0
Much improved	4	5
Improved	17	15
Unimproved	7	10

Inherent in the design of this study were high doses of chlorpromazine, pushed until symptoms of toxicity appeared. In this context, therefore, all patients developed significant drug effects. In all, rigidity of extremities appeared, frequently accompanied by a decrease in facial expression, drooling, and festination. Untoward complications are listed in Table II.

Electroencephalograms were obtained in 20 of the chlorpromazine patients. On adequate doses, concomitant with a change in clinical behavior a moderate amount of low-voltage 4 to 7 cps delta and theta activity was observed. This activity was exaggerated by hyperventilation. In the 3 patients in whom seizures were induced, the delta activity was not significantly different from the remainder of the group. There was a

suggestive relationship between the degree of the induced slow-wave activity and the drug dosage.

TABLE II

COMPLICATIONS

	Chlorpromazine	*Insulin Coma*
Agitation and panic	4	3
Dermatitis, severe	3	–
Seizures	3	5
Refusal of further therapy	2	2
Hypotension	2	–
Secondary reaction, frequent	–	5
Prolonged coma (more than 6 hours)	–	3
Insulin resistance	–	1
Regression of behavior	2	3

It was the conclusion of this study that neither chlorpromazine in high doses nor insulin coma is a specific treatment for schizophrenia. It was noted that these treatments were devices to temporarily alter behavior that had been socially unacceptable. Since chlorpromazine was safer, easier to administer, and more controllable in its effect and had fewer side effects, it was recommended that it replace insulin coma.

Role of electroencephalographic changes in behavioral change

As noted in the following section, a direct relation between changes in electroencephalographic delta and behavioral changes in electroshock had been observed in these laboratories. For this reason, a survey of the role of various newer drug agents was undertaken to determine the potential relationship between behavioral change and electroencephalographic effects.

Chlorpromazine and promazine are effective agents for the induction of changes in motor patterns of behavior. Concomitant electroencephalographic effects are the induction of delta activity, a desynchronization of the record, and a decrease in the amount of fast activity. Both drugs also induce seizure activity spontaneously in patients who have not had seizures prior to the administration of the drugs, and in whom pre-treatment electroencephalograms have not demonstrated dysrhythmic activity.

Reserpine, while inducing a definite parkinsonian syndrome, does not generally induce seizures. At therapeutic levels, the changes in the electroencephalogram are limited to an increase in fast activity. We have not observed delta activity in any patient receiving reserpine.

In patients receiving meprobamate, also, delta activity has not been observed. Records consistently demonstrate high-voltage beta activity, similar to barbiturate. Clinically, meprobamate has some effect in

reducing seizure activity. When dosages are suddenly reduced, we have observed spontaneous seizures in 2 subjects. This observation is similar to that noted in animals.[3]

Electroshock evalution studies

In the course of an extensive evaluation of the electroshock process, a direct relationship has been observed between the degree of induced delta activity and the degree of behavioral change.[4] We observed that serial records taken during the course of electroshock therapy and measured for quantitative changes in delta activity could serve as a guide to the therapeutic outcome. Of 11 patients who were clinically rated much improved, 10 had high-degree delta records in the third and fourth weeks of treatment, whereas of 7 unimproved patients only 1 had such a record. In a subsequent series,[5] these observations were extended in a predictive study. It was suggested by these initial observations that the much improved patients were those in whom high-degree delta activity had been induced early in the course of treatment and sustained. Records taken during the second and third weeks of treatment were assessed. The results in 54 consecutive patients are noted in Table III. Of the patients who developed high-degree delta activity during the second and third weeks of treatment, 67 per cent were rated much improved, whereas only 30 per cent of the patients without such activity were so rated.

TABLE III

PATIENTS WITH HIGH DELTA ACTIVITY IN EEG DURING SECOND AND THIRD WEEKS OF TREATMENT

	Clinical Rating		
EEG Delta	*Much Improved*	*Moderately Improved*	*Unimproved*
Both high (18)	12 (67%)	4 (22%)	2 (11%)
One high (16)	4 (25%)	8 (50%)	4 (25%)
None high (20)	6 (30%)	7 (35%)	7 (35%)

Delta activity in the electroencephalogram reflects the state of brain function, and is a guide to alterations in that state. To verify the relationship between delta activity and behavioral change, concomitant amobarbital tests for altered brain function[6] were done in this series of patients. It was observed that the amobarbital test results were parallel to the electroencephalographic effects.[7] Of patients in the initial series who had been rated as much improved, all had positive amobarbital test reactions after the seventh to ninth weeks of treatment and sustained this response. Of the unimproved patients, however, 15 per cent had

positive amobarbital responses in the third week and 28 per cent in the fourth week, but these responses were not sustained.

A comparison of both electroencephalographic observations and the amobarbital test data, as related to the eventual clinical ratings, is seen in Table IV.[5]

TABLE IV

EEG AND AMOBARBITAL TEST RESULTS DURING SECOND AND THIRD WEEKS OF TREATMENT

	Much Improved	*Moderately Improved*	*Unimproved*
Both positive amobarbital and high EEG delta activity	25	10	3
Either positive amobarbital or high EEG delta activity	8	12	5
Neither positive amobarbital nor high EEG delta activity	0	3	11
Totals	33	25	19

It is apparent that the cluster of positive amobarbital tests, high EEG delta activity, and the much improved clinical ratings is a significant one; equally significant is the cluster of negative amobarbital tests, low to moderate EEG delta activity, and a clinical rating of "unimproved."

In the clinical observations in the electroshock study varied behavioral responses were observed. These included the absence of noticeable symptoms with the return of pre-morbid behavior; hypomania, euphoria, and denial; paranoid states with ideas of reference and delusional formation; confusional states with varying degrees of memory disturbance; increased somatic complaints and preoccupations; states of increased panic, excitement, and agitation; and varying degrees of withdrawal and seclusiveness. Similar psychopathologic reactions were observed in schizophrenic patients undergoing either chlorpromazine or insulin coma treatments, or patients with severe manifest anxiety undergoing reserpine therapy.

In the electroshock group, the degree of behavioral change was directly related to the degree of alteration in neurophysiologic indices. This direct relationship between neurophysiologic change and behavior was even more clearly manifested in a group of patients treated with subconvulsive therapy. In another control study, 27 subjects received subconvulsive therapy instead of grand mal therapy. The electroencephalograms demonstrated either no delta activity or a minimal amount of such activity during the course of treatment. In no patient were moderate or high-degree delta activity records observed. In the amobarbital tests, only 3 patients had positive reactions during treatment, and in each instance this occurred only once. Of the 27 subjects no change in symp-

toms or behavior was noted in 23. Nineteen were later referred for a second course of treatment. Of these, grand mal electroshock induced changes in brain function reflected by high-degree delta activity and/or repeated positive amobarbital tests in 14. All 14 showed significant changes in behavior, whereas of the 5 patients in whom physiologic indices showed only minor changes, only 2 showed a definite behavioral change.

It is important to note that there was no direct relationship between the physiologic changes and a specific type of behavioral change. There was, however, a direct relationship between the degree of induced physiologic change in brain function and the degree of behavioral change. In a further attempt to determine the relationship between the type of behavioral change and other variables, we have carried out studies on the role of personality in the behavorial response.[8] The initial study of the role of personality was devoted to a study of the relation between the characterologic disposition of patients to show denial mechanisms and the clinical results. The relatives of 47 patients were interviewed and denial personality scores were assessed, following a structured interview. Denial scores range from 0 to 25, with a median of 11. The scores were then divided into two groups: scores from 11 to 25 were classed as high denial and those from 0 to 10 as low denial.

Of patients with high denial personality scores, 58 per cent were in the much improved group and only 1 patient was in the unimproved group. The ratings of improvement for the patients with low denial personality scores were random, about one-third appearing in each rating category.

These studies support the present neurophysiologic adaptive hypothesis of the mode of action of electroshock therapy. This hypothesis notes that alteration in brain function is the central effect of electroshock therapy and is a prerequisite to behavioral change. It also notes that under the conditions of the induced change in brain function, altered patterns of adaptation are expressed. The type of adaptation varies, apparently dependent upon the personality organization.

Conclusions

Largely on the basis of these observations, as well as of reports of numerous other observers, the following conclusions regarding the role of physiodynamic therapies in schizophrenia are suggested:

(1) None of the present therapeutic regimes, including insulin coma therapy, electroshock therapy, and the newer drug therapies including chlorpromazine, reserpine, meprobamate, and promazine, are specific for schizophrenic illnesses. No evidence has been educed that any of these therapies have altered the basic schizophrenic process.

(2) Behavorial change in electroshock has been shown to be dependent on an alteration in brain function, as evidenced by serial changes in delta activity in the electroencephalogram. Under these conditions, the pattern of behavioral alteration varies markedly, depending on the degree of induced cerebral dysfunction, the personality of the subject, and the environmental situation.

(3) The newer drug therapies have effects on brain function in direct proportion to their ability to alter behavior as determined by clinical observation. The parallel between electroencephalographic change and behavioral change leads to the proposition that the mode of action of newer drug therapies may be similar to that of electroshock therapy; *viz.*, by altering brain function in a nonspecific manner, behavioral changes are induced.[9] To the extent that the behavioral alteration is of a kind that is rated as improved by the environment, the drugs are considered satisfactory therapeutic agents. In this regard, it is important to note that improvement ratings are but a special case of behavioral change, dependent on the type of adaptation elicited, the expectation of the therapist, administrator, and family, and the tolerance of the milieu.

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