CHANGES IN CATECHOL AMINE RESPONSE TO SUCCESSIVE ELECTRIC CONVULSIVE TREATMENTS*

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CHANGES in sympathetic nervous system responses have been noted to accompany changes in psychological states during psychiatric treatment. Funkenstein, Greenblatt and Solomon, observing the blood pressure response to epinephrine and methacholine, have reported a change in blood pressure patterns on the part of patients who benefited from electric shock treatment (1). Gellhorn has presented evidence that improvement in the psychoses is associated with heightened sympathetic reactivity (2).

Weil-Malherbe and Bone in 1953 introduced a method for the chemical determination of plasma epinephrine and norepinephrine (3), and Weil-Malherbe reported elevations of the plasma levels of both substances immedi-

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ately after electric shock treatment (4). He also reported on the effects of barbiturates and muscle relaxants in altering the catechol amine response.

In the present study, plasma catechol amine responses to electrically induced convulsions have been investigated in psychotic patients receiving electric shock treatment. We have determined catechol amine levels before treatment, changes of level after treatment, and the effect of successive seizures on the amount of amine response. We have also investigated the effect of the drugs used to modify shock treatment on the response, and the relationships between epinephrine and norepinephrine concentrations and various clinical and emotional states.

Subjects and Methods

The subjects of this study were twenty-five in-patients of the Massachusetts Mental Health Center (Boston Psychopathic Hospital), receiving electric shock treatment. Eleven were schizophrenic and fourteen had affective disorders. Patients were treated in the morning, two or three times a week, before breakfast, after sitting fifteen to twenty minutes in the waiting room. The first specimen of venous blood was drawn with the patient lying on a stretcher awaiting application of the treatment electrodes, and the second specimen approximately one minute after the start of electrical stimulation, at the time convulsive movements had largely disappeared. (In a previous study, it was found that peak epinephrine concentrations were recorded at one minute and peak norepinephrine concentrations between two and three minutes after the start of electrical stimulation.) The blood specimens were placed in tubes containing heparin and immediately centrifuged, the plasma then being drawn off and frozen.

With the unmodified form of treatment the only pre-medication was 1·3 mg. of atropine subcutaneously one-half hour before the seizure; no oxygen was given and some degree of cyanosis was usually present after unmodified treatments. With the modified form of shock treatment, atropine was also given one-half hour before the induced convulsion and ·2 to ·4 g. of thiopental sodium (pentothal sodium) and 20 to 50 mg. of succinylcholine chloride administered intravenously just before the convulsion. Thiopental was given to reduce anxiety and succinylcholine to soften the muscular seizure. Oxygen was given by bag pressure just before and after treatment. Fifteen subjects (9 with schizophrenia and 6 with affective disorders) received unmodified treatments and specimens were drawn before and after eighty-five seizures. The remaining ten subjects were given modified treatments and catechol amine levels were determined for seventeen seizures.

The average age of the unmodified group was 40 years and of the modified group 44 years. (The physical condition of both groups was similar, except that four of the ten patients receiving modified treatments had spinal abnormalities on X-ray, such as loss of a disc space or degenerative disc disease.)

With both forms of treatment the convulsive stimulus was given by a Reiter Electrostimulator Model No. RC47c. Subjects received full amperage for five to fifteen seconds, until a tonic state was achieved, and a much reduced amperage for the remaining thirty to forty seconds.

The amount of muscular movement during modified seizures was evaluated on a four-point scale. Zero meant no change from the usual unmodified seizure, 1+ indicated some arm and leg stiffness (during the tonic phase), 2+ arm stiffness but no leg stiffness, and 3+ both arms and legs relaxed and flaccid.

The diagnosis and psychological examination of each patient was recorded before the course of treatments. Changes in the psychological state were noted during the course of treatments and the patients were followed for a period of six months after convulsive therapy in order to determine whether re-hospitalization had taken place in this period.

The method used for the determination of catechol amine concentrations is a modification (5), similar to that described by Aronow and Howard (6), of the Weil-Malherbe and Bone technique (3). Values obtained for epinephrine and norepinephrine by this technique probably include undetermined amounts of other substances as well (7).

In the statistical analysis of the data non-parametric techniques were employed to avoid the assumption of normality of distribution of the material and because of the relatively small size of the samples. The Wilcoxon T test was used to determine the significance of any difference between the catechol amine levels before and after seizures; the Mann Whitney U test was used to test for significance between groups of subjects in terms either of the pre-treatment levels or the amounts of change after treatment. Determinations of the degree of relationship between two variables employed the Spearman Rank Order Correlation.

Observations

Table I presents the mean plasma catechol amine levels before and after unmodified and modified electric shock treatments.

Table I

Mean Plasma Catechol Amine Levels Before and After Unmodified and Modified Shock Treatments

	Epinephrine (micrograms/L.)	(s.d.)	Norepinephrine (micrograms/L.)	(s.d.)	Number of Determinations
Normal resting levels (5) ..	·48	(·13)	1·55	(·59)	12
Unmodified convulsions:					
Pre-convulsive level	·51	(·43)	1·45	(·92)	85
Post-convulsive level	3·45	(·68)	5·08	(1·86)	85
Modified convulsions:					
Pre-convulsive level	1·02	(·68)	1·51	(1·13)	13
Post-convulsive level	1·18	(·79)	1·65	(·86)	13
Post-convulsive level .. .. (modification without 0_2)	2·28	(·23)	1·73	(·40)	4

1. *Catechol Amine Levels Before Treatment*

Psychotic patients awaiting unmodified treatment showed plasma catechol amine levels within normal limits for resting healthy subjects*. The mean epinephrine value was ·51 micrograms/L. and the mean norepinephrine value 1·45.

Table II demonstrates that the pre-seizure *epinephrine* levels rose in the course of successive treatments. Mean levels before the first seizure were significantly ($P<·05$) lower than the levels before the fifth seizure or than the levels before the seventh, eighth, and ninth seizures ($P<·02$). In contrast, there were no changes in the pre-seizure *norepinephrine* levels.

* The mean resting levels for healthy young adults (tested at the conclusion of a basal metabolism test) are given in Table I. After activity the mean values are ·51 micrograms/L. (s.d. ·75) of epinephrine and 3·73 micrograms/L. (s.d. 1·35) of norepinephrine (5).

TABLE II

Pre-seizure Plasma Epinephrine Levels and Rises in the Amount of Post-convulsive Response with Successive Seizures

	Pre-treatment Epinephrine Levels (micrograms/L.)	Amount of Rise in Epinephrine Levels Post-convulsively (micrograms/L.)
First convulsion	·38	2·56
Fifth convulsion	·54	3·00
Seventh, eighth and ninth convulsions	·58	3·42

Patients awaiting the modified treatments had higher mean epinephrine values (1·02 micrograms/L.) than did patients awaiting the unmodified treatments. With the modified treatment there was, as with the unmodified, a tendency for the pre-seizure epinephrine levels to increase with successive treatments (up to the seventh), though the amount of data available is too small for statistical comparison. The pre-seizure norepinephrine level of the modified group (1·51 micrograms/L.) was not significantly different from that of the unmodified group.

2. *Post-Convulsive Catechol Amine Levels*

Significant elevations of the plasma catechol amine levels were noted in the blood specimens drawn after unmodified electric shock treatment. In the eighty-five experiments there was only one instance of failure to record a rise in epinephrine and norepinephrine levels.

There was a significant increase in the amount of epinephrine rise with successive seizures. Table II shows the mean rise following the first, fifth, and seventh, eighth and ninth treatments. (Between the first and fifth $P < ·05$; between the first and seventh, eighth and ninth $P < ·01$.) There was also, as mentioned, an increase in the pre-seizure level of epinephrine with successive seizures.

In the course of successive treatments there was no significant change in the amount of norepinephrine response. The blood specimens were, however, drawn before the known peak of norepinephrine response.

Values were determined for the twenty-fifth treatment in one patient and there was still a significant post-convulsive elevation of both epinephrine and norepinephrine levels.

No correlation existed between the ages of the subjects and the epinephrine or norepinephrine response.

3. *Correlation of Catechol Amine Response with Diagnosis, Psychopathology, and Outcome of Treatment*

The fifteen patients who received modified treatments and on whom the catechol amine responses associated with four or more seizures were determined were first grouped according to diagnosis (whether schizophrenic or affective disorder), then according to presence of paranoid or depressive trends, and finally as to outcome at six months (whether in the community or hospitalized). There were no significant differences between any of the groups in either the mean pre-treatment values or in the response for either of the catechol amines.

The gradual increase in epinephrine levels and responses with successive seizures tended to correspond with the improvement in patients' clinical states, which was usually gradual. There were instances, however, in which clinical

improvement preceded or followed the increase of epinephrine values. Depressed patients, who showed the most improvement both during treatment and six months after, also showed the largest increases in pre-seizure epinephrine levels and post-convulsive responses, although the numbers are too small for statistical comparison.

4. *Effects of Thiopental Sodium and Succinylcholine Chloride on Amine Responses*

The epinephrine response was significantly related to the amount of thiopental administered ($P < \cdot 05$). The larger the dose of thiopental pre-medication the smaller the rise (or greater the drop) of epinephrine post-convulsively. This is shown graphically in Figure 1. There was no significant

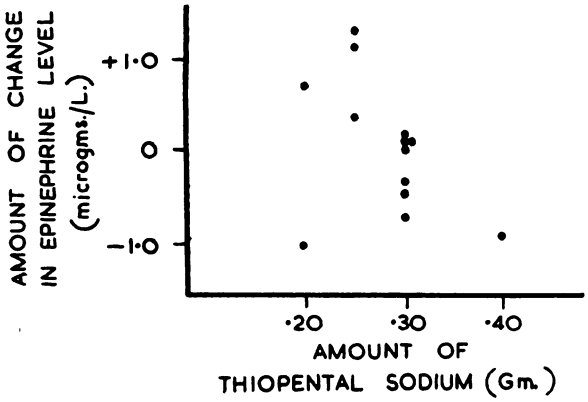

FIG. 1.—Relationship of thiopental dose and amount of change in epinephrine level.

relationship between the norepinephrine response and the amount of thiopental administered.

The norepinephrine response was related to the amount of muscular movement during the convulsion ($P < \cdot 01$). The more complete the modification of the muscular seizure by the succinylcholine chloride, that is the less the muscular movements, the smaller the rise (or greater the drop) of norepinephrine as determined post-convulsively. Figure 2 graphs the amount of change in norepinephrine against the amount of modification.

The epinephrine response to shock treatment was not related to the amount of muscular movement during the seizure.

5. *Effect of Anoxia on Amine Responses*

In an effort to determine the effects of anoxia on the plasma catechol amine response to shock treatment, four modified seizures were given without oxygenating the patients before or after treatment. Table I presents the mean epinephrine and norepinephrine levels following these four modified treatments without oxygen. The post-convulsive level of epinephrine was significantly higher than was the epinephrine level of patients pre-medicated with comparable amounts of thiopental and succinylcholine and given oxygen ($P < \cdot 01$). The norepinephrine level was, however, not significantly higher. The post-convulsive

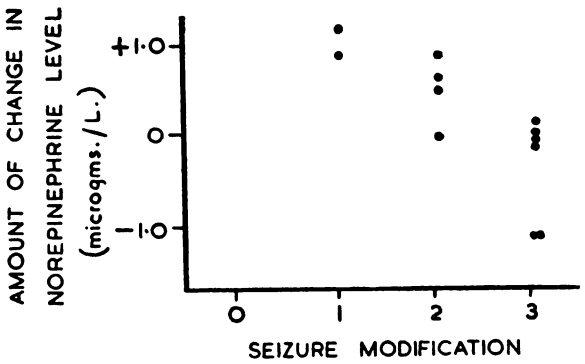

FIG. 2.—Relationship of degree of seizure modification and change in norepinephrine level.

levels of both epinephrine and norepinephrine in patients modified but not given oxygen were lower than the post-convulsive levels of the patients given unmodified seizures ($P < \cdot 01$).

DISCUSSION

The mean catechol amine levels of our psychotic subjects awaiting unmodified shock treatment were within the normal limits for healthy young adults not under stress. Pre-treatment epinephrine concentrations, however, tended to be below the norm early in the course of treatments and to rise above it for the later seizures (see Table II). The amount of epinephrine response to individual seizures also increased with successive treatments.

The findings of an increased pre-treatment epinephrine concentration and an increased epinephrine response with successive treatments support the hypothesis that heightened sympathetic reactivity develops in the course of electric shock treatment. Indirect support of this hypothesis has been provided by the work of Solomon *et al.* (8) on galvanic skin responses and that of Gellhorn and Safford (9) on blood sugar patterns. In addition, Funkenstein, Greenblatt and Solomon have reported a decrease in the hypotensive effect of methacholine and an increased reaction to intravenous epinephrine after successful courses of electric shock treatment, which they explained as the result of heightened sympathetic reactivity to stimulation (1). They also noted a decreased basal blood pressure after successful treatment, which suggested to them a lowered "basal sympathetic tension". The patients in the present study were not tested in a basal state and their rising pre-seizure epinephrine levels may reflect changes in response to the stress of awaiting shock treatment as much as they do changes in "basal sympathetic tension".*

Rising pre-treatment epinephrine levels may suggest an increase of anticipatory anxiety with successive seizures. This explanation of the changes noted in pre-treatment epinephrine levels cannot be fully excluded, but it has not been supported by observations of patients awaiting shock treatment (11). In general, apparent anxiety decreased in the course of treatments.

Michael found the lymphocytic reaction to electric convulsions similar to that of injected epinephrine (12) and Michael and Brown have reported a

* Wenger, Engel and Clemens have recently stressed the importance of separating measures of autonomic balance in a resting state from measures of response patterns to stimuli (10).

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decrease in the amount of lymphocytic rise with successive seizures (13). Altschule, Parkhurst and Tillotson made a similar observation on the eosinophilic response to shock treatment; they found that the usual post-seizure fall in eosinophils tended to decrease if treatments were given every five days or more often (14). One explanation of these results would be a fall in adrenal gland responsiveness with successive seizures. It may be, however, that these studies imply a decrease in the ability of certain systems, such as those which control the lymphocytic and eosinophilic levels, to respond to adrenal hormones or to other stimulating effects of the seizures.

The finding reported here, of an increased or continued adrenal responsiveness over the courses of treatment studies, is in keeping with the work of Holland and Schumann (15) and Zileli *et al.* (16); they noted a rapid re-synthesis of catechol amines in the adrenal medulla after various experimental procedures.

It is not obvious why the epinephrine levels before modified shock treatment should be above those before unmodified treatments. In another study (11), comparing the reactions of patients to modified and unmodified seizures, it was found that patients given modified treatments because of advanced age or physical disabilities expressed greater fear of treatment and were more resistant to accepting it than patients awaiting unmodified seizures. It is therefore possible that the higher pre-treatment epinephrine levels of the modified group in the present study (slightly older and with more physical disabilities than the unmodified group) partly reflect a greater fear of treatment than that experienced by the unmodified group.

The post-convulsive levels found in this study were higher than those Weil-Malherbe has reported (4). This discrepancy may be the result of differences in chemical technique, type of shock-induction, severity of seizures, timing of samples, the degree of hypoxia, or other factors. The possible importance of hypoxia is underlined by some of the present data: when modified patients were not oxygenated before and after treatment there was a greater catechol amine response than when oxygen was given. Satake has also reported that asphyxia is a powerful stimulant to epinephrine secretion (17). These considerations emphasize the danger of assuming that any effects of electric shock treatment (including those chemical effects studied here) are directly the result of electrical stimulation and not secondary to phenomena accompanying the seizure.

Elmadjian and Hope have reported a relationship between aggressive-hostile-active emotional display and the excretion of norepinephrine (18). In the present study a relationship between the amount of muscular movement during a fit and the norepinephrine concentration after it was noted. Convulsions in which there was little modification or reduction of muscular movement were generally followed by large increases of norepinephrine. These results suggest that the patterns of norepinephrine excretion Elmadjian and Hope describe may be a result as much of the muscular activities of the subjects as of their specific emotional states. In the healthy young adults tested to determine the normal values of the chemical method employed for the present study, activity affected the epinephrine values very little, but it produced significant changes in the norepinephrine levels (5). These results are, however, to be contrasted with those of Von Euler and Hellner, who found that physical exercise in healthy subjects produced approximately equal elevations of the urinary excretions of both epinephrine and norepinephrine (19). The differences observed in the present study from those of Von Euler and Hellner may reflect differences in the amount of exercise employed in the two sets of experiments. The subjects of the Von Euler experiments underwent very heavy exercise, as only under

these conditions were the responses of the adrenergic system found to be large enough to show in the urine. It is possible that during very heavy exercise, other factors, such as anxiety, may increase the epinephrine response. It is also possible that the differences in the findings of the two sets of experiments are the result of difficulties in comparing plasma and urinary levels. It is not known, for example, whether the rate of removal of catechol amines from the plasma is the same under the various experimental conditions.

Thesleff has reported that succinylcholine in large doses affects transmission at autonomic ganglia (20). This raises the possibility that the relationship noted here between the norepinephrine response and the degree of effectiveness of succinylcholine in modifying seizures may be a result of direct autonomic effects of succinylcholine. The amounts of succinylcholine required to produce any measurable changes in transmission at autonomic ganglia are, however, many times the amounts used in the present study.

Weil-Malherbe reported that the epinephrine response to electric shock treatment was little changed by the administration of a barbiturate before the seizure (4). In the present study it appeared that the epinephrine response could be reduced or reversed if enough barbiturate were given. Weil-Malherbe also suggested that the production of epinephrine was related to the clinical effectiveness of shock treatment (4). In a separate study, using amounts of barbiturate and succinylcholine which reduce the plasma catechol amine response to seizures, no differences in the clinical outcome of treatment compared with the results of unmodified seizures were observed (11). These data suggest that the production of plasma catechol amines is not an important part of the mode of clinical action of electric shock treatment, although the creation of a state of heightened sympathetic reactivity may be.

Summary

Plasma catechol amine concentrations were determined before and after one hundred and two electric convulsive treatments of twenty-five psychotic patients. The epinephrine and norepinephrine levels of patients awaiting unmodified seizures were within the normal limits for healthy subjects not under stress. Pre-treatment epinephrine levels tended to be below the normal average early in the course of treatments and to rise above it with later seizures.

Significant elevations of both epinephrine and norepinephrine consistently followed unmodified shock treatments. The amount of epinephrine response increased with successive seizures up to the ninth. After as many as twenty-five treatments significant post-convulsive elevations of both amines were still found.

Use of the seizure-modifying agents thiopental sodium and succinylcholine chloride significantly reduced the catechol amine response to shock treatment. The epinephrine response was related to the amount of thiopental administered and the norepinephrine response to the amount of muscular movement during the seizure.

The finding of an increase of pre-treatment levels and post-convulsive elevations of epinephrine with successive seizures gives direct support to the hypothesis that electric shock treatment produces heightened sympathetic reactivity. It cannot be concluded, however, that the *production* of plasma catechol amines is necessary to the clinical action of electric shock treatment, as the results of shock treatment are not changed by agents, such as thiopental and succinylcholine, which decrease the catechol amine response.

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