THE EFFECT OF CONVULSIVE THERAPY ON PLASMA ADRENALINE AND NORADRENALINE

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IT is generally assumed that an activation of the sympathetic system plays an important part in the therapeutic efficacy of convulsive treatments, be it as an unspecific result of stress or owing to a more circumscribed stimulation of specific centres in the hypothalamus and elsewhere. Such an effect has been postulated on the basis of various changes observed after convulsions, such as a rise in blood pressure (Accornero, 1940; Bini and Puddu, 1940; Piette, 1950), hyperglycaemia (Castelluci, 1940; Kessler and Gellhorn, 1941), leucocytosis and lymphocytosis (Gellhorn and Frank, 1948, 1949; Michael, 1949) and eosinopenia (Altschule, Parkhurst and Tillotson, 1949). Pupillary dilatation and contraction of the nictitating membrane have been described in cats (Gellhorn and Darrow, 1939). More direct evidence is provided by the finding that the adrenaline stores of the adrenal medulla are decreased after electrically produced convulsions (Pekkarinen, Hakala and Hyppönen, 1952).

An increase of the adrenaline concentration of peripheral blood in animals and humans following electrical stimulation has also been described (Hann and Kinzius, 1949; Tietz and van Harreveld, 1949; Kinzius and Hann, 1951), but the methods used were lacking in specificity as shown by the fact that the basal values were reported to be up to 2,000 times higher than those now considered probable. The significance of these results therefore cannot be accepted, particularly since we have been unable to confirm the claim of Lehmann and Kinzius (1951) that plasma contains an inactive, protein-bound precursor of adrenaline (Weil-Malherbe and Bone, 1954). Since a reliable and, as we believe, specific method for the estimation of adrenaline and noradrenaline in plasma is now available, the effect of various forms of convulsion treatment on the plasma level of these amines has been investigated. The introduction of muscle paralysants into convulsion therapy, with or without the use of anaesthetics, raises the question of how these modifications affect the sympathetic response. Electrical convulsions were therefore produced (1) without modification ("straight E.C.T."), (2) after barbiturate administration and (3) after the injection of both barbiturate and paralysant. Similarly the effect of leptazol convulsions was studied (1) without modification and (2) after the injection of a paralysant agent.

EXPERIMENTAL

Methods

Electrical convulsions were produced by the application of 90–120 V. for 0·4–0·5 sec. in the usual way.

5–Cyclohex–1–enyl 1,5–dimethylbarbituric acid ("hexobarbitone") was injected intravenously in doses of 0·2–0·3 g.

5–Pentamethylene tetrazol ("leptazol") was injected intravenously in doses of 7–12 ml. of a 10 per cent. solution.

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Bis-2-dimethylaminoethylsuccinate bis-methobromide ("suxamethonium bromide", "brevidil M") was injected intravenously in doses of 20–30 mg. of active cation. It was usually mixed with the hexobarbitone solution in the syringe immediately before the injection.

The corresponding bis-ethobromide compound ("suxethonium bromide", "brevidil E") was injected intravenously in doses of 55–75 mg. of active cation. For use in "modified leptazol therapy" (Berrington and Goldin, 1955) it was mixed in the syringe with, usually, 10 ml. of 10 per cent. leptazol solution immediately before injection.

Venous blood samples (15 ml.) were collected as previously described (Weil-Malherbe and Bone, 1952a). The haematocrit value was determined by centrifugation in Wintrobe tubes at about 2,000 *g* for 45 min. Adrenaline and noradrenaline were determined in plasma by the differential fluorimetric method (Weil-Malherbe and Bone, 1953).

Results

1. *Electroshock.*—The investigations were done on 13 subjects, 10 men and 3 women, all schizophrenics either hitherto untreated or untreated for several months previously. Each patient was submitted in turn to all three forms of treatment at intervals of about 1 week. The three series of results were thus obtained on an identical sample of patients and are strictly comparable. In the first series "straight E.C.T." was used, in the second the current was applied 1–2 min. after the injection of hexobarbitone and the treatment of the third series was "modified E.C.T." as used routinely in this hospital, in which the current is administered 1–2 min. after a combined injection of hexobarbitone and brevidil M. In the last form of treatment one or two oxygen insufflations were given in the interval between injection and stimulation and again after the termination of the fit.

Four blood samples were collected during each treatment, 2 before and 2 after the fit. In the first series ("straight E.C.T.") the first 2 samples were withdrawn with an interval of about 10 min.; a measure of spontaneous variation is thereby provided. In the other two series the first sample was withdrawn before, and the second about 1 min. after the injection, but before the application of the current. The third sample was collected as soon as twitchings or convulsions had ceased and the last sample about 10 min. later.

Fig. 1 shows the mean percentage concentration changes observed in the three series. In straight E.C.T. the plasma adrenaline concentration rises by $75 \cdot 5 \pm 8 \cdot 5$ per cent. above the base level immediately after the fit; 10 min. afterwards it has almost returned to the starting level. The second sample of this series does not differ from the first, indicating the absence of spontaneous change within a similar period of time. The second sample of the other two series shows, within the very short time interval between the injection and the withdrawal of the sample, a remarkable reduction of the adrenaline level amounting to about 60 per cent., although the degree of anaesthesia attained was usually very superficial. The application of the current reverses this effect. The increase above the initial value observed directly after the fit is only slightly below that found after straight E.C.T. The difference from series 1 is not significant for the second series, whereas it is significant at the 5 per cent. level of probability for the third series (Table II). Within 10 min. after the fit the adrenaline concentration has dropped to a value slightly below the base line indicating the persistence of some degree of sedative action. The

difference from series 1 is significant in both cases. Measured by the difference between samples 3 and 4 the height of the adrenaline concentration peak is about equal in all three forms of treatment.

The noradrenaline concentration of plasma, like that of adrenaline, is significantly raised by straight E.C.T. immediately after the fit and is still

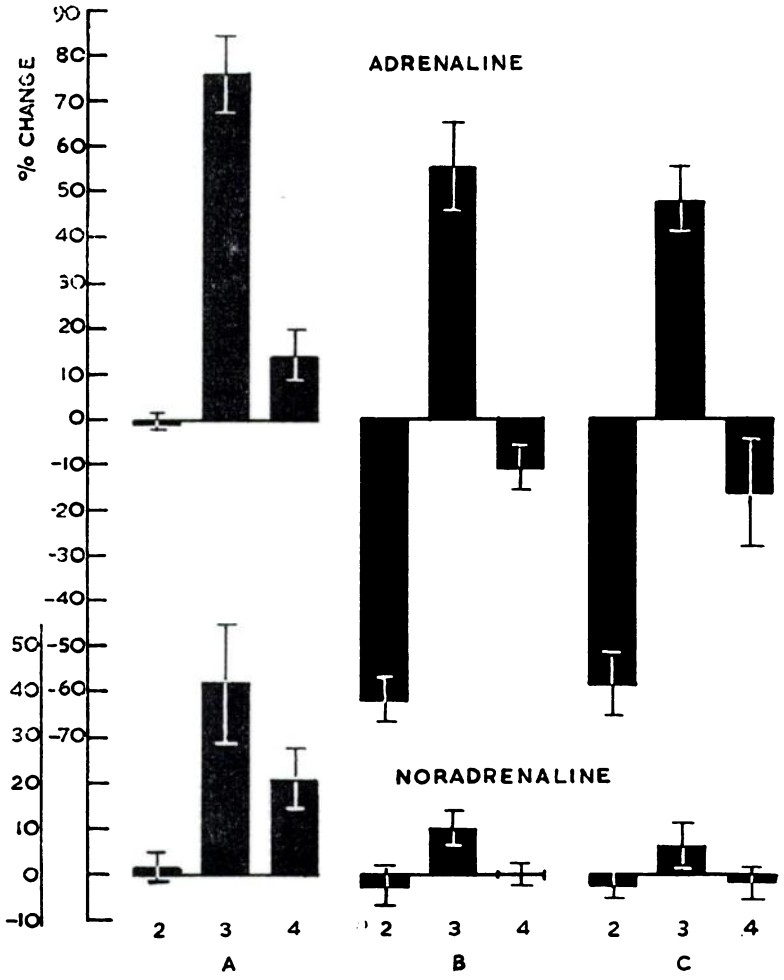

FIG. 1.—The effect of various forms of electroshock on the concentration of adrenaline and noradrenaline in plasma.

The bars indicate the mean percentage concentration changes in samples 2, 3 and 4 of each series. The barred lines indicate the standard error of the mean. A=unmodified E.C.T.; B=E.C.T. after hexobarbitone injection; C=E.C.T. after combined injection of hexobarbitone +brevidil.

Initial values (in μg./l of whole blood):

	A	B	C
Adrenaline	1·51±0·089	1·47±0·085	1·35±0·093
Noradrenaline	3·77±0·22	4·00±0·155	4·01±0·135

elevated 10 minutes later. The increase of the noradrenaline level, though still significant, is much reduced when hexobarbitone is administered, and it is no longer significant when hexobarbitone and brevidil M are combined (Table I). In contrast to the dramatic depression of the plasma adrenaline level

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by the injection of hexobarbitone the fact is of interest that the noradrenaline concentration in sample 2 remains unaffected whether the barbiturate is injected alone or in combination with brevidil.

TABLE I

Significance of differences between means of samples from the same series

Samples compared	"Straight E.C.T."		E.C.T.+ Hexobarbitone		E.C.T.+ Hexobarbitone +Brevidil		Leptazol		Leptazol +Brevidil	
	A	N	A	N	A	N	A	N	A	N
1 v. 2 ..	−	−	+	−	+	−	−	−	−	−
1 v. 3 ..	+	+	+	+	+	−	+	+	+	−
1 v. 4 ..	(+)	+	−	−	−	−	−	(+)	−	−
2 v. 3 ..	+	+	+	(+)	+	−	+	+	+	−
2 v. 4 ..	(+)	(+)	+	−	+	−	−	(+)	−	−
3 v. 4 ..	+	−	+	(+)	+	−	+	−	+	−

Symbols: + ~P≤0·01
(+)~P<0·05>0·01
− ~P>0·05
A=Adrenaline
N=Noradrenaline

The addition of a muscle paralysant to the barbiturate has no significant effect on the response of either the adrenaline or the noradrenaline concentration, compared with the action of the barbiturate alone (Table II).

2. *Leptazol convulsions.*—Two forms of treatment were compared, leptazol alone and leptazol combined with brevidil E. With the exception of 3 cases appearing in both series the subjects of the first series were not the same as

TABLE II

Significance of differences between means of corresponding samples from different series

Series compared	Sample 2		Sample 3		Sample 4	
	A	N	A	N	A	N
"Straight E.C.T." v. E.C.T.+hexobarbitone ..	+	−	−	(+)	+	+
"Straight E.C.T." v. E.C.T.+hexobarbitone+ brevidil	+	−	(+)	(+)	(+)	+
E.C.T.+hexobarbitone v. E.C.T.+hexobarbitone +brevidil	−	−	−	−	−	−
"Straight E.C.T." v. Leptazol	−	−	+	−	−	−
Leptazol v. Leptazol+brevidil	−	−	−	+	−	(+)
E.C.T.+hexobarbitone+brevidil v. Leptazol+ brevidil	+	−	+	−	−	−

Annotation as in Table I

those of the second. The cases of the first series (leptazol alone) consisted of 8 male and 1 female schizophrenics and 3 male manic patients, a total of 12. In the second series (leptazol+brevidil E) there were 7 cases of schizophrenia, 2 of mania and 1 of depression, all males, a total of 10. In both series the first 2 blood samples were collected before the injection, with a 10-minute interval; no significant change of the adrenaline or noradrenaline level was observed within this period. The third blood sample was collected immediately after the

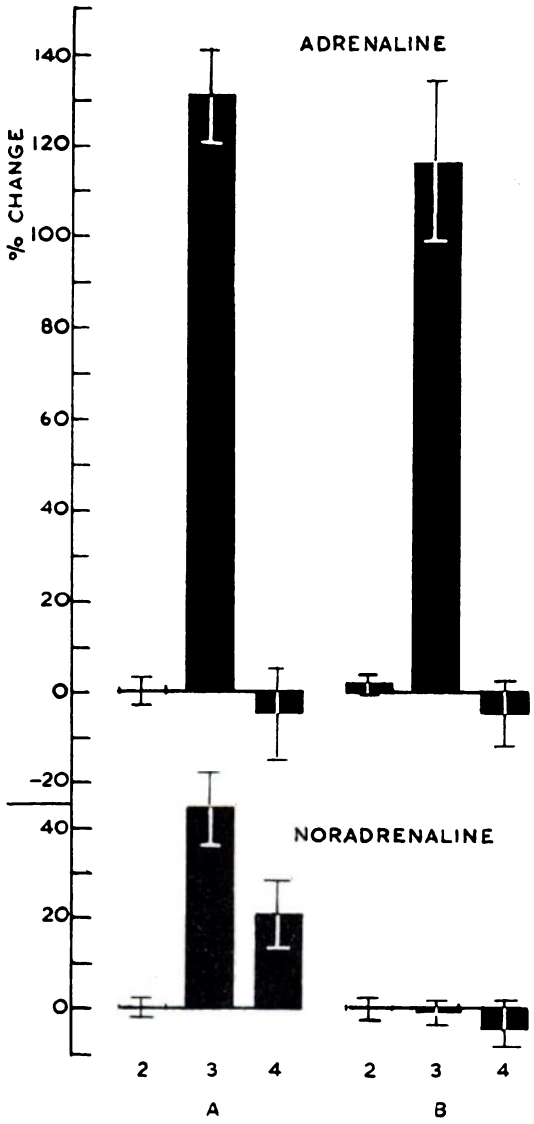

FIG. 2.—The effect of leptazol shock, with (B) and without (A) brevidil, on the concentration of adrenaline and noradrenaline in plasma.
The bars indicate the mean percentage concentration changes in samples 2, 3 and 4. The barred lines indicate the standard error of the mean.
Initial values (in μg./l of whole blood):

	A	B
Adrenaline	1·49±0·080	1·56±0·084
Noradrenaline	4·20±0·127	4·39±0·189

fit, the fourth 10 minutes later. When brevidil was added to leptazol, one or two oxygen insufflations were given after the fit.

The rise of the adrenaline concentration after the fit is almost twice as great as after E.C.T. The effect disappears within 10 minutes. In one experiment brevidil E was replaced by the longer-acting brevidil M; it was injected alone, a blood sample was withdrawn immediately afterwards and finally the leptazol

injection was given. Although barely 1/2 min. elapsed between the first injection and the collection of the blood sample, the plasma adrenaline level was found to be decreased by 45 per cent.; the noradrenaline level was unaffected. The procedure caused considerable distress and apprehension and was therefore not repeated.

The injection of leptazol alone produces a rise of the plasma noradrenaline level which closely corresponds to that following straight E.C.T. Ten minutes later the noradrenaline concentration is still significantly above the basal level. This effect on the noradrenaline concentration completely disappears when leptazol is combined with brevidil E. The suppression of the noradrenaline response can therefore be achieved not only with hexobarbitone, or with hexobarbitone+brevidil, but also with brevidil alone.

Discussion

When the physiological or therapeutic effects of convulsive therapy are considered, it is customary to distinguish between primary and secondary effects, i.e. between those directly connected with the convulsive discharge of groups of neurons and those dependent on the reactions to, or sequelae of, the nervous discharge, such as muscular contractions, cardiovascular changes and anoxia. In the recent modifications of convulsive therapy the secondary effects are minimized by the use of paralysant drugs and artificial respiration without impairment of the curative action. It has been shown in this investigation that, while the increase of the plasma noradrenaline concentration is clearly the result of secondary effects and is suppressed with them, the rise of the plasma adrenaline concentration persists. It therefore seems reasonable to assume that it is due to the stimulation of autonomic centres in the brain. An increased discharge of adrenaline may thus be a component of the therapeutic mechanism, while an increased discharge of noradrenaline is without significance in this respect.

The increase of the plasma adrenaline level is of the characteristic fleeting form associated with the action of adrenaline after intravenous injection. The increased discharge of adrenaline is therefore brief and probably lasts only for the time during which the current flows. Adrenaline estimations carried out on the plasma of patients treated with subconvulsive impulses have shown that the maximum concentration is usually reached while the current is flowing and that the effect has considerably subsided already 1 minute after the interruption of the current (Weil-Malherbe and Bone, 1952b). It is possible therefore that the effect here described was not observed when it reached its peak.

It is of interest to evaluate separately the modifications of the plasma adrenaline and noradrenaline levels by hexobarbitone alone, brevidil alone and by both combined. The rise of the noradrenaline level is as completely suppressed by brevidil alone as by brevidil+hexobarbitone, while hexobarbitone is not quite so efficient in this respect. It is likely therefore that the discharge of noradrenaline is mainly connected with the tonic phase of the convulsions which is inhibited by barbiturates and, to a smaller extent, with the clonic phase which is not.

The reduction of the plasma adrenaline level which so closely follows the intravenous injection of hexobarbitone is also observed after the injection of other barbiturates, such as sodium amytal (unpublished observations) or pentothal. The latter drug, in a dose of 0·75 g., was used in a series of treatments investigated with Dr. J. D. Montagu (cf. Montagu, 1954); it led to a mean reduction of the plasma adrenaline level by $64 \cdot 1 \pm 2 \cdot 9$ per cent. and of the

noradrenaline level by $12 \cdot 5 \pm 3 \cdot 6$ per cent. (19 observations). The effect is thus probably common to all barbiturates and, indeed, to anaesthetics generally, as shown by preliminary observations on patients undergoing various forms of anaesthesia. These and other observations (cf. Weil-Malherbe, 1954) suggest that the activity of the subcortical autonomic centres is geared to the activity of the cortex and that a depression of the latter entails a depression of the former. Some authors, such as Himwich (1951) and Gellhorn (1953), have put forward the opposite view assuming that the cortex inhibits the activity of the centres governing the discharge of adrenaline and that the regression of cortical dominance is coupled with a release of adrenaline. Our results do not support this theory.

Summary

The effect of convulsive treatments on the concentration of adrenaline and noradrenaline in plasma has been investigated. Electroshock was applied (1) without modification, (2) after the injection of hexobarbitone and (3) after a combined injection of hexobarbitone and brevidil ("succinyl choline"). The effect of leptazol was studied (1) without modification, (2) when combined with brevidil.

The unmodified electroshock produces an increase of about 75 per cent. in the plasma adrenaline concentration immediately after the fit; it subsides within about 10 minutes. The plasma noradrenaline concentration is raised by about 40 per cent.; this increase decays more slowly. The injection of hexobarbitone or of hexobarbitone+brevidil leads to a fall of the plasma adrenaline concentration reaching about 60 per cent. within 1 minute. The application of the current reverses this effect, producing a rise of the plasma adrenaline level which is only slightly below that found after an unmodified electroshock. The rise of the plasma noradrenaline concentration is completely suppressed after the injection of hexobarbitone+brevidil, and almost completely after that of hexobarbitone alone.

The injection of leptazol is followed by a mean increase of the plasma adrenaline level amounting to over 130 per cent. The noradrenaline response is similar to that observed after unmodified electroshock. The addition of brevidil does not significantly change the effect of leptazol on the plasma adrenaline concentration, but it completely abolishes the rise of the noradrenaline concentration.

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