AUTONOMIC ACTIVITY AND INDUCED CONVULSIONS.

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SINCE the influence of the autonomic nervous system on epileptic phenomena became the subject of intensive investigations, several contradictory reports have been published. Williams and Russell (1941) and Williams (1941) found that parasympathetic overactivity (induced chemically and registered by electro-encephalography) increases epileptic activity. Darrow (1944) reported opposite results, his observations being based on electrically induced parasympathetic overactivity on animals. He registered his observations by electro-encephalography. Cohen, Thale and Tissenbaum (1944) induced convulsions for therapeutical purposes by administering the parasympathomimetic drug, acetylcholine, and Chatfield and Dempsey (1942) observed the production of fits in cats, when giving acetylcholine and prostigmine together. Though the results were contradictory, the main aim of all these investigations was to establish the cholinergic neurohumoral changes in relation to epilepsy. But, as Williams pointed out, it is impossible to say whether the results are due to a direct central action, are consequent upon changes in the pH or of a respiratory or a circulatory nature. The investigations described in this paper were devised to re-examine these problems clinically. They were based on the hypothesis that if cholinergic overactivity enhances epileptic cerebral activity, the convulsive threshold of the brain should be lowered after administration of anticholinesterases, in particular prostigmine.

METHOD AND RESULTS.

Twenty-five psychotic women ageing from 21 to 50 were chosen; diagnostically they represented a mixed group of chronic psychotics, mainly schizophrenics and psychopaths. They had all received insulin, continuous narcosis or convulsant treatment 12 to 36 months prior to the present investigations. First their threshold to electrically induced convulsions was ascertained by determining the minimal convulsant dosage (MCD). This was again repeated after the investigations had been carried out. The convulsant threshold of the patients on the Ediswan electro-shock apparatus was between 68–95 on the voltage and 0·25–0·55 on the time dial. None of the cases responded with any convulsive phenomena to the subconvulsive dosage (SD) of 55 volts and 0·18 sec. time.

The patients then received 2½ mgm. of prostigmine by rapid intravenous injection. After completion of the injection the S.D., which was standardized to 55 volts and 0·18 sec. time, was applied 50 seconds, 2, 3 and 5 minutes later. After 2, 3 and 5 minutes there was an instantaneous twitch, or a momentarily

dazed attitude, but no fit followed when the S.D. was applied, though the "muscarine action" activated through the prostigmine, especially the circulatory effects, were noticeable. In about 7 minutes after the injection the motor effects of the prostigmine made their appearance in the form of muscular fibrillation, twitchings, increased reflexes and prolonged responses to tap contraction; the S.D. was then reapplied.

It was found, in 9 out of 25 cases, that is to say in 36 per cent., patients responded with a typical fit to the S.D. in 7–10 minutes after $2\frac{1}{2}$ mgm. intravenous prostigmine. It seemed that this response was comparable to the degree of the fibrillation and the allied motor effects of the prostigmine injections. In other words, in most of those who responded to the subconvulsive dosage, the "motor" effects of prostigmine were marked. These effects could be observed in about 7 minutes following the prostigmine injection, and usually decreased after 15 minutes.

In another series of investigations atropine was given together with the prostigmine, to eliminate the "muscarine effects" activated through prostigmine. A combination of $\frac{1}{100}$ gr. of atropine with $2\frac{1}{2}$ mgm. of prostigmine (intravenously) produced only 3 typical fits in 10 cases when S.D. was applied; combination with $\frac{1}{150}$ gr. of atropine produced only 4 typical fits in 10 cases. Finally, on 10 occasions $\frac{1}{100}$ gr. of atropine was given alone, followed within 7 minutes by the M.C.D. The fit produced was always considerably delayed (60 to 120 seconds); no fit was observed when the S.D. followed in 7 minutes the $\frac{1}{100}$ gr. of atropine.

The procedure was repeated on the same group of patients but with phrenazol. Firstly the minimum convulsant dosage of phrenazol was ascertained; this lay between 5·0 and 10 c.c. of phrenazol. As before, $2\frac{1}{2}$ mgm. prostigmine were given intravenously, followed in 7–10 minutes by a rapid injection of 3 c.c. of phrenazol. It was found that 13 out of 25 cases, that is to say 52 per cent., responded with a typical fit, but one control also gave a positive result. No fits occurred either 3 or 5 minutes after the prostigmine was given, and as observed before, there was a fair parallelism between the grade of fibrillation, increased reflex, etc., and the fits. Table I shows the responses as summarized above. It also illustrates that the positive electrical reactions more or less coincide with the positive phrenazol reactions, with a majority of the latter.

Finally, the prostigmine and E.C.T. and then the prostigmine and phrenazol combination were applied to 25 epileptics. Three weeks prior to the investigations their routine anti-convulsant treatment was decreased; it was then found that the average M.C.D. for electrical or chemical means was somewhat lower than in the non-epileptic series. Ten cases of the 25 had a lowered threshold for the prostigmine and E.C.T. combination, and 13 out of 25 cases for the combination of prostigmine and phrenazol.

COMMENTARY.

Thus in a number of cases a fit has been produced by subconvulsive doses of E.C.T. or phrenazol, following prostigmine medication. Similar results were seen, though more frequently, in a series of epileptic patients. There

TABLE I.

No.	E.C.T.		Control S.D.	Atropine.		Phrenazol.		Control S.D.
	M.C.D.	Prost. + S.D.		$\frac{1}{100}$ + Prost. + S.D.	$\frac{1}{200}$ + Prost. + S.D.	M.C.D.	Prost. + S.D.	
1	70 : 2	Fit	—	0	0	5 c.c.	Fit	—
2	80 : 2·5	—	—	..	..	9 c.c.	—	—
3	80 : 3	Fit	—	Fit	Fit	7 c.c.	Fit	—
4	70 : 2	,,	—	0	0	6·5 c.c.	—	—
5	75 : 2·5	—	—	..	..	10 c.c.	—	—
6	70 : 2	—	—	0	0	5·5 c.c.	Fit	—
7	68 : 2	—	—	..	..	7 c.c.	—	—
8	75 : 2·5	Fit	—	Fit	Fit	5 c.c.	Fit	—
9	70 : 2·5	—	—	..	..	5·5 c.c.	,,	Fit
10	90 : 4	—	—	..	..	10 c.c.	—	—
11	80 : 2	—	—	..	..	5 c.c.	Fit	—
12	95 : 4·5	—	—	..	..	7 c.c.	—	—
13	85 : 3·5	—	—	..	0	5·5 c.c.	Fit	—
14	75 : 2	Fit	—	Fit	..	6·5 c.c.	,,	—
15	95 : 5	—	—	..	..	8 c.c.	—	—
16	95 : 5·5	—	—	..	..	10 c.c.	—	—
17	80 : 2·5	—	—	..	..	5·5 c.c.	Fit	—
18	90 : 3·5	—	—	..	..	8 c.c.	—	—
19	70 : 3	Fit	—	Fit	Fit	7 c.c.	Fit	—
20	80 : 2·5	,,	—	0	0	10 c.c.	—	—
21	95 : 5	—	—	..	..	7·5 c.c.	—	—
22	90 : 4·5	—	—	..	..	6 c.c.	Fit	—
23	70 : 2	Fit	—	0	0	5 c.c.	,,	—
24	95 : 5	—	—	..	..	9 c.c.	—	—
25	70 : 2	Fit	—	0	..	5·5 c.c.	Fit	—

seems therefore to be some evidence that prostigmine lowers the convulsive threshold in accordance with Williams's conclusion, namely that parasympathetic over-action increases epileptic activity. In this sense the results oppose Darrow's conclusion.

The above reported experiments do not, however, prove that the seat of action is a central, cerebral one, though it is suggested by several points. First, that the intensity of motor reaction to prostigmine was on the whole best shown by those cases in which there was a lowered convulsive threshold to the convulsants. Secondly, though atropine diminished the obtained positive results, it did not abolish them, or in other words, when the muscarine effect of the cholinergic over-activity was eliminated the lowered convulsive threshold was still noticeable. The fact that some positive results were still obtained after atropine may be interpreted as the result of some central action. The delay of convulsions after atropine medication alone seems similarly to favour the supposition that the antagonistic effects of the atropine-prostigmine combination are not only peripheral. Finally it may be added that in Cushing's and Henderson and Wilson's experiments, centrally activated parasympathetic responses were immediately abolished by intraventricular atropine injections, evidently owing to central action of the atropine (Fulton).

Watterson and McDonald (1939) inhibited induced convulsions by drugs such as carbaminoyl-choline (carbachol) and acetyl-β-methylcholine, attributing the results to cerebral vasodilation. Darrow interpreted his experiments similarly, concluding that acetylcholine in the brain, liberated through parasympathetic overactivity, prevents vasoconstriction locally, thus counteracting epileptic

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activity. It is, however, to be noted that the clinical effects of high acetylcholine concentrations are predominantly circulatory, whilst smaller concentrations, in accordance with Williams' findings, exert their influence on neural elements not involving the vasal mechanisms. Reitman and Richards (1945) demonstrated that induced fits can be prevented in 60 per cent. of cases when cerebral vasodilators are applied, and the writer also found (hitherto unpublished) in a corresponding percentage of cases that the convulsive threshold is lowered when cerebral vasoconstrictors are given; neither the vasodilators, nor the vasoconstrictors were of parasympathomimetic nature. The percentage of cases in which the convulsive threshold was lowered by prostigmine, compared with the above quoted results, is well below the percentage affected by direct action on the cerebral vessels. These findings may therefore be suggestive of a different mechanism for the prostigmine effects, which are probably neural.

Clinical investigations cannot give conclusive evidence in regard to the autonomic nervous system in particular, but they test the autonomic balance by registering the homeostatic tendencies of the organism to a specific autonomic stimulus. All one is therefore able to conclude is, that by disturbing the autonomic balance in favour of the parasympathetic system, the convulsive threshold becomes lowered in a percentage of cases. Finally the usual coincidence of a positive response with a relatively low convulsive threshold does not encourage the use of prostigmine as a therapeutic measure in high threshold cases.

Summary.

1. 2½ mgm. of prostigmine lowered the convulsive threshold to E.C.T. in 36 per cent., and to phrenazol in 48 per cent. of 25 cases.

2. Similar investigations in epileptics did not yield a markedly higher percentage of fits than in normal cases.

3. The results, together with control experiments, may be suggestive that prostigmine has a central neural effect in its reduction of the convulsive threshold for E.C.T. and phrenazol.

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