AUTONOMIC RESPONSES IN PREFRONTAL LEUCOTOMY.

PRELIMINARY REPORT.

By F. Reitman, M.D., D.P.M.

From Netherne Hospital, Coulsdon, Surrey.

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In bilateral prefrontal leucotomy *inter alia* the fronto-subthalamic, the fronto-septal and fronto-hypothalamic (posterior) projections may be severed, together with reciprocally projecting tracts. These may represent the anatomical basis for the altered autonomic visceral disturbances observed following operations. The reports on bilateral leucotomy emphasize the post-operative "improvement in autonomic functions with a tendency to gain weight" (Vonderahe). After lobotomy transient visceral disturbances make their appearance, such as disturbed sphincter control and slightly but permanently decreased blood pressure, whilst vasomotor disturbances and sweating on the contralateral half of the body have been noted following unilateral lobotomy.

No reports, however, have been published regarding the autonomic responses of leucotomized patients under experimental conditions. The present paper describes the effects on leucotomized patients of drugs which obviously influence the autonomic nervous system, and is thus a clinical study of the way in which the severance of the connecting pathways alters the autonomic visceral responses. The rationale of the experiments was as follows:

The autonomic phenomena which have been described as following the operation (sweating, vasodilation, etc.) are of the peripheral type. If drugs are given with peripheral autonomic actions, a difference in the reaction between the leucotomized and not-leucotomized control cases might be expected.

Method.

The drugs used for the experiments may be classified into three groups: firstly anti-cholinesterases; prostigmine as a quaternary and eserine as a tertiary compound. Both of these enhance the effect of the naturally formed acetylcholine, consequently they reinforce cholinergic actions. It may be recalled that the physiological action of prostigmine, when given intravenously, is an enhancement of the action of the cholinergic terminals. Thus lachrymation, miosis, salivation, increased peristalsis, vomiting, the emptying of the bladder and rectum, muscular twitching, and an increase of the tendon reflexes follow. The action of eserine when injected intrathecally is a central stimulation of motor responses; thus after an initial depressive period it increases reflexes, twitchings result, together with enhanced responses to applied sensory stimuli (Kremer). After intravenous administration similar effects can be observed, but they are covered by the early appearance of violent autonomic cholinergic responses.

The second type of drug used was the anti-amino-oxidase ephedrine. This on intravenous administration reinforces the adrenergic terminals and "sympathetic" over-action is the consequence, as shown by mydriasis, vaso-constriction of the skin vessels, rise of blood pressure, compensatory bradycardia, appearance of extra-systoles, etc.

The third group of drugs used were the sympathetico-mimetic amines; of these benzedrine was chosen, its effect being similar to the adrenergic autonomic actions.

When giving these drugs the technique had to be worked out for each of them separately, and as far as is relevant, it will be separately mentioned when the results with each drug are discussed.

The female patients chosen for this enquiry were chronic schizophrenics of the excited and catatonic type. Fifteen cases were selected who had various unsuccessful shock treatments prior to leucotomy. This operation was carried out two to ten months before the investigations. None of these cases had reacted favourably to the operation. Three further cases were studied before and after leucotomy. The control group consisted of five chronic schizophrenics and five other psychotics, none of whom had had the operation.

Results.

Prostigmine.—Five c.c. of prostigmine (2½ mgm.) was the average necessary dosage. Too slow an intravenous injection made the effects indistinct; too rapid administration caused vasomotor collapse. To evade subjectivity, the injection speed was standardized for both leucotomized and control cases at 1 c.c. per 20 seconds. The contrasted responses of a typical control and leucotomized case are illustrated by Table I.

Table I.

Control Case.		Post-Leucotomy Case.	
N.G—, aged 30; *schizophrenia. B.P.* 145/100, *p.* 70.		*K. W—, aged* 28; *schizophrenia. B.P.* 135/95, *p.* 74.	
P.M.		P.M.	
2	2½ mgm. prostigmine intravenously.	2	2½ mgm. prostigmine intravenously.
2.5	Reflexes slightly increased. Complains of twitchings around eye.	2.5	Reflexes slightly increased. Complains of twitchings around eye.
2.7	Pallor. B.P. 125/95, p. 68. Reflexes ++. Tap contractions and moderate muscular fibrillation.	2.7	No pallor. B.P. 135/95, p. 72. Reflexes ++. Tap contractions and moderate muscular fibrillation.
2.9	Lachrymation.	2.9	Lachrymation.
2.10	Salivation; eructations; nausea; B.P. 115/85. Generalized muscular fibrillation. Reflexes +++.	2.10	Moderate miosis; salivation. B.P. 125/85. Generalized muscular fibrillation. Reflexes +++.
2.12	Vomiting.	2.12	B.P. 120/80; eructations.
2.14	B.P. 110/80; vomiting.		
2.16	Defaecation, micturition, fibrillation. Reflexes +++.	2.16	Eructations; fibrillation. Reflexes +++.
2.18	Vomiting again.	2.18	Fibrillation. Reflexes +++.
2.20	Interrupted by 1/75 gm. of atropine and 4 c.c. of coramine given.	2.20	Complains of pains; motor symptoms as above. Pallor.
		2.25	Miosis not increased.
2.30	No autonomic symptoms present. Still muscular fibrillation. Reflexes ++. B.P. 135/100, p. 69.	2.30	Motor symptoms as above; passes urine (normal quantity).
		2.48	Interrupted by 1/75th grain of atropine and 4 c.c. of coramine given.

It can be seen that the leucotomized patient, in contradistinction to the control, did not respond with vomiting, diarrhoea and excessive micturition to the prostigmine. When two or all three of these signs did not appear the result has been classified as a typical post-operative prostigmine response. Table II shows the occurrence of these qualitatively altered prostigmine responses in relation to the total case material. It can be seen that in 60 per cent. of the leucotomized patients gastro-intestinal symptoms such as vomiting and diarrhoea were not produced, but on the other hand about half of the cases responded with transient miosis to prostigmine. In marked contrast 8 out of 10 control cases showed vomiting and diarrhoea, and only 30 per cent. produced transient myosis.

Eserine.—The effective dose was 2½ mgm. in a solution of 2½ c.c. of water given intravenously, but at a slower rate than prostigmine. The circulatory effects of the eserine were, however, more violent than those of prostigmine, and collapse occurred frequently. After a short interval with initial depression of the reflexes, patients complained of " something funny " about their eyes, muscular twitching, increase of reflexes, salivation, lachrymation and vomiting occurred, with faecal and urinary incontinence and a marked fall in the blood pressure, and frequently with vasomotor collapse. There was no regularity in the pupillary changes. These responses were similar in both leucotomized and control cases. But whereas the

TABLE II.

Number.	Leucotomy.	Prostigmine. Miosis.	Saliv.	Vomit.	Diarrh.	Mictur.	T.	Eserine delay.	Ephedrine delay.
1	24 weeks	+	−	−	−	−	×	+	+
2	40 ,,	−	+	−	−	−	×	−	−
3	12 ,,	+	−	−	−	−	×	−	+
4	18 ,,	+	+	−	−	−	×	−	+
5	12 ,,	−	+	+	+	+	..	+	o
6	10 ,,	+	−	−	−	−	×	+	−
7	36 ,,	+	+	−	−	+	×	+	+
8	36 ,,	+	+	−	−	−	×	+	o
9	24 ,,	+	−	−	−	−	×	+	o
10	10 ,,	−	+	+	+	+	..	−	o
11	10 ,,	−	+	+	+	−	..	−	−
12	10 ,,	+	+	+	+	+	..	+	+
13	9 ,,	−	−	−	−	−	×	−	+
14	40 ,,	+	+	+	+	+	..	+	+
15	24 ,,	−	+	+	+	+	..	+	+
1	Control Sch	+	+	+	+	−	..	−	o
2	,, ,,	−	+	+	+	+	..	−	..
3	,, ,,	−	−	+	+	−	..	+	..
4	,, ,,	+	+	−	−	+	×	−	..
5	,, ,,	−	−	+	+	+	..	−	o
6	,, N Sch	+	−	+	+	+	..	−	..
7	,, ,,	−	+	+	+	+	..	+	+
8	,, ,,	−	+	−	−	−	×	−	..
9	,, ,,	−	+	+	+	−	..	−	o
10	,, ,,	−	+	+	+	+	..	−	..

Abbreviations: "T," typical response. "Control Sch," schizophrenic control cases. "O," no extra-systoles. "Control N Sch," psychotic, not schizophrenic control cases.

appearance of the autonomic symptoms in the control cases always started within 14 minutes, the leucotomized patients produced their qualitatively equal responses in 15 to 25 minutes. Thus, whereas the difference in reaction of the leucotomized and non-leucotomized cases to prostigmine was qualitative, to eserine it was in the time and not the intensity of response. Column 4 on Table II shows the number of delayed reactions to eserine, also the association of the positive eserine and prostigmine reactions.

Ephedrine.—The effective dosage was 1½ gm. in a solution of 3 c.c. of water, which was given as a rapid intravenous injection. Only the circulatory changes were recorded, consequently the "differences" described here only related to this one aspect. It was found that 6 out of the 10 control cases developed extra-systoles 1 to 120 seconds after completion of the injection; 3 did not produce extra-systoles, and 1 developed them in 180 seconds. In contrast to these findings 8 out of 15 leucotomized cases responded with extra-systoles between 120–200 seconds after completion of the injection; 3 produced extra-systoles within 100 seconds, and 4 did not respond with extra-systoles at all (see column 5, Table II). The results on such a small number of cases are difficult to assess; it may be that the comparatively delayed response to half the leucotomized cases is significant.

Benzedrine.—20 mgm. benzedrine was given intravenously 20 minutes after 1/100 gr. of intramuscular atropine. It was hoped that in diminishing the cholinergic autonomic activity by atropine, the sympathico-mimetic effects of the benzedrine would become more markedly manifest. Although the blood pressure rose, only 3 out of the total cases (leucotomy and control material) responded with extra-systoles. Though this may be an interesting point in regard to the action of benzedrine, it does not carry forward the present investigations.

Special cases.—Three cases (A, B and C) were investigated before and 3, 4, 5 and 6 weeks after leucotomy. Before leucotomy all the cases responded with the same autonomic symptoms to prostigmine and eserine, as did the control cases,

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and in Cases A and B there was total vasomotor collapse. A bilateral vertical leucotomy was performed on all three cases, using the McGregor and Crombie leucotome. No changes to the drugs were found in any of the three patients three weeks after leucotomy; Cases A and B again responded with vasomotor collapse, as well as with very severe autonomic reactions. After four weeks, however, the autonomic resistance started to manifest itself. All three cases had marked autonomic reactions, but no vasomotor collapse occurred. Five weeks after the operation the responses were less violent, and again no collapse occurred. In six weeks' time Cases A and B showed typical post-leucotomy prostigmine, eserine and ephedrine responses; Case C a typical post-operative prostigmine result, but the other responses were unchanged from before operation. Cases A and C responded with euphoria to benzedrine, and Case B produced extra-systoles under its influence. Up till now all three cases show a definite mental improvement as the result of operation.

Comment.

The above detailed results suggest that in leucotomized patients there is an increased resistance towards drugs which upset the autonomic equilibrium (homeostasis). They seem to point to the fact that no marked autonomic resistance can be expected less than six weeks after the operation, but it appears that the typical results observed are not always in direct proportion to the time which has elapsed after leucotomy.

Gold emphasized the autonomic disbalance in schizophrenics, and showed that after successful insulin treatment there was a tendency to maintain autonomic equilibrium. The 15 patients who were only investigated after leucotomy had failed to show much mental improvement, though with only two exceptions they produced the typical post-operative reactions to one or more of the drugs used. It would therefore seem that the autonomic resistance is not directly dependent upon the calmer mental attitude after the operation of leucotomy, even although there may be a relationship in the case of insulin treatment. It seems probable that the anatomical basis of the resistance are the severed autonomic projection tracts and not only the cortico-thalamic projections. This, however, remains hypothetical until confirmatory post-mortem findings are available. Furthermore, the parallelism of mental improvement and autonomic resistance in the three special cases may emphasize the important role played by the interruption of the thalamic connections.

Notwithstanding the differences observed, these results are only suggestive and not conclusive. Biochemical investigations would expand and give these observations a more definite basis. It also would be out of proportion to draw detailed conclusions based on the outlined investigation; the number of cases (total, 18) is too small for statistical purposes. Nevertheless the results on this sample of clinical material are indicative of the type of response to be expected, and appear to justify further investigations.

Summary.

1. The reactions of 15 leucotomized patients to prostigmine, eserine, ephedrine and benzedrine were investigated.

2. It was found that after leucotomy there is an increased tendency to maintain autonomic equilibrium (homeostasis).

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