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COMPARATIVE ACTION OF E.C.T. AND OF PITUITARY ANTERIOR LOBE HORMONES ON THYROID FUNCTION

BY

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In a previous paper (Reiss, Hemphill, Maggs, *et al.*, 1951) thyroid function in psychoneurotic and psychotic patients has been evaluated by radioactive tracer technique. The present communication deals with the effects of electric convulsion therapy (E.C.T.) on thyroid compared with that of thyrotrophic, adrenocorticotrophic, and sex hormones.

FIG. 1.—Thyroid indices of male patients before and after E.C.T.

Method.—The radioactive tracer method used in all these investigations has been described already (Reiss *et al.*, 1949; Haigh and Reiss, 1950; Reiss *et al.*, 1951). Thyroid function, estimated in this way, is remarkably stable in normal subjects and in untreated stationary psychiatric illness. Table I shows representative results.

TABLE I

Subject No.	Age	Thyroid Investigations		
		First I_t	Interval Between Both Investigations (Days)	Repeat I_t
1	30	14.5	28	16.8
2	33	10.7	21	10.2
3	28	8.0	34	7.4
4	23	6.3	32	6.7
5	28	4.3	356	5.7
6	55	3.3	36	3.4
7	45	0.88	185	0.89
8	30	0.67	354	0.55

In several normal subjects investigated regularly during the past three years thyroid activity did not vary by more than $\pm 10\%$.

The patients investigated belonged to the usual psychiatric material of out-patient clinics and psychiatric hospitals. However, the majority were cases of depression, normally submitted for E.C.T. In these the expectation of recovery with E.C.T. is high. There were also some other cases, complicated by constitutional and reactive factors, in which the prognosis was uncertain.

Results

Figs. 1 and 2 show the levels of thyroid function in male and female patients before, after completion of, and sometimes during electric shock treatment. The extent and trend of the changes after E.C.T. varied, but were most marked when thyroid function was initially high, which in these cases was always reduced. If the thyroid function was initially subnormal the level rose invariably to normal. Where the level of thyroid function was initially normal it sometimes changed, but only within the normal range. In no case that recovered in which the tracer index had been normal before treatment did the I_t value depart from the normal range with impairment of thyroid function. In some cases the thyroid function did not alter significantly and thus there did not seem to be a ready correlation between the effect of E.C.T. on the thyroid and the therapeutic result. In some cases in which the condition of the patient was unaltered or became worse, occasionally a thyroid function, originally in normal range, became reduced to subnormal; in other similar cases the thyroid function did not alter.

Investigations were made in another series of patients in which only the slope of the iodine uptake was measured, as the urine collection could not be completed. The changes of the slope of uptake K were in agreement with the I_t changes shown in Figs. 1 and 2, and wherever the slope was initially outside normal it was found to be within the normal range after successful E.C.T.

For comparison, Fig. 3 shows changes of thyroid activity after treatment with different hormones in patients suffering from varying psychiatric disorders. The second measurement

was not necessarily made at the same point of development of recovery in all cases. In all the patients treated with thyrotrophic hormone the thyroid function was initially subnormal, but after treatment was within

the normal range. Adrenocorticotrophic hormone decreases thyroid activity in different degrees. Its action is thus contrary to that of thyrotrophic hormone. Gonadotrophic hormone of the pituitary anterior lobe was not at our disposal, but treatment with sex hormones, either testosterone and oestrone combined or testosterone or oestrone alone, always reduced thyroid levels.

The results recorded in Fig. 3 show that there is an inverse relationship between the action of thyrotrophic hormone on the thyroid and the action of A.C.T.H. and sex hormones. This fact is confirmed when thyroid function and excretion of steroid hormones during the treatment of patients is studied. Figs. 4 and 5 are examples of such studies which were recently carried out by us on a larger scale (as yet unpublished). Fig. 4 shows that the thyroid activity of a patient suffering from puerperal depression was above normal value, and the 17-ketosteroid and cortin excretion were considerably

below normal value. Determination of 17-ketosteroid and cortin excretion was carried out repeatedly. Ten days later, before there had been any change in the psychiatric picture, 17-ketosteroid and

cortin excretion began to rise spontaneously. This excretion rate continued to increase, and the patient improved and finally recovered. The thyroid activity was once more assessed, and was now within the normal range.

Similar changes were observed during the stages of recovery of another depressive patient treated with testosterone and oestrone (Fig. 5). In this patient there was a negative adrenal cortex response for ketosteroids, a low 17-ketosteroid excretion in 24 hours, and thyroid hyperactivity. Shortly after the beginning of treatment with testosterone and oestrone the ketosteroid and cortin excretion began to rise and after a month thyroid activity was decreased. There was mental improvement. The adrenal cortex response in ketosteroid excretion was then positive. There seems to be an inverse relationship between the ability of the adrenal cortex to produce 17-ketosteroids in the four hours following stimulation and the response of the thyroid to electric shock.

Table II shows examples. Cases 1, 2, and 3 were unable to mobilize A.C.T.H. endogenously and their adrenals did not respond to A.C.T.H. The thyroid function rose after E.C.T. and they improved. Cases 4 and 5 showed a positive response to A.C.T.H. and glucose; their initially elevated thyroid activity decreased after E.C.T. and they improved mentally. All five patients improved clinically with E.C.T., irrespective of the indications of the adrenal cortex response test. In Case 6 the adrenal cortex responded to A.C.T.H., E.C.T. produced no significant effect on the thyroid, and there was no clinical improvement. In Case 7 the adrenal response to A.C.T.H. was positive; there was no change in thyroid activity after E.C.T. but there was therapeutic improvement.

Discussion

The physiological changes produced by electric shock are complicated, and include circulatory and metabolic changes and alterations in endocrine function. It is by no means certain whether all these changes are beneficial, or in what direction an explanation of the therapeutic effect may be sought. There was perhaps a parallel situation in the early days of endocrinology, when crude hormone extracts were used. The physiological effects

FIG. 2.—Thyroid indices of female patients before and after E.C.T.

FIG. 3.—Thyroid indices before and after hormone treatment. TST.=Testosterone. OES.=Oestrone.

were masked by toxic, anaphylactic, and pyrogenous actions due to impurities in the hormone extract which were not related to the specific biological action desired.

Various authors have studied the action of electric shock treatment by investigating its effects on the endocrine system. Most attention has been directed to the pituitary anterior lobe/adrenal cortical regulatory mech-

anism only, and the action of E.C.T. on other ductless glands, including the thyroid, has hardly been investigated.

An increase in the adrenocorticotrophic hormone activity of the pituitary anterior lobe after E.C.T. has been intimated by Hemphill, Macleod, and Reiss (1942), Hoagland, Malamud, Kaufman, and Pincus (1946), Mikkelsen and Hutchens (1948), and Parsons, Gildea, Ronzoni, and Hulbert (1949). The findings of Hemphill and Reiss (1942, 1944), and of Hemphill (1946), that in certain types of involutional melancholia small doses of corticotrophic hormone produce improvement with corresponding increases of 17-ketosteroids, suggest that part of the therapeutic effect of shock treatment in involutional melancholia is due to increased mobilization of A.C.T.H. from the anterior pituitary lobe. Hoagland, Callaway, Elmadjian, and Pincus (1950) compared the adrenal activation in response to injected A.C.T.H. and subconvulsive electric shock. They described, in schizophrenic cases, a statistically significant positive correlation and considered that the more responsive the adrenal pituitary system was the better the prognosis for insulin coma therapy. They put forward the proposition that both insulin shock treatment and E.C.T. represent stresses which, when repeated, act therapeutically by releasing endogenously produced A.C.T.H.

However, as shown in Table II, the responsiveness of the pituitary adrenal cortex system is less consistently related to the therapeutic action of E.C.T. than has been assumed. Furthermore, it is by no means certain that A.C.T.H. (measured recently, by ascorbic acid depletion test only) is one uniform hormone or a mixture of different adrenocorticotrophic hormone components. In our patients not only quantitative relations between the A.C.T.H. dose injected and E.C.T., as shown by Hoagland *et al.*, but also considerable qualitative differences in the adrenal cortex response, have been found (awaiting publication). Finally, the treatment with A.C.T.H. of cases that might be expected to respond well to E.C.T. is not often successful, and it is clear that the complex mechanism of E.C.T. does not operate by mobilizing one hormone only. Investigation of the action of electric shock on the endocrine system requires consideration of other glands besides the adrenal cortex.

Thyrotrophic hormone produces an increase in thyroid activity as measured by radioactive methods (Reiss *et al.*, 1949), and no doubt it is by mobilization of this hormone that the increase in thyroid activity by electric shock is effected.

When thyroid function is low before E.C.T., the thyrotrophic hormone mobilized from the anterior pituitary lobe acts more effectively than when the thyroid function is initially high. This is in agreement with the endocrinological principle that hormones have a greater effect

FIG. 4.—Thyroid activity and the excretion of 17-ketosteroid and cortin in a patient suffering from puerperal depression.

FIG. 5.—Thyroid activity and the excretion of 17-ketosteroid and cortin in a depressive patient treated with testosterone and oestrone.

TABLE II

Case No.	Age and Sex	Investigations before E.C.T.						No. of E.C.T. Before Next Investigation	Investigations after E.C.T.	
		Adrenal Cortex Response Tests 17-Ketosteroid Excretion (mg./hr.)				I _t	I _t		Clinical Change	
		25 mg. A.C.T.H.		150 g. Glucose						
		Before	After 4 hrs.	Before	After 4 hrs.					
1	52 F	0.82	0.58	0.91	0.40	2.5	5	12.0	Improved	
2	56 F	0.34	0.26	0.28	0.20	1.0	4	2.8	"	
3	57 F	0.67	0.39	0.58	0.44	7.1	14	9.8	"	
4	28 F	—	—	0.60	0.84	12.7	5	3.0	"	
5	20 M	0.76	1.2	0.90	1.1	13.3	6	3.3	"	
6	60 F	0.17	0.37	0.31	0.22	6.5	4	4.9	Not improved	
7	36 F	0.56	0.85	0.45	0.88	5.2	6	5.4	Improved	

in underfunction than on normally controlled subjects or in hormone overfunction. Probably when the thyroid function is already above normal range the amount of thyrotrophic hormone mobilized by the action of E.C.T. is not able to increase thyroid function much further, and is perhaps inhibited from doing so by the simultaneous mobilization of A.C.T.H. There appears to be an antagonism between thyrotrophic hormone and A.C.T.H., and A.C.T.H. may inhibit the thyroid. Reiss and Peter (1938) described reduction in blood iodine and atrophy of the thyroid in dogs after treatment with A.C.T.H., and an antagonistic action between thyrotrophic hormone and A.C.T.H. on the blood iodine level. At the same time they noted a decrease in blood iodine in six human cases treated with A.C.T.H., of whom three suffered from Graves's disease. Recent evidence of the antithyrotic action of A.C.T.H. has been reported by R. S. Reiss, Riggs, Thorn, and Forsham (1950).

Probably in many cases E.C.T. operates therapeutically on the anterior lobe/thyroid or anterior lobe/gonadal relationship. It is known that sex hormones in small doses stimulate the anterior pituitary, but large doses inhibit the production of gonadotrophic hormone. The physiological effect of treatment with sex hormones described in this paper may be due to suppression of the production as well as of the function of thyrotrophic hormone by sex hormones acting on the anterior pituitary.

Normal thyroid activity depends on an equilibrium in the production of stimulating and antagonistic hormones. E.C.T. can interfere with the mobilization of pituitary anterior lobe hormones and so influence the total hormone equilibrium. Changes in thyroid activity after E.C.T. are only an indicator for changes in the total hormone equilibrium, irrespective of whether these changes take place inside the normal range only or whether increased or decreased thyroid function is being normalized by E.C.T.

It is not possible at this stage to correlate the therapeutic result of E.C.T. with its physiological effect on one gland. To assume that where the thyroid has been influenced this has been responsible for mental improvement is to imply that a disturbance of thyroid function was originally the cause of the psychiatric illness—an implication not justified without further study. It would be logical to test the supposition by treating psychiatric patients who show a thyroid disturbance from the point of view of this disturbance only. Another way consists in trying to copy the action of the E.C.T. by treating patients with gland concentrates containing all the pituitary anterior lobe hormones.

This is now being attempted in our hospital. Nevertheless, apart from the question of appropriate dosage and the problem of over- and under-sensitivity to hormones, the difficulties are considerable, and deterioration in the progress of the disease and spontaneous remission have to be reckoned with. Our experience shows that thyroid physiology will have to be studied in any further research on the action of E.C.T., and for this the tracer method is convenient and reasonably simple.

Summary

The effect of E.C.T. on thyroid activity has been studied by radioactive tracer technique.

E.C.T. reduces pre-shock hyperactivity and raises pre-shock hypoactivity. Normal pre-shock values are influenced only within the normal range.

This is due to the effect of E.C.T. on the total endocrine equilibrium and especially to the way it influences the antagonism between adrenal cortex and thyroid function.

Relevant problems are discussed and the action of E.C.T. is compared with that of applied hormone therapy.

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THE ANAEMIA OF RHEUMATIC FEVER

BY

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Anaemia is one of the well-recognized features of rheumatic fever. It is of sudden onset: it may be severe, and it regresses as the acute attack subsides. It is usually classified as an anaemia of secondary type and is described as microcytic or microcytic and hypochromic. Anaemia is a common finding in many acute and chronic infective processes, and the anaemia of acute rheumatism has usually been studied from this aetiological aspect.

Investigations to determine whether it is of haemolytic origin or due to suppression of erythropoiesis have been reported. Douglas and Tannenbaum (1930) consider that infection retards erythropoiesis. In their series, which included three cases of acute rheumatism, they found no evidence of an increase in circulating reticulocytes or of a raised icteric index. Kapp and Coburn (1936) studied the excretion of urinary porphyrin in rheumatic fever and found that the urine of their patients contained abnormally large amounts of coproporphyrin. They state that this does not necessarily indicate increased blood destruction, as it may arise partly or wholly from disturbed liver function. Hubbard and McKee (1939), from a study of recrudescences of rheumatic fever in 17 patients, favour the view that the anaemia is due to suppression of erythropoiesis when the disease is most active, followed by increased red-cell formation as evidenced by a slight but significant increase in reticulocytes as the acute stage regresses. From studies of icteric index, serum bilirubin, and urobilinogen excretion they found little or no evidence of increased blood destruction.

Bradley (1938) introduced an entirely new conception of the problem. He studied a patient with signs of mitral