CHANGES IN THE OUTPUT OF 17-KETOSTEROIDS AFTER SHOCK TREATMENT, PRE-FRONTAL LEUCOTOMY, AND OTHER PROCEDURES.*

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THE estimation of the amount of neutral 17-ketosteroids excreted in the urine has attracted considerable attention, since the level of excretion (usually expressed as mgm./24 hours) can be fairly well correlated with the output of androgenic substances determined biologically (Callow *et al.*, 1939*a*, *b*). What constitutes the normal range of daily output is still somewhat uncertain; 1·7 to 12·6 mgm. for females, 3·5 to 15 mgm. for males (Callow, 1939), 4·0 to 15 for normal women (Friedgood and Whidden, 1939), 4·3 to 21 mgm. (Chou and Wang, 1939), 3·5 to 14·6 mgm. for females, 9·4 to 20·4 for males (Patterson, McPhee, Greenwood, 1942) have been quoted. We have conducted investigations in a large number of cases of each sex in the last two years, and have come to regard 6 to 15 mgm. daily as the range for normal adults, females as a rule being lower in the scale than males; after middle age a somewhat reduced output is to be expected. It has been suggested (Patterson *et al.*, 1942) that among normals higher values are related to larger body size, but we are unable to confirm this.

The source of at least the greater part of 17-ketosteroids is believed to be the adrenal cortex, and great departures from the normal range are found where there is hyper- or hypo-activity of this gland; a very large output is common in adrenal cortical tumours, little or none in Simmond's disease. Some reliance has been placed on this estimation in the diagnosis of adrenal disorders in asthenic subjects and in degrees of adrenal virilism and adrenal hyperplasia.

Although individual variations may be wide the day to day excretion of 17-ketosteroids in the same subject is pretty constant and there is little change in output, even during the menstrual cycle (Werner, 1941; Patterson *et al.* 1942). Our own investigations bear this out. In addition to non-mental subjects we have studied the 17-ketosteroids excretion of a series of male mental patients, making estimations at frequent intervals throughout six months. The results formed a fairly flat curve in each case, so that we have felt justified in regarding fluctuations of more than 40 per cent. as evidence of altered rate of output.

The purpose of this paper is to record very considerable increases in 17-ketosteroid excretion which we have observed to follow electrical convulsion therapy, pre-frontal-leucotomy, testicular biopsy, and the administration of corticotrophic hormone.

We hope to amplify our findings at a later date when investigations have proceeded further and therefore regard this paper as a preliminary report.

METHOD.

The technique of the colorimetric method of estimation has been described in detail elsewhere (Callow *et al.* 1939), and need not be repeated; no important modification has been made in arriving at the results recorded here. The total quantity of urine passed in 24 hours was collected, measured and a sample used for the estimation. To insure accuracy, mental patients were put to bed and the urine collected under strict supervision. It was possible in this way alone to guarantee that none was lost. Incontinent and unco-operative subjects were

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rejected. It should be noted that in expressing the quantity of 17-ketosteroids in mgm. excreted in 24 hours, the fluid intake and volume of the urine *per se* do not influence the result. High readings occur in scanty urine if the concentration is high, and vice versa, so that although slight errors in collecting all the urine might give low readings, marked increases cannot be accounted for in this way.

Excretion of 17-ketosteroids after Electro-shock Therapy.

Attention was drawn to a possible influence of shock treatment when it was noticed that more than 20 mgm. of 17-ketosteroids were excreted daily by some chronic schizophrenic male patients previously treated with cardiazol or electrically induced fits. Estimations were therefore made before and after electro-shock treatment in 18 male patients, including 4 who had had a previous course, treatment being given either three or six times weekly.

The effect on ketosteroid excretion with the clinical diagnosis and therapeutic results are indicated in Table I. It will be observed that taking account of changes of not less than 40 per cent., an increased output occurred in 9 subjects, a reduced in none, and that the highest percentage increases were related to the lowest original levels. The initial output of all 4 patients previously treated was above the average and in only one was there any further significant increase. No correlation between the therapeutic result and ketosteroid excretion can be sought in this small series. It did not appear to be of material importance whether fits were induced frequently or at wider intervals.

TABLE I.—*Electro-shock.*

Case.	Diagnosis.	Result.	17-ketosteroids. Before.	17-ketosteroids. After.	Increase.
N—	Depression	Recovery	10·3	15·5	+
W—	,,	,,	2·9	9·6	+
C—	,,	,,	13·9	19·6	+
E—	,,	,,	12·4	17·0	+
No—	,,	,,	10·3	15·5	+
G—	Chronic schizophrenia	Improved	11·7	22·1	+
Wa—	,, ,,	Not improved	5·9	15·0	+
H—	,, ,,	,, ,,	11·7	22·3	+
R—	,, ,,	Improved	4·2	21·0	+
L—	Recent schizophrenia	,,	14·1	11·2	—
Ho—	Hysteria	,,	23·7	19·9	—
Lo—	Depression	Recovered	12·7	9·3	—
Ro—	Chronic schizophrenia	Not improved	16·5	16·9	—
Ha—	,, ,,	,, ,,	11·5	13·4	—
S—	,, ,,	,, ,,	22·9	19·9	—
P—	Recent schizophrenia	,, ,,	12·3	16·9	—
B—	Chronic schizophrenia	,, ,,	8·4	9·8	—
W—	Chronic mania	,, ,,	6·8	5·8	—

Pre-frontal Leucotomy and Excretion of 17-ketosteroids.

Up to the present we have made similar investigations in 6 female cases before and after pre-frontal leucotomy (Table II). An increase was observed in 5 cases, no change in the 6th. The incontinence which is common for weeks after the operation interfered with the collection of urine so that we cannot guess when the output of 17-ketosteroids begins to go up. We have had the opportunity of making several estimations after operation in one case only, and observed that the output was apparently still rising during the third month.

TABLE II.—*Leucotomy—6 Female Cases.*

Ba—	Before operation,	5·8	After 2 weeks,	11·1	After 2 months,	12·4		
Be—	,, ,,	6·9	,, 6 ,,	10·2				
A—	,, ,,	3·5	,, 2 ,,	12·8				
Dc—	,, ,,	3·9	,, 3 ,,	13·4	,, 2 weeks	3·5		
F—	,, ,,	7·1	,, 4 ,,	14·5				
P—	,, ,,	9·2	,, 2 ,,	10·4				

Excretion of 17-ketosteroids after Testicular Biopsy.

An increased output was noticed in a few cases of schizophrenia after the removal of a small portion of tubule tissue from one testis for histological examination. We have investigated 18 of these cases so far, and found no significant change in 13, with an increase of 40 per cent. or more in 5, namely :

3·2 to 16·5 mgm.
5·6 ,, 10·6 ,,
5·7 ,, 15·6 ,,
9·1 ,, 16·5 ,,
8·6 ,, 11·5 ,,

Effect of Cortico-trophic Hormone on the Excretion of 17-ketosteroids.

The use of cortico-trophic hormone in adrenal insufficiency enabled us to investigate its effect on the production of 17-ketosteroids. As cortico-trophic hormone therapy in adrenal failure is being discussed at greater length elsewhere, we are here omitting details of the cases and merely recording the pertinent results.

Table III shows that continued treatment with cortico-trophic hormone in Simmond's disease and post-menopausal hypo-adrenalism produced consistently an increase in 17-ketosteroids output towards if not always up to the normal range.

The cortico-trophic hormone used was not available in large quantities, nor is it certain as yet what the requirements of individual cases may be. It is quite possible that more striking and immediate results might have been obtained by much heavier dosage.

TABLE III.—*Cortico-trophic Hormone—7 Cases.*

Jo—	11.xi.41	2·6	30 units daily.
	28.xi.41	4·6	
	26.i.42	6·9	
	6.ii.42	10·7	
H—	Aug. 1941	Less than 3	40 units daily—24 days.
	12.xii.41	10·0	
	10.ii.42	8·2	
D—	12.xii.41	2·9	25 units daily—14 days.
	13.i.42	3·5	50 ,, ,, 14 ,,
	10.ii.42	4·7	
Ks—	25.ii.42	2·3	50 units daily—20 days.
	20.iii.42	6·3	
M—	6.xii.41	4·2	20 units daily for 28 days.
	2.iii.42	6·7	20 ,, ,, ,, 28 ,,
	5.v.42	8·8	20 ,, ,, ,, 28 ,,
Co—	22.i.42	15·7	50 units daily—10 days.
	12.ii.42	14·5	
Wa—	3.xii.41	5·2	50 units daily for 10 days.
	13.i.42	5·5	

DISCUSSION.

Our investigations may be considered in two parts, those conducted on patients without clinical evidence of endocrine disorder, and on a smaller series suffering from adrenal insufficiency. The latter may be dealt with first.

If the excretion of 17-ketosteroid is an index of some part of the activity of the adrenal cortex, as we are justified in believing it to be, the low excretion rate seen in the hypo-function of adrenals of Simmond's disease and certain post-menopausal syndromes is to be expected. It is our belief that this hypo-adrenalism is due to failure of production of the cortico-trophic principle of the pituitary, a lack which

can be replaced by injected cortico-trophic hormone. It is reasonable to suppose that improvement in the function of the adrenal cortex will be accompanied by an increase in the 17-ketosteroid output; our cases supply evidence of this, and show that it is possible by the use of this hormone to increase the 17-ketosteroids where there was an existing deficiency. This has not been demonstrated before. In most of our cases the rise was not great and was achieved very gradually, but it preceded other objective signs of clinical improvement or gain of weight. In one case, after cortico-trophic hormone had been withheld, the 17-ketosteroid excretion diminished somewhat and the clinical state showed a tendency to relapse. It appears that a good output of 17-ketosteroids is not maintained in these cases unless the adrenal cortex is functioning satisfactorily—a condition that is only obtained if the cortico-trophic principle is supplied adequately from endogenous or exogenous sources.

Three normal cases without symptoms of adrenal insufficiency were treated with cortico-trophic hormone as controls; there was no increase in 17-ketosteroid output. With the admittedly rather empirical dosage of cortico-trophic hormone that was employed, it seems as if the adrenal cortex is unable to respond unless its activity is already subnormal. Similarly in myxoedema thyroid hormone may be active in doses too small to be effective in normal subjects.

In the great majority of cases subjected to an average course of convulsion therapy or pre-frontal leucotomy, the 17-ketosteroid output was significantly increased, to the greatest extent where the original level was low. As this output is usually constant, the increase must be attributed to the treatment. In other words, there has been increased activity in the adrenal cortex as the result of interference with some part of the anterior-pituitary-adrenal-gonadal chain. This increased output could be explained by assuming a hyper-activity of the anterior-pituitary with the production of large quantities of the cortico-trophic principle, for, as we have shown, therapeutic doses effective in hypoadrenalism failed to raise the 17-ketosteroid output in normals.

That shock therapy can influence the endocrines is well known, for it is a common observation that menstruation may return after prolonged amenorrhoea during convulsion therapy unassociated with mental improvement. Among other examples we recall one such case, a married woman, aged 42, childless for 15 years, who had not menstruated since 39, in whom menses returned and who was delivered after leaving hospital of a normal full-term child at 43 years. It seems just to assume that in these cases the anterior pituitary responds to shock therapy by producing gonado-trophic and other fractions. The increased 17-ketosteroid output in the same way could indicate a considerable production of cortico-trophic hormone. In Cushing's disease and possibly in other states of hyperactivity of the anterior pituitary the 17-ketosteroid output is higher, though significantly less than in adreno-cortical tumours. One case of Cushing's disease examined by us excreted 35·0 mgm. per day; other workers have reported similar findings. In three cases of early acromegaly we have seen excretion rates of 26·0, 21·0 and 20·0 mgm. respectively.

It is worth noting that subsequent courses of shock treatment produced little or no further increase, and that the greatest changes were seen where the original levels were low. This is understandable, as with high excretion rates the upper limit of response of the adrenal cortex is already nearly attained.

In speculating on the physiological mechanism responsible for the increased activity of the anterior pituitary the ground is most uncertain. What happens to the brain during one, or a series, of induced fits is far from clear. There are local changes at the site of stimulation, and intense and spreading neural discharge and widespread circulatory and autonomic adjustments before consciousness returns. It is possible that the pituitary is stimulated or that its blood-supply is significantly influenced, and there may be other important factors. But these conditions hardly obtain after pre-frontal leucotomy, and it is probably wiser to regard the pituitary effect in these cases as a sort of release phenomenon due to interruption of nervous connections between the hypothalamus and the frontal lobes. Clinical and electro-encephalographic evidence exists to show that traumatic changes in the frontal lobes occur after metrazol and electro-shock (Cobb, S., 1938; Barrera and Kalinowsky, 1942).

It may very well be that as far as the pituitary is concerned the same sort of

release of control follows shock treatment after the surgical severance of tracts in leucotomy, and combined with the much more widespread systemic and neural disturbances permits considerable hyperactivity of the anterior pituitary.

To explain the increased output of 17-ketosteroid after testicular biopsy, we can suggest either an increased production derived from the gonads or a disturbed balance of the anterior-pituitary-adrenal-gonadal chain, with an increased activity of the anterior-pituitary to restore the function of the traumatized testis.

Endocrinology affords well-known examples of such regulation of the anterior-pituitary. It has previously been observed that improved fertility in animals sometimes results from needling or damaging the testes, and possibly our cases are parallel examples in the human subjects.

We would like to emphasize that although our results are too few to be treated statistically, we have not observed a significant diminution in 17-ketosteroids in a single case, and that change when it occurred was a substantial increase, also that in cases in which subsequent estimations were made the new higher level of 17-ketosteroid was maintained. We feel that these facts offer considerable support for the explanation we have advanced above.

Summary.

1. A considerable increase in 17-ketosteroid output frequently follows convulsion therapy and pre-frontal leucotomy.

2. This probably represents hyper-activity of the adrenal cortex due to increased production of cortico-trophic hormone.

3. It has been suggested that interference with nervous pathways between the frontal lobes and hypothalamus may influence the pituitary to produce this result.

4. Injected cortico-trophic hormone in cases of hypo-adrenalism produced a progressive increase in 17-ketosteroid excretion. It is without effect in normals.

5. 17-ketosteroids were increased after slight trauma of the testes in 5 out of 18 cases.

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