CHAPTER III

METABOLISM OF STEROIDS IN CUSHING'S SYNDROME AND ADRENOCORTICAL SYNDROME

Cushing's syndrome has been considered to be due to abnormally high production of cortisol. However, the hyper function of adrenal cortex could result either from bilateral adrenal hyperplasia, adrenocortical tumour or over secretion of ACTH from the anterior pituitary gland. Other non-endocrinological reason can be the slow clearance of cortisol from the circulation. Therefore the differential diagnosis of this disease is most essential for the prognosis and treatment.

RESUME OF LITERATURE

Secretion and excretion of steroids in patients suffering from Cushing's syndrome:

Cushing's syndrome can be diagnosed easily by the clinical signs and symptoms which are very characteristic of the disease. The difficulty arises in pin pointing the etiological factors. Cushing's syndrome can arise due to adrenal hyperplasia; such patients do not necessarily secrete high amounts of adrenal steroids. It has been observed that in adrenal hyperplasia, the excretion of 17-KS was normal or slightly elevated; rarely, however, does this approximate the high excretion of steroids observed in patients with malignant adrenocortical tumours. Plotz et al
determined urinary 17-KS in a group of 25 patients with Cushing's syndrome. The values of 17-KS varied from 0 to 20.6 mg per 24 hours and the average figure was 10.8. In six patients with benign adrenal adenoma the average values were 4.8 mg per 24 hours, and in eleven patients with bilateral adrenal hyperplasia the average value was 15.1 mg. The 24 hour excretion of 11-oxy-steroids in six cases ranged from 0.86 to 6.3 mg which was much higher than normal levels (0.5 to 1.5 mg per 24 hours). Several reports on the excretory values of 17-KS in Cushing's syndrome have appeared in the literature but such measurements help only partially if at all in the diagnosis of the etiological factor of this disease.

Fractionation of urinary 17-KS:

Kovacic et al. 16 carried out fractionation of urinary 17-KS and observed that two adult patients with cortical hyperplasia had a high concentration of 3β-hydroxy-17-ketosteroids (3β-OH-17-KS) i.e. DHEA and epiandrosterone; on the other hand, two patients with adrenal cortical adenoma had low concentrations of 3β-OH-17-KS. The concentration of 3α-hydroxy-17-ketosteroids (3α-OH-17-KS) i.e. androsterone and etiocholanolone were similar in both these groups. They were able to differentiate adrenal hyperplasia from adenoma as in former there was an increased excretion of DHEA and epiandrosterone. Further, in hyperplasia the ratio of 3β-OH-17-KS to 3α-OH-17-KS was greater than one, while in
adenoma it was less than one. On the other hand, Vande Wiele et al⁷ and Jailer et al⁸ did not find detectable quantities of DHEA in the urine of five out of seven patients with adrenal hyperplasia but an abnormally large amount of DHEA was found in the urine in one of the remaining patients. They further observed an absolute increase in the urinary excretion of 11-oxygenated 17-KS, 11β-hydroxyandrosterone and the ratio of etiocholanolone to androsterone was approximately four times greater than that observed in normal subjects. Bouliex et al⁹ observed an increased ratio of 11-oxy-17-KS/11-desoxy-17-KS in Cushing's syndrome due to adrenal cortical hyperplasia and Vande Wiele et al⁷ found a similar pattern in 17-KS fractions in patients with adrenal hyperplasia and with adrenal carcinoma. Thus fractionation of urinary 17-KS failed to distinguish adrenal hyperplasia from adrenal adenoma or carcinoma.

Measurement of urinary corticosteroids:

One of the characteristics of Cushing's syndrome is an increased excretion of corticosteroids and their metabolites. Dyrenfurth et al¹¹ reported increased urinary content of tetrahydrocortisone, tetrahydrocortisol, cortisol and corticosterone in their patients affected with Cushing's syndrome. During intramuscular administration of ACTH all these steroids including corticosterone and cortisol were increased. Heider et al¹² observed in 51
cases of suspected Cushing's syndrome, a higher excretion of 17-KS and 17-KGS. After ACTH administration the 17-KS excretion increased from 300-900 percent. The 17-KGS values which ranged from 3 to 60 mg per 24 hours in the control state, increased and ranged between 19 to 125 mg per 24 hours after ACTH administration. Such data indicated a hyperfunctioning of the adrenal cortex but were insufficient to throw light on the differentiation of adrenal hyperfunction. It is well established that in most patients with Cushing's syndrome due to adrenal hyperplasia the adrenal cortex responded with an increase in corticosteroid secretion in excess of the normal range when given ACTH.

Suppression of adrenocortical function:

Attempts have been made to suppress the hypercortical function in Cushing's patients by the administration of cortisone. Five patients with adrenal cortical hyperplasia were given 200 mg of cortisone intramuscularly daily for 5 days; the control values of urinary 17-KS ranged from 11.7 to 27.6 mg per 24 hours (mean 20.5 mg) declined to a range of 4.7 to 19.2 mg per day with a mean value of 15.9 mg following cortisone administration. In two cases of adrenal adenoma, the control urinary 17-KS were 22.4 and 5.7 mg per 24 hours and these values were 32.2 and 5.0 mg after administration of cortisol. Similarly, in two patients with adrenal carcinoma, a 17-KS excretion of 43.9 and 6.7 mg
per day did not fall after administration of cortisol. In a group of patients reported by Laidlaw et al. no decrease in the urinary excretion of 17-KS and 17-OHCS occurred following treatment with 9α-fluoro-cortisol, and only partial suppression of 17-OHCS was observed by Cope and Harrison and Cope in three patients with adrenal hyperplasia. The 17-OHCS excretion in one patient with adrenal carcinoma did not decrease following 9α-fluoro-cortisol therapy. Gennes et al. demonstrated distinct suppression in the excretion of urinary steroids by administering 6 mg of 9α-fluoro-Δ-dehydrocortisol per day to a patient with Cushing's syndrome. A partial suppressive response to Δ6-methyl-9-fluoro-21-desoxy-cortisol administration was also observed in a patient with bilateral adrenal hyperplasia. Grant was successful in suppressing the pituitary-adrenal function in patients with adrenal cortical hyperplasia by increasing the dose of Δ9-fluoro-cortisol and dexamethasone (Δ9-fluoro-16-methyl-cortisol) but patient with adrenocortical tumour did not respond to these compounds. On the other hand, a patient with pituitary adenoma showed definite suppression of the pituitary-adrenal function during treatment with large doses of Δ-fluoro-cortisol and dexamethasone; This test could have been of specific diagnostic value in Cushing's patients due to adrenal hyperplasia or adrenal tumours but it did not differentiate pituitary adenoma from adrenal hyperplasia.
Measurement of plasma 17-OHCS:

The excretion of steroids in the urine of Cushing's patient fluctuates from day to day and measurements of steroids in the urine may not assess true adrenal secretion 23, 4, 24. Lindsay et al 25 employed the determination of plasma 17-OHCS to study adrenal function in Cushing's syndrome. Two patients, one with adrenal adenoma and the other with adrenocortical hyperplasia did not show diurnal variation of these steroids in plasma as in normal subjects 26, 27. These two patients responded to exogenous ACTH while in a patient with adrenal carcinoma the plasma 17-OHCS did not increase after administration of ACTH. Eik-Nes et al 28 were, however, the first to demonstrate a high response to ACTH in a patient with Cushing's syndrome due to adrenal adenoma. The control value of plasma 17-OHCS in this patient was 32.0 µg per 100 ml without diurnal variation and the plasma 17-OHCS, rose to 110 µg per 100 ml after 25 I.U. of ACTH given intravenously over a period of 6 hours. Soffer et al 29 were unable to demonstrate changes in plasma 17-OHCS in cases of adrenal adenoma or carcinoma following ACTH administration.

Nugent et al 24 and Doe et al 30 observed absence of diurnal variation in some Cushing's patients while in others it was present but of a low magnitude. Recently, Steinbeck 31 studied steroid excretion and plasma 17-OHCS in patients with Cushing's syndrome due to adrenal cortical
hyperplasia, adrenal adenoma and adrenal carcinoma and discussed the limitations of diagnostic importance of measuring these steroids before and after stimulation with ACTH.

B) Biosynthesis of steroids in Cushing's syndrome:

It has been fairly established that in Cushing's syndrome due to adrenal cortical hyperplasia, a defective steroidogenesis of adrenal cortex exists, and a high concentration of cortisol in blood or increased excretion of corticosteroids in the urine is seen. It is suggested that it may be due to excessive secretion of ACTH where the feedback mechanism would fail or the adrenal cortex would be hyper-responsive to normal or decreased amounts of ACTH. Thus the adrenal cortex in Cushing's syndrome may show increased responsiveness to an exogenous ACTH than the normal. The adrenal cortex in this disease thus appears to be hyper-responsive to endogenous ACTH and accelerates the reaction from cholesterol \( \rightarrow \) pregnenolone \( \rightarrow \) progesterone \( \rightarrow \) 17α-hydroxyprogesterone \( \rightarrow \) cortisol.

In case of Cushing's syndrome due to adrenal adenoma, it is suggested that the adrenal cortical tumour produces higher amounts of cortisol and corticosteroids which subsequently inhibit the production of ACTH. In the absence of ACTH and due to maintenance of high concentration of cortisol in the blood it is believed that the contralateral adrenal undergoes atrophy. The enzyme reactions
in the adrenal cortex which convert cholesterol to cortisol may be accelerated and made independent of ACTH stimulation.

In Cushing's syndrome due to pituitary adenoma high amount of ACTH is secreted which would lead to the hypertrophy of adrenal cortex. The production of pregnenolone will be thus increased which would be converted to cortisol and corticosterone. The high concentration of cortisol in blood would not inhibit the secretion of anterior pituitary since the functions of tumour are not controlled by cortisol secretion\textsuperscript{35}. 
MATERIAL

(A) Cushing's syndrome:

Three cases of Cushing's syndrome of different etiology were investigated. Patient KK was studied over a period of 6½ years while patients TN and SD were studied for a period of two years and one year respectively. In these patients the basal excretion of 17-KS, 17-KGS was observed repeatedly and the excretion of pregnanetriol and pregnanetriol-11-one was investigated before an ACTH test and before hormonal treatment. The ACTH infusion test was furthermore, carried out in all the three plasma 17-OHCS and urinary 17-KS, 17-KGS, pregnanetriol and pregnanetriol-11-one was investigated.

Patient KK was studied before adrenalectomy, after unilateral adrenalectomy and during cortisol and prednisone treatment. Patient SD was investigated before and after the removal of a tumour of the left adrenal and also while being on cortisol therapy. Finally, patient TN was investigated before and after deep X-ray therapy to an adenoma of the pituitary gland.

(B) Adrenogenital syndrome:

In two cases of adrenogenital syndrome the excretory patterns of 17-KS, 17-KGS, pregnanetriol and pregnanetriol-11-one as well as plasma levels of 17-OHCS were determined (Table VII). ACTH infusion was carried out
on patient SR and the effect of ACTH was observed by estimating the same steroids in urine and plasma as indicated above. Both patients were subjected to prednisolone treatment, over a long period and the excretion of 17-KS and 17-KGS were determined in order to evaluate adrenal function and to regulate the dosage of prednisolone needed for controlling the diseased state.
RESULTS

Cushing's syndrome:

(A) Plasma 17-OHCS

17-OHCS in plasma were estimated repeatedly in three cases of Cushing's syndrome. The control values ranged from 27.4 to 40.0 μg per 100 ml of plasma (Table XX). After ACTH infusion these values increased which ranged between 40.1 and 66.5 (Fig. 13).

Patient TN, who had adenoma of the anterior pituitary gland was subjected to deep X-ray therapy to the hypophysis and after a tumour dose of 2100 r., the resting level of 17-OHCS had decreased from 40 to 11.1 μg. An ACTH infusion carried out at this time resulted in a three-fold increase in plasma 17-OHCS. Three weeks after a full tumour dose of 3300 r the control value of 17-OHCS was 17.5 μg and after ACTH it increased to 52.5 μg per 100 ml of plasma (Fig. 14).

After the removal of the left adrenal tumour in patient SD the concentration of 17-OHCS dropped from 28 to 2.5 μg per 100 ml of plasma.

(B) 17-KS, 17-KGS and pregnanediol in urine:

In patient KK the values of 17-KS, estimated on 5 different occasions ranged from 4.9 to 5.9 mg per 24 hours, and the value of pregnanediol was 0.5 mg per 24 hours, estimated on two occasions only. Adrenalectomy was performed on
Table XX

**Plasma and urinary steroidal values in Cushin's syndrome**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Plasma 17-OHCS (μg/100 ml)</th>
<th>17-KGS (mg/24 hr.)</th>
<th>17-KS (mg/24 hr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.N.</td>
<td>F</td>
<td>38.5, (40.0)</td>
<td>20.8</td>
<td>9.9</td>
</tr>
<tr>
<td>K.K.</td>
<td>F</td>
<td>31.6, (30.0)</td>
<td>6.0, (5.8)</td>
<td>3.8, (4.1)</td>
</tr>
<tr>
<td>S.D.</td>
<td>F</td>
<td>30.0, (27.5)</td>
<td>20.0</td>
<td>7.4</td>
</tr>
</tbody>
</table>
RESPONSE TO ACTH IN CUSHING'S SYNDROME

Fig. 13
RESPONSE TO ACTH IN CUSHING'S SYNDROME (T.N.)

PLASMA 17-HYDROXYCORTICOSTEROIDS
μg/100ml

TIME IN HOURS

0 1 2 3 4

Fig. 14
this patient in September 1953, when the left adrenal was completely removed and 7/8 of the right gland excised. The 17-KS value dropped to 2.9 mg per 24 hours. The 17-KS excretion increased to its original concentration by April 1959, when the values ranged from 3.8 to 4.8 mg per 24 hours, and after ACTH administration the 17-KS and the 17-KGS were 5.1 and 29.9 mg per 24 hours respectively.

The excretion of 17-KS and 17-KGS in patient TN was 9.9 and 20.8 mg per 24 hours respectively. After a full tumour dose of 3,300 r to the anterior pituitary gland, 17-KS were 11.3 mg and the 17-KGS were 10.8 mg per 24 hours.

Finally, in patient SD the values of 17-KS and 17-KGS were 7.4 and 20.0 mg which, after ACTH administration, became 9.6 and 16.8 mg per 24 hours respectively. After the removal of the left adrenal tumour the value of 17-KS was reduced to 2.9 mg and the 17-KGS decreased to 3.0 mg per 24 hours.

**Pregnanetriol and pregnanetriol-11-one excretion in patients suffering from Cushing's syndrome and adrenogenital syndrome:**

The excretion of pregnanetriol was determined in three Cushing's patients. Patient KK had hyperplasia and showed an excretion rate of pregnanetriol of 1.88 mg per 24 hours and 4.37 mg per 24 hours after infusion of ACTH.

Patient SD who had a non-malignant tumour of the left adrenal
showed a basal excretion of 2.12 mg per 24 hours and 1.88 mg during ACTH infusion. Similarly, in the case of patient Th who had adenoma of the anterior pituitary gland the values were 3.17 mg per 24 hours before and 3.50 mg after ACTH infusion. Out of these three patients, KK and Th showed a positive test for the excretion of pregnanetriol-11-one before and after ACTH, while patient SD did not show pregnanetriol-11-one excretion even after ACTH.

The estimations of pregnanetriol and of pregnanetriol-11-one were carried out in two patients suffering from the adrenogenital syndrome. Both patients showed a high control excretion of these steroids and in patient SR a substantial increment was found following ACTH administration (Table VII). The high amounts of pregnanetriol and 17-KS and the presence of pregnanetriol-11-one might be due to defective steroidogenesis in the adrenal cortex probably, a partial block at 21- and/or 11-hydroxylase enzyme action in this disease.
DISCUSSION

In Cushing's syndrome there is high secretion of cortisol and most of the signs and symptoms of this disease have now been produced in non-endocrine patients by the administration of cortisol. The various causal factors which lead to increased production of corticosteroids are illustrated diagrammatically in Fig. 15. The differentiation of the etiological causes underlying adrenocortical pathology is of practical importance in the therapeutic management of this disease. In the present study, there was a close resemblance in the clinical appearance of the three patients (KK, TN and SD) showing signs of Cushing's syndrome though the mechanism involved in each case appeared quite different.

Adrenal hyperplasia: Patient KK

Urinary 17-KS:

This was a classical case of adrenal hyperplasia as evident by the histological studies of the surgically removed adrenal gland as well as by the excretory patterns of steroids. The urinary excretion of 17-KS was within the normal range and varied between 4.9 to 5.9 mg per 24 hours. The values decreased after partial adrenalectomy. This patient had a recurrence of Cushing's disease 5 years following adrenalectomy when the urinary excretion of 17-KS ranged from 3.8 to 4.8 mg per day. These values increased
POSSIBLE CAUSES OF CUSHING'S SYNDROME

Fig. 15

STEROIDOGENESIS IN ADRENAL CORTEX (BILATERAL ADRENAL HYPERPLASIA)

Fig. 16
only to 5.1 mg per day after administration of ACTH. On the other hand, urinary 17-KGS and plasma 17-OHCS showed a higher response to exogenous ACTH than normal subjects.

**Urinary 17-KGS and plasma 17-OHCS:**

In patient KK the urinary excretion of 17-KGS was within normal limits as assessed by repeated determinations of urinary 17-KGS on different days. This is contrary to the high plasma 17-OHCS in this patient. Similarly, after ACTH administration both urinary 17-KGS and plasma 17-OHCS increased above the normal response. A probable pathway of steroidogenesis in adrenal cortex in patient KK (adrenocortical hyperplasia) has been shown in Fig. 16. In this particular case it is possible that adrenal cortical steroids may be metabolised at a slower rate. This statement can be verified from detailed experiments where plasma 17-OHCS were determined following administration of cortisol dose and determining the decay rate of the injected material. The metabolism of cortisol depends on its concentration in the metabolic environment as indicated by Plager et al. In other patients with Cushing's disease (TN, SD) the plasma 17-OHCS and urinary 17-KGS correlated well and were always high. Patient KK excreted a normal amount of 17-KS before adrenalectomy. Since the excretion of adrenal steroids depends on the functional state of the liver as well as the kidney, it is possible that these functions were defective in patient KK. This probably explains the high plasma 17-OHCS.
associated with normal excretion of 17-KS and 17-KGS.

**Urinary pregnanetriol and pregnanetriol-11-one:**

As shown in Fig. 17 cortisol is synthesised from progesterone by progressive oxidation at 17, 21 and 11 positions. Pregnanetriol is formed by the reduction of 17α-hydroxyprogesterone at position 20 and at the α,β positions in ring A. Fotherby and Love\(^{37}\) observed that approximately 50% of the administered 17α-hydroxyprogesterone was converted to pregnanetriol in normal subjects while 11-desoxycortisol was not converted to this steroid. In adrenal hyperplasia enzymatic deficiencies in the adrenal cortex are believed to impair hydroxylation particularly at position 11 and 21. As a result various metabolites of the obligate precursors for cortisol appear in the urine like pregnanediol, pregnanetriol and pregnanetriol-11-one as shown in Fig. 17.

Since none of these precursors of cortisol possess the ability of cortisol to inhibit the secretion of ACTH, excessive quantities of ACTH are secreted leading to defective steroidogenesis in the adrenal cortex. In this way the enhanced excretion of 17-KS, pregnanediol, pregnanetriol in adrenal hyperplasia could be explained. The pregnanetriol excretion in patient KK in a control state (without ACTH administration) was within normal limits but increased twice to that of normal level after ACTH administration.
METABOLITES FROM THE OBLIGATORY PRECURSORS OF CORTISOL

**Fig. 17**
Pregnanetriol-11-one is an abnormal steroid metabolite and it has not been detected in the urine of normal men and women or of the pregnant women. Hence, the detection of this steroid in the urine has a definite significance and pointing to defective steroidogenesis due to adrenal cortex. This steroid was present in the urine of patient KK in the control state as well as after the administration of ACTH indicating defective steroidogenesis in the adrenal cortex. This may be probably because the precursors of cortisol such as 17α-hydroxyprogesterone might be getting hydroxylated at position 11 before the hydroxylation at position 21. It is known that 11-hydroxyprogesterone or Δ⁴-pregnene-11β-17α-diol-3, 20-dione is a poor precursor for cortisol synthesis. These steroids are reduced at Δ⁴-3-keto-position, hydroxylated at position 20 and oxidised at position 11 in the liver and excreted.

**Adrenal adenoma: Patient SD.**

**Urinary 17-KS:**

Patient SD had a benign adrenal cortical tumour and had signs and symptoms belonging to Cushing's syndrome. The peculiarity of this patient was that urinary 17-KS excretory level was normal and was not elevated after administration of ACTH.

**Urinary 17-KGS:**

The excretion of 17-KGS in the urine of this patient was significantly increased, as shown in Table XX.
This suggested hyperactivity of adrenal cortex. Although estimation of 17-KGS in urine proved to be a more sensitive index of this disease than the estimation of urinary 17-KS, it does not however help to distinguish between various causative factors of this disease.

**Plasma 17-OHCS:**

The concentration of plasma 17-OHCS in this case was significantly higher than normal as shown in Table XX. These values did not increase after the administration of ACTH. These results indicate that there is hyperactivity of adrenal cortex which seemed to be independent of ACTH secretion as shown in Fig. 18. After surgical removal of adrenal tumour the excretion of 17-KS as well as 17-KGS reduced considerably. The concentration of plasma 17-OHCS reduced from 30 to 2.5 μg per 100 ml on eleventh day following adrenalectomy (the cortisone therapy was discontinued two days before this estimation was done). The left adrenal was found atrophic and hence the patient was given exogenous cortisone for few months. In this case suppression of adrenocortical function by administration of 9-fluorocortisol or dexamethasone or other compounds having metabolic properties of cortisol would have been helpful in differentiating the etiological causes underlying this disease.

**Urinary pregnanetriol and pregnanetriol-11-one:**

Patient SD excreted higher amounts of pregnanetriol than normals which was increased after the administration of ACTH. The excess amounts of pregnanetriol excretion may
STEROIDOGENESIS IN ADRENAL CORTEX
(ADRENAL ADENOMA)

ACETATE -------► CHOLESTEROL

- ACTH

PREGNENOLONE

17α-HYDROXY-PREGNENOLONE

PROGESTERONE

11α-DESOXYCORTICOSTERONE -------► CORTICOSTERONE

DEHYDROEPI-ANDROSTERONE

17α-HYDROXYPROGESTERONE

11-DESOXYCORTISOL -------► CORTISOL

INCREASED INHIBITION OF ANT. PITUITARY

Δ4-ANDROSTENEDIONE

TESTOSTERONE

11β-HYDROXY-ANDROSTENEDIONE

Fig. 18
also reflect decreased 21-hydroxylase activity of the adrenal cortex. This patient did not excrete pregnanetriol-11-one even after administration of ACTH.

**Pituitary adenoma: Patient TN:**

**Urinary 17-KS:**

The excretion of 17-KS of patient TN was slightly higher than that of normal subjects. This patient had a pituitary adenoma. The urinary 17-KS did not decrease even after irradiation of tumour (3300 r) of the anterior pituitary gland.

**Urinary 17-KGS:**

The urinary values of 17-KGS in patient TN were significantly higher than normals which suggested hyperadrenocortical function. These values did not increase by the ACTH administration indicating a presence of adrenocortical or pituitary tumour.

**Urinary pregnanetriol and pregnanetriol-11-one:**

The excretory level of pregnanetriol was higher than normal and did not increase after the administration of ACTH, as shown in Table VII. It is interesting to note that patient TN excreted pregnanetriol-11-one before and after administration of ACTH. If the adrenal cortex in this case was normal and the hyperadrenocortical function was due to excess secretion of ACTH by anterior pituitary tumour, the presence of pregnanetriol-11-one in the urine of this patient was not expected. The abnormal steroidogenesis of
adrenal cortex might be due to stimulation of this gland by an unknown factor secreted by the anterior pituitary tumour.

**Plasma 17-OHCS:**

This patient had a very high concentration of plasma 17-OHCS (40.0 µg/100 ml) which showed very little response to ACTH administration as shown in Fig. 13. In this state the adrenocortical cells are functioning at maximum capacity because of high endogenous secretion of ACTH by the pituitary tumour. Additional exogenous ACTH, therefore, failed to stimulate further production of plasma corticosteroids. After X-ray irradiation of 2100 r to anterior pituitary the level of plasma 17-OHCS reduced to 11.1 µg per 100 ml and the response of ACTH test was within the normal limits. This could be explained on the basis that the adrenal cortex in such cases is physiologically not abnormal but it is constantly stimulated by the excessive secretion of ACTH from anterior pituitary gland. A probable pathway of steroidogenesis in such cases is illustrated in Fig. 19. There was considerable improvement in the physical condition of the patient, three weeks after X-ray therapy, the plasma 17-OHCS was normal and ACTH-corticosteroid response test at this state suggested that the adrenal function had reverted nearly to normal as a result of deep X-ray therapy.

The plasma 17-OHCS values at control state (without ACTH administration) in the various etiological categories
STEROIDOGENESIS IN ADRENAL CORTEX
(PITUITARY ADENOMA)

\[
\begin{align*}
\text{ACETATE} & \quad \rightarrow \quad \text{CHOLESTEROL} \\
& \quad \rightarrow \quad \text{ACTH} \\
\text{PREGNENOLONE} & \quad \rightarrow \quad 17\alpha\text{-HYDROXY-PREGNENOLONE} \\
& \quad \rightarrow \quad \text{DEHYDROEPI-ANDROSTERONE} \\
& \quad \rightarrow \quad 1\beta\text{-ANDROSTENEDIONE} \\
& \quad \rightarrow \quad \text{TESTOSTERONE} \\
\text{PROGESTERONE} & \quad \rightarrow \quad 11\beta\text{-DESOXYCORTICOSTERONE} \\
& \quad \rightarrow \quad \text{CORTICOSTERONE} \\
& \quad \rightarrow \quad 11\beta\text{-DESOXYCORTISOL} \\
& \quad \rightarrow \quad \text{CORTISOL} \\
\end{align*}
\]

Fig. 19
of hypercorticism did not appear to differ in any characteristic manner in our three cases, adrenal hyperplasia, adrenal adenoma and pituitary adenoma. This is in contrast to the findings of Perkoff et al.⁴⁰ who reported different levels of plasma 17-OHCS in different categories of hyper adreno-cortical activities. ACTH test was found useful in differentiation of various etiological causes of Cushing's syndrome and for the management of its treatment.
**SUMMARY**

1. Determination of urinary 17-KS and 17-KGS were of little use in the diagnosis of Cushing's syndrome. On the other hand, estimation of plasma 17-OHCS in control state and after the administration of ACTH was important to distinguish adrenal hyperplasia from adrenocortical adenoma or pituitary adenoma which are the etiological causes of Cushing's syndrome.

2. Higher than normal amounts of pregnanetriol in the urine of all Cushing's patients and the presence of pregnanetriol-11-one in urine of patients having adrenal hyperplasia and pituitary adenoma indicated defective steroidogenesis in the adrenal cortex in this disorder.

3. Attempts have been made to differentiate the etiological causes of Cushing's syndrome and the importance of such differential diagnosis by determination of various steroid hormones or their metabolites have been discussed.
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