VIRILIZING SYNDROMES

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FIG. 1.—Biosynthetic pathways of steroids in adrenal, ovary and testis.

Virilization implies that a person has been influenced by an excess of androgen. Although this may be comparatively easily recognized in children and women, it is extremely difficult to detect in men.

The naturally occurring substances which are known to have androgenic activity and which are of importance in man are, in decreasing order of activity: testosterone, androstenedione, dehydroepiandrosterone and 11-hydroxyandrostenedione. Androsterone has also been suggested as arising in the adrenal, but the evidence for its production by this gland is limited to two observations with incomplete identification.^{17, 8}

Apart from androsterone, all these substances have been isolated from adrenal glands, though in the case of testosterone it was from an adrenal tumour.

The Origin of Androgens

Androgenic substances are produced by three glands, the adrenal, testis and ovary. One substance is common to all three glands, namely, androstenedione (Fig. 1). In the testis this is converted to testosterone, in the ovary it is on the pathway to oestradiol and in the adrenal it appears to be one of the definitive androgens produced by

this gland.²⁶ The biosynthetic pathway to androstenedione is shown in Fig. 1. In the adrenal the dominant pathway is to hydrocortisone (cortisol) (Fig. 2) and this is controlled by the pituitary hormone, ACTH (corticotrophin). In its turn ACTH is depressed by cortisol; by this feedback mechanism the production of cortisol is controlled at the appropriate level.

By administration of ACTH production of cortisol can be greatly increased. In younger children this treatment produces only a very small increase in androgen excretion. With the onset of puberty the adrenal response to corticotrophin changes towards the adult pattern and appreciable androgen production is found. After loss of the pituitary in the adult the adrenal androgen response to ACTH reverts to that of a young child. In contrast to this, some women with simple hirsutism have an exaggerated androgen response to ACTH. It has been suggested by Prunty²² and Mills²⁰ that these data might be explained by the existence of a second pituitary hormone which comes into play at puberty and which acts synergistically with ACTH to increase adrenal androgen secretion. This hormone might reasonably be called the androgen-stimulating hormone.

The qualitative similarity of the steroid path-

FIG. 2.—Structures of steroids.

ways in the gonads and adrenals was first suggested by Samuels,²³ and it is quite possible that the increased androgen production by all three at the time of puberty might be controlled by the same pituitary hormone.

In young animals approaching puberty androstenedione appears in spermathecal vein blood before testosterone does and is increased by treatment with chorionic gonadotrophin. However, the latter trophic hormone will not effect the conversion of androstenedione to testosterone.¹⁸ After puberty chorionic gonadotrophin in male animals and man increases the secretion of testosterone and not that of androstenedione. This evidence is in support of the view that one pituitary hormone stimulates androgen synthesis as far as androstenedione, but another is necessary to convert the androstenedione to testosterone. One of these hormones is interstitial cell-stimulating hormone (ICSH). The pathway from progesterone to androgen in human ovarian tumour tissue has been demonstrated by Savard *et al.*²⁵ and Mills *et al.*²¹ It was found by Meyer¹⁹ that both androstenedione and 19-hydroxyandrostenedione are converted to oestrogen and it seems probable, therefore, that 19-hydroxyandrostenedione is an intermediate between androgen and oestrogen. In the ovary the administration of FSH either *in vivo* or *in vitro*¹⁵ stimulates the conversion of androgen to oestradiol.

Adrenal androgen production differs in certain important ways from ovarian or testicular androgen secretion. The compound dehydroepiandrosterone (DHA) is characteristic of the adrenal (see Fig. 1). What part it plays as an androgen is obscure. In adrenal vein blood Short²⁶ found it is sometimes present to a greater extent than androstenedione and sometimes to a lesser extent. However, the greater androgenicity of androstenedione made it always the dominant androgen. Another important characteristic of the adrenal is the

presence of an enzyme system for attaching a hydroxyl group on carbon atom 11 of the steroid nucleus (see Fig. 2). This enzyme system may operate as the last stage in cortisol synthesis or it may work after removal of the side chain and convert androstenedione to 11-hydroxyandrostenedione. In so doing it would decrease the androgenicity of the androstenedione. The 11-hydroxylating enzyme system has only rarely been demonstrated in gonadal tissues.²⁴

Metabolism of Androgen

The similarity in the steroid pathways in adrenal and gonads complicates the problem of detecting the source of excess androgen secretion in the various virilizing syndromes. Androstenedione and testosterone are interconvertible in some tissues and both are excreted in the urine as the 17-ketosteroids androsterone and aetiocholanolone (Figs. 2 and 3). The presence of these 17-ketosteroids in the urine (and they are the major ones) gives no information as to the gland secreting the parent compound. However, DHA and the 11-oxygenated 17-ketosteroids (Fig. 3) are characteristic of the adrenal and the ratio of these to the androsterone and aetiocholanolone may well give an indication as to which gland is secreting the excess androgen. If either the testis or the ovary is producing testosterone or androstenedione excessively the proportion of the total 17-ketosteroids that is DHA would be expected to be abnormally small. In practice this ratio is found to be very variable in normal people, probably because DHA may be converted to androstenedione and appear in the urine as androsterone or aetiocholanolone. The reverse situation, however, gives valuable information, i.e. a markedly raised DHA excretion definitely indicates that the adrenals are secreting excess androgen.

Study of the 11-oxygenated 17-ketosteroids is complicated by the fact that some arise from the

FIG. 3.—Androgens and their urinary excretion products.

FIG. 4.—The ratio $\frac{11\text{-hydroxy androsterone}}{11\text{-oxygenated aetiocholanolones}}$ in the urine of normal individuals and patients with virilism. C = normal controls, H = idiopathic hirsutism, S-L = Stein-Leventhal syndrome, A-G = adrenogenital syndrome.⁷

metabolism of 11-β-hydroxyandrostenedione and some from cortisol (Fig. 3). However, if the 11-oxygenated ketosteroids are separated into the three compounds, one finds that 11-hydroxyandrostenedione leads mainly to 11-hydroxyandrosterone,⁵ but the small fraction of cortisol which is excreted as 17-ketosteroid is found mainly as

11-hydroxy or 11-keto-aetiocholanolone.¹⁰ If, therefore, adrenal secretion is directed more towards androgen secretion than to cortisol secretion, one would expect the androsterone and aetiocholanolone or the 11-hydroxyandrosterone to be high relative to the 11-oxygenated aetiocholanolones which arise mainly from cortisol. This divergence

FIG. 5.—The ratio $\frac{11\text{-deoxy 17-ketosteroids}}{11\text{-oxygenated aetiocholanolones}}$ in the urine of normal individuals and patients with virilism. Symbols as for Fig. 4.⁷

BIOSYNTHESIS OF CORTICIDS IN CONGENITAL ADRENAL HYPERPLASIA

FIG. 6.—The biosynthetic pathway in patients with the adrenogenital syndrome.

FIG. 7.—The relation between 17-ketosteroids and 17-ketogenic steroids. Data for control days and the first, third and fourth days of ACTH gel 20 u. b.d. I.M. are plotted.

is exaggerated during ACTH administration.⁷ The ratios are abnormal in congenital adrenal hyperplasia and idiopathic hirsutism (Fig. 4). They are also abnormal in some patients with the Stein-Leventhal syndrome (Figs. 4 and 5),⁷ which suggests that the adrenal as well as the ovaries may be abnormal in this condition.

In congenital adrenal hyperplasia (the adrenogenital syndrome) the primary defect, as first shown by Bartter *et al.*,² is that there is interference with cortisol synthesis (Fig. 6) and ACTH secretion rises and stimulates the adrenal to secrete more androgen. The hold-up in cortisol synthesis is at the stage of 17-hydroxyprogesterone.¹⁶ This steroid is then metabolized to give rise to pregnanetriol and 17-hydroxypregnanolone (Fig. 6). In normal individuals only very small amounts of pregnanetriol are excreted (except during pregnancy, when it is not of adrenal origin¹⁴). The ketogenic steroid technique¹¹ measures pregnanetriol as well as cortisol and its metabolites in the urine. The ratio of ketogenic steroids to pregnanetriol is therefore a measure of the efficiency of cortisol synthesis. This ratio is very low in the adrenogenital syndrome.

In one other respect adrenal androgen differs from gonadal and that is in its response to ACTH. Only adrenal androgen is increased in response to ACTH. However, the rise in 17-ketosteroid excretion when ACTH is administered depends upon the amount of androgen-stimulating hormone.

The response is best assessed in relation to the corticoid response. In children and patients with hypopituitarism the 17-ketosteroid response is poor (Fig. 7). In some patients with idiopathic hirsutism it is greater than normal (Fig. 7). When the testes are removed the androgen-stimulating hormone apparently rises because the 17-ketosteroid response to ACTH is unusually good (Table 1).

Conversely, if there is a tumour producing excess androgen, this appears to suppress the androgen-stimulating hormone so that the 17-ketosteroids rise very poorly when ACTH is given (Table 2). The response to ACTH, therefore, is a very useful test in patients with virilizing conditions.

Clinical Assessment

Virilization may become apparent in three different ways: (a) at birth, (b) as precocious puberty, (c) in adults.

(a) At Birth

Female infants may be born with partial masculinization of the external genitalia (female pseudohermaphrodites). This may include enlargement of the clitoris or labial fusion or both. It may be so severe that the vagina and urethra open into a common urogenital sinus or the child may appear like a male with hypospadias. The corresponding condition in the male (macrogenitosomia) consists of enlargement of the genitalia, especially the

TABLE 1
RESPONSE TO ACTH IN A MAN SOME YEARS AFTER
BILATERAL ORCHIDECTOMY AND WITHOUT REPLACEMENT
THERAPY

Therapy	17-keto-steroids mg./day	17-ketogenic steroids mg./day
None	11.0	9.8
"	10.9	9.1
ACTH gel 20 u. b.d. I.M.	27.2	29.4
" " " " " "	30	35
" " " " " "	36	44
" " " " " "	36	39

TABLE 2
RESPONSE TO ACTH IN A WOMAN WITH AN ANDROGEN-
SECRETING OVARIAN TUMOUR

Therapy	17-keto-steroids mg./day	17-ketogenic steroids mg./day
None	11.3	5.8
"	8.4	8.2
ACTH gel 20 u. b.d. I.M.	8.1	17.3
" " " " " "	10.1	14.5
" " " " " "	13.2	12.7
" " " " " "	14.2	38.6

penis, and this may easily be overlooked. There are three causes of these conditions: (i) Congenital adrenal hyperplasia (the adrenogenital syndrome). (ii) Congenital abnormalities without hormonal disturbance. (iii) Administration of androgenic substances to the mother during pregnancy. The second can only be diagnosed by excluding the other two, but even if the third is suspected it is still essential to exclude congenital adrenal hyperplasia.

CONGENITAL ADRENAL HYPERPLASIA

The age of presentation depends upon the severity of the condition. The most severely affected have genital abnormalities at birth. It is difficult to explain these just on the basis of a defect in cortisol synthesis.

Diagnosis. It is important to diagnose the condition as early as possible so that treatment with cortisone may be started. This will prevent further virilization and completely normal development will then ensue. Fertility in the female then appears to be unimpaired and children born to such mothers have been normal, although relatives of patients with the adrenogenital syndrome do seem to have minor defects in cortisol synthesis.⁹

The diagnosis is confirmed firstly by persistence of raised 17-ketosteroid excretion after the first few weeks of life and secondly by excretion of pregnanetriol of more than a few hundred microgrammes per day. Both these abnormalities are suppressed by cortisone treatment. Administra-

TABLE 3
THE INCIDENCE OF THE VARIOUS CAUSES OF PRECOCIOUS
PUBERTY*

Cause	Females	Males	% (both sexes)
Idiopathic ..	401	111	62
Congenital adrenal hyperplasia ..	58	42	12
Ovarian tumours ..	78	—	9
Intracranial lesions	18	51	8
Albright's syndrome	33	2	4.2
Adrenal tumours ..	4	16	2.4
Testicular tumours	—	18	2.2

*Based on Wilkins.²⁷

tion of ACTH usually causes increased 17-keto-steroid excretion in contrast to the response in normal children. This also suggests that there must be some other factor besides the defect in cortisol synthesis. Girls with enlargement of the clitoris should not be rashly subjected to amputation unless the enlargement is really gross. With control of the excessive androgen secretion and normal growth of the rest of the body, the clitoris may not be out of proportion some 20 years later.

ANDROGENS DURING PREGNANCY

Partial virilization of females has been reported not only after administration of methyl testosterone,³ but also when certain synthetic progestational agents have been given for threatened abortion. Some of these progestational agents are androgenic, especially 17-ethinyl testosterone ('Ethisterone') and 17-ethinyl 19-nortestosterone ('Norlutin'), as reported by Grumbach *et al.*¹³ Two mothers given progesterone have had virilized infants, but this may have been coincidence considering the number of women given progesterone during pregnancy who have had normal infants.

The children are in all hormonal respects normal and the only treatment required is minor surgery if the labia are fused. The same applies to infants with non-hormonal congenital abnormalities.

(b) Precocious Puberty

In children virilization may present as precocious puberty. In girls there is usually enlargement of the clitoris first, followed by appearance of pubic hair. In boys the penis is usually first affected: it increases in size and pigmentation. Erections become more frequent, the scrotum darkens and pubic hair appears. In both sexes acne may develop. Much later axillary hair appears and then the voice deepens. Only rarely does facial hirsutism appear in children. The bone age increases and growth has the typical puberty spurt. Early on, therefore, the children are taller than others of the same age, but epiphyseal closure comes early and the final stature is shorter than

normal. Mental age is unaffected and usually tooth development is not advanced.

The incidence of the various causes of precocious puberty is shown in Table 3 (based on Wilkins²⁷).

IDIOPATHIC (CONSTITUTIONAL)

The changes are those of normal puberty. The excretion of 17-ketosteroids, oestrogens and gonadotrophins are as found at adolescence. It occurs predominantly in girls and may begin as early as the time of birth, but most commonly arises about four or five years of age. It may be necessary to exclude the other causes (see below).

CONGENITAL ADRENAL HYPERPLASIA

If the children do not have genital abnormalities at birth, they usually present about the age of two or three years, either with enlargement of the clitoris or penis or with development of pubic hair. By this time they will show more rapid growth than normal and, in particular, advanced bone age. The diagnosis is made as mentioned above. The pregnanetriol excretion becomes increasingly valuable and especially its relationship to the total ketogenic steroids when ACTH is given. In normal individuals the ratio $\frac{\text{pregnanetriol}}{\text{total ketogenic steroids}}$

is between 9 and 30 during ACTH administration and in congenital adrenal hyperplasia it is usually under two.⁷ Treatment with normal replacement doses of cortisone should be started as soon as the diagnosis is confirmed. Without this the females will rarely menstruate and boys will not develop active spermatogenesis. Both will occur regardless of chronological age if cortisone therapy is commenced after the bone age has reached 12 years.

A few children with the adrenogenital syndrome are hypertensive, and in two of these it has been shown that the metabolic block is in the conversion of 11-deoxycortisol to cortisol (see Fig. 6). The corticosterone which is made in small amounts by the normal adrenal also fails to undergo 11-hydroxylation and so desoxycorticosterone is formed. It is thought that this compound is responsible for the hypertension. Treatment with cortisone in the early stages gradually allows the blood pressure to return to normal.

Another small group of patients with the adrenogenital syndrome includes those who are 'salt-losing'. They present as in adrenal crisis and are very likely to die undiagnosed. They need excessive amounts of sodium-retaining steroid and added salt as well. Some have defective aldosterone synthesis.⁴ Extensive search for a sodium-losing steroid in them has failed to reveal one and recent studies on renal handling of sodium sug-

gest that the presence of one need not be postulated.¹

OVARIAN TUMOURS

The commonest ovarian tumour in childhood is the granulosa cell tumour. It may cause precocious sexual development at any age from five months upwards. Uterine bleeding is almost invariable and this excludes an adrenal cause for the sexual development. The 17-ketosteroid excretion is normal or only slightly raised (1.6 to 3.5 mg./day in the reported cases), but, on the other hand, urinary oestrogen levels are usually high. In every case there has been a palpable pelvic tumour by the time the child presented with obvious symptoms and signs.

Other ovarian tumours in childhood are exceedingly rare. A few cases of teratoma have been described and clinically resemble granulosa cell tumour. Chorionepithelioma is even rarer. The patients have marked wasting associated with sexual precocity and sometimes menstruate. As might be expected, there is a high titre of chorionic gonadotrophin in the urine.

INTRACRANIAL LESIONS

These form a surprisingly high proportion of the cases of precocious puberty when it is not constitutional. Clinically they resemble exactly idiopathic precocity unless neurological signs are present. The hormonal changes that occur are precisely those of normal puberty. The intracranial lesions have all been in the region of the hypothalamus or if they originate in surrounding structures, e.g. pineal, they encroach upon the hypothalamus. The tumours have mostly been gliomas or astrocytomas. Sometimes they are associated with other hypothalamic disturbances e.g. polydipsia, polyphagia, obesity, sleep disturbance. The same syndrome may arise after encephalitis or miliary tuberculosis or in association with congenital brain defects. If there is a history of encephalitis in a child presenting with precocious puberty further investigations should be carried out to confirm or exclude, if possible, hypothalamic damage.

ALBRIGHT'S SYNDROME

Precocious puberty is one aspect of this syndrome. Puberty is in all respects similar to the normal, but may occur at any age from a few months upwards. The other features of the condition are brownish areas of skin pigmentation which are present from birth and patchy areas of rarefaction in the bones ('polyostotic fibrous dysplasia'). There may be sclerosis of the base of the skull, but there are no abnormalities of calcium or phosphorus metabolism.

TABLE 4

RESPONSE TO ACTH IN A BOY AGED THREE WITH AN ANDROGEN-SECRETING ADRENAL TUMOUR

Therapy	17-keto-steroids mg./day	17-ketogenic steroids mg./day
None	35	8.3
" " " " " "	28	5.2
ACTH gel 20 u. b.d. I.M.	36	11
" " " " " "	23	62
" " " " " "	39	62
" " " " " "	26	129

ADRENAL TUMOURS

In children virilizing tumours of the adrenal are frequently malignant, though they may remain encapsulated for a long time. Presenting symptoms include more rapid growth in height and muscular development. In boys the penis increases in size and becomes pigmented and in girls the clitoris hypertrophies. Pubic hair may also be present. These patients are readily distinguished from those with idiopathic precocity because they excrete large amounts of 17-ketosteroids. These are not suppressed by cortisone and the pregnanetriol is normal: this differentiates them from patients with congenital adrenal hyperplasia. Usually fractionation of the urinary 17-ketosteroids will reveal appreciable amounts of dehydroepiandrosterone. This excludes the testis (or ovary) as the gland responsible for the virilization. With pure androgen-secreting tumours the rest of the adrenal is normal and shows a normal hydrocortisone response to ACTH, but the 17-ketosteroids are unaffected (Table 4).

INTERSTITIAL CELL TUMOUR OF TESTIS

These tumours are comparatively rare. The children resemble those with the adrenogenital syndrome or with androgen-secreting tumours of the adrenal. The tumour is usually unilateral and not malignant. If it is large enough, one testis will appear larger than the other. The size of the tumour has varied from less than 1 cm. to 12 cm. The smaller ones may be difficult to detect. The urinary 17-ketosteroids are raised, but the dehydroepiandrosterone is not. The corticoid response to ACTH is that of a normal child and the 17-ketosteroids are not suppressed by cortisone. Pregnanetriol excretion is normal. These chemical tests serve to differentiate patients with these tumours from those with adrenal tumours or with congenital adrenal hyperplasia. It is important to remember that some of the latter may have testicular enlargement associated with what some authorities call 'adrenal rests' and others call 'clumps of Leydig cells'. The cortisone

suppression test is essential to distinguish the two conditions.

CUSHING'S SYNDROME

In children this is not usually associated with virilization, whereas the features of cortisol excess are quite obvious.

(c) Adults

The differential diagnosis here is somewhat more difficult. Causes of virilization in the adult include the following (in approximate order of frequency):

- (1) Idiopathic hirsutism.
- (2) Stein-Leventhal syndrome.
- (3) Cushing's syndrome.
- (4) Ovarian tumours.
- (5) Congenital adrenal hyperplasia.
- (6) Adrenal tumours.

The study of the clinical picture and the chemical investigations are directed towards deciding which gland is responsible for the excessive androgen secretion and whether surgical intervention is indicated. It is rapidly becoming apparent that there may not be any good correlation between histology of a tumour and the hormones produced by it (e.g. testicular tumour secreting only cortisol,²⁴ ovarian tumour with cells resembling granulosa cells but secreting testosterone²¹).

In general, it may be said that severe virilization, if due to adrenal androgen, is associated with high 17-ketosteroid excretion; if it is associated with normal 17-ketosteroid excretion the androgen most probably comes from the ovary and probably includes testosterone.^{25, 21}

The data required to differentiate the various conditions causing adult virilization are shown in Table 5. The ratios of 11-hydroxyandrosterone to 11-oxygenated aetiocholanolones and 11-deoxy 17-ketosteroids to 11-oxygenated aetiocholanolones have been reported by Brooks and Prunty⁷⁷ and Figs. 4 and 5 are based on their results.

(1) IDIOPATHIC HIRSUTISM

This diagnosis is best reserved for those women who have hirsutism beginning after puberty, usually around the age of 20. They usually have normal menstrual cycles and do not have enlargement of the clitoris. Their resting 17-ketosteroids are usually around the upper normal levels, but when given ACTH some of them have exaggerated 17-ketosteroid responses (Fig. 7). Their 17-ketosteroids can be suppressed with cortisone and their pregnanetriol excretion is often around or just above the upper limits of the normal range (up to 2 mg./day). Fractionation of the 17-ketosteroids suggests increased production of 11-

TABLE 5
THE DIFFERENTIAL DIAGNOSIS OF ADULT VIRILISM

	17-ketosteroids					Preg- nanetriol	Menstrua- tion	Pneumo- peritoneum
	Resting	ACTH Response	Suppression Test	Ratio I*	Ratio II*			
Idiopathic Hirsutism	Normal or high	Normal or high	Suppress	Increased	Increased	Normal	Normal	
Stein-Leventhal	Normal or high	Normal or high	Suppress	Increased	Normal or increased	Normal	Irregular or absent	Enlarged ovaries
Cushing's	Normal or high	Normal or high	May suppress	Increased	Normal	Normal	Irregular or absent	
Ovarian tumour	Normal or high	Normal or low	Poor suppression	Normal	Increased	Normal	Irregular or absent	Enlarged ovary or palpable tumour
Adrenogenital	Normal or high	Normal or high	Suppress	Increased	Increased	High	Normal or absent	
Adrenal tumour	High	No change	No change	Normal or increased	Increased	Normal	Normal or irregular	

* Ratio I = $\frac{11\text{-hydroxyandrosterone}}{11\text{-oxyaetiocholanolones}}$

* Ratio II = $\frac{11\text{-deoxy 17-ketosteroids}}{11\text{-oxyaetiocholanolones}}$

hydroxyandrostenedione and the precursors of androsterone and aetiocholanolone.

Long-term suppression of 17-ketosteroids with cortisone with or without oestrogen in addition causes diminution of hair growth in some individuals. The results are certainly not dramatic.

(2) STEIN-LEVENTHAL SYNDROME

This will be dealt with in greater detail elsewhere in this issue. The point that should be emphasized here is that it may be very difficult to differentiate these patients from those with idiopathic hirsutism. The data of Brooks and Prunty⁷ show that the same adrenal disturbance may occur in both groups of patients. Menstrual disturbance is common in the Stein-Leventhal syndrome, but the diagnosis can only be established if the typical polycystic ovaries are demonstrated. Either vaginal examination or pneumoperitoneum may reveal ovarian enlargement.

(3) CUSHING'S SYNDROME

In severe cases there is very little problem in distinguishing between Cushing's syndrome and other causes of hirsutism. However, the milder cases may well present difficulties. Presence of purple striae would be very much in favour of Cushing's syndrome. Hypertension and plethoric facies may also occur with some ovarian tumours (see below) and obesity is sometimes associated with the Stein-Leventhal syndrome. The final

diagnosis will sometimes depend upon the urinary corticoid excretion and its response to a normal ACTH-suppressing dose of dexamethasone. In all cases except Cushing's syndrome the urinary corticoids would be suppressed by 2 to 3 mg. of dexamethasone in divided doses every six hours for two days. The 17-ketosteroids often take longer to fall even if they are of adrenal origin.

(4) OVARIAN TUMOURS

It is much more important to establish that an ovarian tumour is the cause of virilization than to predict before operation what type of tumour might be found.

The 17-ketosteroids are rarely much raised in patients with ovarian androgen excess. This suggests that when virilization is severe a very potent androgen is being secreted. It has been shown that testosterone was being synthesized by two ovarian tumours.^{25, 21}

An ovarian tumour is frequently large enough to be palpable, but sometimes it is not and then various tests may suggest that the androgen excess originates in the ovary. With ACTH the rise in 17-ketosteroids is poor (see Table 2). This may be because the androgen-stimulating hormone is suppressed by the ovarian androgen. On the other hand, the 17-ketosteroids are not well depressed by suppressing endogenous ACTH with cortisone. If the 17-ketosteroids are fractionated, the ratio of 11-hydroxyandrosterone to the 11-oxygenated

aetiocholanolones is normal, while the ratio of 11-deoxy 17-ketosteroids to the 11-oxygenated aetiocholanolones is high. This is because 11-oxygenation of ovarian hormones does not normally occur. Menstruation is frequently interfered with: this may lead either to amenorrhoea, oligomenorrhoea or occasionally intermenstrual bleeding.

Arrhenoblastoma. This is the commonest ovarian tumour producing androgen excess. Virilization is severe, usually with marked hirsutism, enlargement of the clitoris and deepening of the voice coming on in the space of a few months. The tumour is usually palpable and may contain multilocular cysts. There is a gradation between the true arrhenoblastoma and the granulosa cell tumour. Some tumours have been described which contain both types of histology and for these the term *gynandroblastoma* was proposed by Meyer. The arrhenoblastoma is frequently malignant, but is slow to metastasize.

Masculinovoblastoma. This tumour has many names: virilizing lipid cell tumour, adrenal cortical cell tumour, luteoma, hypernephroma of the ovary. The clinical features are identical with those of the arrhenoblastoma. Sometimes there is excess excretion of oestrogen and pregnanediol. These latter features are of value when, as sometimes happens, the tumour causes the characteristics of Cushing's syndrome, including polycythaemia, hypertension, obesity and even impaired glucose tolerance. These characteristics may appear before the ovarian tumour is palpable, but the virilization is frequently more severe than in Cushing's syndrome. The tumour is very rare.

Hilus cell tumour (sympatheticotrophic cell tumour). There is no way clinically of differentiating this tumour from other virilizing ovarian tumours. Histologically it is of interest because the cells resemble the Leydig cells of the testis, even to being in close association with non-myelinated nerves and having crystalloids of Reinke.

Dysgerminoma. This has never been shown to be producing hormones, but it is sometimes associated with pseudohermaphroditism.

(5) CONGENITAL ADRENAL HYPERPLASIA

The diagnosis of this condition has previously been discussed. However, it is important to realize that the condition may first manifest itself after puberty^{12, 6} and that regular menstruation

may then occur. In all biochemical respects these patients have the characteristics of the congenital variety of the disease, but there is no evidence of excessive androgen secretion before puberty. Pregnanetriol excretion, especially in response to ACTH, is most valuable diagnostically.

(6) ADRENAL TUMOURS

The main characteristics useful in diagnosis have been described under the section on precocious puberty. In the adult the differentiation from an ovarian tumour is made by the high excretion of dehydroepiandrosterone. The urinary 17-ketosteroids are not stimulated by ACTH nor depressed by cortisone.

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