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DIAGNOSIS, COURSE AND TREATMENT**

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ADRENAL CORTICAL HYPERPLASIA WITH VIRILISM: DIAGNOSIS, COURSE AND TREATMENT^{1, 2}

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INTRODUCTION

The clinical differentiation of patients with adrenal cortical hyperplasia and adrenal cortical carcinoma is often difficult because both of these lesions may give rise to a symptom complex (1 to 4) known as adrenal cortical virilism or as the adrenogenital syndrome.³ The characteristics of the syndrome usually are accelerated growth and skeletal maturation in children, amenorrhea and lack of breast development in girls, and excessive development of masculine secondary sex characteristics, acne, hirsutism, and increased musculature in individuals of both sexes. Rarely, patients with carcinoma of the adrenal cortex show abnormal feminization instead of masculinization.

The possibility of differentiating hyperplasia from carcinoma by chemical measurements was suggested by investigators who isolated and identified certain steroids in unusual quantities from the urine of patients with adrenal cortical carcinoma (5 to 10). The isolation and identification of urinary steroids, however, requires special facilities which are not available in most clinical laboratories. On the other hand, relatively simple procedures are available for the fractionation and colorimetric assay of some of the urinary steroidal constituents (11). Preliminary observations have been reported from this laboratory on the clinical usefulness of urinary steroid assay in differential diagnosis (12).

If the diagnosis is carcinoma of the adrenal cortex, surgical removal of the tumor is clearly the treatment of choice. However, surgical removal of a significant amount of adrenal tissue does not

appear to be of permanent benefit to patients with adrenal cortical hyperplasia (1, 3, 12, 13). On the other hand, suggestively beneficial effects have been obtained by the administration of estrogenic hormones to female patients with virilism associated with adrenal cortical hyperplasia. Dorfman, Wilson and Peters (3) noted a temporary fall in the urinary excretion of male hormones (androgens) and a slight development of the breast tissue in one girl who received large quantities of one of the natural estrogens, estrone. Lisser (14) has also reported that a 17-year-old girl was feminized by injections of the synthetic estrogen, diethylstilbestrol.

The present communication confirms and extends our previous observations (12) by reporting measurements of the pregnanediol and of the alpha and beta alcoholic, non-alcoholic, and total 17-ketosteroid excretion per day of 12 patients with adrenal cortical hyperplasia and 3 patients with adrenal cortical carcinoma.⁴ Additional data are cited from the literature. The study also presents some observations on 2 girls and 1 boy with adrenal cortical hyperplasia, before and after the oral administration of diethyl stilbestrol.

MATERIAL AND METHODS

Of the 12 patients listed under the diagnosis of adrenal cortical hyperplasia (Figure 1), 11 were studied in this laboratory⁵; Case 13 was reported by Fraser, Forbes, Albright, Sulkowitch and Reifenstein (15); Case 6 was investigated both in our laboratory (case 6b) and by Fraser *et al.* (case 6a). All presented the characteristic evidences of adrenal cortical virilism. In 7 of this group, the diagnosis was confirmed by surgical exploration; in

¹ Read before the American Pediatric Society, Skytop, Pennsylvania, May 2, 1942.

² This work was aided by a grant from the Commonwealth Fund of New York.

³ This clinical entity is to be distinguished from Cushing's syndrome which may also be associated with adrenal cortical dysfunction.

⁴ We are greatly indebted to the following physicians for urine samples and case summaries on the following cases reported here: Dr. F. Albright, Cases 13 and 15; Dr. H. Friedgood, Case 16; Dr. R. Ganz, Case 3; Dr. S. Werner, Cases 4, 5 and 12; Dr. G. Twombly, Case 7; Dr. J. Warkany, Case 1; Dr. W. A. Reilly, Case 8.

⁵ Detailed data relating to these patients are on file in this office.

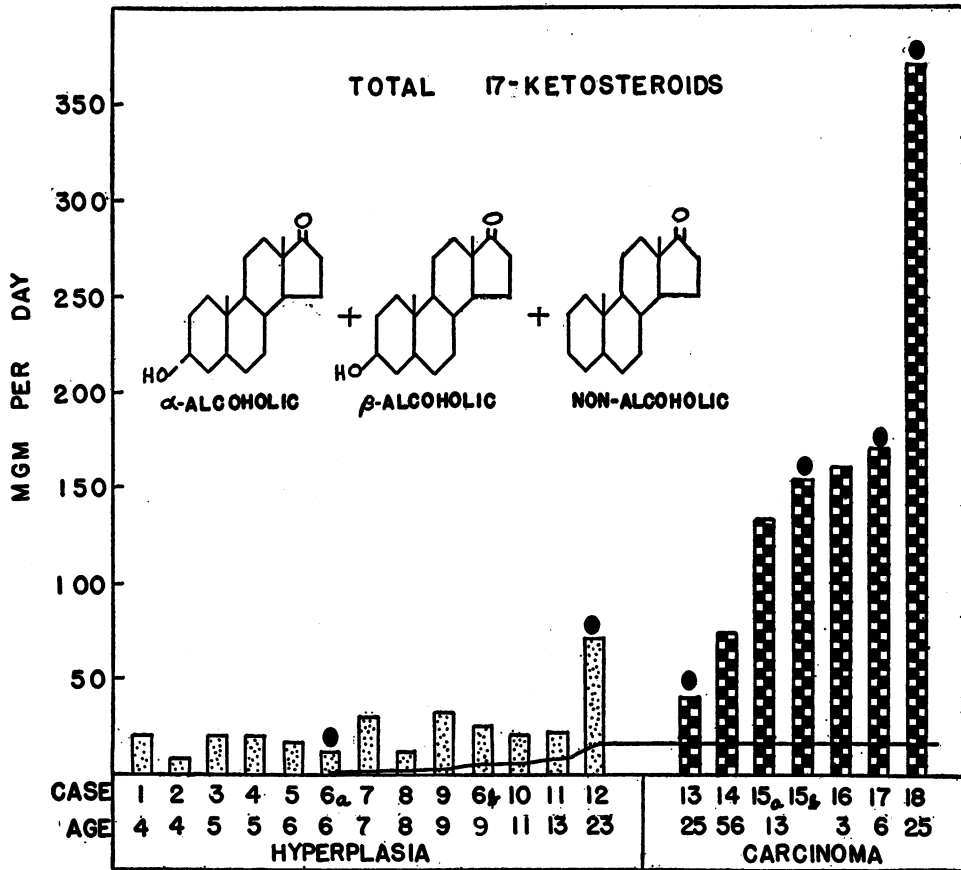


FIG. 1. TOTAL URINARY 17-KETOSTEROID OUTPUT PER DAY BY PATIENTS WITH ADRENAL CORTICAL HYPERPLASIA (SPECKLED COLUMNS) AND WITH ADRENAL CORTICAL CARCINOMA (CHECKERED COLUMNS) AS GIVEN BY THE ORDINATE

A black circle over a column indicates that the measurement was taken from the literature. Cases 6_a and 12, reference 15; cases 13 and 17, reference 5; case 15_b, reference 10; case 18, reference 16; case 19, figure 4, reference 9. The semi-horizontal curve represents the approximate upper limit of normal 17-ketosteroid output per day by normal individuals of the same or of an older age.

the remainder, a presumptive diagnosis was made on the basis of the clinical findings and the prolonged course of the disease.

Three of the 7 patients with adrenal cortical carcinoma (Figures 1 to 4) were studied in this laboratory.⁶ Case 15 was studied both in our laboratory and by Wolfe, Fieser and Friedgood (10). Urinary excretion data on the other 4 were taken from the literature (6, 7, 9, 16). Of these patients, 5 had signs and symptoms of adrenal cortical virilism. On the other hand, Cases 13 and 14 had a different syndrome, commonly known as Cushing's disease, which in these patients was associated with carcinoma of the adrenal cortex.

Estimations of the approximate upper limit of normal

⁶ Detailed data relating to these patients are on file in this office.

urinary total 17-ketosteroid output are derived from over 200 determinations, on 80 normal persons of both sexes ranging in age from a few hours to 45 years. The normal values for the various 17-ketosteroid fractions represent measurements made on 40 individual specimens, and on 7 pooled specimens, each one of which was made up to be representative of a different age group. The maximum normal pregnanediol value is derived from 22 determinations made on males of different ages and on girls who had not reached the menarche.

All determinations in this laboratory were made according to procedures described elsewhere (11, 17). With the exception of Case 18 the urinary excretion data on the carcinoma patients taken from the literature represents values obtained by chemists who isolated and identified the urinary steroids.

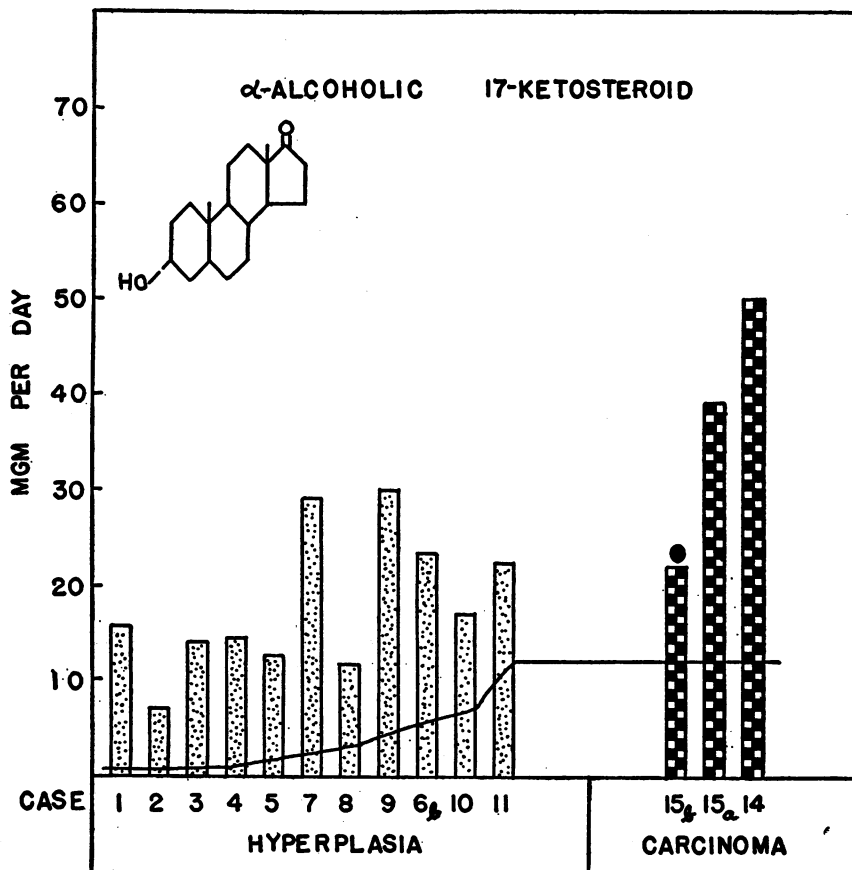


FIG. 2. ALPHA-ALCOHOLIC URINARY 17-KETOSTEROID OUTPUT PER DAY
The various symbols have the same significance as in Figure 1.

RESULTS

A. Daily urine excretion of steroids

Table I gives the data on the urines of abnormal subjects assayed in this laboratory. Figures 1 to 5 present these data and those culled from the literature, together with the approximate upper limit of excretory values for normal subjects of corresponding age. Near the top of each figure is a diagram describing the chemical structure of the substance or substances mentioned in the title of the figure. It will be noted that in Figure 1 the term, total 17-ketosteroids, includes steroids which possess a carbonyl group (ketone) at position 17 (top right hand end of the steroid molecule). The 17-ketosteroids may be divided into alcoholic and non-alcoholic substances. The alcoholic 17-ketosteroids which have an hydroxyl group at position 3 (lower left hand end of the molecule) are further subdivided into alpha- and beta-alcoholic

steroids according to the spatial position of the hydroxyl group, which determines their precipitability by digitonin. The ordinate for each figure gives a scale of the milligrams of the designated steroid excreted per day. On certain of the urines from cancer patients the results are reported in terms of milligrams per liter.⁷ The height of each column in the figures thus indicates the approximate daily output of steroid by the patient whose case number is given along the abscissa. The columns for patients with the diagnosis of adrenal cortical hyperplasia are speckled; those for patients with carcinoma of the adrenal cortex are checkered. A solid black circle over a column indicates that the value is taken from the literature. The curve running upwards in a semi-horizontal direction from left to right, in Figures 1 to 4, describes the approximate upper limit of

⁷ Cases 15 and 19 are so reported.

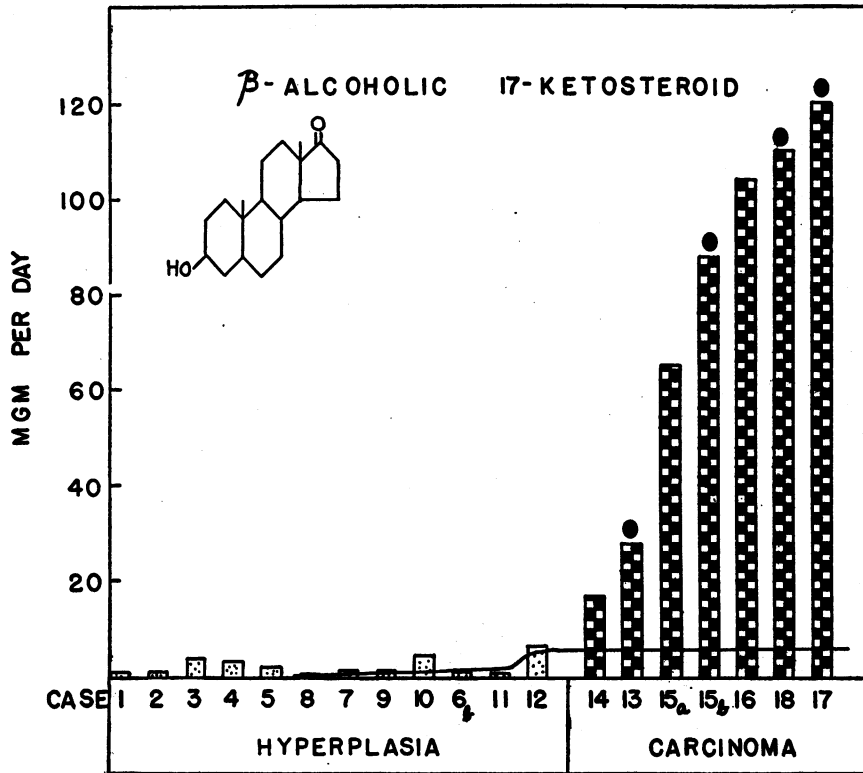


FIG. 3. BETA-ALCOHOLIC URINARY 17-KETOSTEROID OUTPUT PER DAY
The various symbols have the same significance as in Figure 1.

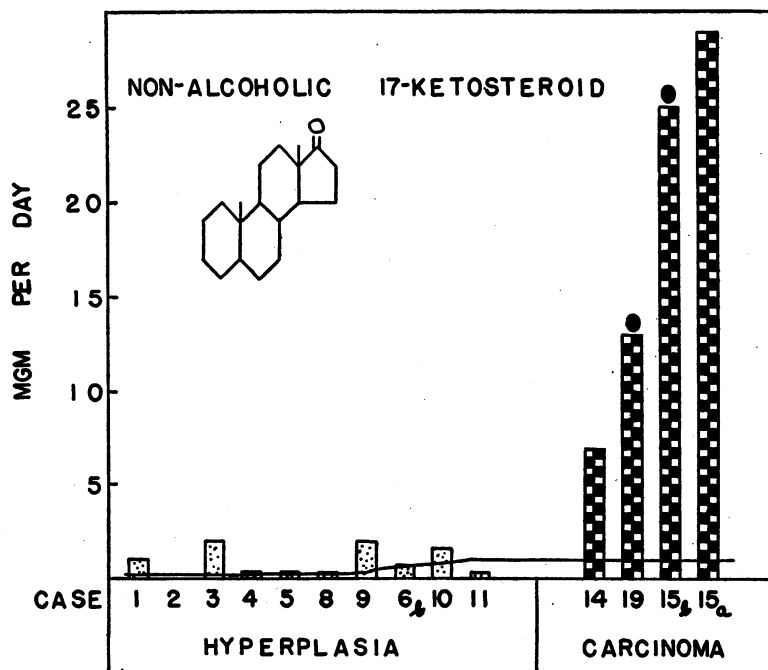


FIG. 4. NON-ALCOHOLIC URINARY 17-KETOSTEROID OUTPUT PER DAY
The various symbols have the same significance as in Figure 1.

TABLE I

Daily excretion of urinary 17-ketosteroids and of pregnanediol by patients with adrenal cortical hyperplasia and adrenal cortical carcinoma

The results are expressed in milligrams per day.

Case number	Sex	Diagnosis	Diagnosis		17-Ketosteroid output				Pregnanediol
			Proven	Presumptive	Total	Alpha alcoholic	Beta alcoholic	Non-alcoholic	
ADRENAL CORTICAL HYPERPLASIA									
1	M	ACV*		+	18.0	15.5	1.3	1.2	0.8
2	M	ACV	+		7.8	7.0	0.8	0.0	0.4
3	M	ACV	+		20.3	14.1	4.1	2.1	0.2
4	F	ACV	+		19.2	15.5	3.4	0.3	0.6
5	F	ACV		+	16.7	13.0	3.3	0.4	2.2
7	F	ACV		+	31.0	(29.0)†	2.0		
8	F	ACV	+		11.7	11.4	0.0	0.3	0.0
9	M	ACV	+		33.4	29.8	1.6	2.0	3.3
6b	F	ACV		+	25.2	23.4	1.2	0.6	0.0
10	F	ACV	+		23.4	17.2	4.6	1.6	
11	F	ACV	+		23.4	22.3	0.7	0.4	1.0
12	F	ACV		+	72.4		6.6		
ADRENAL CORTICAL CARCINOMA									
14	F	C*	+		74.0	51.0	16.0	7.0	
15a	F	ACV	+		133.0	39.0	65.0	29.0	
16	F	ACV	+		160.0		104.0		

* ACV signifies Adrenal Cortical Virilism; C indicates Cushing's syndrome.

† This value includes the non-alcoholic as well as the alpha-alcoholic 17-ketosteroids.

normal values for individuals of the same or of an older age. These maximum values for normal individuals, ranging between 4 and 17 years of age or older, are for the total 17-ketosteroids 0.8 to 17 mgm.; for alpha-alcoholic 17-ketosteroids 1.7 to 15 mgm.; for beta-alcoholic 0.4 to 5.0 mgm.; and for non-alcoholic 17-ketosteroids from 0.1 to 1.7 mgm.

The data show that patients with adrenal cortical hyperplasia and those with carcinoma both excreted abnormally large amounts of total (Figure 1) and alpha-alcoholic (Figure 2) 17-ketosteroids. Patients with carcinoma of the adrenal cortex tended to excrete larger quantities of these substances than did those with hyperplasia of the gland. It is observed, however, that the minimum values of the carcinoma patients approximately coincide with the maximum values of the hyperplasia group.

On the other hand, it is seen that only patients with carcinoma of the adrenal cortex excreted definitely excessive quantities of beta-alcoholic (Figure 3) and non-alcoholic (Figure 4) 17-ketosteroids. Little or no tendency towards an overlap in the maximum and minimum values of the two types of patients is evident.

The measurements of pregnanediol excretion are given in Figure 5. The horizontal line inter-

secting the ordinate at 0.5 milligrams indicates that normal girls, who have not menstruated, and nor-

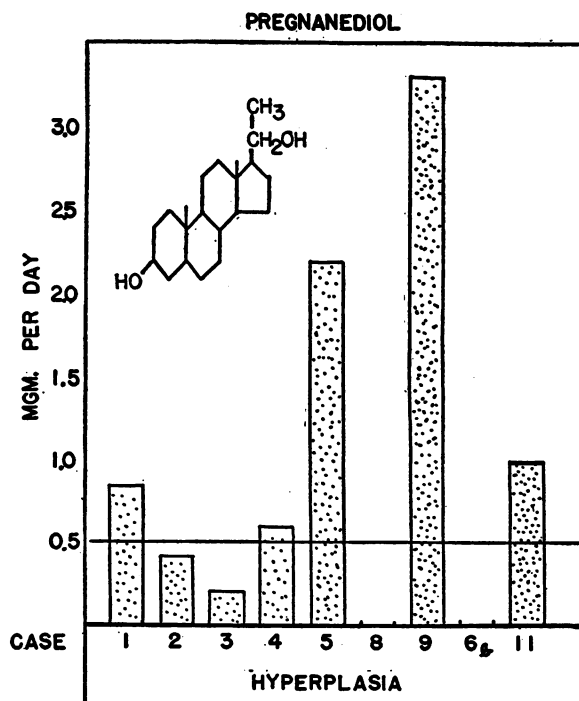


FIG. 5. URINARY PREGNANEDIOL OUTPUT PER DAY

The various symbols have the same significance as in Figure 1.

mal boys excreted not more than 0.5 mgm. per day of apparent pregnanediol,⁸ a portion of which may be interfering chromogens. Four of the patients with adrenal cortical hyperplasia excreted less than this amount of pregnanediol; 5 excreted between 0.5 and 3.5 mgm. per day. The excretion

⁸ Unpublished observations on non-pregnant females, who were having normal menstrual periods, show that these individuals excreted between zero and 10 mgm. of pregnanediol per day, depending upon the phase of the menstrual cycle.

of pregnanediol by adrenal cortical hyperplasia patients thus appears to be variable.

B. Observations on the spontaneous course and on the influence of unilateral adrenalectomy in children with adrenal cortical hyperplasia

Serial measurements of the height and skeletal age⁹ and of the total urinary 17-ketosteroid out-

⁹ The height and skeletal ages were determined by referring to normal standards giving the average age of

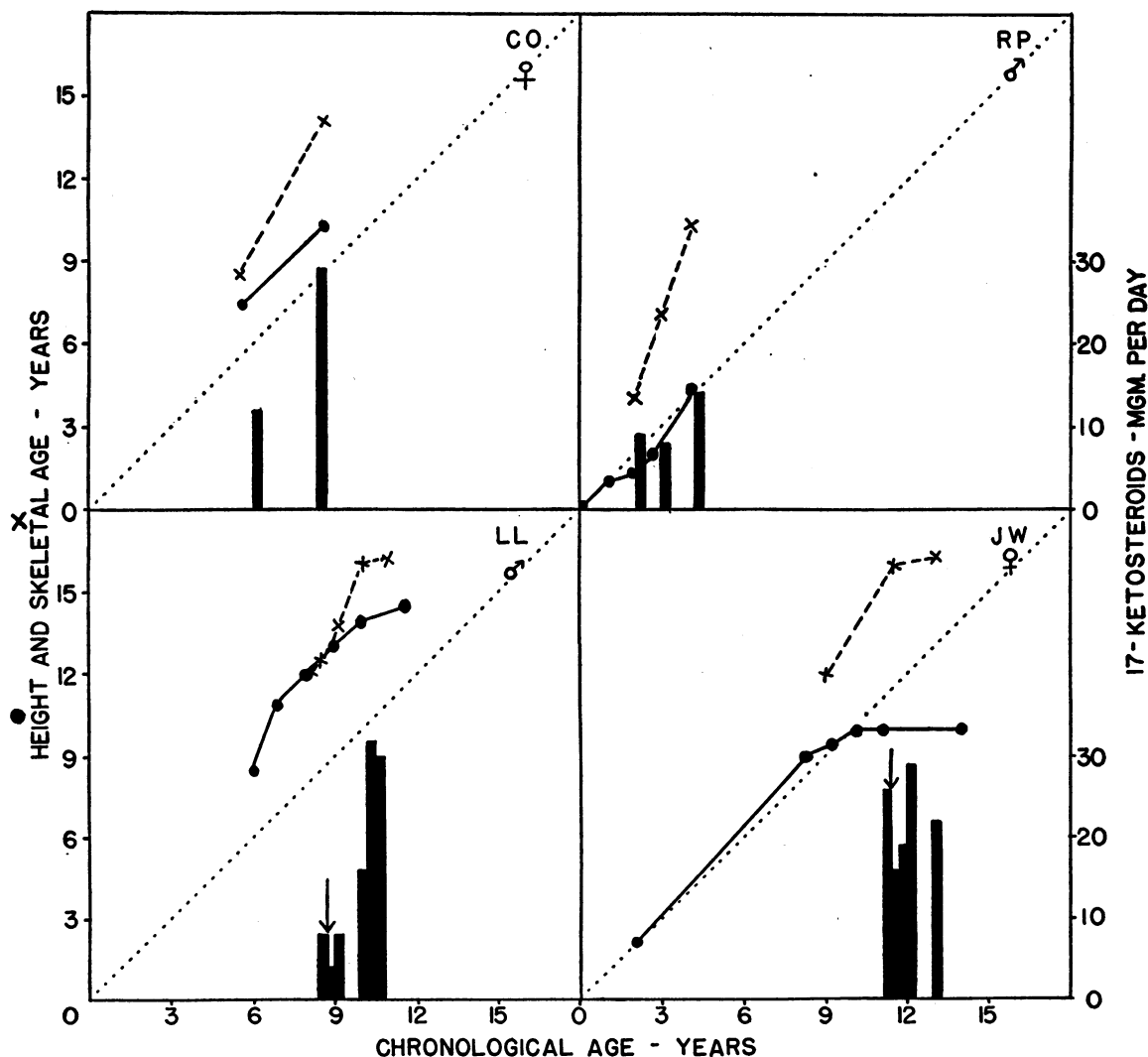


FIG. 6. OBSERVATIONS ON THE HEIGHT AND SKELETAL AGES AND THE TOTAL URINARY 17-KETOSTEROID OUTPUT OF 4 CHILDREN WITH HYPERPLASIA OF THE ADRENAL CORTEX

C. O. is case 6b; R. P. is case 2; L. L. is case 9; and J. W. is case 10. The height age is represented by the black circles, the skeletal age by the crosses, and the 17-ketosteroids by the black columns. The diagonal dotted lines in each square show where the black circles and crosses would fall if the height and skeletal age of the patient corresponded exactly to the chronological age. The arrows in the 2 lower squares indicate that an unilateral adrenalectomy was performed at that time.

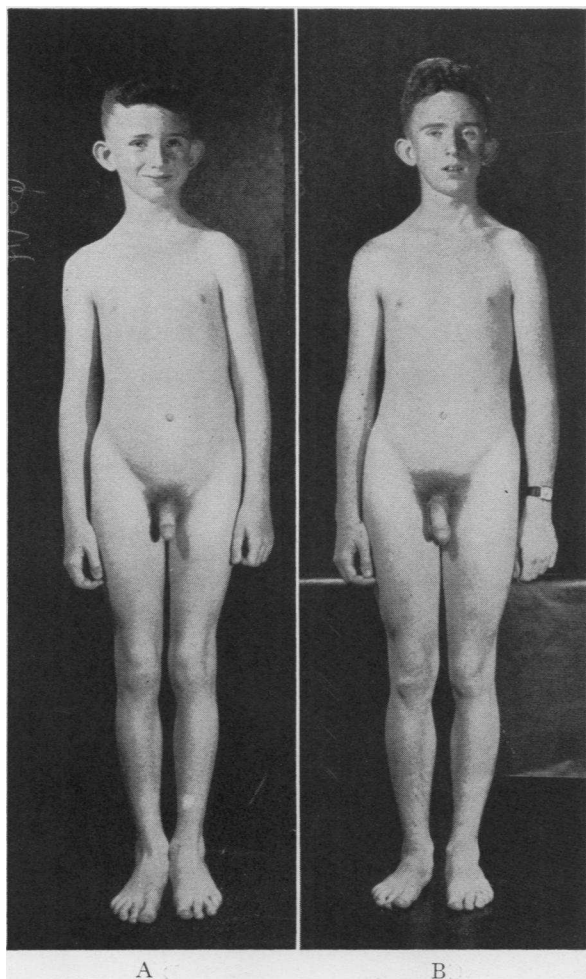


FIG. 7. CASE 9 (L. L.). ADRENAL CORTICAL VIRILISM DUE TO HYPERPLASIA OF THE ADRENAL CORTEX

A. Patient at $7\frac{1}{2}$ years, shortly before unilateral adrenalectomy. B. Patient at $11\frac{1}{2}$ years. Note increase in size of testes.

put per day of 4 children with hyperplasia of the adrenal cortex are plotted as ordinates against their chronological age as abscissae, in Figure 6. The height ages of each patient are represented by black circles connected by solid lines while the skeletal ages are given by crosses connected by broken lines. The 45 degree diagonal dotted lines describe points where the height and skeletal ages would fall if they were exactly equal to their chronological ages. The total 17-ketosteroid output is indicated by the vertical black columns.

children of the same sex and height (18) or skeletal development (19).

The arrow in the 2 lower squares indicates that an unilateral adrenalectomy was performed at that time.

The data of Figure 6 indicate that there was a progressive tendency for the skeletal age of these patients to be advanced beyond the chronological age by 3 or more years and for the total urinary 17-ketosteroid output to reach higher levels as the patients grew older. The height age also tended to exceed the chronological age until closure of the bone epiphyses at a skeletal age of approximately 16 years interfered with further growth. The curves show that the operative removal of one adrenal gland in 2 patients (J. W. (Case 10) and L. L. (Case 9)) did not permanently alter the precocious growth and development. Moreover, there was only a temporary drop in the total 17-ketosteroid output. Furthermore, as shown in Figures 7A and B and 8A, B and C, no regression in the masculine secondary sex characters had become evident 2 or more years postoperatively. The left hand photographs (7A, 8A) in these figures were taken just prior to the operation; the photographs designated 7B, 8B and C were made two or more years later. No breast development took place in the girl, and the clitoris of the girl and the penis of the boy failed to diminish in size.

It is noteworthy that the testes of the boy patient (Case 9, Figure 7) had been of normal size for his chronological age from the onset of his symptoms. Thus at approximately 12 years of age, the testes, which had been small in comparison to the abnormally large penis, enlarged, with the result that he then closely resembled a normal adolescent boy in external appearance.

C. Observations on the effect of orally administered diethyl-stilbestrol on patients with adrenal cortical hyperplasia

Some of the physical changes observed in the girl patients, J. W. (Case 10) and C. O. (Case 6), within 6 months after they had started to take 5 to 10 mgm. of diethyl-stilbestrol by mouth daily, are depicted in Figures 8D and 9B. There was a definite and marked increase in mammary gland tissue and in the size of the nipples. The nipples of the latter patient became deeply pigmented. The clitoris of each patient shrank in

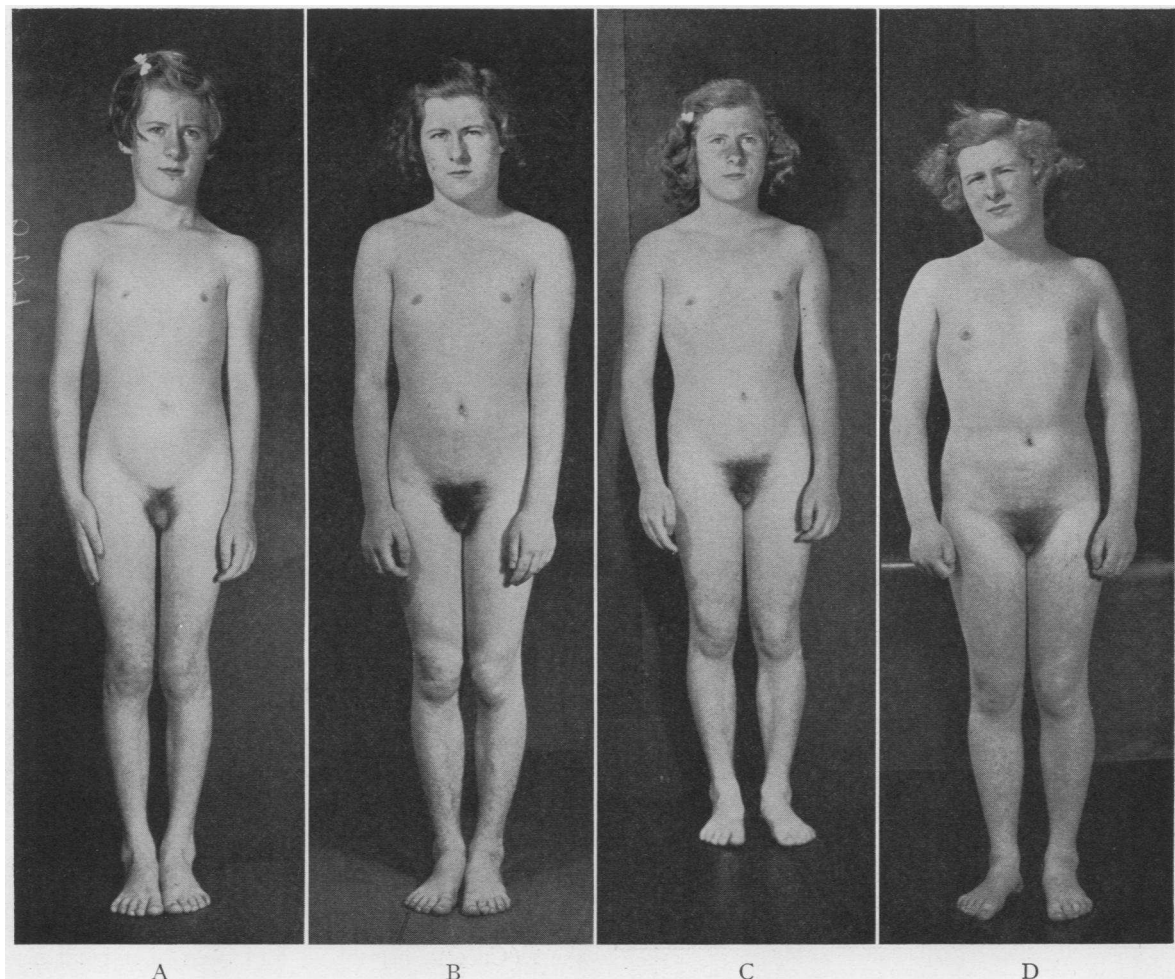


FIG. 8. CASE 10 (J. W.). ADRENAL CORTICAL VIRILISM DUE TO HYPERPLASIA OF THE ADRENAL CORTEX

A. Patient at 8 years, shortly before unilateral adrenalectomy. B. Patient at 11½ years. C. Patient at 12¾ years, immediately before oral diethyl-stilbestrol therapy. D. Patient 6 months after diethyl-stilbestrol, in daily doses of 5 mgm., was started. Note breast and nipple development.

size. The labia increased in size. There was no definite change in the hirsutism but the acne retrogressed. Patient J. W. (Case 10) did not have any nausea or menstrual bleeding during the period when diethyl-stilbestrol therapy alone was given. Furthermore, discontinuation of this therapy did not result in menstruation. However, 3 days after a 10-day period during which she was given 60 mgm. of anhydro-hydroxy-progesterone¹⁰ in addition to 5 mgm. of diethyl-stilbestrol by mouth per day, she had a 3-day period of menstrual flow. On the other hand, patient C. O.

¹⁰ We are indebted to Dr. M. Gilbert of the Schering Corporation for a generous supply of this material.

(Case 6), after receiving only diethyl-stilbestrol for a period of 3 months, had 2 periods of menstrual bleeding, lasting 4 days each. The personality of these girls also underwent an apparent change. Before therapy was started, these children were morose and reticent and gave the impression that they were self-conscious and unhappy. At about the time that breast development first became evident, they became more effective individuals as evidenced by a more cheerful disposition, a more self-confident demeanor, and, particularly, an unexpected improvement in school work.

During a control period of 3 or more days,

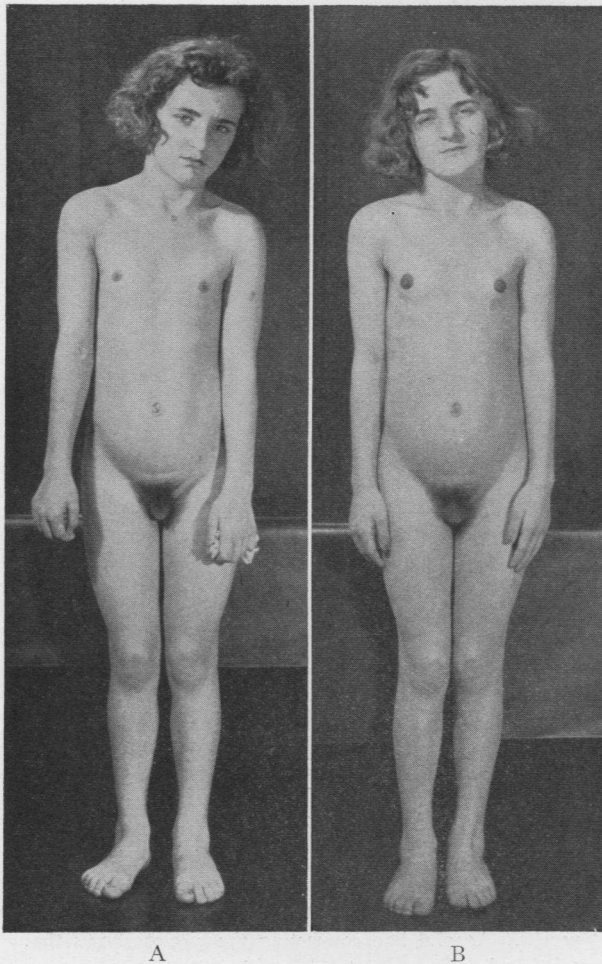


FIG. 9. CASE 6 (C. O.). ADRENAL CORTICAL VIRILISM PROBABLY DUE TO HYPERPLASIA OF THE ADRENAL CORTEX

A. Patient at 9 years, immediately before therapy. B. Patient after 5 to 10 mgm. of diethyl-stilbestrol had been given daily by mouth for 6 weeks. Note enlargement of breasts and nipples with pigmentation of areolae of nipples.

preceding the administration of diethyl-stilbestrol and at various intervals after the drug was started, urine samples representing 24-hour intervals of time were collected and assayed for their total 17-ketosteroid content. The results obtained on the foregoing 2 girls and on a boy (R. P., Case 2) with adrenal cortical hyperplasia are given in Figure 10. The abscissa shows the time intervals. The height of the solid black areas along the abscissa depicts the milligrams per day of diethyl-stilbestrol, as given by the stilbestrol ordinate scale. The height of the circles and crosses, con-

nected by the lines, gives the total 17-ketosteroid output per day, corresponding to the 17-ketosteroid ordinate scale. The double vertical line running through the initial (average control) 17-ketosteroid value given for each patient indicates the range of values obtained during the control period.

The figure shows that there is a tendency for the total 17-ketosteroid output to diminish during periods when diethyl-stilbestrol is being given, and for the level to rise when the therapy is discontinued. However, the changes in 17-ketosteroid levels are neither striking nor consistent.

DISCUSSION

The data presented indicate that quantitative analysis of specific fractions of the urinary 17-ketosteroids reveals more striking differences between patients with adrenal cortical hyperplasia and adrenal cortical carcinoma than does assay of the total 17-ketosteroids alone. Whereas the pattern of the 17-ketosteroids excreted by individuals with hyperplasia of the gland corresponds roughly to the normal, the pattern observed for individuals with carcinoma of the adrenal cortex veers widely from the normal. This abnormal pattern appears to be characteristic of carcinoma of the adrenal cortex, whether associated with adrenal cortical virilism or Cushing's syndrome. Thus there appears to be an alteration in biochemical function, corresponding to the differences in the cellular morphology of hyperplastic and of carcinomatous adrenal cortices. The importance of these observations in differential diagnosis is clear.

The observations on the clinical progress of children with adrenal cortical hyperplasia raise questions of interest from the point of view of therapy. The enlargement of the testes of the boy patient (Case 9) suggests that the precocious masculinization of hyperplasia may not be a serious complaint for boys. If this gonadal growth and gradual transition from precocious virilism to seemingly normal maturation is characteristic of male patients with the disease, it may explain the low recorded incidence of adrenal cortical virilism in adult males. However, it is possible that the adrenal cortical androgens upset the normal pituitary-gonadal relationships, thereby causing a disturbance in gonadal function which has not as yet been recognized.

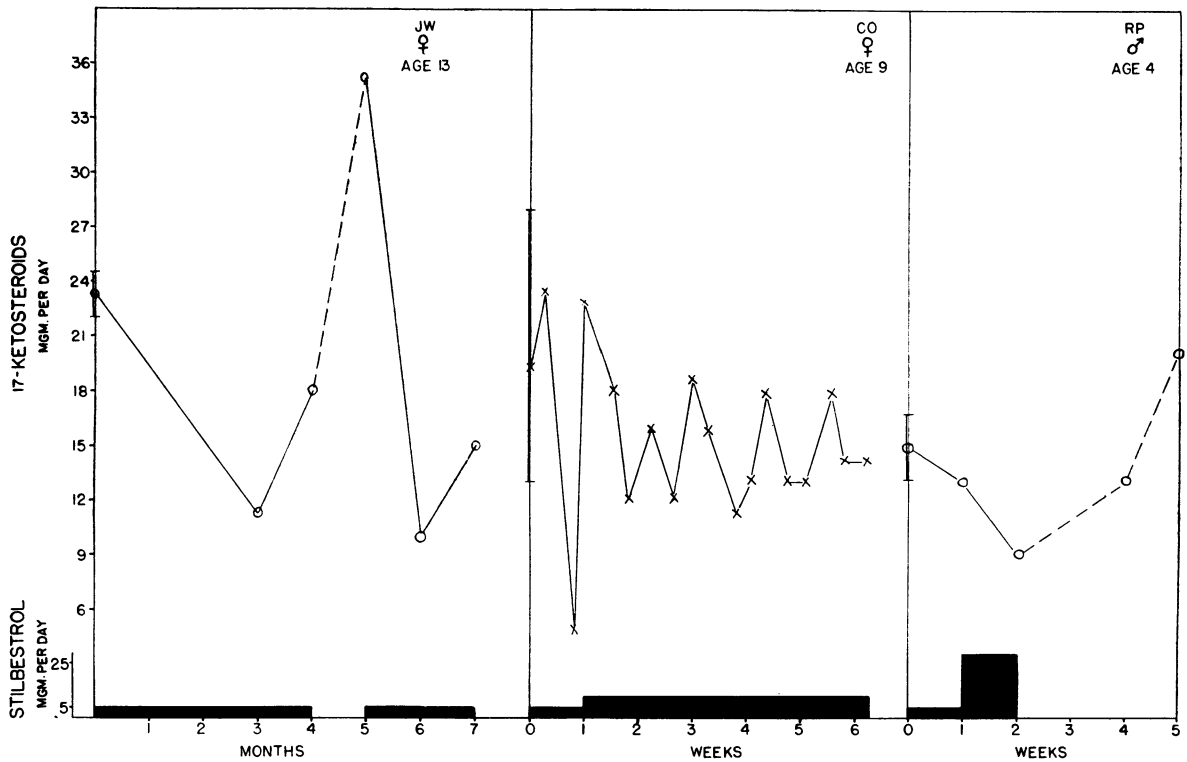


FIG. 10. INFLUENCE OF ORALLY ADMINISTERED DIETHYL-STILBESTROL ON TOTAL URINARY 17-KETOSTEROID EXCRETION PER DAY BY 3 CHILDREN WITH HYPERPLASIA OF THE ADRENAL CORTEX

J. W. is case 10; C. O. is case 6*b*; and R. P. is case 2. The duration of therapy is given by the abscissa. The dosage of diethyl-stilbestrol is shown by the height of the solid sections at the bottom of the figure. The total 17-ketosteroid output is given by the circles and crosses. The double vertical line at the left hand of each section indicates the range in 17-ketosteroid values during a control period. A solid line connecting the circles shows that diethyl-stilbestrol was being given; a broken line represents periods when it was not being given.

On the other hand, the prognosis for girls with virilism due to adrenal cortical hyperplasia is much less favorable. The tendency to masculinization persists and no normal feminine maturation takes place during the adolescent age period or later. Because the hyperplastic adrenal cortical tissue is believed to be the source of the excess androgenic hormones responsible for the masculinization in these patients, attempts to alleviate the condition by partial adrenalectomy were logical. Unfortunately, however, subtotal adrenalectomy has not proved to be permanently effective. This finding suggests that the adrenal cortical hyperplasia and hyperactivity may not reflect a primary disease of the adrenal cortex, but may result from adrenal cortical stimulation by nervous or humoral agents such as pituitary adrenocorticotrophic hormones. Complete adrenalectomy is, of course, incompatible

with life. This failure of surgical therapy led to the therapeutic trial of diethyl-stilbestrol, which is a potent, inexpensive, and apparently non-toxic estrogen. It would appear that the drug is capable of transforming girls with the masculinization of adrenal cortical virilism into persons with predominantly feminine characteristics. This is probably a purely cosmetic transformation, unaccompanied by the changes in ovarian function necessary for fertility or by the striking changes in adrenal cortical activity which would have been suggested by definite alterations in the urinary 17-ketosteroid output. It would thus appear that the feminization resulted from the artificial increase in the concentration of circulating estrogenic hormones. A continuation of this feminine development would, therefore, seem to depend on prolonged estrogen therapy.

There is experimental evidence that estrogens may cause hypertrophy of the adrenal cortex (20) and that estrogen therapy may not be physiologically ideal. For this reason the effectiveness of agents which may produce atrophy of the adrenal cortex (20, 21) should be investigated as such agents become available for clinical use.

SUMMARY AND CONCLUSIONS

The total urinary 17-ketosteroid excretion is abnormally increased in patients with adrenal cortical hyperplasia or adrenal cortical carcinoma.¹¹ However, the magnitude of the total 17-ketosteroid excretion is not always a reliable index of the exact nature of this hyperactivity. On the other hand, the urinary output of the beta-alcoholic and the non-alcoholic 17-ketosteroids has been found to be markedly elevated in patients with adrenal cortical carcinoma, whereas their output was either normal or but slightly elevated in patients with cortical hyperplasia. Assay of the excretion of these latter 2 fractions therefore appears to be of diagnostic value in differentiating patients with adrenal cortical hyperplasia from those with carcinoma of the adrenal cortex.

In agreement with the observations of others (22 to 24) the urinary pregnanediol values are not consistently elevated in patients with adrenal cortical hyperplasia.

Adrenal cortical virilism, when due to hyperplasia of the adrenal cortex, usually persists without a tendency to spontaneous remissions. Children of both sexes may tend to grow rapidly in the early stages of the disease, but cease growing at an abnormally early age because of premature closure of the epiphyses. There is a probability that the boys will become normal appearing adult males but whether or not they will attain fertility is uncertain. If left untreated, the girls tend to remain chronically masculinized.

¹¹ Unpublished observations are available on eight children with sexual precocity apparently due either to accelerated normal physiologic processes or to central nervous system lesions. The sexual precocity in these children differed from that observed in the adrenogenital syndrome in that the gonads rather than the adrenal cortex appeared to be the source of the sex hormones responsible for the secondary sex development. The total 17-ketosteroid values of this group were not markedly elevated, but corresponded approximately to values obtained on normal individuals of the same physiologic age.

The treatment of choice for patients with a carcinoma of the adrenal cortex is surgical removal. On the other hand, surgery does not appear to be indicated in the treatment of patients with adrenal cortical hyperplasia. In girls with this latter disease, orally administered diethylstilbestrol causes development of the female secondary sexual characteristics and improvement in psychological outlook. On the other hand, there appears to be little indication for such therapy in the male.

Addenda: Since this paper went to press, additional measurements have been made on 2 adult women with adrenal cortical virilism. The first patient had proven adrenal cortical hyperplasia. She excreted a total of 46.8 mgm. of 17-ketosteroids per day. Of these, 6.4 mgm. were beta-alcoholic 17-ketosteroids. The second patient had a proven adrenal cortical carcinoma. Her total 17-ketosteroid output was 74.0 mgm. per day. Of these, 28.5 were beta-alcoholic 17-ketosteroids.

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