Amenorrhea Due to Defects in Steroid Biosynthesis*

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Amenorrhea as the first manifestation of a steroid biosynthetic defect is rather unusual. The common forms of congenital adrenal hyperplasia are classic examples of steroid biosynthetic defects. Yet in genotypic females, this disorder is usually evident from birth because of virilization. Effective treatment usually ensues and amenorrhea is only a problem when control is inadequate. However, there are individuals whose disorder will be manifest for the first time in the postnatal or adult period. In addition, multiple other steroid defects have now been clearly delineated. Many of these individuals will have amenorrhea, virilization, or sexual ambiguities as part of the clinical picture. This paper will describe some of the more clearly delineated steroidal biosynthetic defects. Also, the clinical management of patients with postnatal onset of 21-hydroxylase deficiency form of congenital adrenal hyperplasia will be discussed.

Steroidogenesis. One can better appreciate the biochemical defects and clinical manifestations of these various steroid defects by having a rudimentary knowledge of the basic steroid pathways involved. To pinpoint the individual defects, it is helpful to recall the numbering sequence of the carbon atoms of the steroid molecule as shown in Figure 1. For the purposes of this discussion, one can consider cholesterol as the basic substance from which steroids are derived. It is at the point of its conversion to pregnenolone that tropic hormones have their effect; that is, ACTH for the adrenal cortex, and the gonadotropins for the gonads (Fig. 2). When circulating levels of glucocorticoids or sex steroids reach sufficient levels for physiologic functions of the individual, the classic negative feedback mechanisms become operative so that further releasing hormones from the hypothalamus are held in abeyance, and the specific tropic hormones from the pituitary are not released until there is further need for additional hormones.

In the biosynthetic defects discussed here, the steroid end products necessary for physiological function are not formed in optimum amounts. This triggers release of releasing factors from the hypothalamus which in turn causes secretion of the tropic hormones from the pituitary. Next, stimulation of the target glands (adrenal and/or gonads) leads to excessive intermediate products being elaborated up to the point of the defect. Clinical manifestations of these disorders are due to a deficiency of a normal end product, an excess of intermediate substances with the possible peripheral conversion to other hormones, or usually both. In defects involving steps early in the biosynthetic pathways, the adrenals and gonads are involved. Abnormalities occurring later in the order of flow usually involve only one gland or the other. Important sex steroid precursors and weak androgens may be formed by the adrenal and converted to more potent androgens and even estrogens in certain of these disorders. Such conversions apparently occur in the liver and skin and possibly other tissues. However, the gonads do not form glucocorticoids.

Specific Defects. Brief descriptions of biosynthetic defects will be outlined starting at the more

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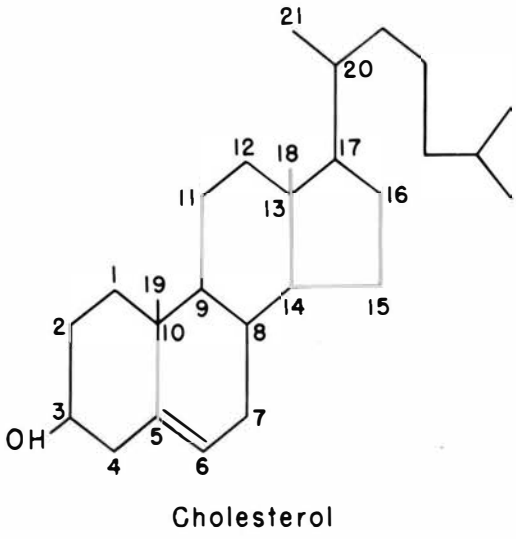

Fig. 1—Numbering sequence for the first 21 carbon atoms in steroid nomenclature. Useful in locating biosynthetic steroid defects described in this paper.

primitive, or early, stages of steroid biosynthesis and proceeding to later-stage defects. Accordingly, the order of presentation bears no relationship to relative frequency or importance of these disorders.

C-20 block with lipoid adrenal hyperplasia (Desmolase deficiency CAH) (Fig. 3). Being unable to convert cholesterol to pregnenolone, affected individuals lack life-sustaining steroids; hence the disorder is fatal. The condition is of interest to the gynecologist in that it supports Jost's work regarding virilization of the genital tracts. Being a primitive (early) defect, it involves steroidogenesis in the gonads as well as in the adrenals. The fetal testes are unable to form adequate androgens to virilize the genitalia fully, leading to genital ambiguity in genetic males. This is in contradistinction to the findings in the more common 21- and also 11-hydroxylase forms of congenital adrenal hyperplasia where genetic females are often born with ambiguous genitals. Cholesterol accumulates in the adrenal of affected individuals; hence the designation "lipoid." Theoretically, the treatment would be the administration of glucocorticoids and mineralocorticoids with the addition of appropriate sex steroids at the time of pubescence. Prader, Gurtner, and Siebenmann (1, 2) reported two patients with this disorder and collected five additional cases. All seven died before the eighth month of life with adrenal insufficiency even though treatment with gluco- and mineralocorticoids had been employed. Although other steroid abnormalities may be present, it is probable that the main defect is in the transformation of cholesterol to pregnenolone (3). Early fatalities preclude this form of CAH in the differential diagnosis of amenorrhea, though ultimately a mild form of the defect with survival might be anticipated.

Three β-hydroxysteroid dehydrogenase deficiency (Fig. 4). Being unable to convert pregnenolone to progesterone, these individuals present with many of the features of the previously described desmolase deficiency. Salt loss has been a prominent feature of the adrenal insufficiency with the result that fatalities are usual. Inadequate testosterone leads to ambiguous genitals in genetic males whereas mild virilization of affected females has been attributed to testosterone being formed from increased amounts of dehydroepiandrosterone (DHA) and other precursors. Since it is a primitive defect, gonadal steroidogenesis is also affected. In Bongiovanni's series (4), three females out of a total of six individuals with this form of CAH were surviving. He postulated a partial defect as did Kenny and his coworkers (5). The latter authors also showed increasing 3β-hydroxysteroid dehydrogenase activity with increasing age. Steroid excretion patterns in these patients would suggest the development of alternate pathways which allow for survival of some infants. The presence of pregnenetetrol (with a hydroxyl group at C 21) suggests the ability of 17-hydroxylase and 21-hydroxylase to act on this "primitive" molecule (6). This compound is not excreted in increased amounts in the usual 21-hydroxylase deficiency (7). Since this enzyme also plays an important part in the gonadal biosynthesis of sex hormones (6), its absence would necessitate substitutional sex-hormone therapy at pubescence. Obviously sterility can be anticipated.

Seventeen α-hydroxylase defect (Biglieri syndrome) (8) (Fig. 5). This being a primitive block, the gonads and adrenals are involved. Absence of adequate sex steroids leads to hypogonadism and elevated gonadotropins. The elevated levels of desoxycorticosterone (DOC) and corticosterone lead to hypokalemic alkalosis and hypertension, thus turning off the renin-angiotensin mechanism with resultant low or absent aldosterone. This defect is clinically ex-

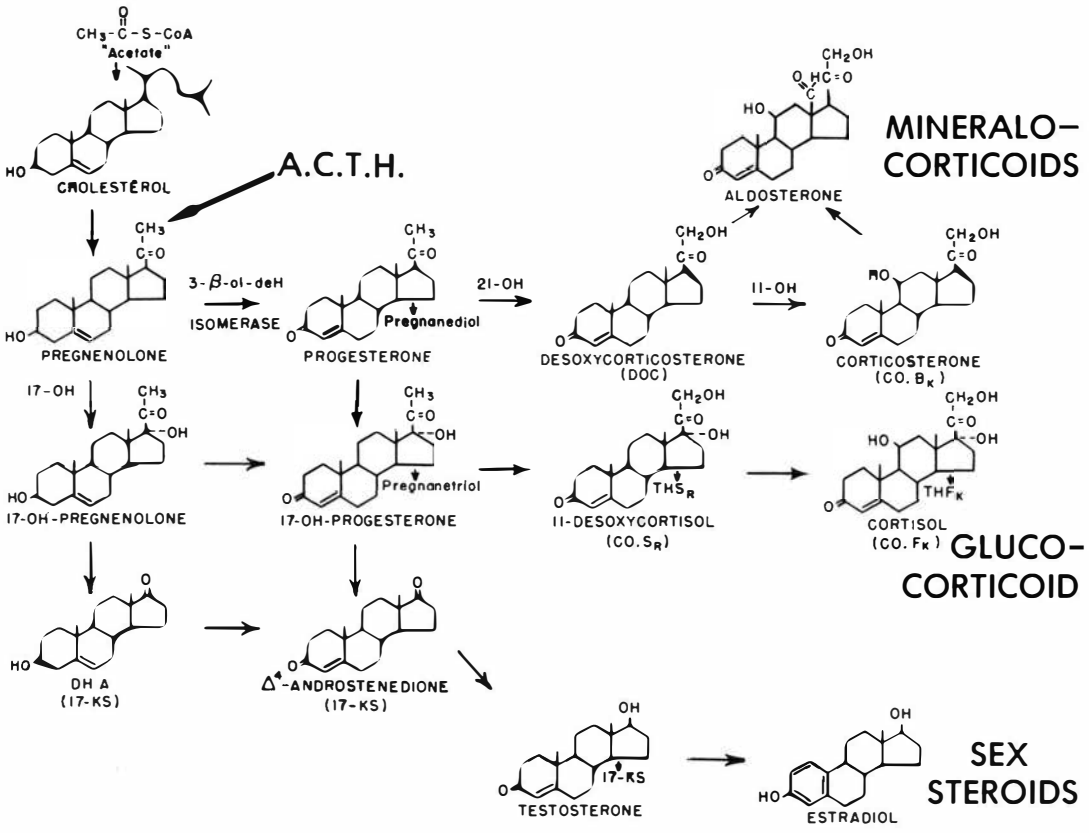

Fig. 2—Abbreviated steroid flow sheet of major steroids produced in the human. Mineralocorticoids are regulated by a mechanism involving osmolar and pressor receptors and in turn the renin-angiotensin mechanism and only to a minor degree by ACTH. The glucocorticoid (cortisol) plasma levels are modulated by negative feedback influence of the 11-hydroxyl group on the hypothalamus and in turn its releasing factor for ACTH. The major sex steroids, testosterone and the estrogens, typified by estradiol, are produced from adrenal DHA and androstenedione in tissues peripheral to the adrenal such as the liver and the skin. Some degradation products of major steroids are pointed out by small arrows beneath the individual steroids.

pressed in the genetic female by hypertension and the absence of puberty. In addition to the elevated gonadotropins, blood progesterone is high. In the genetic male, ambiguous genitalia and absence of puberty result from the inability to make either androgens or estrogens; hence it is a cause of male pseudohermaphroditism (9). This syndrome in genetic females is similar to the feminizing testicular syndrome in the absence of secondary sex hair, but differs in that breast development is absent and hypertension is present. The treatment in females is adequate substitutional therapy with glucocorticoids. Preference is given to one without significant mineralocorticoid activity; for example, prednisone. Addition of sex steroids at pubescence is indicated, but infertility can be expected. It would appear that these patients could be monitored for effectiveness of therapy by the measurement of plasma progesterone.

Simple virilizing congenital adrenal hyperplasia (mild 21-hydroxylase defect) (Fig. 6). Being unable to form optimal amounts of cortisol and corticosterone, these individuals exhibit augmented ACTH production which leads to shunting towards the androgen pathway and ultimate virilization. Aldosterone and cortisol (hydrocortisone) are formed in suboptimal amounts so that overt adrenal insufficiency may not be necessarily manifest (10, 11). The majority of female patients will have exhibited considerable evi-

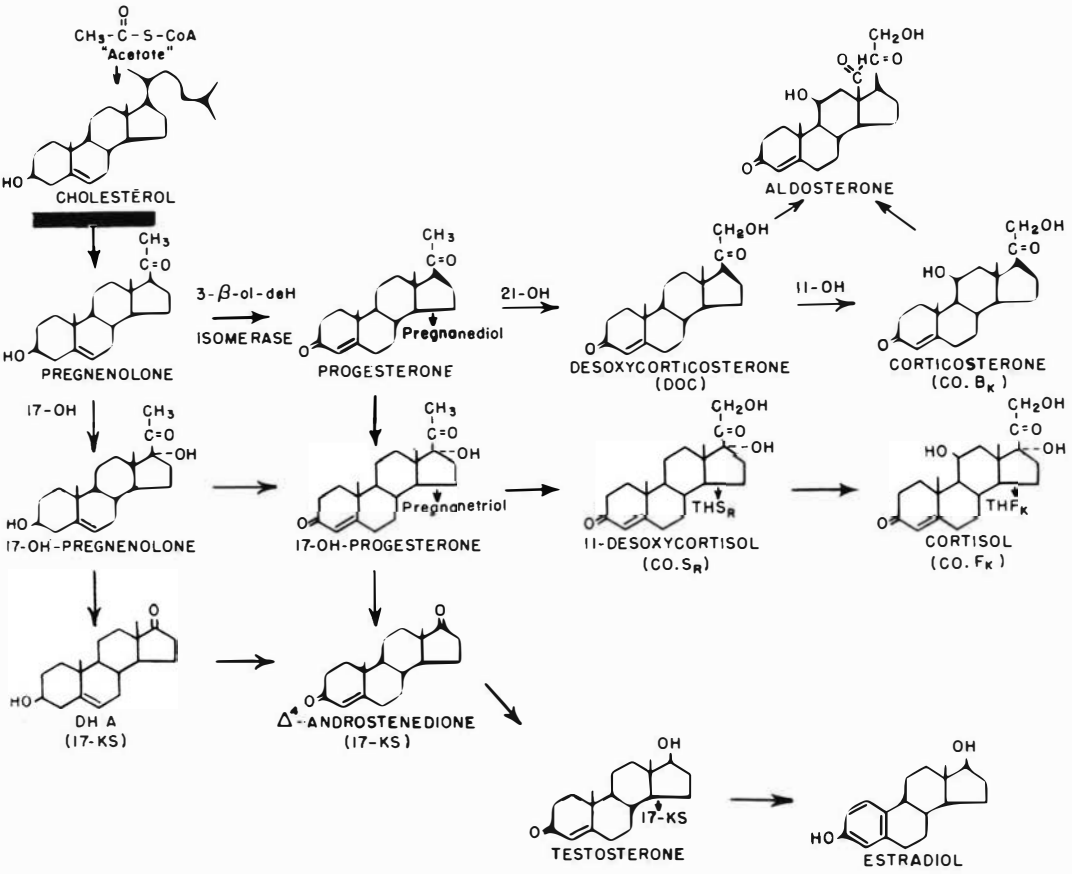

Fig. 3—Desmolase defect (also called lipoid adrenal hyperplasia due to accumulation of cholesterol in adrenals). Usually fatal due to deficiency of both mineralocorticoids and glucocorticoids. Leads to sexual ambiguity in males due to deficient testosterone to masculinize in utero.

dence of virilization and usually sexual ambiguity at birth, leading to prompt diagnosis and treatment. In the affected male, however, the external genitalia are normal and the diagnosis of CAH is therefore less obvious. This doubtless accounts for the predominance of the disorder in females; that is, males may die of undiagnosed hypoadrenalism.

Diagnosis and treatment depend largely on suppressibility of the hyperactive hypothalamic-pituitary-adrenal axis by exogenous administration of 11-hydroxylated glucocorticoids. Androgens are elevated in plasma and urine. Estrogen excretion may be elevated in these individuals (12, 13). Such estrogenic activity is not clinically manifest. Presumably, the excessive androgens effectively override the estrogenic activity. Most investigators have held that urinary gonadotropins are suppressed by the excessive androgens (13, 14). However, Stevens and Goldzieher (15) found detectable and often adult levels of gonadotropins in 4 of 5 children with CAH and variable levels in adults. Steroid suppressive therapy led to a fall of FSH in 3 of 6 patients whereas LH was unchanged in 5 and rose in 2, suggesting that compensatory pituitary hyperactivity in CAH is not limited to the pituitary adrenal mechanism but has repercussions in gonadotropin regulation as well. In

any event, once adequate suppressive therapy is instituted, postpubertal females rapidly feminize and become ovulatory.

Diagnosis can be suspected on the basis of baseline urinary 17-ketosteroids (17-KS). Normal adult females ordinarily have values between 2 and 12 mg/24 hours. Patients with obesity, stress situations, essential and familial hirsutism or Stein-Leventhal syndrome may have levels to 25 or even 30 mg/24 hours whereas patients with CAH usually will have baseline values on the order of 50 mg/24 hours. Patients with adrenal adenomas ordinarily will have values of approximately 100 mg, and patients with virilizing adrenal carcinomas will have values of 200 mg or up. The degradation metabolite of 17 hydroxyprogesterone (17OH-P), pregnanetriol, was found to be elevated in the urine of these patients and has been used for years to confirm the diagnosis and to monitor therapy. Most laboratories report normal values in adult females to be 4 mg or less per 24 hours. Patients with CAH have values from modestly above 4 mg up to manyfold this level. The suppressibility of this steroid as well as 17-KS by 2 mg of dexamethasone every 6 hours for two days proves the ACTH dependence of the disorder and differentiates it from the autonomous virilizing adenomas and carcinomas (16). However, it appears that pregnanetriol is not a primary intermediate in the formation of an-

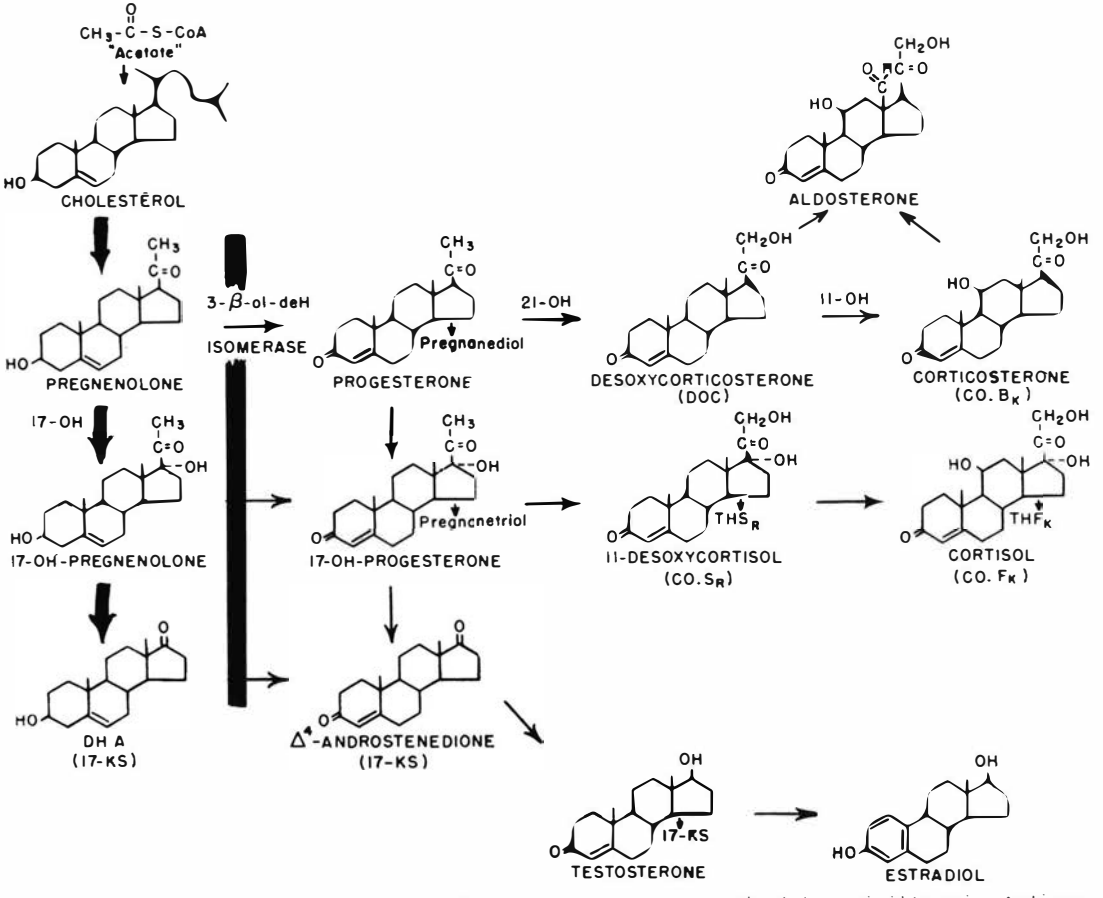

Fig. 4—Defect of 3β ol-dehydrogenase-isomerase. Fatal due to decreased mineralocorticoid and glucocorticoid formation. Ambiguous genitals in males due to deficient androgen production to fully masculinize in utero. Partial virilization of females due to peripheral conversion of DHA to androgens.

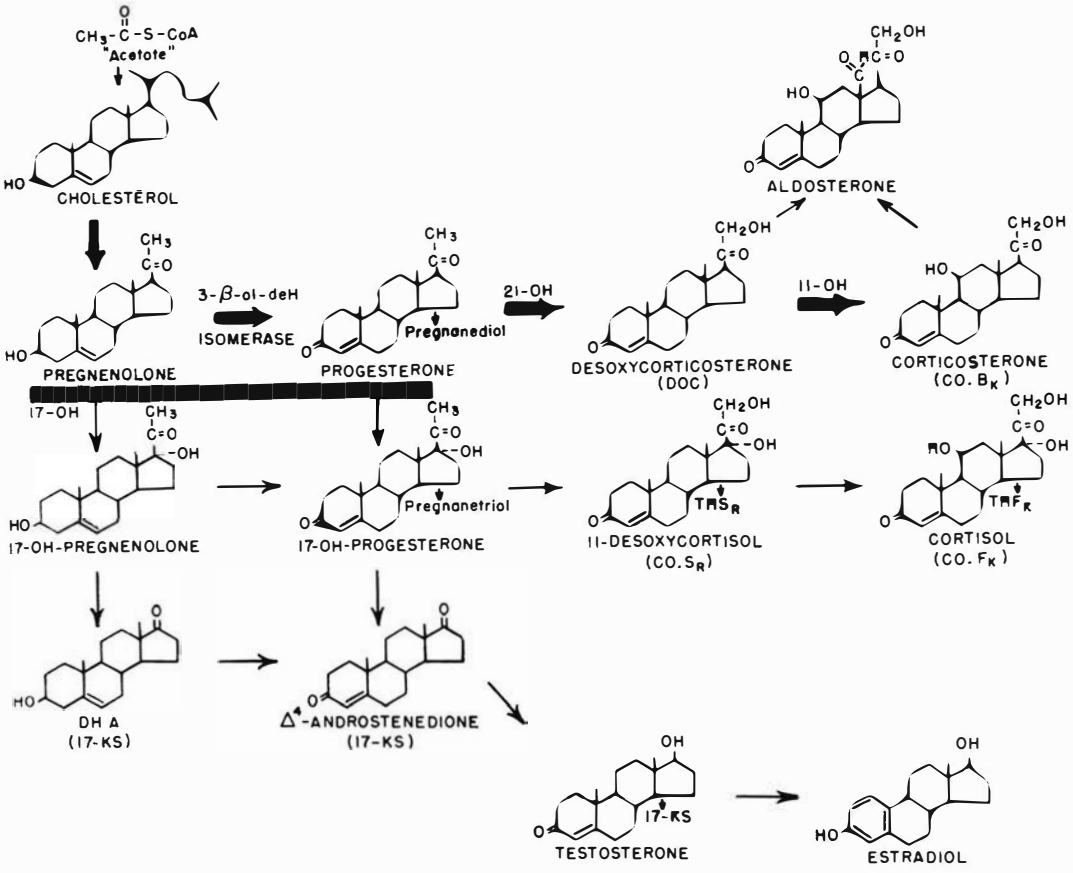

Fig. 5—Seventeen α-hydroxylase defect (Biglieri syndrome). Accumulation of mineralocorticoids leads to hypertension and deficiency of sex steroids to absence of secondary sex characteristics in females and failure to develop external genitalia in males.

drogens (17) suggesting that the major pathway is through DHA and androstendione. Although 17OH-P has been known to be elevated in this disorder for years (18), its measurement as a practical matter has been of more recent vintage (19, 20). The bother and inaccuracy of collection of 24-hour urine specimens for steroid assays has led to the measurement of plasma 17OH-P, progesterone, and testosterone in diagnosing and monitoring these patients. Lippe and co-workers point out multiple factors that may affect serum steroid determinations (21); hence they suggest that where virilization is a prominent feature in amenorrheic women, long-term adrenal suppression tests with measurement of several plasma steroids (for example, 17OH-P and testosterone) be utilized. Normal adult patients ordinarily have plasma 17OH-P levels of up to 200–400 ng% whereas patients with CAH and blocks of C-21 or C-11 hydroxylation will have levels severalfold that amount when untreated or if out of control (for example, 1–4 μg%) (19).

A subvariant of the mild 21-hydroxylase deficiency is that of the postnatal onset of the disorder. Sporadic cases have been reported (22, 23, 24) and described. It would appear that these individuals have a milder form of the disorder which becomes manifest only upon their being stressed.

Other subvariants of the 21-hydroxylation deficiency include periodic fever in association with

elevated plasma etiocholanolone (25) and "late" sodium loss (26). Hypoglycemia probably is not a separate subvariant but a manifestation of hypoadrenalism.

Severe 21-hydroxylase defect (salt-losing congenital adrenal hyperplasia) (Fig. 7). This variant of the 21-hydroxylase defect is more complete so that a deficiency of mineralocorticoids including aldosterone exists. Shunting to the androgenic pathway is also present leading to virilization. The defect, being of more profound degree, leads to even higher ACTH levels than in the simple virilization syndrome so that hyperpigmentation may ensue and indeed has been used as a clinical sign in addition to steroid assays in the monitoring of therapy. Diagnosis is the same as with the mild form, but treatment differs. In addition to suppressive therapy with a glucocorticoid, a mineralocorticoid and often salt supplementation are necessary. It has been suggested that different 21-hydroxylation defects may exist in the salt losers as opposed to the nonsalt losers (27).

Eleven-hydroxylase deficiency (hypertensive congenital adrenal hyperplasia) (Fig. 8). In addition to the shunting along the androgenic metabolic pathway as in the 21-hydroxylase defects, the mineralocorticoid, DOC, accumulates, leading to salt retention and hypertension. These patients also frequently pigment

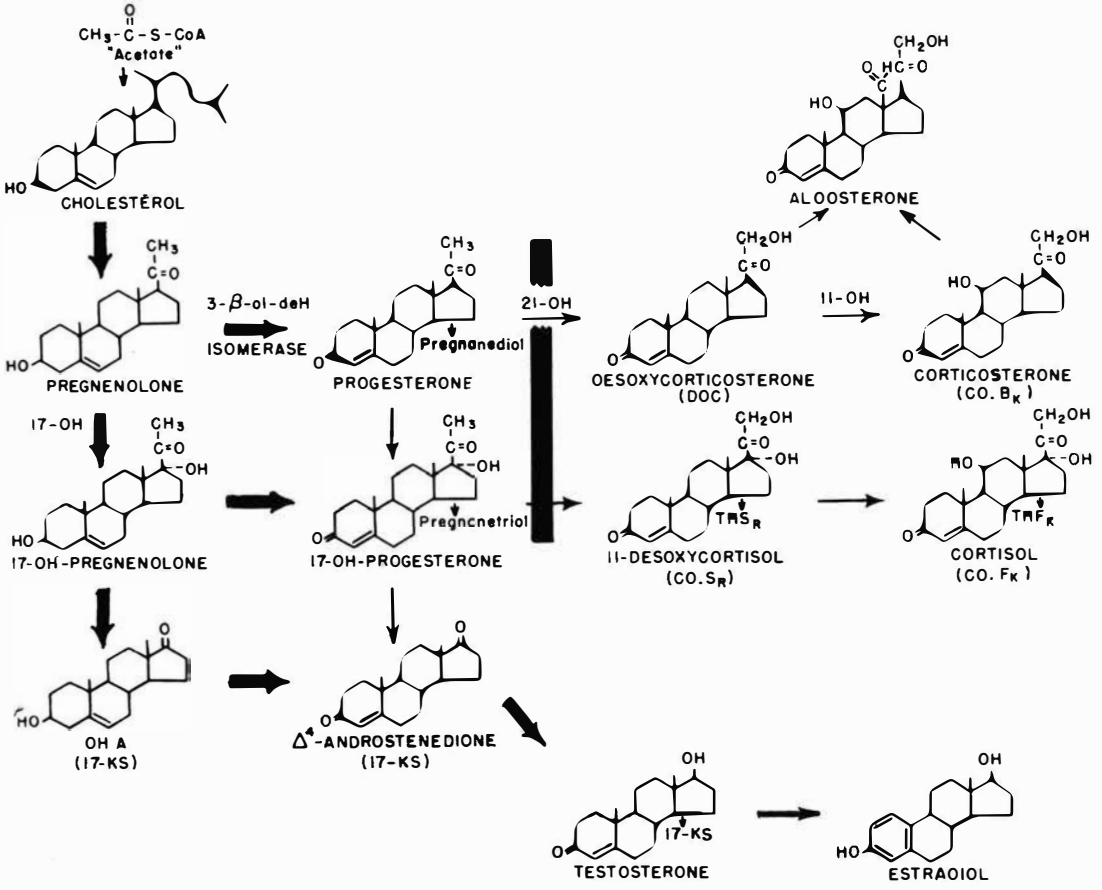

Fig. 6—Mild 21-hydroxylase defect. Glucocorticoids and mineralocorticoids may be formed, but at expense of adrenals becoming hyperplastic with overt production of androgen precursors which are converted to testosterone. This leads to virilization in adults, somatic precocity and pseudohermaphroditism in female infants.

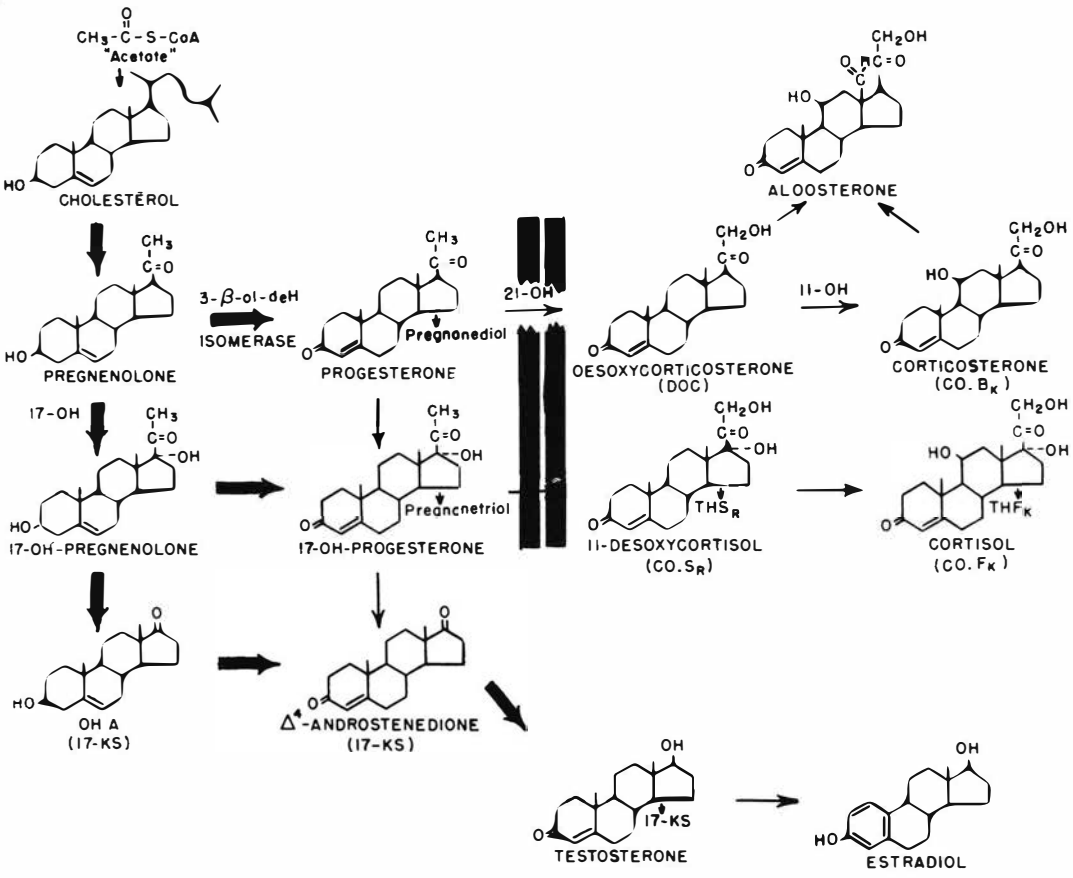

Fig. 7—Severe 21-hydroxylase defect. Virilization findings similar to the mild form but additionally salt loss occurs due to the mineralocorticoid deficiency including aldosterone.

from the excessive ACTH activity. Clinically, these patients present as the 11-hydroxylase patients except for hypertension and salt retention. Diagnosis can be suspected on the basis of hypertension. Biochemical confirmation is by the finding of elevated levels of tetrahydro-S (the degradation product of 11-desoxycortisol) in the urine. More specific radioimmunoassays for DOC and 11-desoxycortisol may simplify diagnosis in the future.

Late onset of this disorder has also been reported (28, 29). Zachmann and co-workers extensively studied an infant girl with an 11-hydroxylase deficiency who was normotensive and had normal levels of DOC though compound S was excessively high. This suggested to them a selected inhibition of the 11β-hydroxylation of 17α-hydroxylated steroids (30).

Eighteen-hydroxylase dehydrogenase defect (Fig. 9). Ulick (31) described this disorder accompanied by low aldosterone resulting in low serum sodium, high potassium, dehydration, hypotension, high renin activity, and elevated levels of hydroxycorticosterone. This disorder should not enter into the differential diagnosis of amenorrhea and the virilizing congenital adrenal hyperplasias.

Seventeen β-hydroxysteroid dehydrogenase defect (deficient testicular 17-ketosteroid reductase activity) (Fig. 10). Goebelsmann and co-workers (32)

described a 46-year-old married phenotypic female with clitoral enlargement, hirsutism, breast development, and a blind vaginal pouch. Chromosomal karyotype was 46 XY. Abdominal testes were removed. Prior to operation, testosterone was at low normal male levels, though considerably above female levels. Urinary 17-KS were 33 mg/24 hours. The finding of androstenedione of 1.02 μg/100 ml (being tenfold above normal male levels) suggested testicular 17β-hydroxysteroid dehydrogenase deficiency. More recently, Givens and associates (33) described two additional patients (sisters) with primary amenorrhea, hirsutism, clitoral enlargement, 46 XY karyotype, but lacking breast development. They, too, found grossly elevated androstenedione levels along with elevated urinary 17-KS and plasma estrone, but subnormal amounts of testosterone and estradiol. In vitro incubation of testicular tissue from their second case confirmed a partial defect in testicular 17-KS reductase activity and documented increased 3β-hydroxysteroid dehydrogenase activity. They felt that failure of breast development was probably due to lower estrogen levels than in previously reported cases. Accordingly, when one finds elevated 17-KS in an amenorrheic individual, further delineation of the defect by steroid biochemical assays seems warranted. Indeed, such investigations may show the Reifenstein syndrome as well as other forms of male

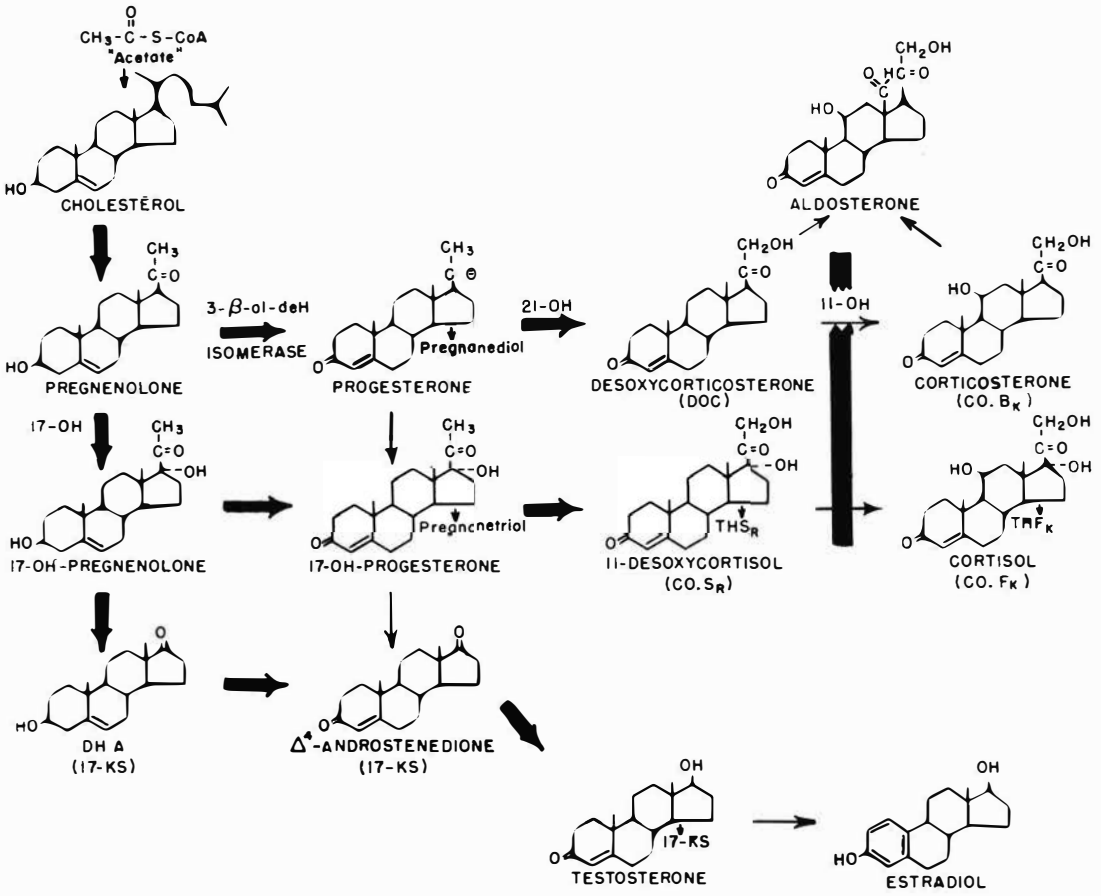

Fig. 8—Eleven-hydroxylase defect. Virilization due to shunting of adrenal precursors to androgenic pathway. Hypertension results from accumulation of mineralocorticoids—principally desoxycorticosterone.

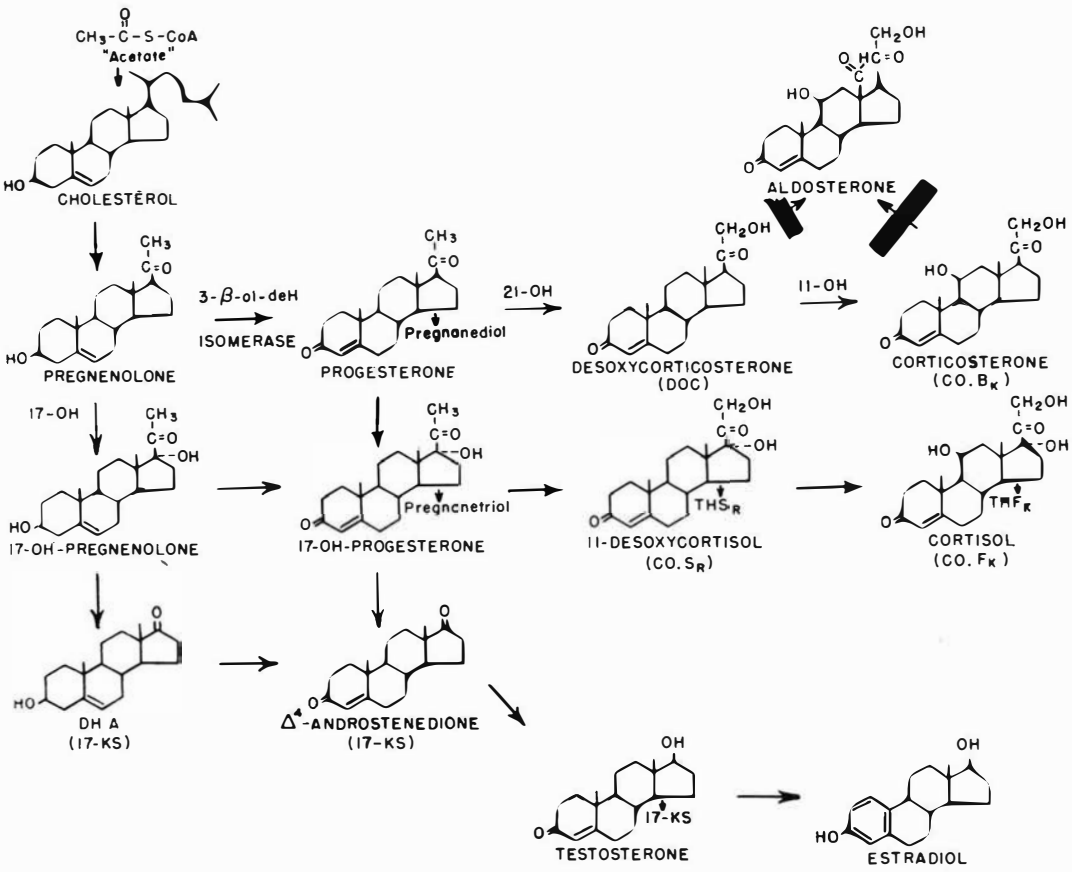

Fig. 9—Defect of 18-hydroxylase dehydrogenase. Aldosterone deficit leads to decreased plasma sodium, high potassium, dehydration, hypotension, and high renin activity. No direct gynecologic endocrinopathy association.

pseudohermaphroditism to be due to this disorder of steroid biosynthesis.

Stein-Leventhal syndrome (Fig. 11). Early workers dealing with in vitro studies showed an accumulation of DHA and testosterone in incubation studies on ovarian tissue from patients with this syndrome. These studies suggested a partial defect in the aromatizing enzyme to convert testosterone to estradiol as well as an inadequacy of 3β-ol dehydrogenase activity. However, such observations were not interpreted to imply the uniform existence of invariable, all-or-none enzyme defects in the polycystic ovarian tissue (34). Accumulating evidence would suggest, however, that the issue is much more complex. Probably there are patients now classed with this syndrome whose disease primarily resides in the adrenal cortex, others who have primarily an ovarian defect; but the majority have a defect in hypothalamic function. Accordingly, it is felt that there is no such neat demonstration of a consistent biochemical defect as outlined in Figure 11 in spite of early works suggesting such.

Case Presentations. *Post-pubertal simple virilization.* Patient M.S.H., Duke Unit #5-59154 (Fig. 12). A 17-year-old female was seen on referral November 1, 1961, with defeminization. Menarche was at 11 years with regular menses for two years. At age 13, the patient had mumps and measles during a two-

week period. Infrequent and scant menses, averaging one per year followed. Acne and hirsutism steadily progressed after age 11. Loss of scalp hair had progressed for 5 months. Patient was said to be the product of a normal term delivery, though she was adopted. Pertinent laboratory findings are noted in Table I. Two rest days intervened between the ACTH, metapyrone, and dexamethasone tests. Suppressive therapy was started, and the patient had an ovulatory spontaneous menstrual period 6 weeks later proved by endometrial biopsy. She was married, and while on suppressive therapy, delivered spontaneously on January 1, 1967, under pudendal block anesthesia, a 5 lb. 8 oz. normal male infant and on November 21, 1968, a 6 lb. 15 oz. normal female infant by Dr. William A. Peters. Her pelvis was normal by x-ray pelvimetry. During each delivery, the patient was supported by parenteral hydrocortisone, and her oral glucocorticoid was doubled then gradually tapered to maintenance level during the immediate puerperium. In that the patient appeared so normal and was cycling spontaneously, glucocorticoid therapy was discontinued in September 1969. She has continued to have cyclic menses without evidence of virilization. During the past year, her urinary 17-KS were 13.7 mg/24 hrs on two occasions, and her 17-hydroxycorticosteroids (17OH-CS) 2.9 and 4.3 mg/24 hours.

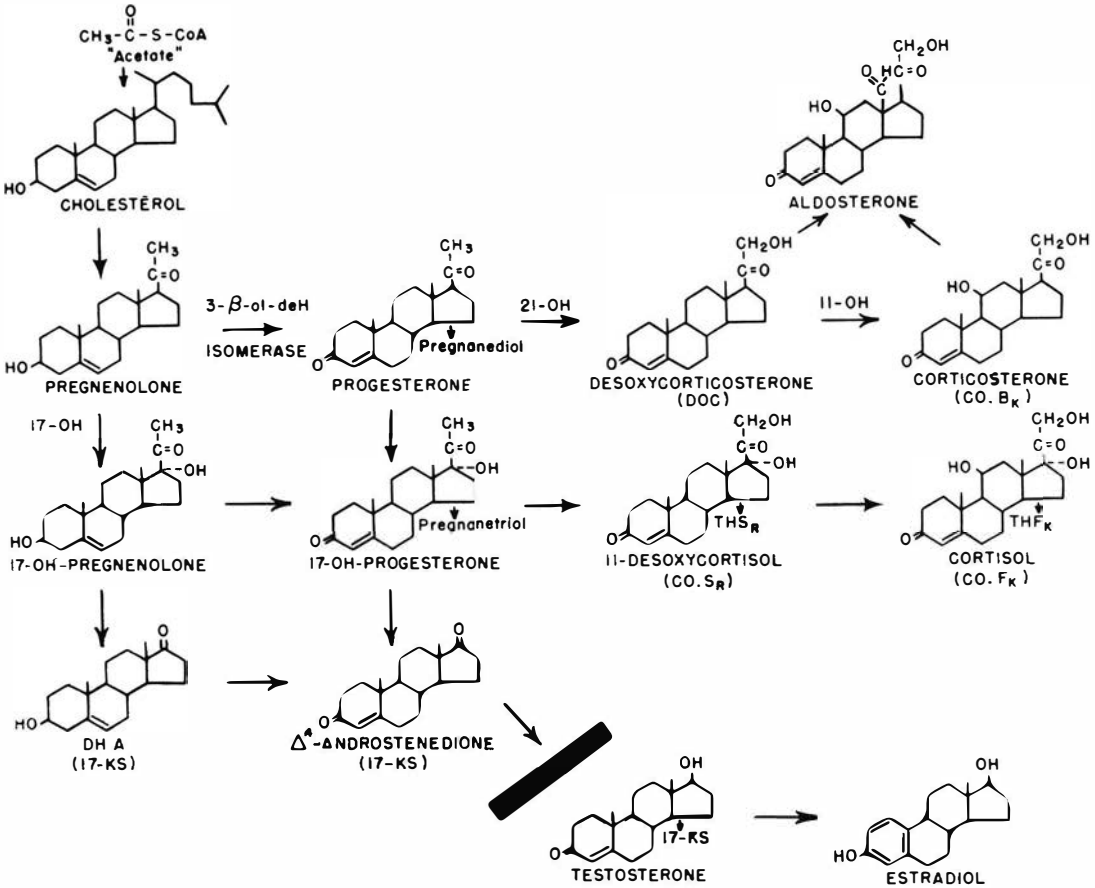

Fig. 10—Defect of 17β-hydroxysteroid dehydrogenase. Extremely rare steroid defect where androstenedione increased some tenfold over normal levels while achieving low normal testosterone. Reported in male pseudohermaphrodites, hence a consideration in differential diagnosis from common forms of CAH.

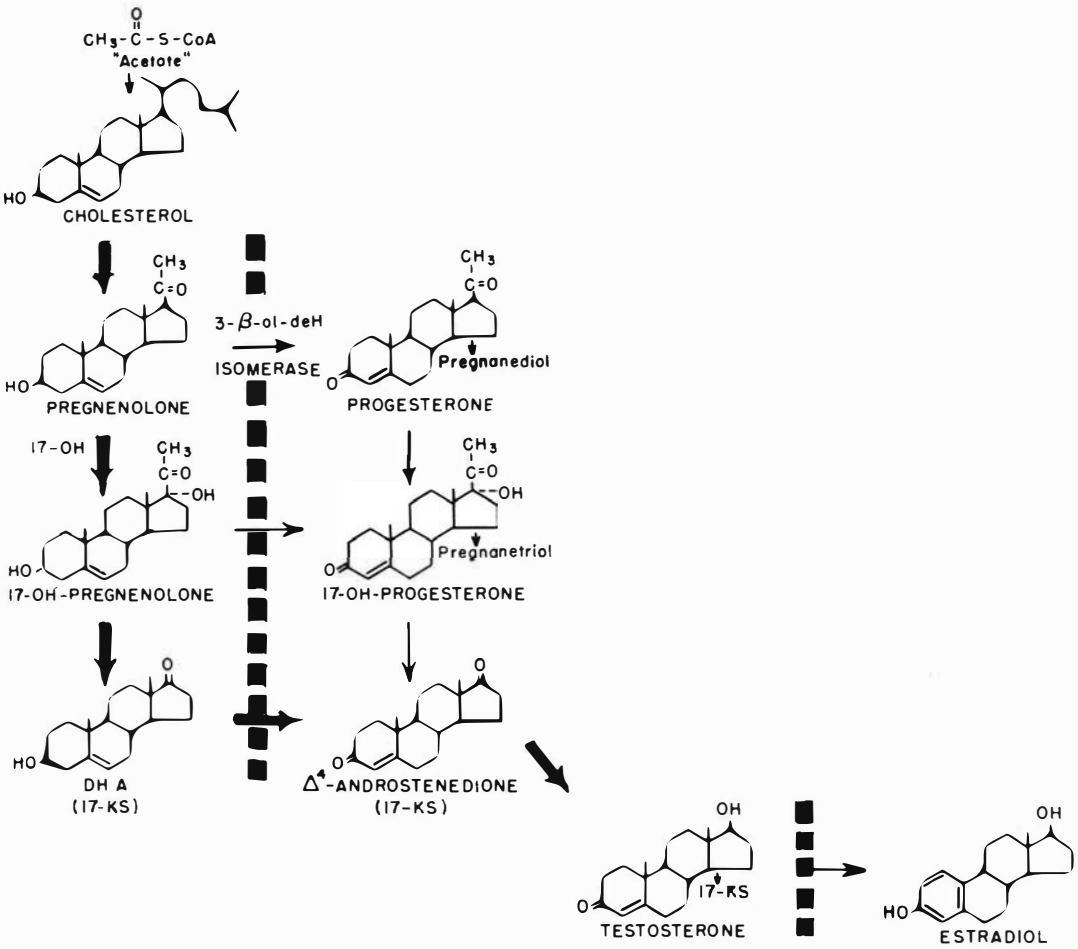

Fig. 11—Aromatization defect leading to excessive accumulation of testosterone and partial 3β-ol dehydrogenase defect causing elevated levels of DHA described inconsistently with Stein-Leventhal syndrome.

Comment. Postnatal virilization of the female is more commonly due to an autonomous tumor or ingestion of hormones than due to the postnatal (acquired) form of congenital adrenal hyperplasia. However, ready suppressibility of this patient's greatly-elevated abnormal steroids bespeaks the nature of her disorder. Since her onset occurred after most, if not full, statural growth had been achieved, she was not stunted, nor was her pelvic capacity compromised. Accordingly, delivery was spontaneous. Her children have been assessed for the possibility of congenital adrenal hyperplasia, and this has been ruled out. The chances of offspring having the disorder are remote, since the prevalence of the gene for the disorder is on the order of 1 in 128 for heterozygotes and 1 in 67,000 for the overt disease (35). However, the frequency will be on the increase in that affected individuals with proper treatment will no longer be sterile (36). This patient is remarkable in that she has remained apparently normal for a protracted period of time off of therapy in spite of a severe abnormality of steroidogenesis when first diagnosed. Her 17-KS are now upper limits of normal and her 17OH-CS are low bespeaking the fact that she

probably is just minimally compensated. However, she has undergone the stress of rearing two small children and moving to Europe without decompensating. Accordingly, our original hypothesis of decompensation due to psychologic stress of adolescence may be questioned (37).

Postnatal simple virilization. Patient K.S.S., Unit # 61682 (Fig. 13). A 13-year-old white female was seen January 18, 1963, because of "virilizing syndrome." She was born prematurely. Development was normal until age 4 when pubic and axillary hair became apparent. Her 17-KS were elevated, and glucocorticoid therapy was given elsewhere for two years, but discontinued by the mother when Cushingoid features developed. These rapidly disappeared, but were followed by progressive hirsutism. One brother had prostatic hypertrophy diagnosed at age 19.

Suppressive therapy was started January 23, 1963, and the patient was hospitalized elsewhere April 3, 1963, with right lower quadrant abdominal pain. Fifteen days later, menarche occurred and was followed by regular menses and rapid budding of breasts. Hirsutism gradually decreased, but her voice remained unchanged. Significant laboratory data are shown in Table I. Iliac crests were fused on the abdominal film. With her last menstrual period in May 1967, and after an adequate trial of labor, patient was delivered by cesarean on February 5, 1968, of a 5 lb. 7 oz. normal female. Opera-

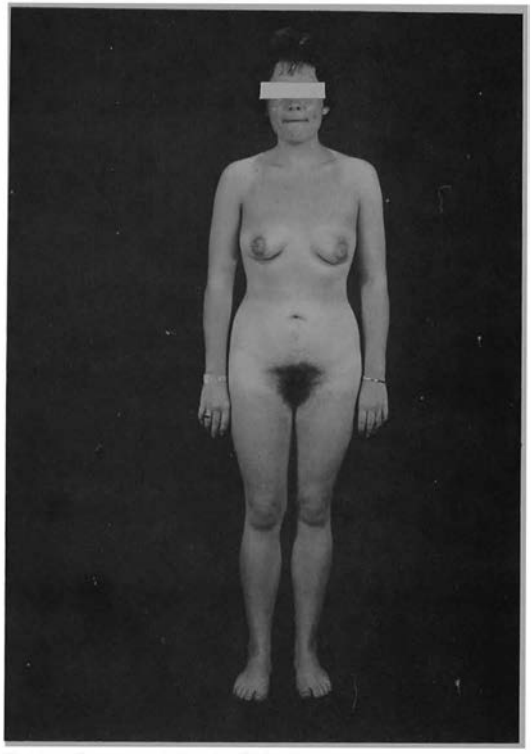

Fig. 12—Patient M.S.H., #F-59154. Normal feminine contour and endocrine measurements existed with comedones and facial hirsutism. B.P. 120/70. Weight 61 kg.

TABLE I

Patient	Age	Therapy	Urinary Steroids 17-KS	17-OH-CS	17-Ketogenic	Pregnanetriol
M.S.H.	17	None	82.8	11.4	15.7	9.7
		ACTH Gel 40 U IM q. 12 hrs. × 3 days	164.7	31.0	156.6	24.9
		Metapyrone 500 mg q. 4 hrs. × 2 days	77.4	41.8	128.0	43.2
		Dexamethasone 0.5 mg. q. 6 hrs. × 2 days	41.8	1.4	9.8	2.9
		Dexamethasone 2 mg. q. 6 hrs. × 2 days	7.8	0	3.6	0.5
K.S.	13	None	40.1			71.3
		Dexamethasone 0.5 mg q. 6 hrs. × 2 days	18.3		107.8	
		Dexamethasone 0.5 mg q. 6 hrs. × 2 days	7.6		31.4	
		Dexamethasone 2 mg. q. 6 hrs. × 2 days	5.7	2.7	11.6	1.4

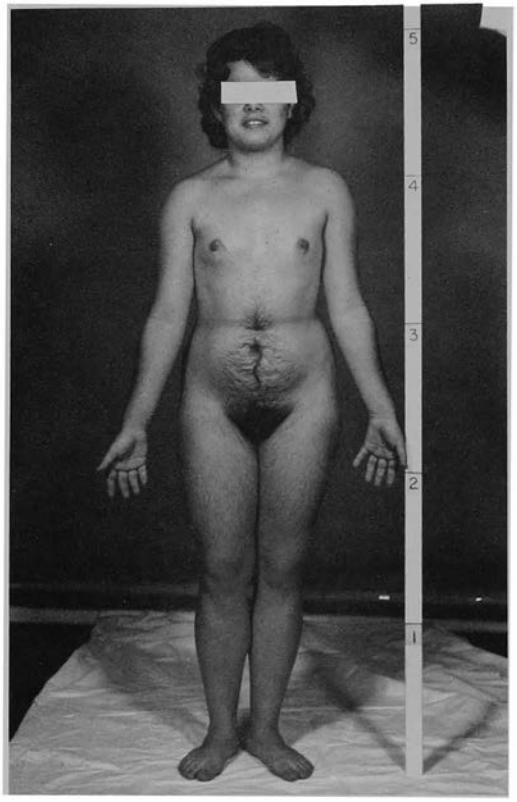

Fig. 13—Patient K.S.S., # 61682. Shows stunted growth, facial hirsutism, and android escutcheon. Chest was shaved prior to photography. Muscle hypertrophy was present and breast development absent. Voice was baritone. B.P. 150/90. Weight 55.5 kg. Height 152 cm. Span 151 cm. Lower segment 76 cm.

tion was necessary due to a moderately contracted pelvis of somewhat android configuration.

The patient has been maintained on prednisone 5 mg at bedtime. She continues to cycle normally. Her plasma 17OH-P of 216 ng%, plasma progesterone 1.4 μg% in luteal phase with plasma estradiol 20.3 ng%, suggest ovulation. However, her plasma testosterone persisted in the range from 80 to 120 ng% bespeaking continuing excessive testosterone production. Accordingly, an additional 2.5 mg of prednisone is being added in the morning.

Comment. Failure to continue glucocorticoid therapy as prescribed by her physician led to premature closure of this patient's epiphyses and ultimate stunting from excessive sex steroids. In turn, this probably necessitated delivery by cesarean because of cephalo-pelvic disproportion. In the past, some patients with adrenal hyperplasia who could not tolerate steroid therapy have been subjected to adrenalectomy. However, such surgical therapy is no longer warranted, for proper monitoring should be achievable so that the disease can be brought under control without significant side effects from the medication. Hayek and associates have suggested the single dose of a long-acting suppressive agent at midnight for therapy of this disorder with good results; hence simplifying therapy (38). Such therapy is appealing and rational. However, one must use a fairly long-acting steroid; therefore, oral hydrocortisone, the naturally occurring hormone that is missing, can not be utilized. Problems persist in such patients as this who have their sleep-wake patterns altered by work habits (she is a telephone operator working swing shifts). This may account for the need for an additional a.m. dose. Reversibility of some signs of virilization occur (the patient has lost much body hair, though some facial shaving is still necessary). Rapid feminization as shown by breast development and ovulatory menses is to be expected once adequate therapy is instituted. Her hospitalization was for suspected appendicitis, but the pain was apparently mittelschmerz, since she had her menarche two weeks later. Clitoromegaly and deep voice have persisted in this patient, since such changes, once they occur, do not reverse. Contraception in this patient, as well as in the first, is by intrauterine device. Estrogen-containing oral contraceptives should be avoided in as much as they confound steroid monitoring of such patients by altering steroid binding proteins. This patient was found to be hypertensive when initially seen, raising the question of a possible 11-hydroxylase block. However, measurement of tetrohydro-S showed no significant amounts of this in the urine. Prolonged hypertension following cessation of desoxycorticosterone therapy in CAH has been reported (39); however, we feel that this is highly unlikely in this patient, since initial therapy had been discontinued for almost a decade before she was found hypertensive.

Patient L.O.T., Unit # 235684-5. A 38-year-old nulliparous obstetrical nurse was seen on referral because of inadequate control of adrenal hyperplasia while taking divided doses during the day. Some evidence of virilization probably was present at birth (clitoromegaly), though hirsutism did not become

manifest until after age 5. In 1954, the patient elsewhere underwent vaginoplasty, abdominal exploration, and clitoridectomy with the findings of follicular cyst of the ovary with occasional ova and a hypertrophic clitoris (5 cm.). The adrenals were thought normal to palpation. The patient was empirically treated with Premarin® and thyroid and had withdrawal bleeding. All therapy was discontinued in 1964, and she had spontaneous regular menses for one year with flow lasting 3–5 days and on occasion had associated cramping. Her baseline 17-KS were 51 mg. rising to 109 with ACTH and suppressing to 13.4 mg. with Decadron®. She was discharged on 25 mg. cortisone per day and was later changed to prednisone. However, she was seen on referral, and her urinary pregnanetriol was 31.5 mg/24 hrs. She was shaving twice daily. The patient was working swing shifts as a registered nurse. She was advised to take 5 mg. prednisone before going to bed and 2.5 on arising and an additional 2.5 mg during the day if necessary. Since institution of this therapy, her plasma testosterone has ranged from 16 to 28 ng% with concomitant loss of chest and arm hair, though facial shaving is still needed. Her plasma estradiol has been between 2 and 43 ng%, though she has remained anovulatory while cycling, as shown by plasma progesterones repeatedly less than 400 ng%. Her 17OH-P has ranged from 118 to 496 ng%.

Comment. Patients working swing shifts can experience considerable difficulty in controlling their excessive androgen production since the ACTH surge may come at a time when they are not receiving their larger dose of suppressive steroid. Also, changing shifts alter diurnal variation and may in itself be a stressful situation causing further decompensation. If even suppression is not obtained by giving a dose prior to anticipated ACTH surge, consideration of longer-acting injectable therapy such as utilized in infants may be considered. Neither this patient, nor our patient undergoing cesarean, had evidence of classical Stein-Leventhal type ovaries, although CAH has been noted associated with polycystic ovaries (40). The thickened capsules in such patients have been attributed to excessive androgens.

Patient P.B., Unit # 233484-2. A 23-year-old gravida II, para 1, abortus 0 had menarche at age 12 and cyclic menses until age 16 when she started skipping menses. At age 17, she had ovarian wedge resections elsewhere with diagnosis of Stein-Leventhal syndrome. However, menses did not resume. She was seen by another physician who treated her with prednisone. Menses then resumed, and the patient spontaneously achieved a pregnancy only to have mid-trimester loss with prolapsed cord, intrapartum death, and delivery by cesarean. On physical examination, the patient had considerable facial hirsutism, modest clitoromegaly, but normal size ovaries. The patient was again studied off therapy with elevated 17OH-P of 4.4 μg%. Her plasma progesterone was 132 ng%. With adequate suppression, plasma progesterone rose to 1.7 μg% (ovulatory level) and 17OH-P fell to 160 ng% (normal). The patient spontaneously resumed menses and became pregnant with last menstrual period November 11, 1974. On January 8, 1975, continuing the same dose of 5 mg prednisone at bedtime, her plasma testosterone was 80 and plasma 17OH-P 137 ng%, and her plasma progesterone was greater than 1.6 μg%.

Comment. Patients with congenital adrenal hyperplasia being adequately treated will be unable to have plasma or urinary estriols as an index of fetal well-being in as much as these steroids cross the placental barrier and suppress fetal-adrenal activity—a most important source of precursors for pregnancy estriol. Differential suppression tests should be able to delineate patients with primarily ovarian disorders as opposed to those with primarily adrenal disorders and prevent unnecessary wedge resections in the future.

Patient L.H., Unit # 235525-8. A 27-year-old patient was seen in consultation because she had developed Cushingoid features as a result of being on prednisone for persistent amenorrhea. Menarche was at age 12 with an average of one cycle per year until age 18 when she was placed on oral contraceptives with regular withdrawal bleeding for three years. Upon discontinuance, the patient remained amenorrheic for one year when she was seen by a gynecologist and had bilateral wedge resection of ovaries. She remained amenorrheic for another year except for scant spotting on rare occasion. The patient was admitted to another university center and underwent dexamethasone suppression test with 17-KS, suppressing from 21 mg/24 hours to 6 mg on the first day of high-dose dexamethasone. She also had adrenal and ovarian vein catheterization, showing adrenal venous plasma testosterones quite elevated with some elevation of ovarian and peripheral values. She was placed on prednisone 10 mg every other day with spontaneous menses occurring approximately every 6–7 weeks. She then relapsed into

amenorrhea. Medication was discontinued for retesting, and after one month off of therapy, her plasma 17OH-P was 1.8 μg% (approximately five to tenfold the normal values) with plasma testosterone 79 ng% (upper limits of normal for adult females in our laboratory are 60 ng%), plasma cortisol 10 μg% at 8 a.m., plasma estradiol 24.1 ng% (normal proliferative phase value), plasma progesterone 94.5 ng% (anovulatory value). On suppressive therapy, 17OH-P fell to 165 ng%, testosterone was 71 ng%, and plasma estradiol remained at 22.9 ng% with progesterone 78 ng%. Stimulation with Clomid®, escalating doses to a maximum of 150 mg/day times five days, indicates the patient remains anovulatory with progesterone 50.5 ng%, plasma estradiol 24 ng%, while 17OH-P has remained 112 to 216 ng% during the time she is being maintained on p.m. suppressive prednisone.

Comment. This patient with a mild form of 21-hydroxylation defect with first manifestations in postnatal period did not achieve smooth suppression with alternate-day therapy. Even though nighttime therapy has brought about normalization of 17OH-P and near normal values of plasma testosterone, she remains anovulatory and unresponsive to Clomid® at this time. In this patient, the elevation of 17OH-P in the plasma out of proportion to the progesterone would indicate that her primary pathway to 17OH-P is through 17-hydroxy-pregnenolone rather than through progesterone. Also, findings would suggest that even though near-optimal biochemical control of the disorder can be achieved, fertility does not automatically ensue. She probably needs further suppressive therapy. If optimum control is then achieved as shown by normal plasma testosterone, 17OH-P, and urinary 17-KS, then a search for other causes of amenorrhea are warranted, for they can be subject to such disorders as hypothalamic amenorrhea.

Patient J. L., Unit # 161059. An 11-year-old patient was seen in consultation after she had seen a group movie at school on sexual development in which a photograph of abnormal external genitalia was shown. She persisted in telling her teacher that she had such abnormal genitalia. Although "show and tell" in its fullest sense did not occur, this experience led to her being referred where the disorder was well characterized. She is now on suppressive therapy.

Comment. Clitoromegaly of this degree, had it been present at birth, surely would have been recognized, though possibly some physicians may attempt to downplay its importance. However, the clinical course of this patient, that is, the onset of hirsutism and facial acne just prior to her evaluation, would suggest postnatal onset of her disorder.

Patient C. G., Unit # 172230-1. A 20-year-old patient had onset of virilization at age 11, and the diagnosis of congenital adrenal hyperplasia was made at a medical university well known for its large series of congenital adrenal hyperplasia patients. Initial attempts to control her here by continuing cortisone acetate which had been instituted elsewhere failed, and she was switched to prednisone in 1970, taking 2.5 mg every eight hours. However, when seen in February, 1974, her 17OH-P was greater than 1.4 μg%, and her plasma progesterone greater than 1.6 μg%, with plasma testosterone 72 ng%. She was anovulatory as shown by endometrial biopsy and basal body temperature charts. Five mg. of prednisone at bedtime still failed to achieve suppression with plasma 17OH-P of 3.7 μg%, therefore, prednisone has been increased to 7.5 mg/day while sterility investigation is being pursued.

Discussion. Differential diagnosis of congenital adrenal hyperplasia includes disorders of adrenal and gonadal origin. Rarely are such entities as Morgagni-Stewart-Morel syndrome or Achard-Thiers syndrome of any importance in the differential diagnosis, if indeed they represent true syndromes.

Cushing's syndrome is readily differentiated by overnight dexamethasone suppression test in most patients and by baseline values of glucocorticoids. Rarely is virilization of the degree seen with CAH present in patients with Cushing's syndrome. Exogenous administration of virilizing hormones can present a problem particularly when the patient does not know what she has received. Anabolic steroids have been given in wasting diseases, osteoporosis, and to improve libido. The differentiation of ovarian hyperandrogenic syndromes including Stein-Leventhal syndrome can generally be made on the basis of differential suppression tests employing glucocorticoids to suppress the adrenal component and combination estrogen-progestogen preparation such as Enovid® E for the ovarian component (41, 42). True hermaphroditism usually is not much of a problem since prepubescent hirsutism is not usually evident even though ambiguous genitalia may exist. Steroid assays readily differentiate the conditions. Occasionally, patients with gonadal dysgenesis with a Y stem line (usually) may present with signs of hirsutism and clitoromegaly. This has been particularly

true of patients with gonadoblastomas or Teter's gonocytomas III and IV. Again, steroid assays readily differentiate the condition. In patients with virilizing ovarian tumors such as an arrhenoblastoma, elevated androgens will not suppress with exogenous administration of glucocorticoids. Further, their urinary 17-KS are generally not of the magnitude of those seen with CAH.

Summary. Enzymatic defects of adrenal and gonadal steroidogenesis have been described, many of which lead to amenorrhea and sexual ambiguity. Seven patients with congenital adrenal hyperplasia are presented who were first diagnosed at times far removed from the neonatal period. One such patient had dramatic onset of hirsutism, amenorrhea, and profound elevation of androgens. After suppression, she achieved two pregnancies, delivered, and subsequently has gone off therapy and continues to have cyclic menses in spite of borderline steroid values. The usefulness of a single nighttime long-acting glucocorticoid in achieving smooth suppression in patients with adrenal hyperplasia appears rational and is meeting with success. Diagnosis and monitoring of therapy of such patients has been facilitated by the availability of immunoassays for 17OH progesterone, and testosterone in lieu of urinary 17-KS, and urinary and plasma pregnanetriol assays.

Authors' note: Since preparation of this presentation, 5α reductase deficiency has been described in association with male pseudohermaphroditism. (Walsh et al, Familial incomplete male pseudohermaphroditism, type 2, decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias, *N Engl J Med* 291:944–949, 1974).

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