CONGENITAL ADRENAL HYPERPLASIA

HISTORY

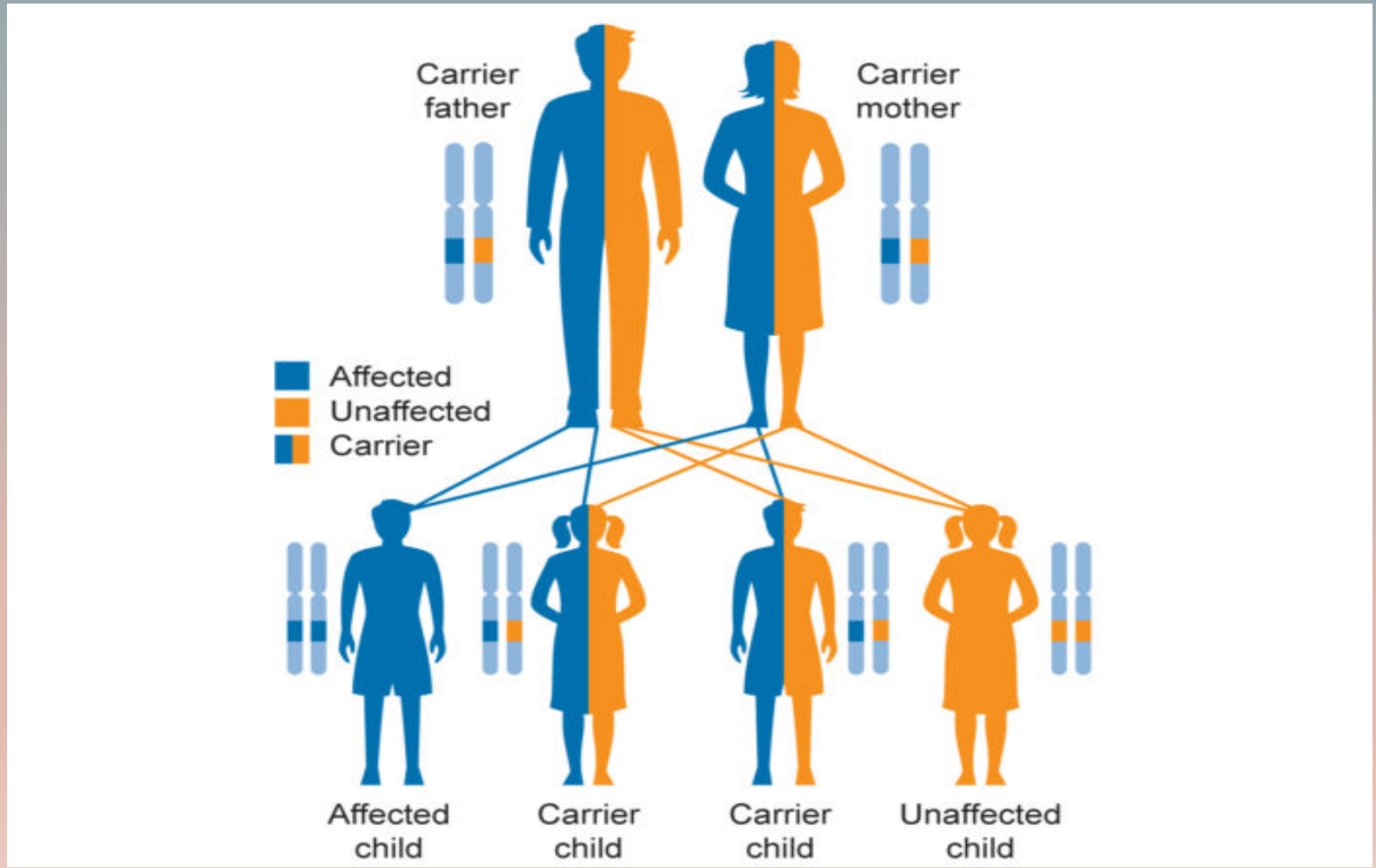
The first report of non-salt wasting congenital adrenal hyperplasia (CAH), initially described in **1865** by Luigi de Crecchio[1]

Much has been learned over the past 150 years about CAH

1978 ,location of the gene discovered to be located on the short arm of 6th chromosome

1989, Texax included CAH in its newborn screening program

CAH is a family of AR disorders of cortisol biosynthesis.



Cortisol deficiency increases secretion of ACTH, which in turn result in adrenocortical hyperplasia and overproduction of the intermediate metabolites.

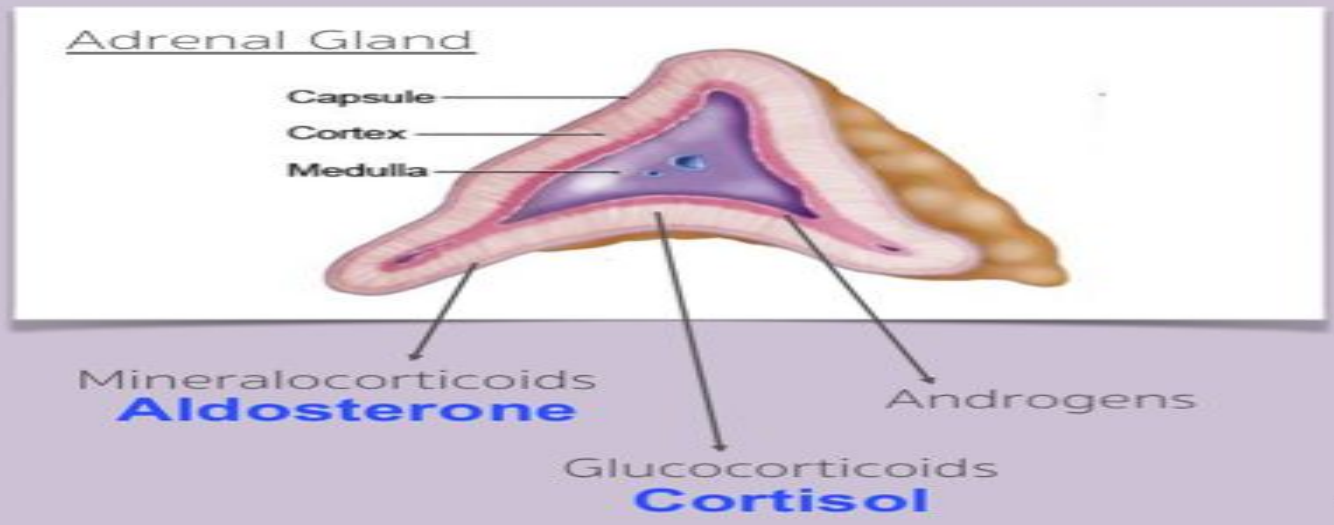
Depending on the enzymatic step that is deficient,

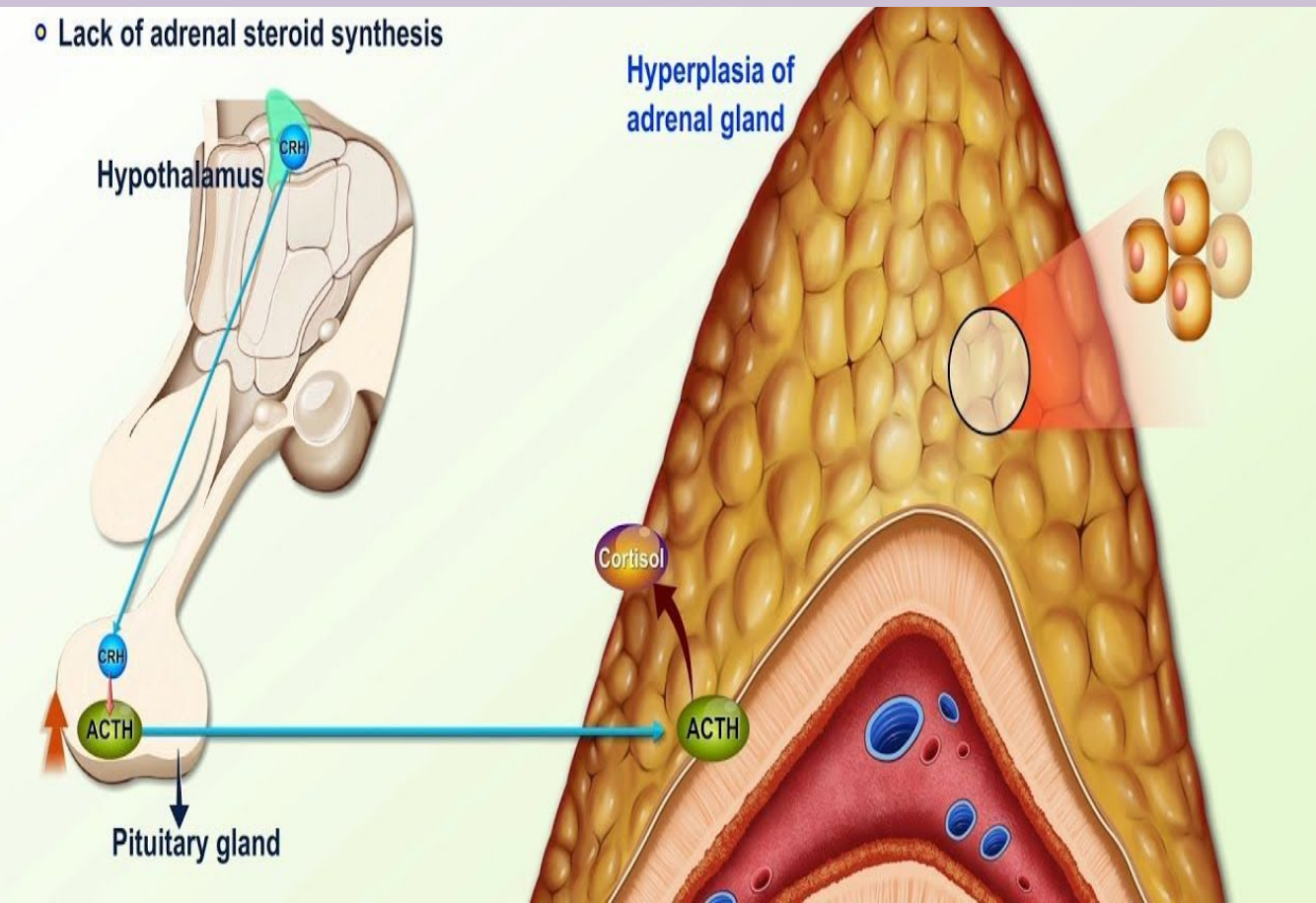
There may be signs, symptoms, and laboratory findings of:

*mineralocorticoid deficiency or excess;

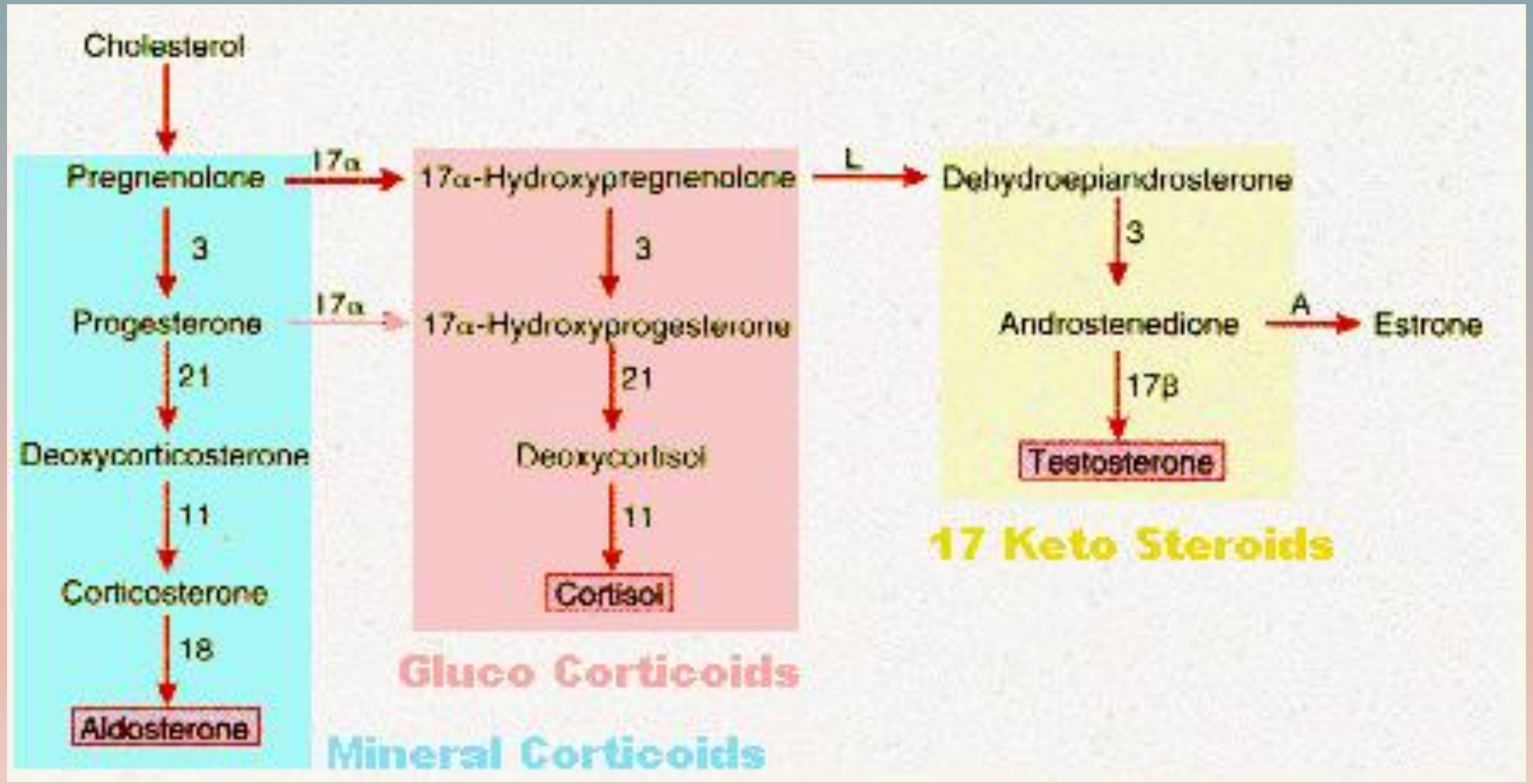
*incomplete virilization or premature puberty in affected males; and

*virilization or sexual infantilism in affected females.





Pathways of Adrenal steroid synthesis



Congenital Adrenal Hyperplasia Caused By 21-hydroxylase Deficiency

Etiology:

It accounts **>90%** of CAH cases.

It caused by deficiency of 21-hydroxylase which is a P450 enzyme (CYP21, P450c21) that ....

hydroxylates progesterone & 17-hydroxyprogesterone (17-OHP) to

yield 11-deoxy-corticosterone (DOC) & 11-deoxycortisol respectively,which eventually yield aldosterone and cortisol respectively

The incidence // 1 in 15,000 live births.

Path.:

It can be divided into classical & non-classical.

- *Classical 21-hydroxylase deficiency* involves 2 types according to the degree of gene mutation & enzyme activity:-
- **Salt-wasting disease** (70%) is the most severe form; it is due to deficiency of both hormones (i.e. aldosterone and cortisol).
- **Simple virilizing disease** (30%) is less severe form; the patients are able to synthesize adequate amounts of aldosterone but they also have elevated levels of androgens of adrenal origin.

- *Non-classical disease* is more common than the classical one; patients have only mild elevation of androgens and may have signs of androgen excess after birth

C.M. ❖ Patients with **Classic disease** have the following manifestations:-

- **Aldosterone and Cortisol deficiency:** Both hormones are deficient in

"salt-wasting" disease → **anorexia, vomiting, dehydration, weakness, hypotension, hypoglycemia, hyponatremia,hyperkalemia, and progressive weight loss.**

These problems are typically develop as early as **10-14 days** of life & if patient is untreated; shock, cardiac arrhythmias, and death may occur within days or weeks.

Prenatal Androgen Excess: The steroid precursors are accumulated up to **hundreds times of normal** including **17-OHP & progesterone**.

17-OHP is shunted into the pathway of **androgen biosynthesis** →

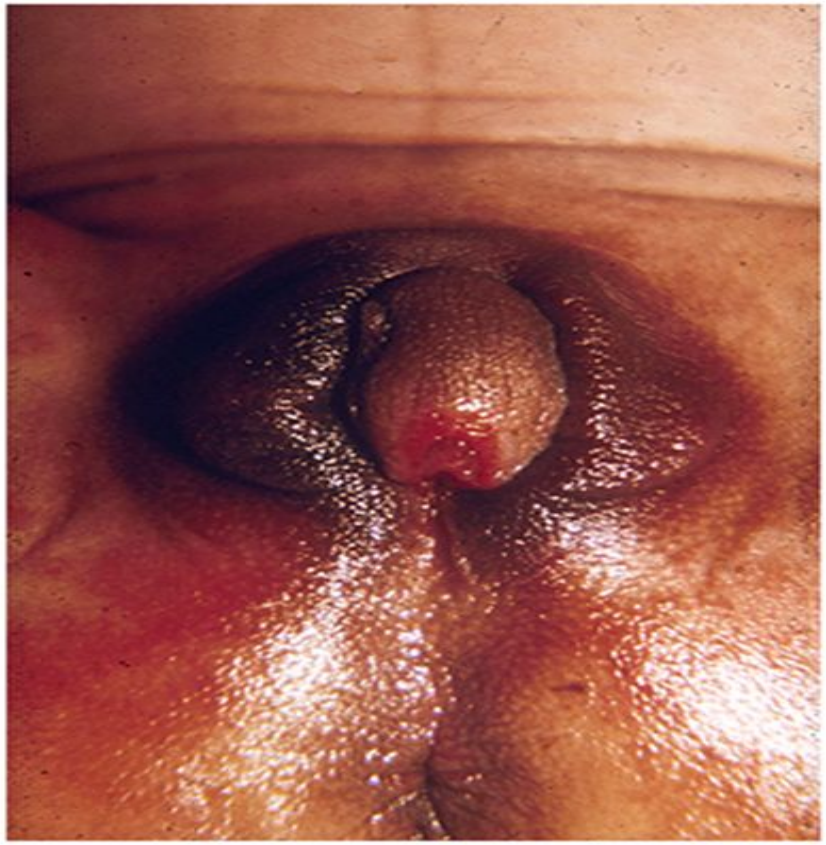
high levels of androstenedione which converted outside the adrenal gland into **testosterone.**

This problem begins as early as **8-10 wk of gestation** → masculinized of external genitalia of the affected **female** e.g. **enlargement of clitoris** with partial or complete **labial fusion.**

The vagina usually has a common opening with the urethra (urogenital sinus); however, the

internal genital organs are normal as female. !!

Atypical genital appearance



Clitoromegaly in a 46,XX infant with congenital adrenal hyperplasia due to 21-hydroxylase deficiency.

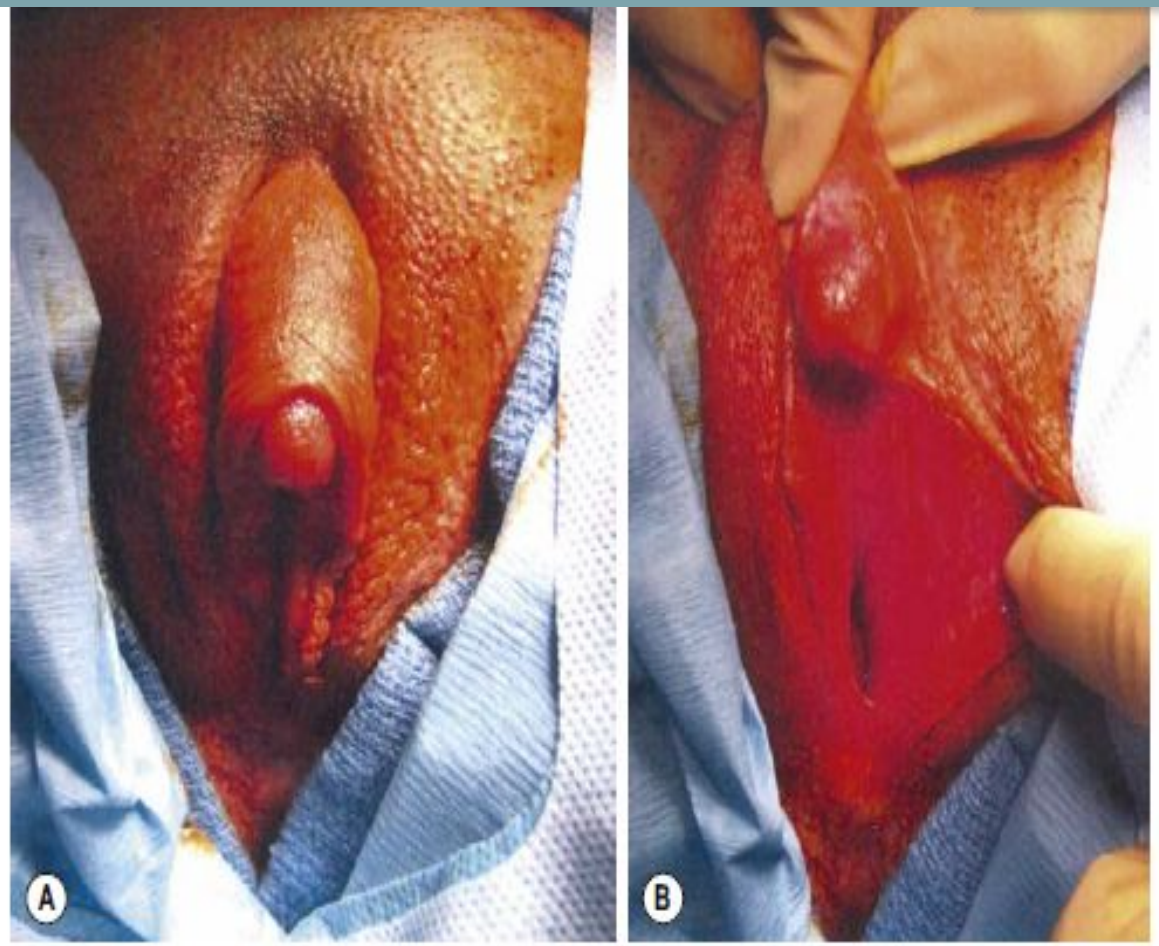


Fig. 62.7 Ambiguous genitalia (**A,B**). The patient has congenital adrenal hyperplasia, 21-hydroxylase deficiency (**A**). Note the enlarged phallus. (**B**) With labio-scrotal folds distracted, note the single opening of the urogenital sinus..

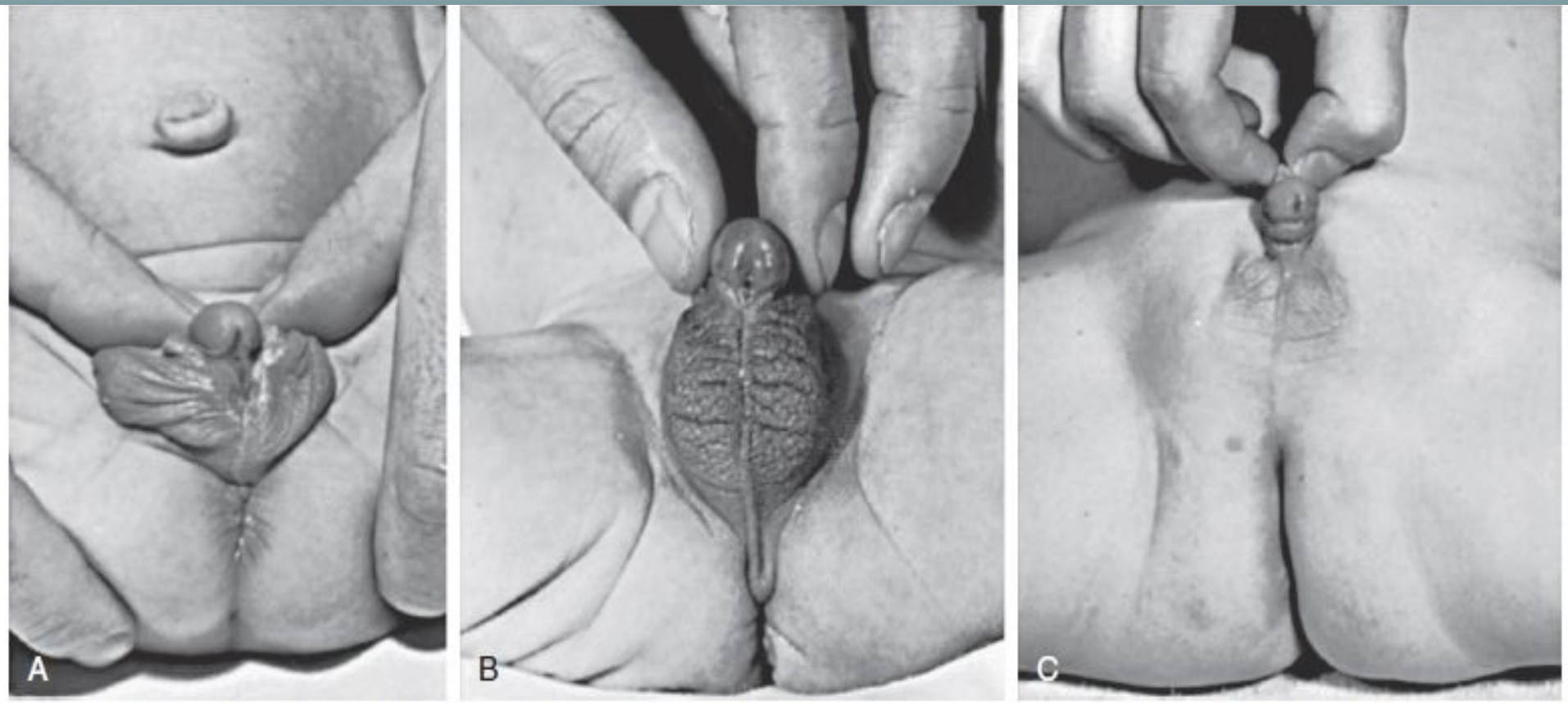
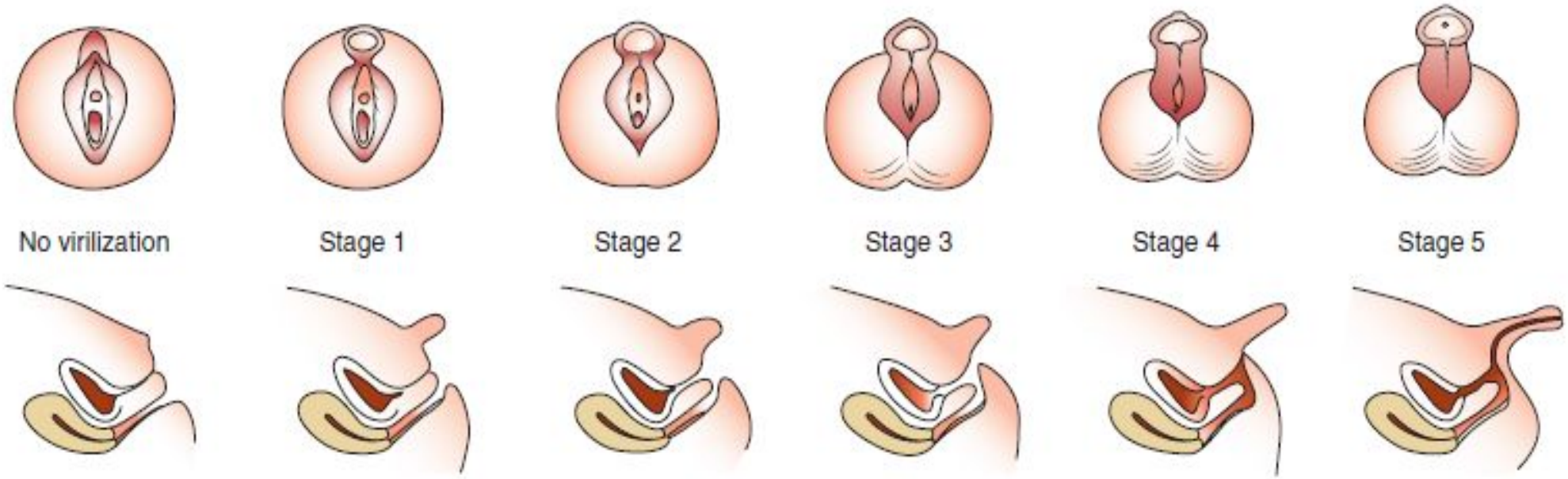


Fig. 594.2 Three virilized females with untreated congenital adrenal hyperplasia. All were erroneously assigned male sex at birth, and each had a normal female sex-chromosome complement. Infants **A** and **B** had the salt-wasting form and received the diagnosis early in infancy. Infant **C** was referred at 1 yr of age because of bilateral cryptorchidism. Notice the completely penile urethra; such complete masculinization in females with adrenal hyperplasia is rare; most of these infants have the salt-wasting form.

Prader scale



• **Fig. 89.6** Prader scale reflecting the degree of virilization of the external genitalia. The internal genitalia reflect the changes in the urogenital sinus that may be seen with a 46,XX DSD such as congenital adrenal hyperplasia. (From Allen L. Disorders of sexual development. *Obstet Gynecol Clin North Am.* 2009;36:25-45.)

> ***Note:*** *Since urethra opens below urogenital sinus, some affected females may mistakenly presumed to be*
>
> *males with hypospadias & cryptorchidism*

Male infants appear normal at birth, thus, Dx may not be made in them until signs of adrenal insufficiency develop, whereas those with simple virilizing form have even more delay in Dx because they appear normal and rarely develop adrenal insufficiency.

Hence, **NEWBORN SCREENING** is essential in every infant by measuring **17-OHP at birth**

Postnatal Androgen Excess:

Prenatal exposure of the brain to high levels of androgens may influence the subsequent **behavior** in affected

females who tend to be interested in the male toys.

Signs of androgen excess include: excessive muscular development,

rapid somatic growth and accelerated skeletal maturation; thus,

affected patients are tall in childhood but premature closure of epiphyses causes growth to stop relatively early, and adult stature will be stunted.

Pubic and axillary hair may appear; acne and deep voice

may develop.

In male,

the penis, scrotum, and prostate may become enlarged,

except testes which usually remain prepubertal in size due to absence

of gonadotropine (FSH & LH) stimulation, so that they appear

relatively small in contrast to the enlarged penis.

Occasionally, an ectopic adrenocortical cells in the testes become hyperplastic in response to excessive ACTH

resulting in "**testicular adrenal rest tumors**".

IN FEMALE,

although the internal genital structures are normal, breast

development and menstruation may not occur unless the excessive production of androgens is suppressed by adequate therapy.

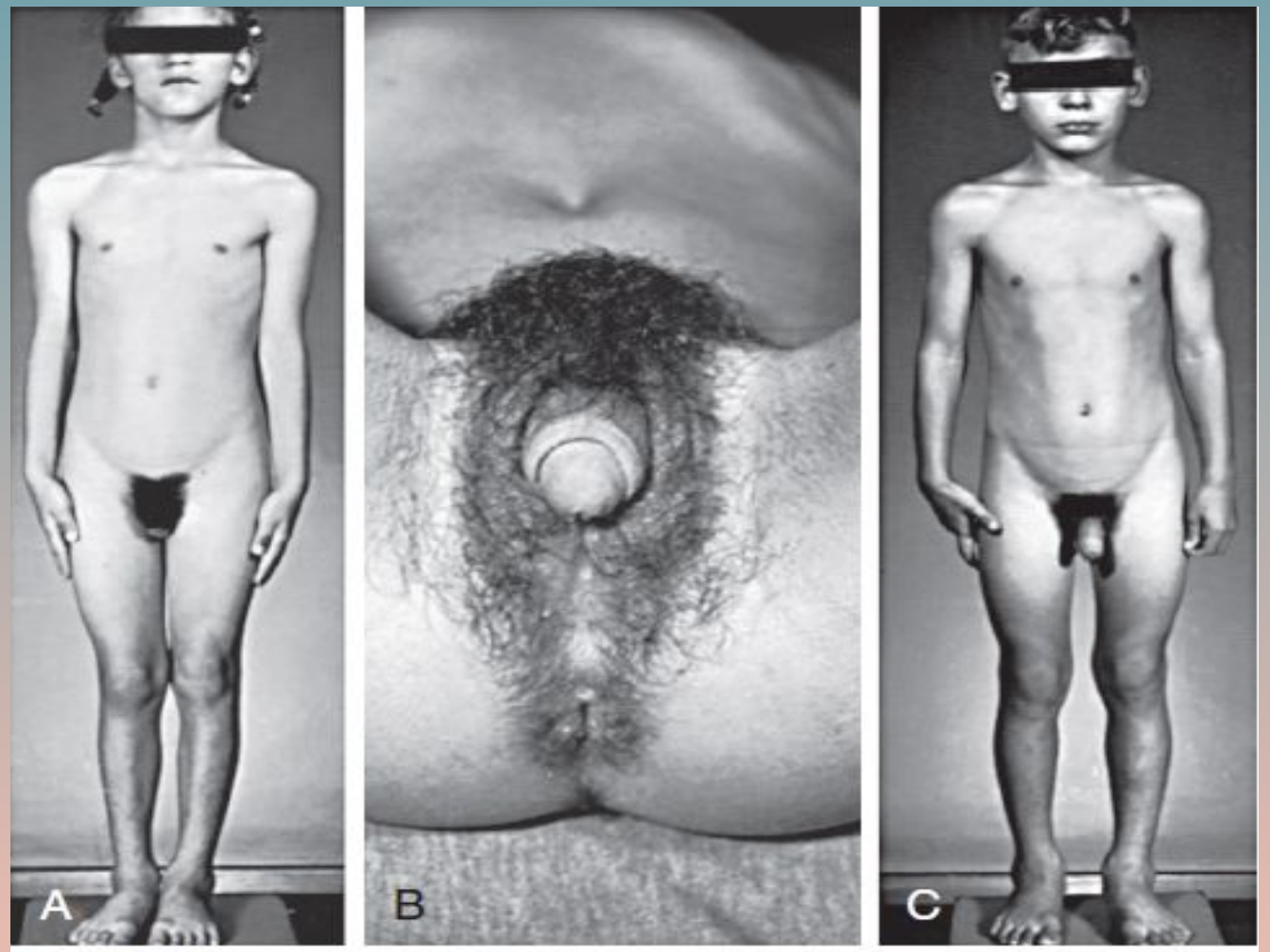


Fig. 594.1 **A,** A 6 yr old girl with congenital virilizing adrenal hyperplasia. The height age was 8.5 yr, and the bone age was 13 yr. **B,** Notice the clitoral enlargement and labial fusion. **C,** Her 5 yr old brother was not considered to be abnormal by the parents. The height age was 8 yr, and the bone age was 12.5 yr.

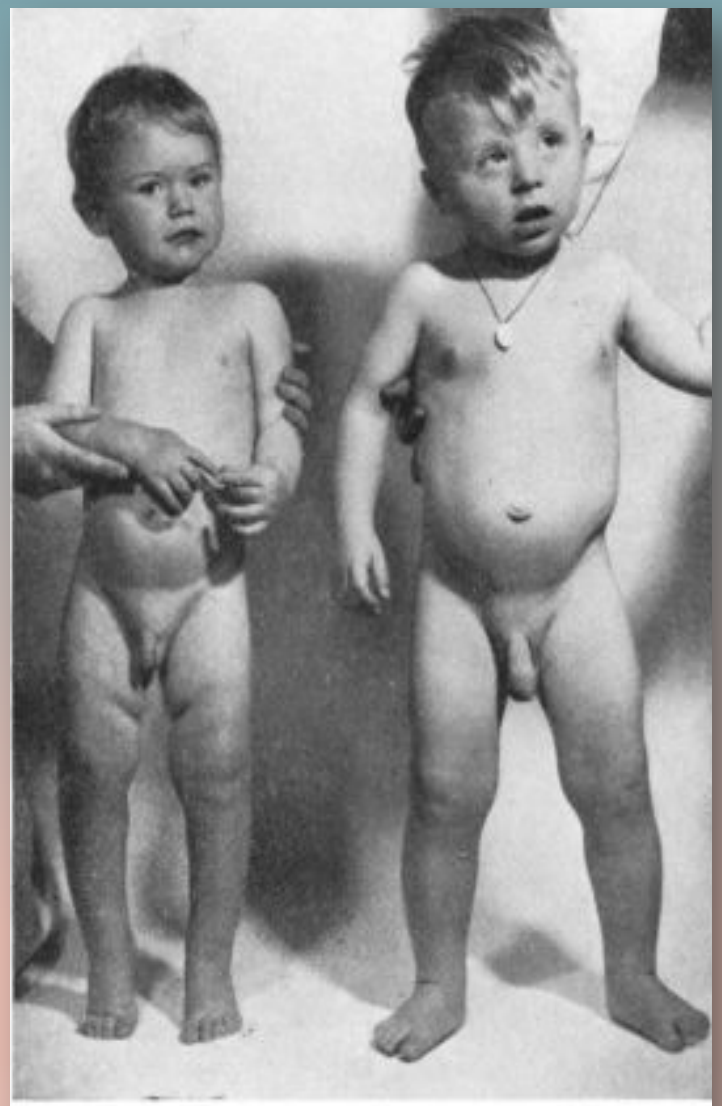


FIG. 3.—Case 3, aged 1 year 3 months.

Case . This male child was born on July 8, 1958, and was the fourth child of a full cousin marriage. The neonatal period was uneventful. He grew rapidly and when he was I year and 3 months his parents observed early pubic hair and penile enlargement (Fig. 3). Clinical examination at this time showed a child, tall for his age, muscular and with slight breast enlargement. Bone age was 4 years. Blood pressure was normal. Urinary excretion of 17-oxosteroids was 5 5 mg. per day. He was given cortisone 50 mg. daily for one month and thereafter 25 mg. daily. 17-oxosteroid output was then 1 3 mg. per day. When seen six months later, growth had proceeded unchecked. His weight age was 41 years, height age 21 years and bone age 6 years. Urinary steroid excretion was again raised (Table 1). Cortisone was increased to 75 mg. daily. His parents alleged that this high dosage was maintained till he was next seen at 3 years of age. His bone age was then equivalent to 10 years. Under strict in-patient supervision cortisone was increased over six months to 300 mg. daily. Nevertheless, his bone age continued to advance to 11 years. Cortisone was then withdrawn abruptly without obvious ill effects. He was then given dexamethasone 2 mg. daily plus cortisone 50 mg. daily.

Adreno-medullary Dysfunction: Development of adrenal medulla requires exposure to extremely high cortisol levels. Thus patients with classic CAH may have abnormal adrenomedullary function e.g. blunted epinephrine responses, hypoglycemia, & lower HR with exercise.

Patients with **Non-classical** 21-hydroxylase deficiency **show similar**

but milder signs of androgen excess.(in which there is 20 to 50% 21-hydroxylase enzyme activity)

In this attenuated form,

Cortisol and aldosterone levels are **normal** and affected females have normal genitals at birth.

However later in life, females and males either remain**asymptomatic** or may present with signs of **precocious pubarche** e.g.early development of pubic and axillary hair, hirsutism, acne, and in females, menstrual disorders and infertility may occur.

*prevalence**.....as high as 1 in 200**

Dx;17-hydroxyprogesterone — An early morning baselineis a good screening test for nonclassic CAH and may obviate the need for an ACTH test.

A very elevated (>1500 ng/dL [45 nmol/L]) is diagnostic of NCCAH.

MX:

children, hydrocortisone 10 to 15 mg/m^2 divided into 3 daily doses.Asymptomatic children who are diagnosed genetically due to family genotyping studies do not require treatment

premature pubarche without advanced bone maturation can be monitored every six months without treatment

For most adult women who are not pursuing fertility, we suggest OCs as first-line therapy for(hirsutism). Antiandrogens can be added after six months if the response to OCs is inadequate

For sexually active women, hydrocortisone, prednisone, or prednisolone are suggested because dexamethasone crosses the placenta

In women who do not ovulate with glucocorticoid therapy alone, we suggest

INV.

Patients with salt-losing disease have typical laboratory findings

associated with **cortisol & aldosterone deficiency** e.g.

hyponatremia, hyperkalemia, metabolic acidosis, and hypoglycemia, but these abnormalities can take 10-14 days or longer

to develop **after birth.**

Blood levels of 17-OH Progesterone are markedly elevated

which may be hundreds times of normal, but levels of this hormone are normally high during 1st 2-3 days of life (even in unaffected infants);

Measuring of 17-OHP before and after 30 or 60 min of IV bolus of cosyntropin (ACTH**) is the most reliable method for Dx.**

INV.

Androstenedione & testosterone are also elevated in affected females; whereas in male infants, testosterone is not usually elevated because it is already in high level normally.

Other tests include:

urinary 17-ketosteroids and **pregnanetriol** levels

are elevated but are now rarely used clinically.

ACTH levels are elevated

Plasma levels of **renin** are also elevated

serum aldosterone is inappropriately low for the high renin level.

- **Genotyping** is available but expensive and may take weeks

ACTH stimulation test

●A cosyntropin (ACTH) stimulation test is indicated to rule out rare disorders of steroidogenesis.

●Although a cosyntropin stimulation test is the gold standard to diagnose all forms of congenital adrenal hyperplasia (CAH), it is not always necessary to make the diagnosis of classic 21OHD; infants with classic 21OHD have levels of basal adrenocortical hormone and cortisol precursors that are already markedly elevated due to a highly stimulated adrenal cortex.

To assess borderline cases, the standard high-dose (250 mcg cosyntropin) test, not the low-dose (1 mcg) test, should be used. This is preferred over genetic testing and can be done in an outpatient setting by a pediatric endocrinologist

NEWBORN SCREENING

Because 21-hydroxylase deficiency is often undiagnosed in affected males until they have severe adrenal insufficiency,

all states in the United States and many other countries have instituted newborn screening programs(mandatory). These programs analyze

17-hydroxyprogesterone in a dried, filter paper blood spot. preferably between two and four days after birth.

Most affected neonates have random concentrations greater than 3500 to 5000 ng/dL (105 to 150 nmol/L)

APPROACH TO PATIENT WITH AM GENITALIA:

Prenatal diagnosis ***of*** ***21 hydroxylase deficiency*** **is usually indicated when the parents have already an affected infant. It is done by DNA analysis obtained late in the 1st trimester by chorionic villous sampling or during the 2nd trimester by amniocentesis.**

A thorough **physical exam** to define the anatomy of the genitals including palpation of scrotum (or labia) and the inguinal regions for palpable gonads which almost always indicate the presence of testicular tissue and thus that the infant is a genetic male.

US is helpful in demonstrating the presence or absence of uterus and can often locate the gonads (ovaries or intra-abdominal testes). Injection of **contrast** medium into the urogenital sinus of virilized female can demonstrate the vagina and uterus.

Rapid **karyotype** e.g. FISH technique can quickly determine the genetic sex of the infant.

Note: *The results of the above tests are likely to be available before the results of hormonal testing (which may take several days to be evident, except 17-OHP); results can allow the clinical team to advice parents about the genetic sex of infant.*

TREATMENT:

Glucocorticoid Replacement Therapy

Cortisol deficiency can be treated with glucocorticoids which also **suppress excessive production of androgens** by the adrenal cortex (through suppression of ACTH by the negative-feedback mechanism) and thus minimizes virilization problems.

This often requires **larger** glucocorticoid doses, typically **15-20 mg/m$_2$/24 hr of hydrocortisone** daily orally in 3 divided doses.

Double or triple the dose during periods of stress

Glucocorticoid Rx must be continued indefinitely in all patients with classical disease but may not be necessary in non-classical disease unless signs of androgen excess are present.

Therapy must be individualized.

Pubertal development should be **monitored by periodic exam & skeletal maturation**

Hormone levels,

especially 17-OHP and androstenedione

Children with **"simple virilizing disease"**, especially males, are…

frequently not diagnosed until **3-7 yr** of age,

Furthermore, some children, especially if the bone age is ≥ 12 yr, may

develop **spontaneous gonadotropin-dependent "true" puberty when treatment is instituted** because Rx will suppress the production of adrenal androgens which stimulate the release of pituitary gonadotropins. This form of superimposed true precocious puberty may be treated with **gonadotropin hormone-releasing hormone analog**

e.g. leuprolide.

Mineralocorticoid Replacement Therapy

mineralocorticoid replacement with **fludrocortisone**.

usually in dose **0.1-0.4 mg/day ÷ 2**

(with **sodium** supplementation).

Older infants and children are usually maintained with **less** dose, 0.05-0.1 mg.

TABLE 89.8 Treatment Guidelines for Neonate With Salt-Wasting Congenital Adrenal Hyperplasia (CAH)

Glucocorticoids: hydrocortisone	Maintenance: 12-20 mg/m^2 per day PO divided three times a day Stress dosing: Acute illness with stable hemodynamics: 40 mg/m^2 per day PO/IV/IM divided q 6-8 h Severe stress, such as major surgery or sepsis, or if hemodynamically unstable: 100 mg/m^2 (or 25 mg) IV/IM STAT once, then 25 mg/m^2/dose q 6 h for 24-48 h. Assess the need for ongoing stress dosing as per clinical status General anesthesia (either for surgery or procedure): 50 mg/m^2 IV/IM once 30-60 minutes before anesthesia induction
Mineralocorticoids: fludrocortisone	0.05-0.2 mg/day PO once or twice daily
Sodium chloride	0.5-5 mmol/kg per day divided in 4-6 doses as tolerated

SURGICAL MANAGEMENT OF AMBIGUOUS GENITALS:

Significantly virilized females usually undergo surgery **between 2- 6 mo** of age.

If there is severe clitoromegaly, it is reduced in size,

whereas moderate clitoromegaly may become much less noticeable as the patient grows.

Vaginoplasty and correction of the urogenital sinus can also be done.

Revision of surgery during adolescence is often necessary.

In adolescent and adult females with poorly controlled 21-hydroxylase deficiency,

bilateral laparoscopic adrenalectomy with hormone replacement can be done.

PRENATAL THERAPY !

COUNSELING Parents should be offered counseling as soon as the diagnosis of CAH is established. If the infant presents with atypical genitalia, immediate and ongoing counseling by an expert team is particularly important.

mothers with pregnancies at risk can be given **dexamethasone as early as 6th wk of gestation**, i.e. before the above tests are done. Dexamethasone suppresses secretion of steroids by fetal adrenal, including androgens, thus it ameliorates virilization of the external genitals in affected females.

However, because adverse effects of prenatal therapy several groups have concluded that prenatal therapy should be regarded as experimental and undertaken only by a highly experienced team

Chorionic villus biopsy is then performed to determine the sex and genotype of fetus,

then therapy is continued **only if the affected fetus is female**.

The determination of sex and genotype of the fetus can also be made in **early** pregnancy by DNA analysis of fetal cells isolated from plasma of the mother.

WHAT HAPPENS NEXT?

Long term follow up monitoring is essential for children with CAH.

They will need regular **blood tests** to monitor hormone levels in the body and **adjustments of steroid replacement** doses.

Men usually have normal fertility provided they have been optimally treated,

but **some women** with CAH may have problems conceiving so may require additional help to have children. Once pregnant, women with CAH should carry the baby to term but may require a caesarean section to deliver.

Quality of life — Quality of life is broadly reduced in adults with 21OHD . In a report of 151 adults, decreased quality of life was associated with the use of prednisolone or dexamethasone treatment (versus hydrocortisone) and with markers of obesity and insulin resistance .

These associations were found in patients with both classic and nonclassic forms. Another study from the same group found dexamethasone treatment to be associated with greater insulin resistance

Mortality — A study from Sweden of 588 adults with classic 21OHD found approximately a two- to fourfold increase in mortality compared with population norms . The major causes of death were adrenal crisis (42 percent), cardiovascular (32 percent), cancer (16 percent), and suicide (10 percent). Mortality was highest among men and among patients with the most severe ("salt-wasting") disease.

CAH Due To 11β-hydroxylase Deficiency

Et. Deficiency of this enzyme which convert 11-deoxycortisol to cortisol

→ **accumulation of 11-deoxycortisol and deoxycorticosterone** →

shunting to the androgen biosynthesis (as above);

aldosterone biosynthesis is not affected.

C.M. It accounts **≈ 5%** of CAH & mainly is presents in a **classical, severe form** .

All signs and symptoms of androgen excess that are found in 21-hydroxylase deficiency usually also occur in 11-hydroxylase deficiency.

Although cortisol is not synthesized efficiently, aldosterone synthetic capacity is normal; thus, it is unusual for patients to manifest signs of adrenal insufficiency

About **65% of patients become hypertensive** due to elevated levels of deoxycorticosterone

Inv. Plasma levels of cortisol is low, consequently, ACTH level is high.

11-deoxycortisol and deoxycorticosterone are elevated

and plasma renin activity is suppressed, consequently, aldosterone levels are low

Hypokalemic alkalosis occasionally occurs.

Rx. Hydrocortisone is given in doses **similar** to those used for 21 hydroxylase deficiency.

Mineralocorticoid replacement is sometimes transiently required in infancy after glucocorticoids Rx (due to sudden suppression of deoxycorticosterone secretion); however, it is rarely necessary otherwise.

Hypertension often resolves with glucocorticoid Rx but may require

additional therapy if it is of long standing by calcium channel blockers.

Congenital Adrenal Hyperplasia Caused By 3β-hydroxysteroid Dehydrogenase Deficiency

ETIOLOGY

Deficiency of (3β-HSD) occurs in fewer than 2%

Thus deficiency of the enzyme results in decreased synthesis of cortisol, aldosterone, and androstenedione but increased secretion of DHEA

More than 30 mutations in the *HSD3B2* gene have been described in patients with 3β-HSD deficiency.

C.M.: infants are prone to **salt-wasting crises.**

males are incompletely virilized. Varying degrees of hypospadias may occur

females are mildly virilized, with slight to moderate clitoral enlargement.

Postnatally, continued excessive DHEA secretion can cause precocious adrenarche.

During adolescence and adulthood, hirsutism, irregular menses, and polycystic ovarian disease occur in females.

Males manifest variable degrees of hypogonadism.

LABORATORY FINDINGS The hallmark of this disorder is the marked elevation of the Δ5 steroids (such as 17-hydroxypregnenolone and DHEA) Patients may also have elevated levels of 17-hydroxyprogesterone because of the extraadrenal 3β-HSD activity that occurs in peripheral tissues; these patients may be mistaken for patients with 21-hydroxylase deficiency.

TREATMENT Patients require glucocorticoid and mineralocorticoid replacement with hydrocortisone and fludrocortisone, respectively, as in 21-hydroxylase deficiency.

Incompletely virilized genetic males in whom a male sex of rearing is contemplated may benefit from several injections of 25 mg of a depot form of testosterone every 4 wk early in infancy to increase the size of the phallus. They may also require testosterone replacement at puberty.

Congenital Adrenal Hyperplasia Caused By 17-hydroxylase Deficiency

The rare variant (CAH) known as 17-hydroxylase deficiency was first described in the 1960s in patients with sexual infantilism and **hypertension**. It has also been described to present in the setting of male pseudohermaphroditism.

ETIOLOGY Less than 1% of CAH cases are caused by 17-hydroxylase deficiency, but the condition is apparently more common in Brazil and China.

Patients have alterations in their *CYP17* gene

This enzyme plays a central role in steroidogenesis.

Thus, patients with 17-hydroxylase deficiency have reduced secretion of cortisol, androgen, and estrogen, with adrenal and gonadal steroidogenesis impairment

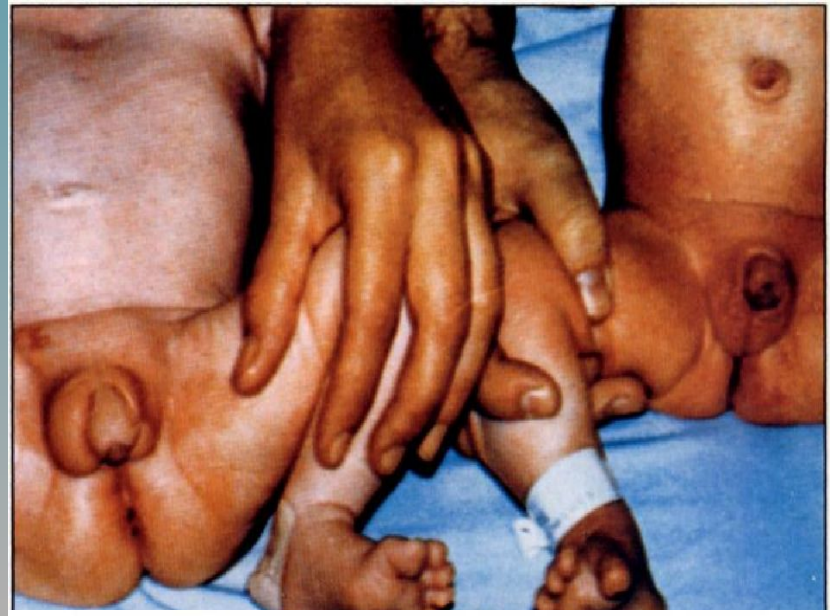
C.M And Lab.Findings

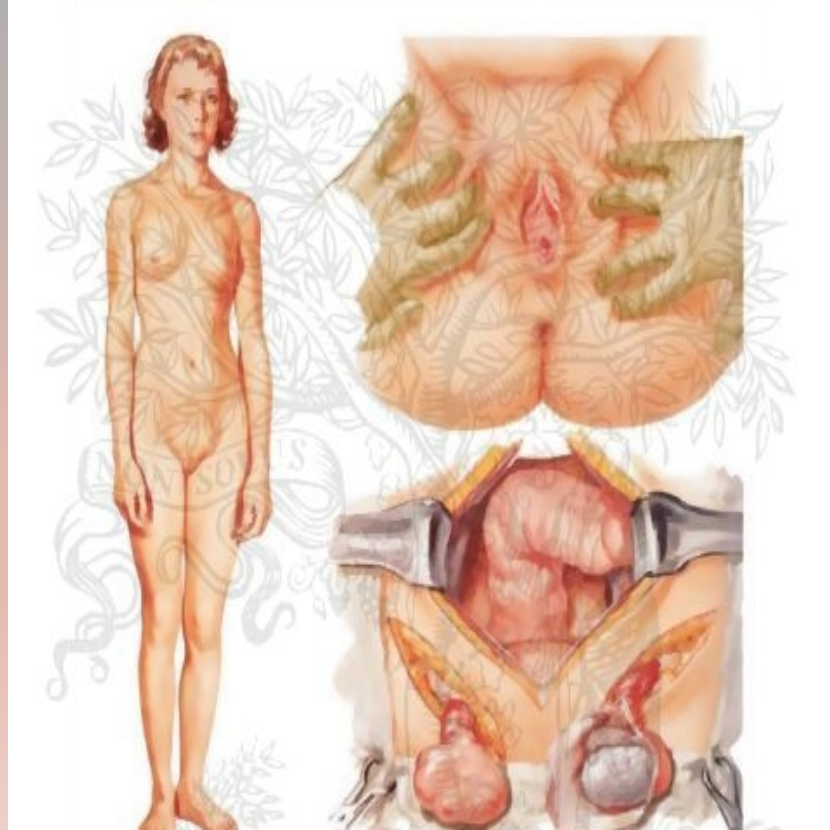
low cortisol

Deoxycorticosterone excess This can cause **hypertension**

Low androgens …Affected **males are incompletely virilized** and present as phenotypic females or with sexual ambiguity.

Affected females usually present with **failure of sexual development** at the expected time of **puberty.**





TREATMENT: Patients with 17-hydroxylase deficiency require glucocorticoid replace-ment with hydrocortisone to suppress secretion of deoxycorticosterone and thus control hypertension.

Additional antihypertensive medication may be required.

Females require estrogen replacement at puberty.

Genetic males may require either estrogen or androgen supplementation depending on the sex of rearing.

Surgery!

Table 594.1 Diagnosis and Treatment of Congenital Adrenal Hyperplasia

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
21-Hydroxylase deficiency, classic form	*CYP21* 6p21.3	Glucocorticoid deficiency	↓ Cortisol, ↑ACTH ↑↑ Baseline and ACTH-stimulated 17-hydroxy-progesterone	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
21-Hydroxylase deficiency, nonclassic form	*CYP21* 6p21.3	May be asymptomatic; precocious adrenarche, hirsutism, acne, menstrual irregularity, infertility	↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone ↑ Serum androgens	Suppression with glucocorticoids
11β-Hydroxylase deficiency	*CYP11B1* 8q24.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated 11-deoxycortisol and deoxycorticosterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
		Hypertension	↓ Plasma renin, hypokalemia	Suppression with glucocorticoids

3β-Hydroxysteroid dehydrogenase deficiency, classic form	*HSD3B2* 1p13.1	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated Δ5 steroids (pregnenolone, 17-hydroxy-pregnenolone, DHEA)	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females and males	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Precocious adrenarche, disordered puberty	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Suppression with glucocorticoids
17α-Hydroxylase/17,20-lyase deficiency	*CYP17* 10q24.3	Cortisol deficiency (corticosterone is an adequate glucocorticoid)	↓ Cortisol, ↑ ACTH ↑ DOC, corticosterone Low 17α-hydroxylated steroids; poor response to ACTH	Glucocorticoid (hydrocortisone) administration
		Ambiguous genitalia in males	↓ Serum androgens; poor response to hCG	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Sexual infantilism	↓ Serum androgens or estrogens	Sex hormone replacement consonant with sex of rearing
		Hypertension	↓ Plasma renin; hypokalemia	Suppression with glucocorticoids

Congenital lipoid adrenal hyperplasia	*STAR* 8p11.2	Glucocorticoid deficiency	↑ ACTH Low levels of all steroid hormones, with decreased or absent response to ACTH	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↓ Aldosterone, ↑ plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in males	Decreased or absent response to hCG in males	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Poor pubertal development or premature ovarian failure in females	↑ FSH, ↑ LH, ↓ estradiol (after puberty)	Estrogen replacement

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Thank you