

Adrenal Disorders

A. General principles of adrenal function

1. The **adrenal gland** is composed of two parts, the **adrenal cortex**, which synthesizes a multitude of different steroid compounds, and the **adrenal medulla**, which produces catecholamines (i.e., epinephrine).
2. **Three major pathways** in the adrenal cortex result in the production of **mineralocorticoids** (aldosterone), **glucocorticoids** (cortisol), and **androgens** (dehydroepiandrosterone [DHEA]), as outlined in **Figure 6-5**.
3. **Glucocorticoid and androgen synthesis** are regulated by a negative feedback loop by the **hypothalamic–pituitary–adrenal axis** via adrenocorticotropin hormone (ACTH). **Mineralocorticoid synthesis**, however, is controlled by the **renin–angiotensin system** and **is independent** of the pituitary gland and ACTH.
4. Children may present with disorders of adrenal insufficiency and with disorders of glucocorticoid excess.

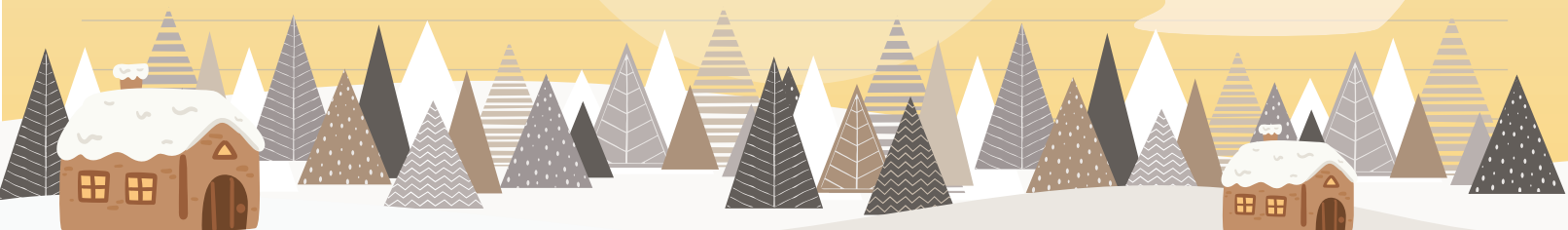
B. Classification of adrenal insufficiency. Adrenal insufficiency may be **primary** or **secondary**, each with different clinical manifestations.

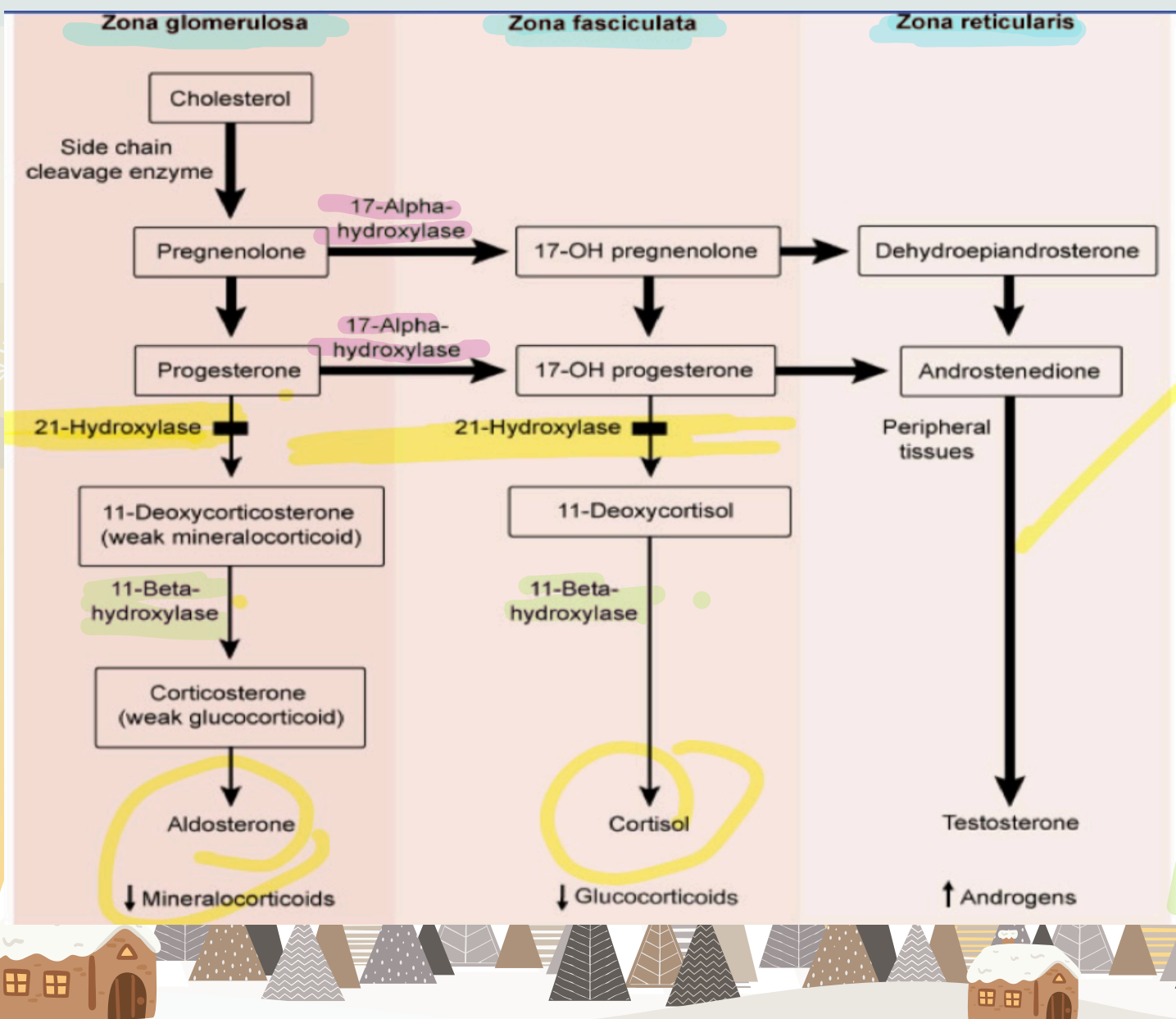
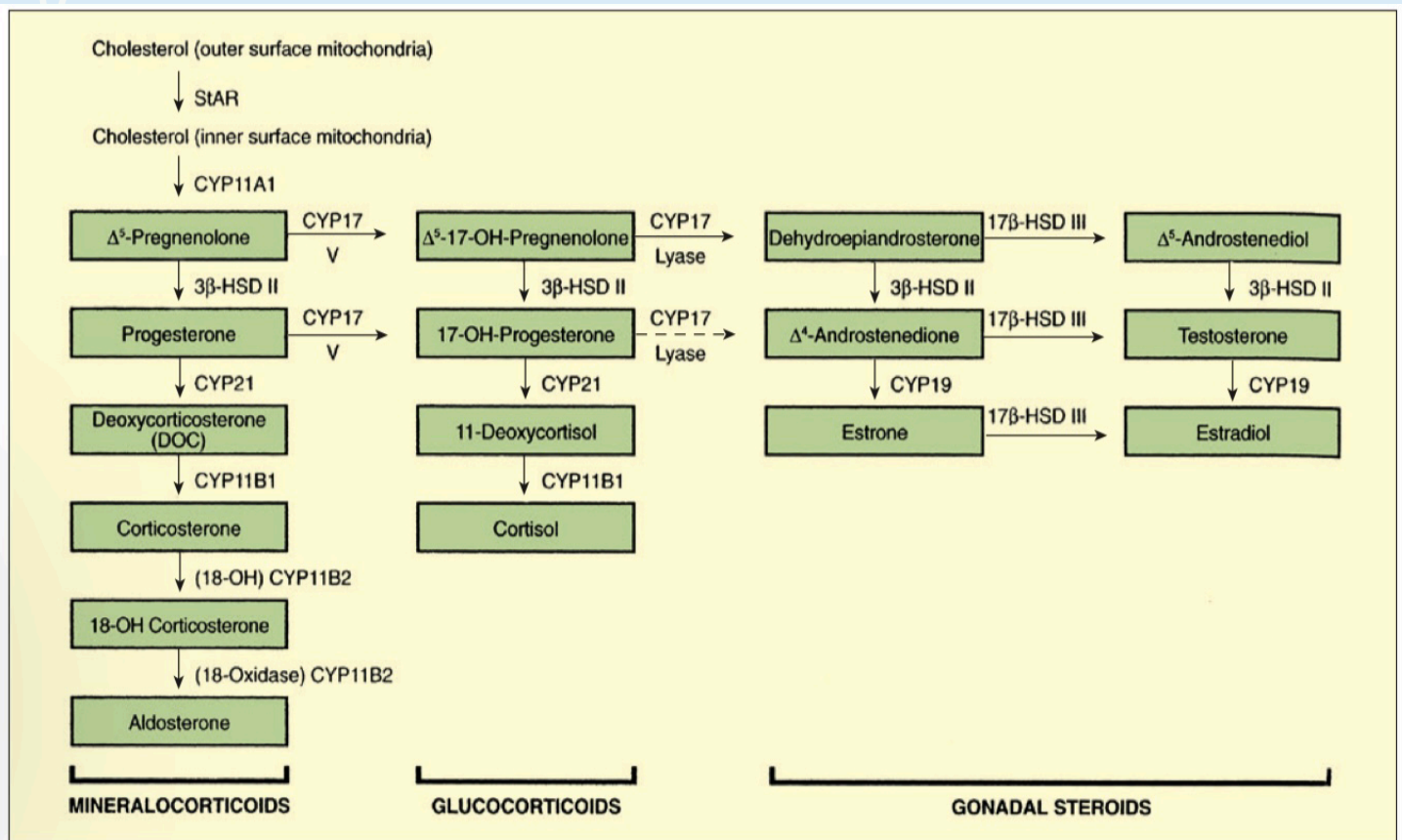
1. Primary adrenal insufficiency

- a. This condition results from destruction of the adrenal cortex or from an enzyme deficiency (i.e., a problem at the level of the adrenal gland).
- b. Patients present with signs and symptoms of both **cortisol deficiency** (anorexia, weakness, hyponatremia, hypotension, and increased pigmentation over recently healed scars) and **aldosterone deficiency** (failure to thrive, salt craving, hyponatremia, and hyperkalemia).
- c. **Examples** include **Addison disease**, **CAH**, and **adrenoleukodystrophy** (rare, X-linked recessive disorder with neurologic deterioration).

2. Secondary adrenal insufficiency

- a. This condition results from any process that interferes with the release of cortisol-releasing hormone (CRH) from the hypothalamus or ACTH from the pituitary (i.e., a problem at the hypothalamic or pituitary level).
- b. In contrast to primary adrenal insufficiency, *serum potassium may be normal* in secondary adrenal insufficiency because there is **no aldosterone deficiency**, given an intact renin–angiotensin system. However, these patients are still prone to developing acute adrenal crisis similar to that in primary adrenal insufficiency patients.
- c. **Examples** include pituitary tumors, craniopharyngioma, and Langerhans cell histiocytosis. However, **the most common cause is iatrogenic**; this occurs when the **hypothalamic–pituitary axis** has been suppressed by exposure to long-term dosages of glucocorticoids (usually longer than 2 weeks).





Congenital adrenal hyperplasia

C. CAH

1. This **autosomal recessive congenital enzyme deficiency in the adrenal cortex** is a classic example of primary adrenal insufficiency of childhood. **CAH is also the most common cause of DSD in XX infants with no palpable gonads (i.e., virilized females).**
2. The enzyme deficiency in patients with CAH may lead to underproduction of cortisol or aldosterone and a buildup of precursors that shunt into androgen pathway leading to an **increased production of androgens** (see **Figure 6-5**).
3. **Multiple enzyme deficiencies** may lead to CAH, and the clinical presentation varies depending on which enzyme is affected. The three main types include:
 - a. **21-OH deficiency** (accounts for **>90% of cases**). Three different subtypes of 21-OH deficiency affect the clinical presentation. There is some degree of correlation between the mutation and clinical phenotype.
 1. **Classic salt-wasting CAH (i.e., both mineralocorticoid and glucocorticoid pathways are affected, resulting in both cortisol and aldosterone deficiency).** Girls present with virilization (mainly varying degrees of clitoromegaly), and at 1–2 weeks of life both boys and girls present with failure to thrive, vomiting, and electrolyte abnormalities. Boys may have no apparent genital abnormality. (Key point: Male infants presenting with salt-wasting crisis can be confused for pyloric stenosis. Patients with salt-wasting CAH have a metabolic acidosis, whereas patients with pyloric stenosis have a metabolic alkalosis.)
 2. **Simple virilizing CAH (i.e., only the glucocorticoid pathway is affected, resulting only in cortisol deficiency).** Because there is no aldosterone deficiency, there is usually no electrolyte abnormality. Girls present with virilization at birth, and boys present later in life (1–4 years of age) with tall stature and precocious puberty.
 3. **Nonclassic CAH (i.e., late-onset with mild cortisol deficiency and no mineralocorticoid involvement).** These patients usually present at 4–5 years of age. Girls present with premature adrenarche, clitoromegaly, acne, rapid growth, hirsutism, and infertility. Boys present with premature adrenarche, rapid growth, and premature acne.
 - b. **11 β -OH deficiency** (accounts for 5% of cases). These patients present similarly to patients with the more common 21-OH deficiency, except that they are **hypertensive** and *hypokalemic*. Here the enzymatic defect is further down the mineralocorticoid synthetic pathway. The excess precursor metabolite is 11-deoxycorticosterone.
 - c. **3 β -hydroxysteroid dehydrogenase deficiency** (rare). These patients present with salt-wasting crises, glucocorticoid deficiency, and ambiguous genitalia as a result of an early block in all three adrenal cortex steroid pathways.



TABLE 178.1 Clinical Manifestations of Adrenal Insufficiency

Cortisol deficiency
Hypoglycemia
Inability to withstand stress
Vasomotor collapse
Hyperpigmentation (in primary adrenal insufficiency with excess of adrenocorticotrophic hormone)
Apneic spells
Muscle weakness, fatigue
Aldosterone deficiency
Hyponatremia
Hyperkalemia
Vomiting
Urinary sodium wasting
Salt craving
Acidosis
Failure to thrive
Volume depletion
Hypotension
Dehydration
Shock
Diarrhea
Muscle weakness
Androgen excess or deficiency (caused by adrenal enzyme defect)
Ambiguous genitalia in certain conditions

Enzyme deficiency	Hormonal abnormalities	Symptoms
21-hydroxylase	• ↓ Cortisol & aldosterone • ↑ Testosterone • ↑ 17-hydroxyprogesterone	• Ambiguous genitalia in girls • Salt wasting (vomiting, hypotension, ↓Na⁺, ↑K⁺)
11β-hydroxylase	• ↓ Cortisol & aldosterone • ↑ Testosterone • ↑ 11-deoxycorticosterone (weak mineralocorticoid) & 11-deoxycortisol	• Ambiguous genitalia in girls • Fluid & salt retention, hypertension
17α-hydroxylase	• ↓ Cortisol & testosterone • ↑ Mineralocorticoids • ↑ Corticosterone (weak glucocorticoid)	• All patients phenotypically female • Fluid & salt retention, hypertension

4. **Diagnostic workup** varies with the type of CAH (see [Figure 6-5](#)):
 - a. Patients with **21-OH deficiency** have increased **17-OHP levels**.
 - b. Patients with **11β-OH deficiency** have increased levels of **11-deoxycortisol** and **11-deoxycorticosterone**.
 - c. Patients with **3β-hydroxysteroid dehydrogenase deficiency** have increased levels of **DHEA** and **17-hydroxypregnenolone**.
5. **Management**
 - a. **Hydrocortisone** is administered at a dose that sufficiently suppresses ACTH production so that androgen production decreases, but is not excessive enough to interfere with proper growth. For most patients, this will require doses of 10–20 mg/m² per day of hydrocortisone. This is greater than the physiologic dose of hydrocortisone of 6–8 mg/m² per day. See [section IV.D.3](#) for management of adrenal crisis.
 - b. If patients are also aldosterone deficient, **mineralocorticoid replacement** (fludrocortisol) in combination with salt supplements (in young children) may be given at a dosage that normalizes the plasma renin activity (PRA).
 - c. **Frequent follow-up is essential**, and growth velocity, physical examination, bone age, and laboratory tests (17-OHP, PRA, androgens, etc.) should be monitored carefully. Parents should be educated and warned about the importance of compliance with medicines and how febrile episodes, vomiting, and surgical operations may require additional steroid therapy to prevent adrenal shock.



D. Acquired adrenal insufficiency

1. Etiology. Causes are multiple.

- Chronic supraphysiologic steroid use** (usually greater than 2 weeks)
- Addison disease** is adrenal insufficiency resulting **from autoimmune destruction of the adrenal cortex by lymphocytic infiltration**. Antibodies to the adrenal gland may be detected (i.e., 21-OH antibodies), and there may be other associated endocrinopathies, including Hashimoto thyroiditis and type 1 diabetes mellitus (DM) (**type I polyglandular syndrome**), or hypoparathyroidism and chronic mucocutaneous candidiasis (**type II polyglandular syndrome**).
- Less common causes** of acquired adrenal insufficiency are **acute adrenal hemorrhage** in the neonate and **septicemia** (especially associated with meningococcemia, known as **Waterhouse–Friderichsen syndrome**).

2. Evaluation

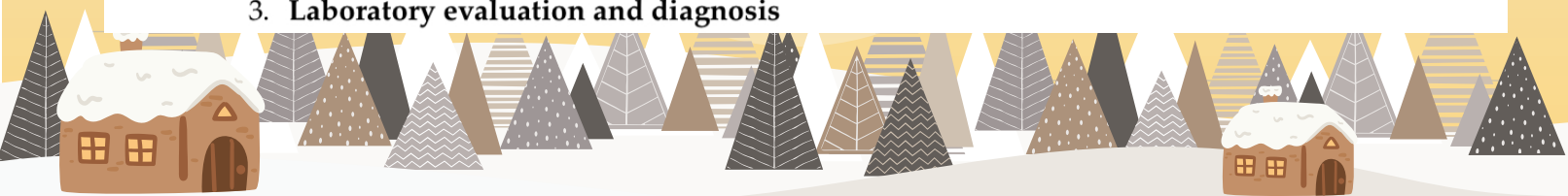
- A **high index of suspicion is necessary** because the symptoms may be subtle and the conditions can be life-threatening. Patients with Addison disease can present with **unusual hyperpigmentation** due to **simultaneous stimulation of melanocytes from elevated ACTH levels**, resulting from lack of cortisol feedback at the level of the pituitary.
- History of prior steroid use or autoimmune disorders** should raise clinical suspicion.
- Random plasma cortisol levels are usually not helpful (although a cortisol level $> 20 \mu\text{g/dL}$ in the presence of stress excludes adrenal insufficiency).
- ACTH stimulation test** is the **test of choice** and measures adrenal cortisol reserve by comparing the baseline cortisol level with the cortisol level 1 hour after ACTH injection. Normally, a cortisol value $> 18\text{--}20 \mu\text{g/dL}$ after ACTH stimulation is considered an adequate response.

3. Management

- Some patients may present with **adrenal crisis (hypotension, hypoglycemia, severe lethargy)**, and this is a medical emergency!
- Prompt treatment requires **intravenous fluids with 5% dextrose in normal saline** to correct hypotension and hyponatremia, and to prevent hypoglycemia.
- Parenteral steroids** (commonly referred to as “stress doses”) are given in adrenal crisis until the patient is stabilized ($50\text{--}100 \text{ mg/m}^2$ per day of hydrocortisone). **Oral mineralocorticoids and dextrose-containing fluids should be given as well.**
- For patients not in adrenal crisis, replacement with oral hydrocortisone ($\sim 8 \text{ mg/m}^2$ per day) and mineralocorticoids is sufficient.

E. Glucocorticoid excess

- Clinical features** include poor growth with delayed bone age, central obesity, moon facies, nuchal fat pad, easy bruisability, purplish (hemorrhagic) striae, hypertension, and glucose intolerance.
- Major causes of hypercortisolism**
 - Iatrogenic.** The **most common cause of glucocorticoid excess is iatrogenic**, as seen in patients who have been treated with long-term steroids for chronic diseases, such as asthma, inflammatory bowel disease, and juvenile idiopathic arthritis.
 - Cushing syndrome.** This is excessive glucocorticoid production caused by **benign or malignant adrenal tumors**. Note that most adrenal tumors are virilizing, but on occasion, they may also feminize.
 - Cushing disease.** This is excessive glucocorticoid production caused by **excessive ACTH production** by a pituitary tumor, such as a microadenoma.
- Laboratory evaluation and diagnosis**



- a. **Elevated free cortisol in 24-hour urine collection.** Depression, alcohol consumption, and obesity may lead to false positives.
 - b. Absence of the expected cortisol suppression seen in an **overnight dexamethasone suppression test** (i.e., dexamethasone given in the evening normally suppresses the following morning's physiologic rise in cortisol)
4. **Key point: Cortisol excess states may be confused with obesity. Hypercortisolism presents with growth impairment and delayed bone age, but obese patients have normal to fast growth and an advanced bone age.**

B. Establish the Cause of Hypercortisolism:

- **ACTH testing** is the best initial test to determine the cause (source) or location of hypercortisolism.

- Following are indicators of the source of the hypercortisolism:

- o ACTH level **low**: This means the origin is in the **adrenal gland**. Scan the gland with a CT or MRI and remove the adenoma that you find.

- o ACTH level **high**: This means the origin is either in the **pituitary gland** or from the **ectopic production of ACTH**.

Decreased ACTH level = adrenal source

- The next step is a **high-dose dexamethasone suppression test**:

- o If high-dose dexamethasone **suppresses** the ACTH, the origin is the **pituitary**. Scan the pituitary. Remove the adenoma if it is visible.

- o If high-dose dexamethasone **does not suppress the ACTH**, the origin is an **ectopic production of ACTH** or a **cancer that is making ACTH**. Scan the chest for lung cancer or carcinoid. Remove the cancer if possible.

- If the tests point to a pituitary source but the scanning is indeterminant, **inferior petrosal sinus sampling** is used to confirm it. Petrosal sinus sampling is also used to **localize the lesion**, as well to see which half of a pituitary should be removed.

- Many people have incidental **adrenal and pituitary lesions**. If you start with a scan, you might remove the wrong part of the body, and you cannot put it back!

- You must always confirm the **source of hypercortisolism with biochemical tests** before you perform **imaging studies**. At least **10% of the population has an abnormality of the pituitary on MRI**. If you start with a scan, you may remove the pituitary when the source is in the adrenals.

▪ Other Laboratory Testing in Hypercortisolism:

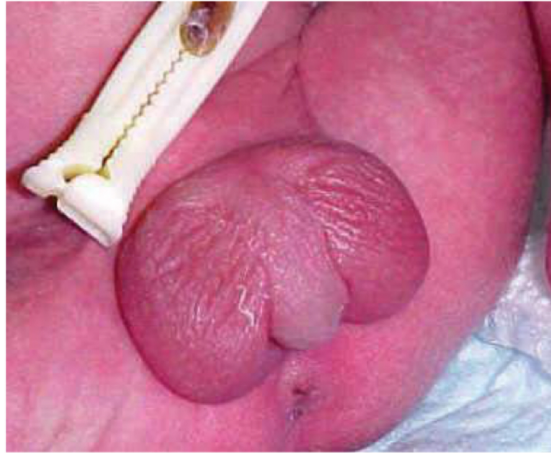
- Cortisol is a stress hormone that is an **anti-insulin**. In addition, **there is some aldosterone like effect of cortisol** that has an effect on the kidney's distal tubule of excreting potassium and hydrogen ions.

- Effects of hypercortisolism include:

- o **Hyperglycemia**.
- o **Hyperlipidemia**.
- o **Hypokalemia**.
- o **Metabolic alkalosis**.
- o **Leukocytosis** from demargination of white blood cells. At least half of white cells in the blood are on the vessel wall waiting for an acute stress to come into circulation. They are like parked police cars waiting to be called.

This infant has classic **congenital adrenal hyperplasia** (CAH) caused by **21-hydroxylase deficiency**, which results in:

- Inhibited conversion of progesterone to 11-deoxycorticosterone, a precursor to aldosterone: Decreased aldosterone causes **dehydration** (eg, sunken fontanelle, dry mucosa) and **salt-wasting** (eg, hypotension, hyponatremia, hyperkalemia) (**Choices A and C**).
- Inhibited conversion of 17-hydroxyprogesterone to 11-deoxycortisol, a precursor to cortisol: Decreased cortisol results in fasting hypoglycemia (**Choice D**).
- Increased conversion of 17-hydroxyprogesterone to androstenedione, a precursor to testosterone: Increased testosterone causes **virilization** and ambiguous genitalia in female infants. Male infants typically have no abnormal newborn genital findings, although they may have an enlarged penis or scrotal hyperpigmentation.



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Figure 16-1. Ambiguous Genitalia Seen in Congenital Adrenal Hyperplasia

