

## Enzymatic pathways and genetic disease

### Introduction

Enzymes typically do not function autonomously, but as part of biochemical (or metabolic) pathways. These pathways exist to take a precursor molecule and convert it into one or more end products through multiple chemical steps.

This reading introduces you to a human biochemical pathway involving several enzyme-catalyzed steps. It describes a medical disorder resulting from problems that occur with enzymatic steps in this pathway. The reading is an excerpt from the American Academy of Family Physicians website, <http://www.aafp.org/afp/990301ap/1190.html>

### Directions

Prior to reading the attached article, review the material on metabolic pathways in your textbook (section 6-4, p. 108). The article describes several types of genetic mutations in enzymes involved in a metabolic pathway. Since we do not cover genetic mutations until chapter 10, you may want to review the material in section 10.4 of your text (p. 179-180) before reading the article.

In class, our discussion will focus on the pathway figures presented in the article.

Questions to consider (in the event you are asked graded clicker questions on this assigned reading):

- Why do patients with 21-hydroxylase deficiency have insufficient amounts of cortisone (cortisol) and aldosterone?
- Why is there accumulation of 11-deoxycorticosterone and 11-deoxycortisol as a result of an 11- $\beta$  hydroxylase deficiency?
- When looking at the symptoms of this disorder in females, what can explain such characteristics as acne, taller than normal, hirsutism, infertility, and clitorimegaly?



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## Congenital Adrenal Hyperplasia: Not Really a Zebra

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[▶ A patient information handout on congenital adrenal hyperplasia, written by the authors of this article, is provided on page 1199.](#)

Congenital adrenal hyperplasia was once considered a rare inherited disorder with severe manifestations. Mild congenital adrenal hyperplasia, however, is common, affecting one in 100 to 1,000 persons in the United States and frequently eluding diagnosis. Both classic and nonclassic forms of the disease are caused by deficiencies in the adrenal enzymes that are used to synthesize glucocorticoids. The net result is increased production from the adrenal gland of cortisol precursors and androgens. Even mild congenital adrenal hyperplasia can result in life-threatening sinus or pulmonary infections, orthostatic syncope, shortened stature and severe acne. Women with mild congenital adrenal hyperplasia often present with hirsutism, oligomenorrhea or infertility. Congenital adrenal hyperplasia is diagnosed by demonstration of excess cortisol precursors in the serum during an adrenal corticotrophic hormone challenge. Diagnosis of congenital adrenal hyperplasia in fetuses that are at risk for congenital adrenal hyperplasia can be determined using human leukocyte antigen haplotype or by demonstration of excess cortisol precursors in amniotic fluid. Treatment includes carefully monitored hormone replacement therapy. Recognition of the problem and timely replacement therapy can reduce morbidity and enhance quality of life in patients that are affected by congenital adrenal hyperplasia.

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Classical congenital adrenal hyperplasia is rare, affecting only one in 14,000 patients, but mild forms of the disease may occur in one of every 100 to 1,000 persons.<sup>1,2</sup> The condition is caused by a deficient synthesis of cortisol; most cases are related to 21-hydroxylase or 11- $\beta$  hydroxylase deficiency<sup>3-5</sup> (*Figure 1*). The affected enzyme can be totally or partially impaired. The degree of enzyme insufficiency determines the severity of the condition.<sup>2,5</sup>

The hallmark of congenital adrenal hyperplasia is inadequate production of glucocorticoids.<sup>1</sup> Patients with mild congenital adrenal hyperplasia are frequently unable to mount sufficient stress responses to trauma and infection. Glucocorticoid precursors accumulate in these persons and are converted to androgenic steroids, causing shortened stature, early puberty, severe acne, and virilization and infertility in females.<sup>2,3,5,6</sup> Mineralocorticoid synthesis can also be affected, resulting in electrolyte disturbances, hypotension and syncope.<sup>5,6</sup>

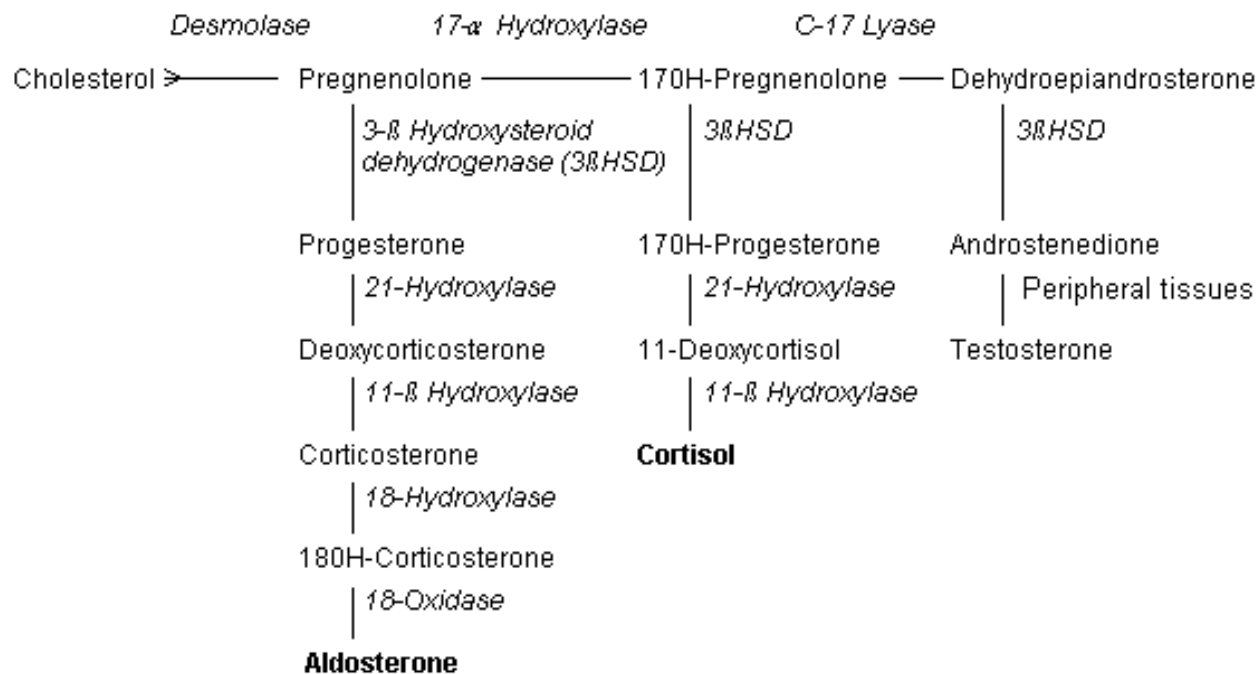
## Enzyme Pathways and Genetics

### 21-Hydroxylase

Ninety percent of patients with congenital adrenal hyperplasia have 21-hydroxylase deficiency.<sup>2-4,6</sup> Because this enzyme functions in both glucocorticoid and mineralocorticoid synthesis, some patients with 21-hydroxylase deficiency have insufficient amounts of cortisone and aldosterone (*Figure 2*). These persons have the "salt-wasting" form of congenital adrenal hyperplasia, with hyponatremia, hypovolemia, hyperkalemia and hypotension.<sup>1-4,6</sup> The enzyme 21-hydroxylase is a chromosome 6, human leukocyte antigen (HLA)-linked, cytochrome P450 enzyme that is found in the smooth endoplasmic reticulum. Its DNA sequence can be altered by at least nine mutations, many of which leave the enzyme impaired but not totally inactive.<sup>2,3,6</sup>

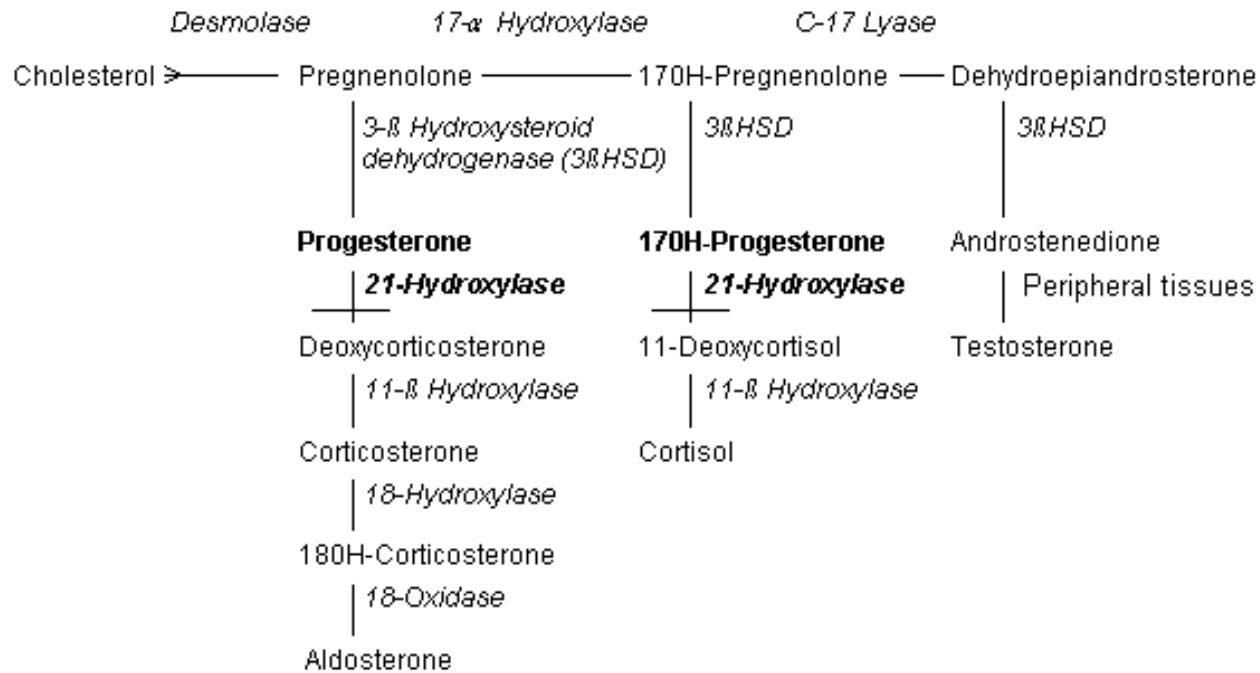
Ninety percent of cases of congenital adrenal hyperplasia are the result of a deficiency of the enzyme 21-hydroxylase.

### Enzymatic Pathway for Cortisol and Aldosterone



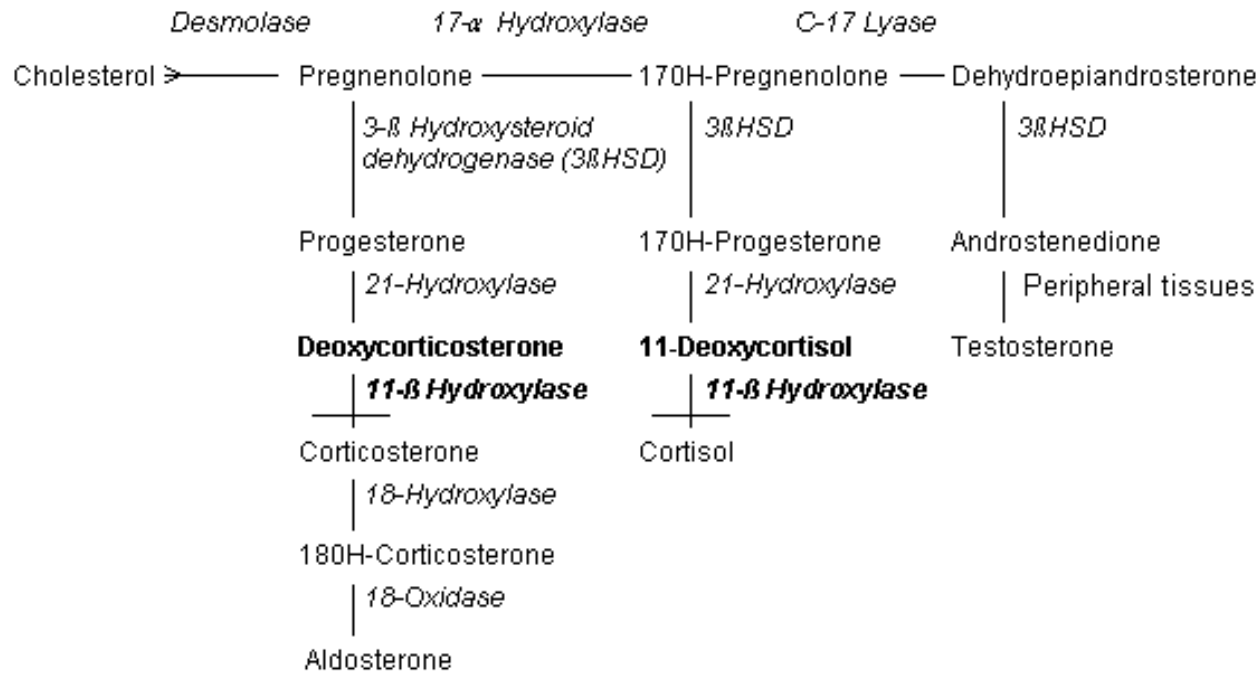
**FIGURE 1.** Enzymatic pathway for biosynthesis of cortisol and aldosterone, beginning with cholesterol. Italics denote enzymes.

### Result of a 21-Hydroxylase Deficiency



**FIGURE 2.** Accumulation of progesterone and 17-hydroxyprogesterone as a result of a 21-hydroxylase deficiency. Italics denote enzymes.

### Result of an 11- $\beta$ Hydroxylase Deficiency



**FIGURE 3.** Accumulation of 11-deoxycorticosterone and 11-deoxycortisol as a result of an 11- $\beta$  hydroxylase deficiency. Italics denote enzymes.

The incidence of classic congenital adrenal hyperplasia is especially high in Madagascar and certain areas of Alaska. Mild congenital adrenal hyperplasia occurs more frequently in Ashkenazi Jews, and in Hispanic, Slavic and Italian populations.<sup>2,3,6</sup>

### 11- $\beta$ hydroxylase

Deficiency of 11- $\beta$  hydroxylase is found in 8 to 9 percent of patients with congenital adrenal hyperplasia.<sup>2,5</sup> Glucocorticoid synthesis remains impaired but, in this disorder, deoxycortisol accumulates (*Figure 3*). Deoxycortisol and its metabolites have mineralocorticoid properties and may cause hypertension when they accumulate.<sup>2,3,7</sup> Thus, simple blood pressure measurements may help determine the underlying type of congenital adrenal hyperplasia. The enzyme 11- $\beta$  hydroxylase is a chromosome 8, cytochrome P450 enzyme located in the mitochondria. Known gene abnormalities include insertions, deletions, mis-sense/nonsense codons, and point mutations. Some of these abnormalities result in severe dysfunction of the enzyme while others result in only partial impairment.<sup>3-5</sup>

Classic 11- $\beta$  hydroxylase deficiency occurs in approximately one per 100,000 births and occurs more frequently in Moroccan Jews. Mild congenital adrenal hyperplasia due to 11- $\beta$  hydroxylase deficiency is more common, however, and may be responsible for 1 to 2 percent of cases of hirsutism and oligomenorrhea in women.<sup>3-5</sup>

## Manifestations and Recognition

### Classical Congenital Adrenal Hyperplasia

The classic form of congenital adrenal hyperplasia occurs when cortisol synthesis is extremely low. The disorder usually manifests in childhood. Hypersecretion of adrenal androgens causes masculinization of the external genitalia of the female fetus. Affected infants can have ambiguous genitalia or even erroneous gender assignment. Because testicles are not present to produce müllerian inhibiting factor, the internal female organs are intact.<sup>1,2,4</sup>

Children with classic congenital adrenal hyperplasia may lack sufficient amounts of cortisol to mount a stress response, and they frequently succumb to minor illnesses. Those who survive to adulthood experience premature puberty. Premature closure of the epiphyses results in short stature even though these children grow at an accelerated rate when young. Severe acne is also a frequent problem. Adult women with classic congenital adrenal hyperplasia may have pronounced hirsutism and amenorrhea.<sup>1-4,6</sup>

### Mild Congenital Adrenal Hyperplasia

Mild congenital adrenal hyperplasia is much more common than the classic form.<sup>2,3,5,6</sup> Men and women with mild congenital adrenal hyperplasia may have normal height compared with the general population, yet shortened stature when compared with their parents. Near-syncope may be a chronic or recurrent problem in these patients, and they frequently have a history of severe acne and mild hyperpigmentation. Some people with mild congenital adrenal hyperplasia can mount limited glucocorticoid stress responses and are thus never recognized as having the disorder. Others, however, have frequent illnesses and decompensate when challenged by common infections or minor trauma.<sup>1-4,6</sup>

Women with congenital adrenal hyperplasia may have clitorimegaly and poorly developed vaginal labia. These women may also be hirsute and frequently present with oligomenorrhea, infertility or polycystic ovary syndrome.<sup>1-7</sup>

## TABLE 1 Signs and Symptoms Suggesting Mild Congenital Adrenal Hyperplasia

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### Children

- Moderate to severe recurrent sinus or pulmonary infections
- Severe acne
- Hyperpigmentation, especially of the genitalia
- Tall for age
- Early onset of puberty

### Adults

- Childhood history as defined above
- Syncope or near-syncope
- Shortened stature compared with either parent
- Hypotension (21-hydroxylase deficiency)
- Hypertension (11- $\beta$  hydroxylase deficiency)

### Women

- Clitorimegaly