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# General Hormone Manufacture

## The First and Basic Steps

It will be helpful to print out a chart of steroid hormone synthesis. A Google search for "steroidogenesis" under the Images section will yield a number of choices. There is a good one in Wikipedia. Any biochemistry text and many lay books on menopause and hormones have these charts.

**Cholesterol: The basic molecule and the origin of the word steroid**.

All the steroid hormones are made from LDL **cholesterol**. If it is in short supply, hormone manufacture will be reduced. Impoverished people subsist on a diet largely of vegetables and grain based starch. With chronic caloric restriction, there is very little body fat. Although it is possible for the body to manufacture fat from carbohydrate and protein, this only occurs if there is adequate or excess caloric supply. In the United States, very few people are so poor that they have inadequate calories in their food, but starvation and caloric restriction have historically been a reproductive problem and is still a problem is some areas of Africa and Asia.

**The First Step:**

The first step in all steroid hormone synthesis is the conversion of cholesterol into **Pregnenolone**. This takes place in the **mitochondria** of the steroid producing cells, mostly in the ovary, testes and adrenal glands. The tropic hormones, FSH, LH and ACTH attach to the outside of the cell membrane. This stimulates the conversion of ATP to Cyclic AMP, which travels to the mitochondria. There, Cyclic AMP stimulates the P450scc and P450c11 enzymes to convert LDL cholesterol into Pregnenolone. (*This step is energy dependent. It is theorized by some physicians that Chronic Fatigue-Adrenal Exhaustion-Fibromyalgia syndrome is an adrenal mitochondrial problem. For this reason, some physicians give supplemental Pregnenolone to get around this step*.) Pregnenolone then moves into the cytoplasm. The rest of steroid synthesis takes place on the **endoplasmic reticulum**. Further steps often involve the removal of carbon atoms but never the addition of carbon to the basic structure.

**Two Pathways:**

After Pregnenolone there is a branch. One pathway takes Pregnenolone to Progesterone and the other takes Pregnenolone through 17OH-Pregnenolone to DHEA. In the Adrenal gland, Progesterone is converted to Corticosterone and then into Aldosterone. In the Adrenal, Ovary and Testicle, both pathways can lead back to Androstenedione. From there, Androstenedione is converted to either Testosterone or Estrone. There is a conversion square. 17beta-hydroxysteroid dehydrogenase converts Androstenedione to Testosterone and converts Estrone to Estradiol.

**VERY IMPORTANT:**

P450aromatase converts Androstenedione to Estrone and Testosterone to Estradiol. **Aromatase is a very important enzyme and occurs in a number of tissues**. It works, of course, in the ovaries, testicles and adrenal. In addition, brain cells can aromatize Testosterone in men to estradiol and stimulate memory and learning in the Hippocampus. Aromatase in abdominal fat changes adrenal androgens into estrogens. Aromatization in various tissues is controlled and affected by cytokines, cyclic nucleotides, gonadotropins, glucocorticoids and growth factors.

There now exist pharmaceuticals that inhibit the actions of Aromatase. Two such aromatase inhibitors are anastrozole and letrozole. Used mostly to treat breast cancer, these drugs form an intense blockage of estrogen production and affect many different tissues.

Benzene is a ring of six carbons that share their electrons. Glucose is also a ring of six carbons but the electrons are not shared. Benzene has a strong odor while the sugars, like glucose, do not. Compounds with a ring of shared electrons are called aromatic because of the smell from the benzene related compounds. Of the steroid hormones, only the estrogenic compounds have the unsaturated shared electrons in ring #1; an aromatic ring.

**Environmental note:** Many organic compounds have aromatic benzene rings including DES, DDT, most insecticides, most herbicides, dioxin, and chemicals that keep plastics soft, many detergents and other industrial and household chemicals. **Nearly all these chemicals act as estrogens inside the body!!**

**Hormones in the blood:**

The two main pathways go through Progesterone and DHEA. Although large amounts of Progesterone are made as an intermediate step in hormone manufacture, very little is released into the blood. Only during ovulation and pregnancy is Progesterone released. Men have low blood levels. DHEA, dehydroepiandrosterone, is the most abundant steroid hormone in the circulation. It is made mostly by the Adrenal gland. Serum levels can be 20,000 times those of estrogen. It is a mild androgen. It is converted into the main androgens and those androgens are converted by aromatase into the estrogens. Why some intermediates are released into the circulation and others are not is unclear.

**The conversion enzymes: Individual variations**

The various P450, 17beta and aromatase enzymes are proteins. They are made of long strings of amino acids that are coded for by large segments of DNA. Over the generations, mutations have occurred. There are significant differences among individuals, families and ethnic groups in the relative strengths of these various enzymes. This may account for the variations in breast and penile size, muscle development and hair growth patterns. It has become popular for some people to take supplements containing DHEA, which is available without a prescription. I find that some women convert much of it into Testosterone, some convert much of it all the way to Estradiol and Estrone while other women simply raise their DHEA levels. I attribute these differences to the various strengths of the individual versions of the various converting enzymes. **It is important to keep individual variation in mind when prescribing any hormones. You never know what is going to happen until you test follow-up levels in that specific individual.** This is true for hormone manufacture, conversion, metabolism and excretion. Robert P. Goldman, M.D.