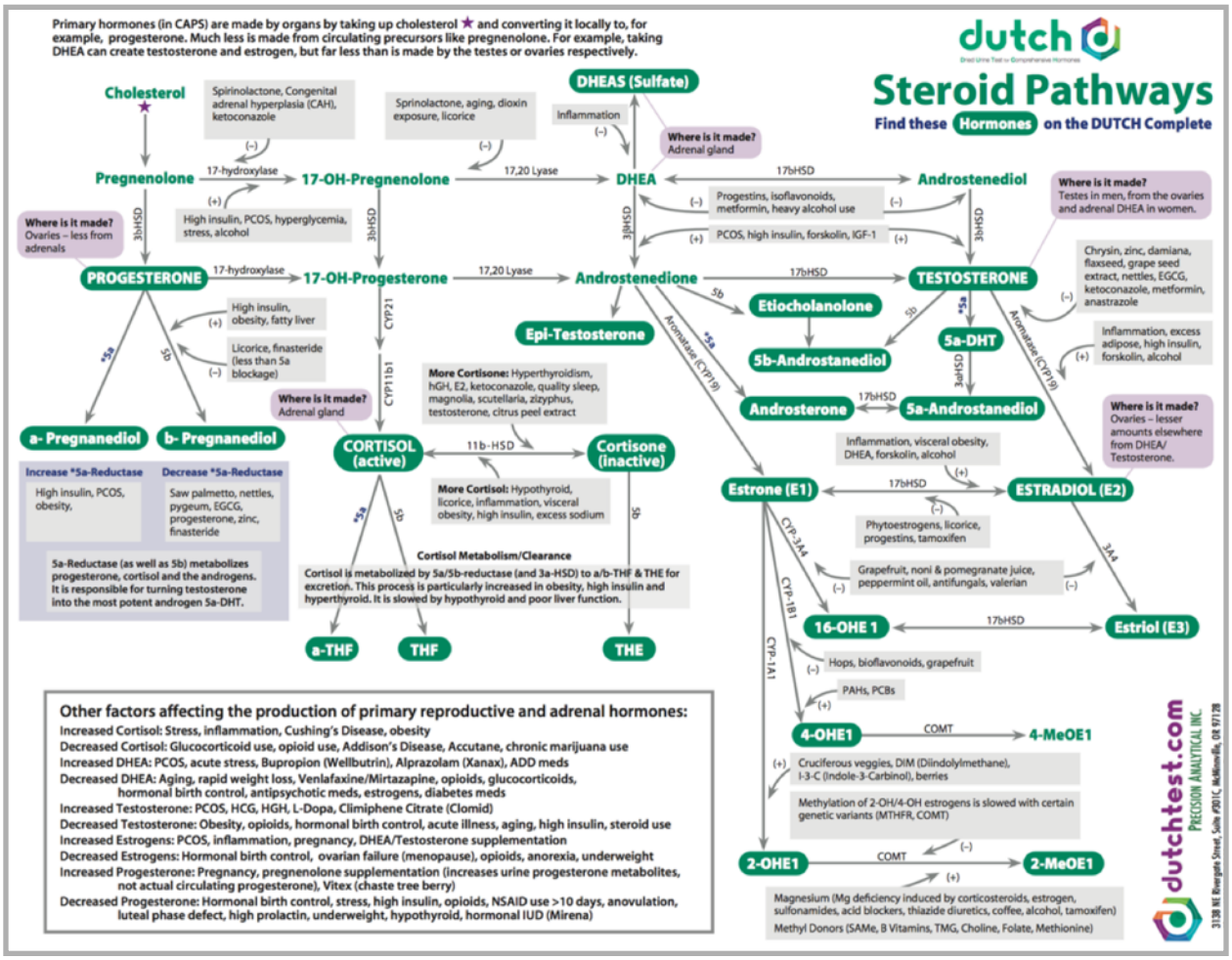
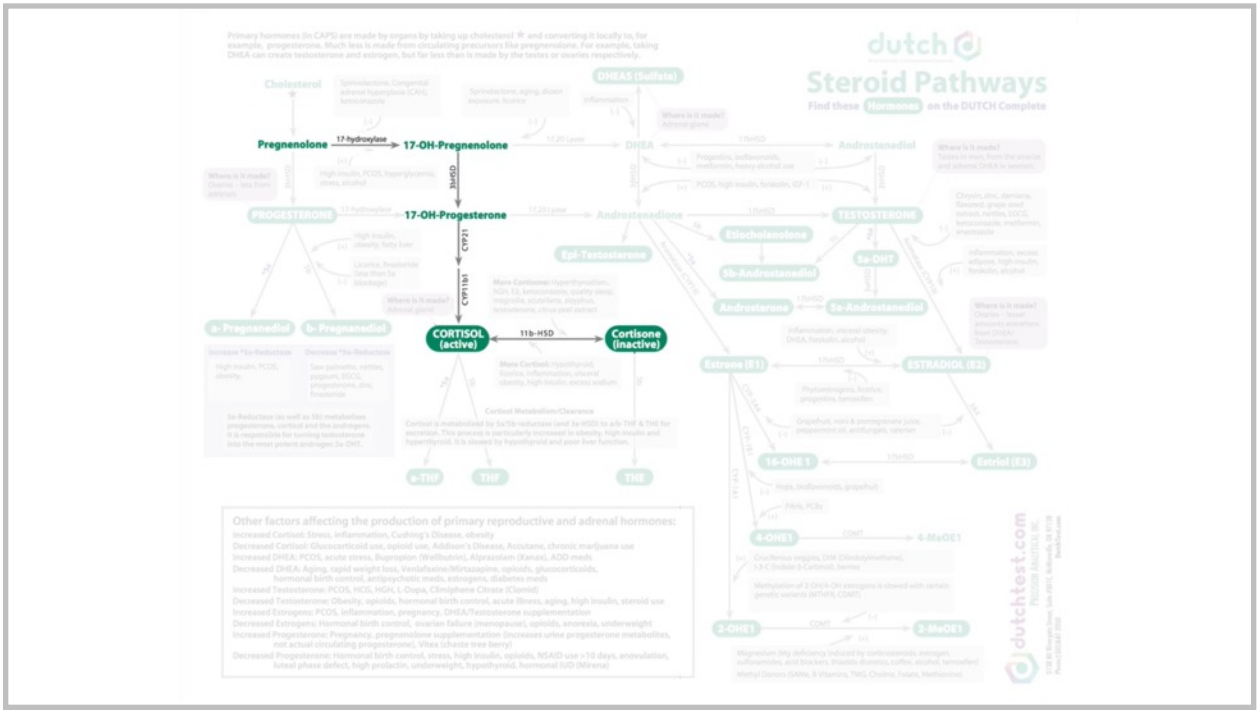
HPA-D: HPA Basic Physiology - Part 6

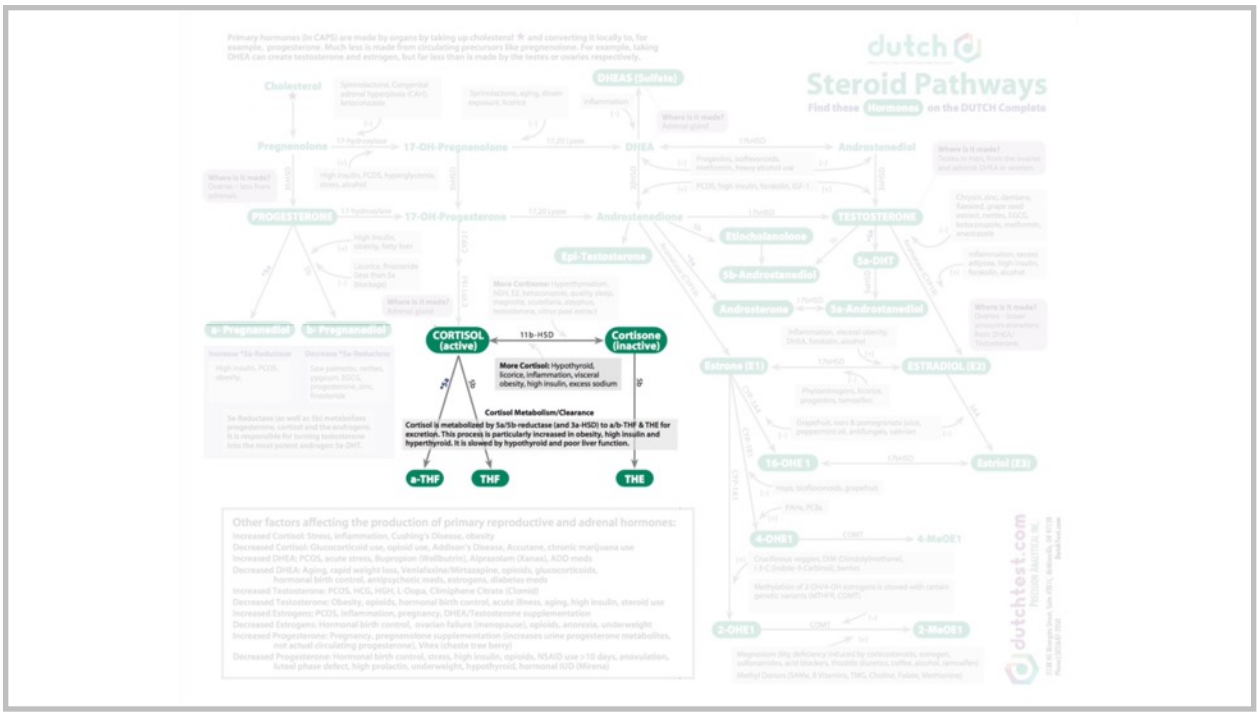


Okay, now let's take a closer look at the metabolism steroid hormones with a focus on adrenal steroid hormones, along with some of the factors that affect their conversion. In the very detailed, complex diagram on the slide, which was created by Mark Newman, the director of Precision Analytical, which is the lab that offers the DUTCH test that I'll be teaching you later in this section, as you can see, this steroid hormone metabolism is very complex, and this is actually a simplified diagram of what's going on. So let's start at the top left, where all steroid hormone production begins, and that's with the conversion of cholesterol into pregnenolone. This primarily happens in the organs themselves, like the adrenal glands and the gonads. Much less of the downstream hormones are made from circulating precursors like pregnenolone or DHEA. This is really important to understand because when you know that the conversion of cholesterol into pregnenolone primarily happens in the organs and glands, not in the bloodstream, that explains

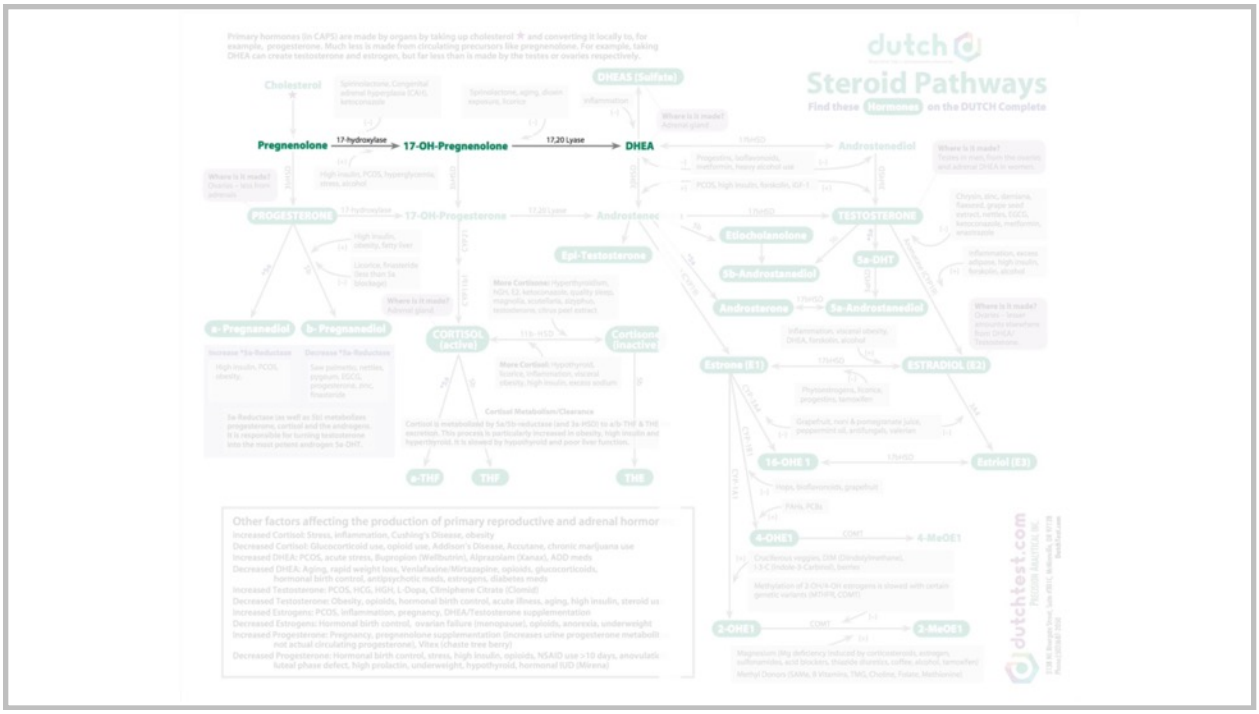
why taking supplemental DHEA and pregnenolone don't significantly increase estrogen and testosterone levels, and we'll talk more about that in the treatment section.



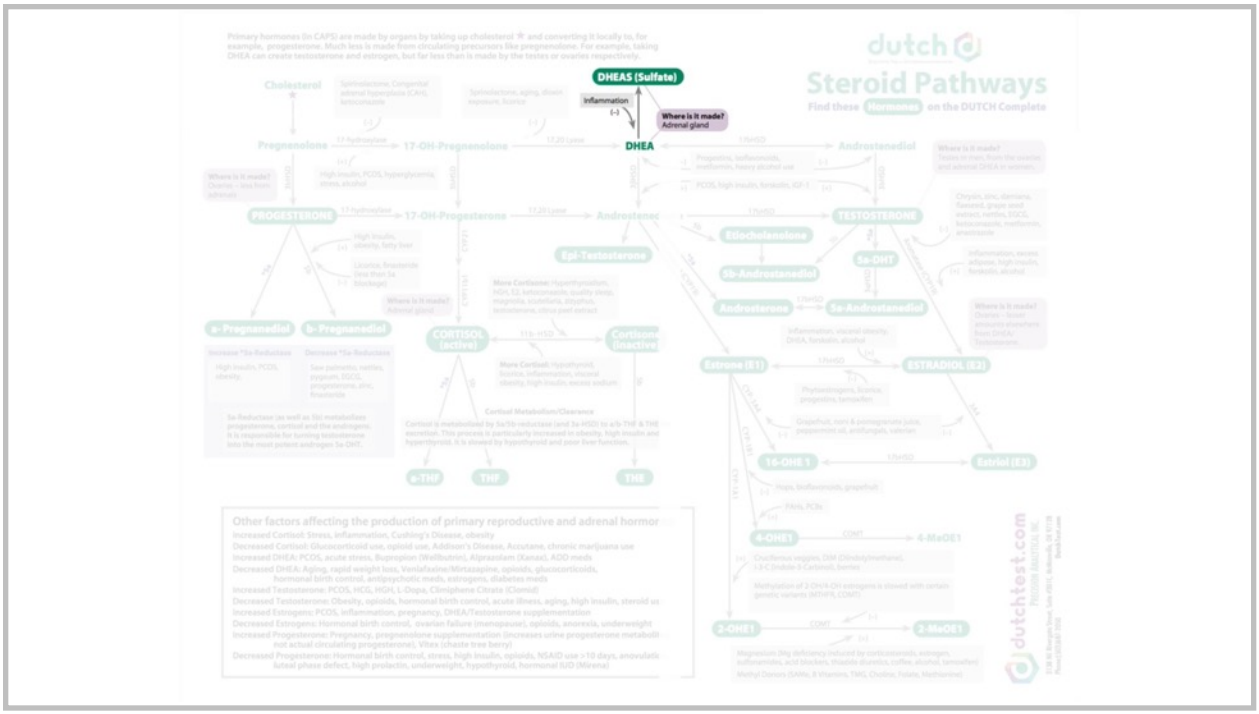
All right, let's start with cortisol. In the adrenal gland, cholesterol is converted into pregnenolone, which is then converted into 17-OH-pregnenolone, then converted into 17-OH-progesterone, which is then finally converted into active cortisol. Conversion of pregnenolone to 17-OH-pregnenolone is reduced by drugs like spironolactone or ketoconazole and by hereditary conditions like congenital adrenal hyperplasia. The conversion of pregnenolone to 17-OH-pregnenolone is increased by high insulin levels, PCOS, hyperglycemia, stress and alcohol. So already we can see how all of the conditions I just mentioned can lead to high cortisol levels. Active cortisol can be converted into cortisone, which is, as we discussed, relatively inactive and weak compared to active cortisol, and we talked already about the factors that favor more cortisone. These include hyperthyroidism, human growth hormone, estradiol, good sleep, drugs like ketoconazole, and then adaptogenic herbs like magnolia, scutellaria, and ziziphus, and then finally testosterone. The factors that favor more cortisol, again, include hypothyroidism, inflammation, visceral obesity, high insulin, excess sodium, and licorice, which increases the half-life of circulating cortisol.



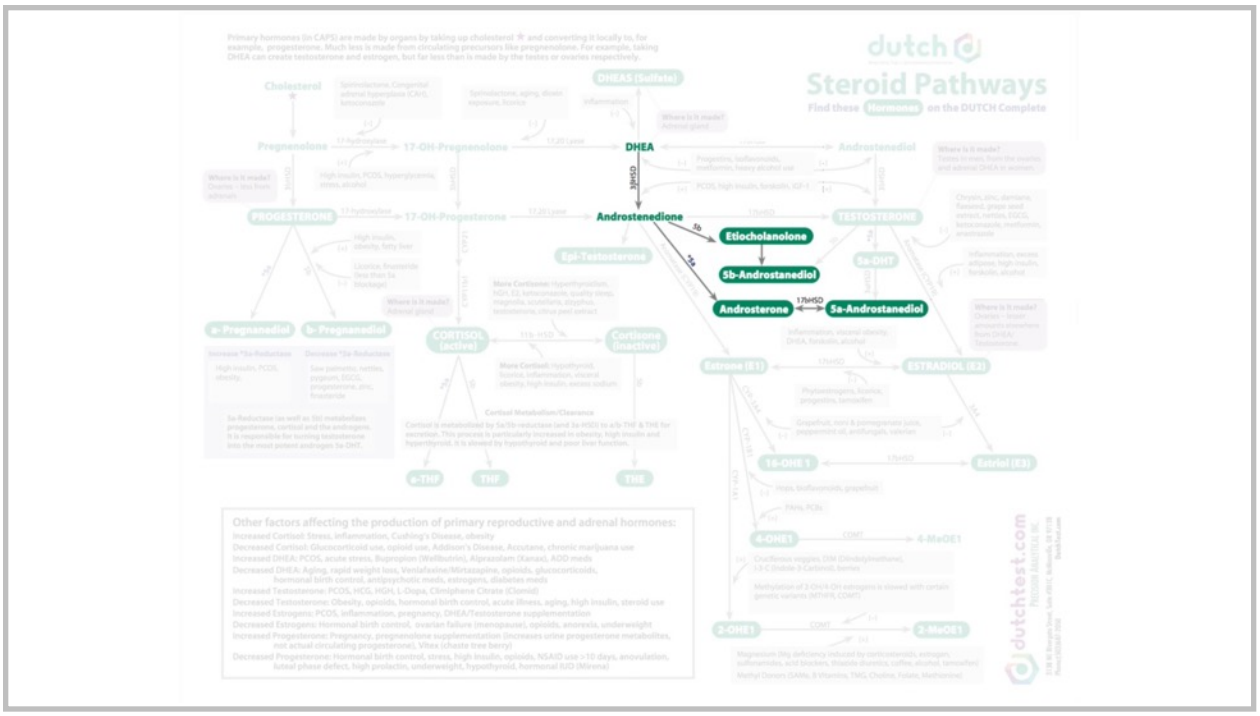
Cortisol is metabolized by a 5-alpha and 5-beta reductase as well as 3-alpha-hydroxysteroid dehydrogenase, to two different metabolites: allo-tetrahydrocortisol, or ATHF, and tetrahydrocortisol, which is just abbreviated as THF, and then these are excreted in the urine. Cortisone is metabolized by a 5-beta reductase to tetrahydrocortisone, or THE, for excretion in the urine. Both of these processes are increased in obesity, high insulin, and hyperthyroidism, and they are decreased in hypothyroidism and poor liver function. So just make a mental note of this; it's going to turn out to be important for interpreting the DUTCH urine test results later, but we'll talk about it a lot more at that point.



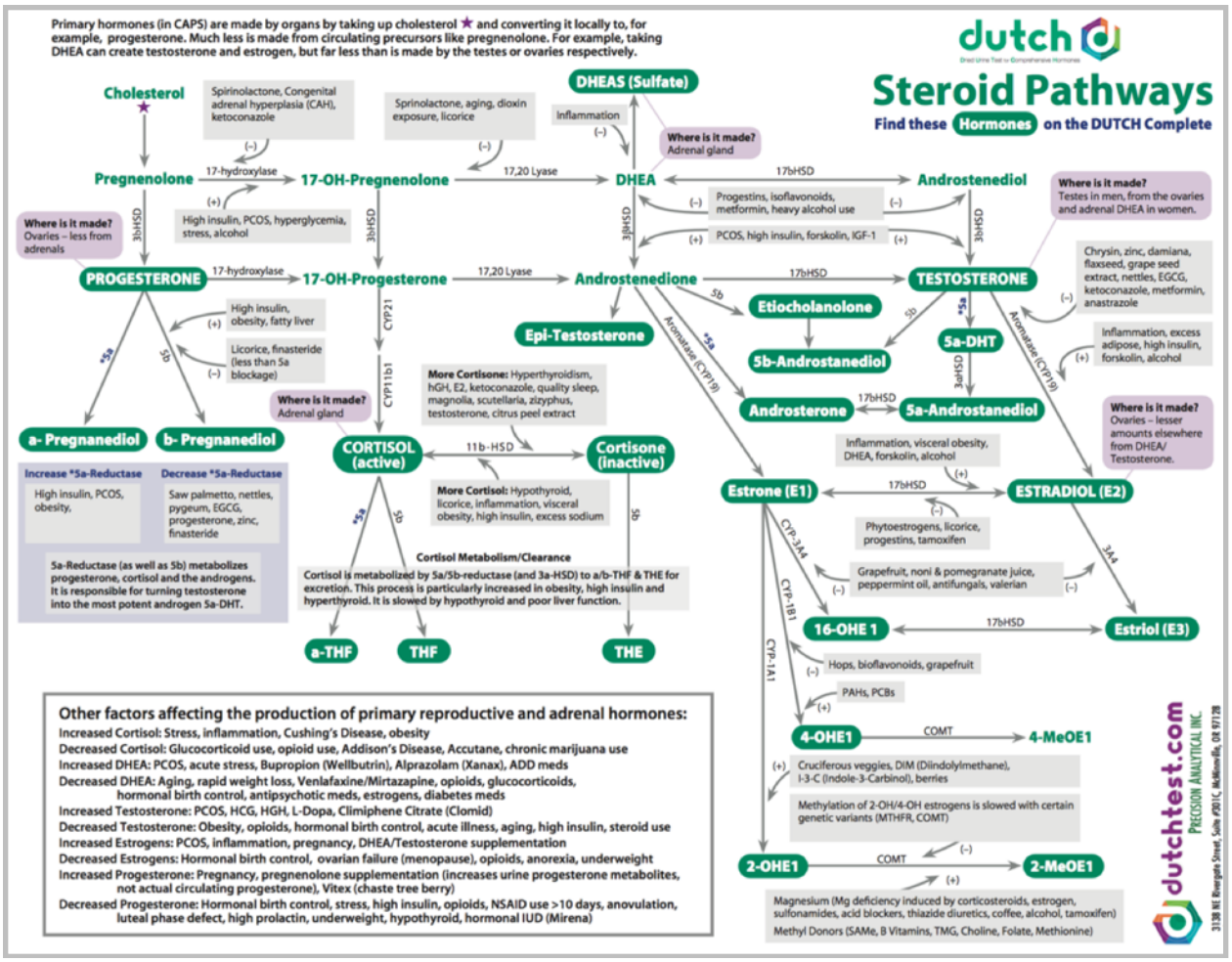
DHEA is produced in the adrenal gland, cholesterol is converted into pregnenolone, which is then converted into 17-OH-pregnenolone, which is finally converted into DHEA. Since this conversion pathway also involves conversion of pregnenolone to 17-OH-pregnenolone, it's also impaired by spironolactone, ketoconazole, and congenital hyperplasia. The conversion of 17-OH-pregnenolone to DHEA is inhibited by spironolactone in addition to exposure to dioxins, which are persistent in environmental pollutants that come from smelting, chlorine bleaching of paper pulp, and herbicides and pesticides, and by licorice root, which is a relatively unknown effect of licorice, and aging.



DHEA has several metabolites; one is DHEA sulfate, which is produced by the addition of a sulfate group to DHEA, and like DHEA, DHEA sulfate is also produced in the adrenal gland. DHEA itself is not present in the urine, but DHEA sulfate is, and that's what's measured in urine tests that measure DHEA, including the DUTCH panel. The conversion of DHEA to DHEA sulfate is inhibited by inflammation, so it's possible to have normal DHEA but low DHEA sulfate when inflammation is present, and that's one downside of urine testing for DHEA, but there are a few ways around that, which we're going to talk about later in the section. I've also seen some cases where DHEA sulfate is elevated but DHEA itself is normal; it's not entirely clear what causes this, but as a side note, DHEA sulfate appears to have a diurnal rhythm in urine and saliva, but not in blood, and it's also not clear why that's happening at this point.



DHEA is also converted into several other metabolites, all of which are weak androgens and function mostly as intermediates in the bioconversion of DHEA to testosterone and estrogen. One is androstenedione; the conversion of DHEA to androstenedione is inhibited by progestins, so that would include synthetic progesterones like birth control, isoflavonoids, metformin, and heavy alcohol use. The conversion of DHEA to androstenedione is increased by things like PCOS, high insulin levels, IGF1, and forskolin, which is a chemical found in the roots of the coleus forskoli plant, which is traditionally used to treat cardiovascular disorders and asthma. Androstenedione is converted into other weak androgens, namely etiocholanolone, which in turn is converted into 5-beta-androstenediol and androsterone. These conversions are catalyzed by 5-beta reductase in the case of etiocholanolone and 5-beta reductase in the case of androsterone, but less is known about the specific actions of these hormones.



Let's look a little more specifically at the 5-alpha and 5-beta reductase pathways, because they're so important in this hormone cascade. 5-alpha reductase metabolizes progesterone, cortisol, and some of the androgens. It's responsible for turning testosterone into DHT, which is the most potent androgen. It's 10 times more potent than testosterone. Upregulated 5-alpha reductase metabolism is associated with prostatitis and prostate cancer in men, hirsutism and PCOS in women, and other conditions caused by elevated androgens. The factors that increase 5-alpha reductase metabolism include high insulin, PCOS, and obesity. In this pattern, you'll see high active cortisol, alpha-tetrahydrocortisol, alpha-pregnanediol, which is a metabolite of progesterone, androsterone, and 5-alpha DHT. Agents that are known to decrease 5-alpha reductase activity include saw palmetto, nettle, IGM, EGCG, progesterone, zinc, and finasteride. Less is known about 5-beta reductase, but it's seen as a more favorable conversion pathway for androgen metabolism than the 5-alpha pathway. When 5-beta reductase is favored, you'll see higher tetrahydrocortisol relative to alpha-tetrahydrocortisol and tetrahydrocortisone, which is the less active form of cortisol, as well as higher levels of etiocholanolone and 5-beta androstenediol. The significance and importance of all these relationships that we've just discussed will become a lot more clear when we start looking at DUTCH test results in more detail, but before we do that, we need to talk a little bit more about the

etiology of HPA axis dysfunction and the dysfunction of the SAS in more detail, as well as the shortcomings of the adrenal fatigue concept, and that's what we're going to do next. See you then.