



# Androgens and the Nuances of Androgen Metabolism

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# Disclaimer

This lecture and the cited scientific literature, when referring to women/females, are referring to individuals born biological females; when referring to men/males, this lecture is referring to individuals born biological males.



# Objectives

At the end of this presentation, attendees should have a better understanding of, and gain insights into:

- The definition of “androgen” and the effects that these sex hormones have in both the male and female body.
- How to best evaluate androgen activity in the body through the use of urinary androgen testing.



# What is an “Androgen”?

From Oxford Languages:

- An “androgen” is a male sex hormone, such as testosterone.





# What is an “Androgen”?

Androgens include, but not limited to:

- Testosterone
- 5a-DHT
- 5a-androstenediol
- 5b-androstenediol
- Androstenedione
- DHEA
- DHEA-S
- Etiocholanolone
- Androsterone



# What is an “Androgen”?

Androgens are responsible for male sex characteristics.

- “The production of testosterone at about 9 weeks of gestation results in the development of the reproductive tract and the masculinization (the normal development of male sex characteristics) of the brain and genitalia.”

Institute of Medicine (US) Committee on Understanding the Biology of Sex and Gender Differences; Wizemann TM, Pardue ML, editors. Exploring the Biological Contributions to Human Health: Does Sex Matter? Washington (DC): National Academies Press (US); 2001. 3, Sex Begins in the Womb. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK222286/>



# What is an “Androgen”?

Androgens are responsible for primary MALE sex characteristics:

- Penis
- Testes

Institute of Medicine (US) Committee on Understanding the Biology of Sex and Gender Differences; Wizemann TM, Pardue ML, editors. Exploring the Biological Contributions to Human Health: Does Sex Matter? Washington (DC): National Academies Press (US); 2001. 3, Sex Begins in the Womb. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK222286/>

# What is an “Androgen”?

Androgens support secondary **MALE** sex characteristics:

- Facial hair
- Chest hair
- Increased body hair
- Pelvic build (lack of rounded hips)
- Upper body muscular build
- Ability to generate muscle mass at a faster rate than a female
- Voice changes



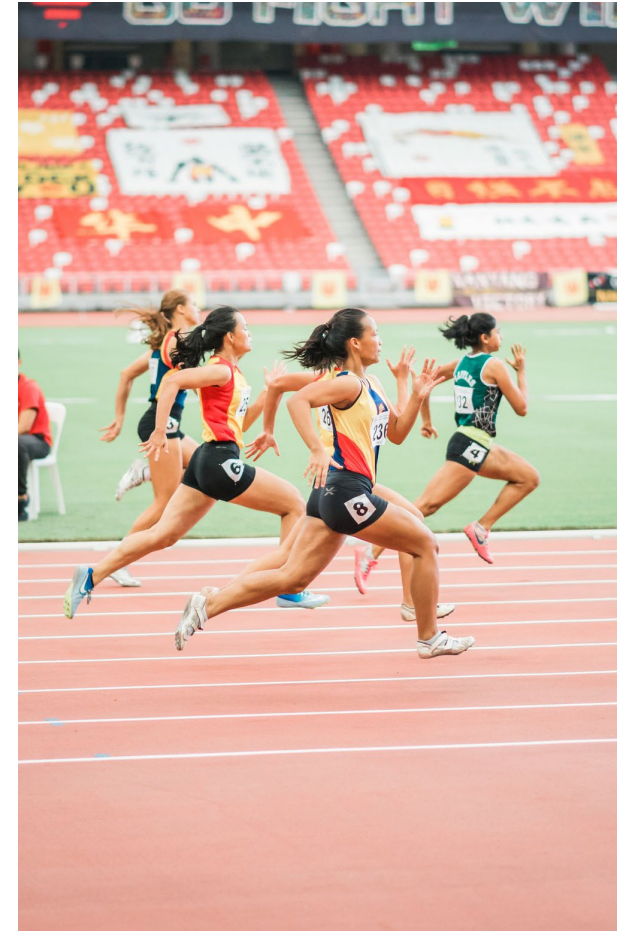
Julia E. Richards, R. Scott Hawley. “Chapter 8 - Sex Determination: How Genes Determine a Developmental Choice.” In *The Human Genome: A User’s Guide* (Third Edition), edited by Julia E. Richards, R. Scott Hawley, 273-298. Amsterdam: Academic Press, 2011.



# What is an “Androgen”?

In **MALES** and **FEMALES**, androgens support:

- Muscle, strength, stamina, healthy weight
- Bone mineral density
- Skin, hair
- Memory, cognition
- Sexual function, libido
- Fertility
  - sperm production (males)
  - follicle development (females)
- Cardiovascular health
- Immune health



# Healthy Androgens

Jeremy



Androgen keep Jeremy healthy.

- Muscle, strength, stamina
- Healthy weight
- Bone mineral density
- Skin, hair
- Memory, cognition
- Sexual function, libido
- Fertility
- Cardiovascular health
- Immune health

# Androgen Deficiency

In **MALES** and **FEMALES** androgen deficiency may result in:

- Inability to build muscle mass, poor strength and stamina, poor exercise recovery
- Weight gain
- Osteopenia/osteoporosis
- Memory issues, brain fog
- Mood issues, low mood, fatigue
- Low libido, erectile issues
- Infertility
- Cardiovascular disease
- Immune dysregulation



# Androgen Deficiency

Jed



Jed has low androgens.

- Fatigue
- Erectile issues
- Obese, gynecomastia
- Brain fog
- High cholesterol



# Androgen Excess

In **MALES** and **FEMALES** androgen excess may result in:

- Acne
- Scalp hair loss
- Increased facial hair growth and body hair growth
- Mood issues, irritability, anger
- **Males: prostate issues**
- **Females: irregular cycles, fertility issues, hirsutism**



# Androgen Excess

Amy



Amy has high androgens.

- High prolactin
- STRESSED OUT
- Hair thinning
- Acne
- Irritability

# Androgen Excess

Emily



Emily has high androgens.

- PCOS
- High insulin
- Overweight
- Irregular cycles
- Infertility



# Key Points

- Androgens are male sex hormones, such as testosterone.
- Androgens are important for primary and secondary male characteristics.
- Both males and females produce androgens.
- In both males and females, androgens are involved in muscle mass, strength, stamina, facial and body hair growth, mood, cognition, memory, skin, nails, bone mineral density, sexual function, libido, fertility, cardiovascular and immune health.
- Androgen deficiency and androgen excess can negatively affect both males and females.



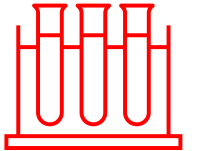
# How do we measure androgens?

DUTCH urine metabolites (7 total):



- Testosterone
- 5a-DHT
- 5a-androstanediol
- 5b-androstanediol
- DHEA-S
- Etiocholanolone
- Androsterone

Common serum (blood) tests:



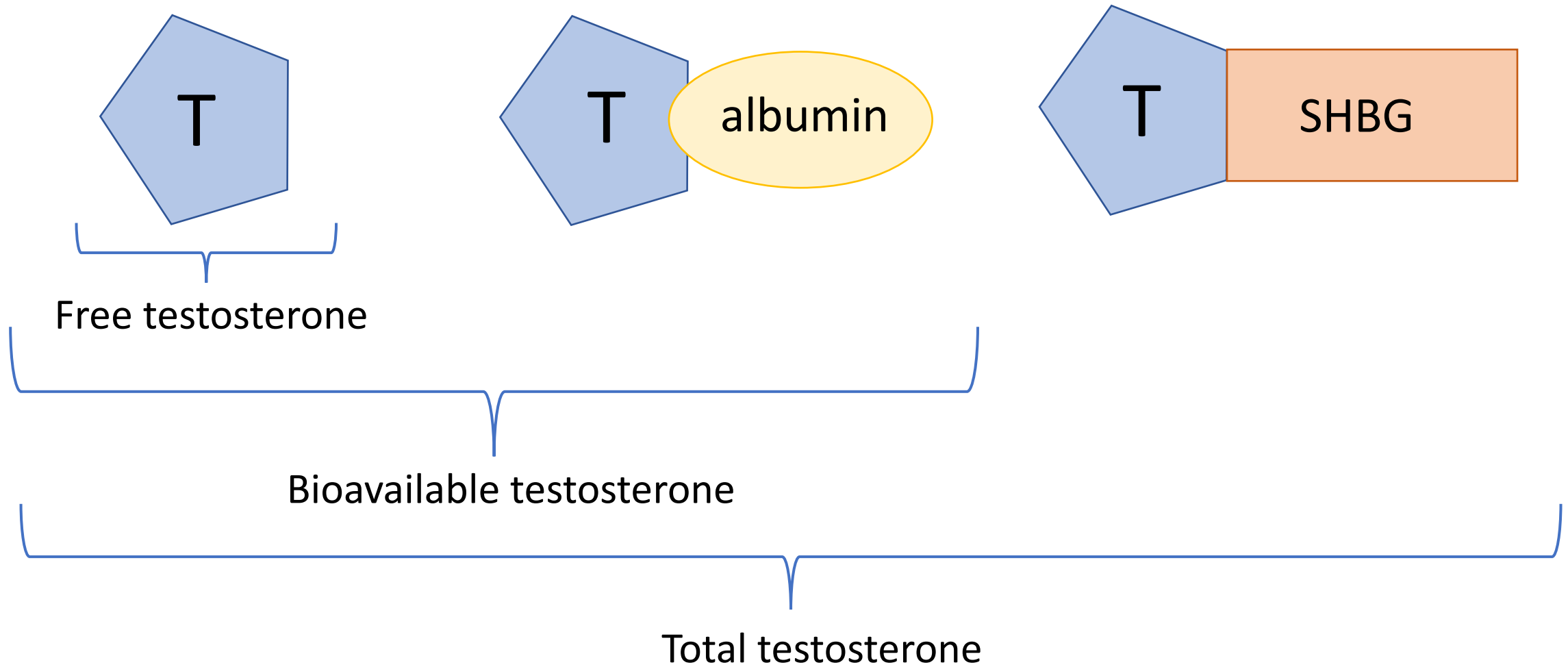
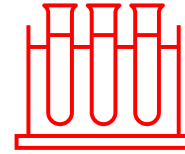
- Total testosterone
- Bioavailable testosterone
- Free testosterone
- DHEA
- DHEA-S

# How testosterone circulates in the blood

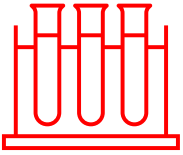
- Testosterone can circulate in its free form or bound to a protein (albumin or SHBG).
- Free testosterone is “active.”
- Testosterone loosely bound to albumin can readily dissociate and become “active.”
- Testosterone tightly bound to SHBG doesn't readily dissociate.



# Binding Globulins



# How do we measure androgens?



Common serum (blood) tests:

- Total testosterone
- Bioavailable testosterone
- Free testosterone
- DHEA
- DHEA-S



# What do I do with these androgens??

DUTCH urine metabolites (7 total):



- Testosterone
- 5a-DHT
- 5a-androstanediol
- 5b-androstanediol
- DHEA-S
- Etiocholanolone
- Androsterone



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# What do I do with these androgens??



DUTCH urine metabolites (7 total):

## Testosterone metabolites\*

- Testosterone
- 5a-DHT
- 5a-androstenediol
- 5b-androstenediol

## DHEA metabolites\*

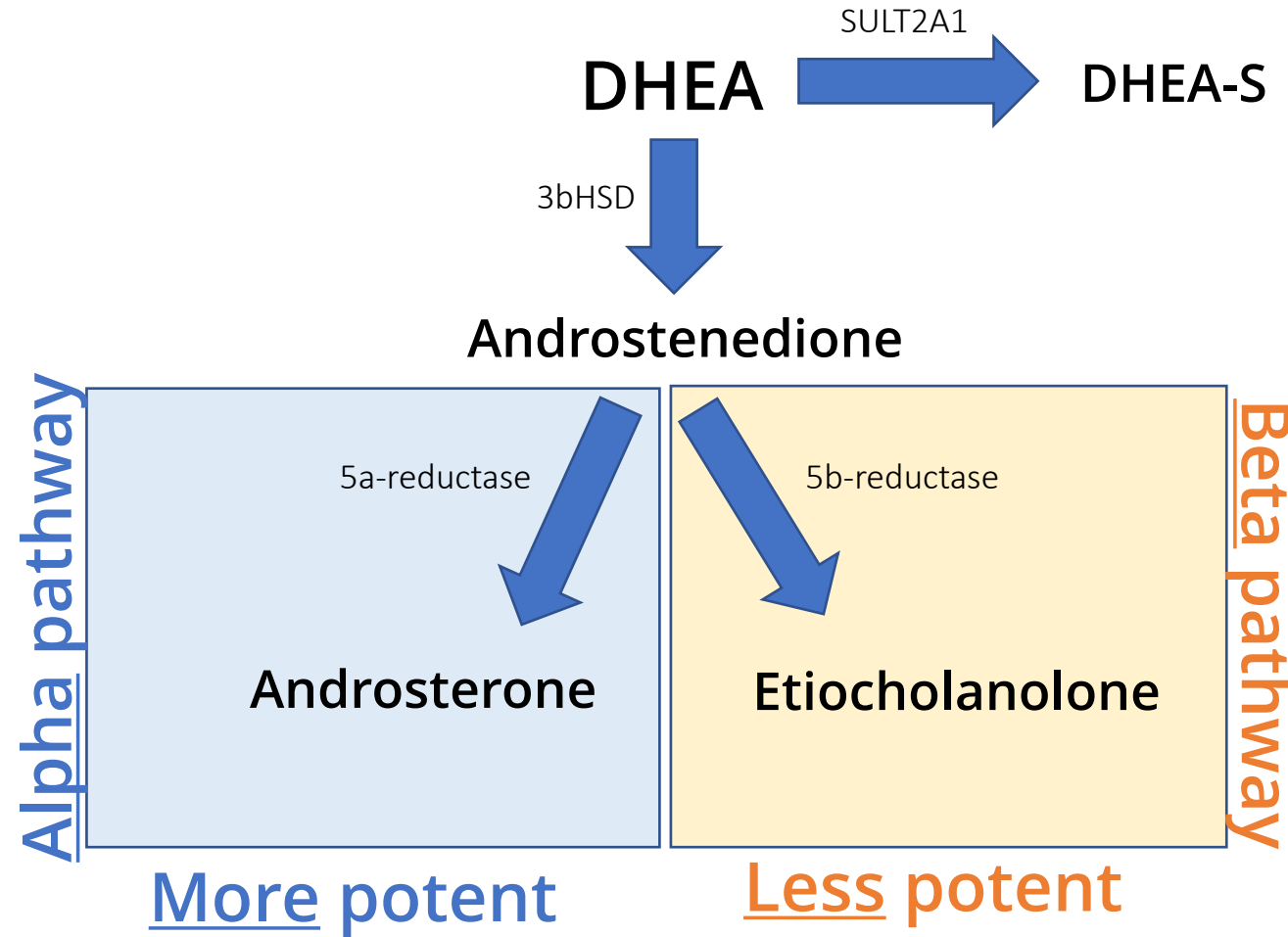
- DHEA-S
- Etiocholanolone
- Androsterone

\*Note that DHEA can influence testosterone metabolite levels and testosterone can influence etiocholanolone and androsterone levels.

# DHEA urine metabolites



“alpha male”





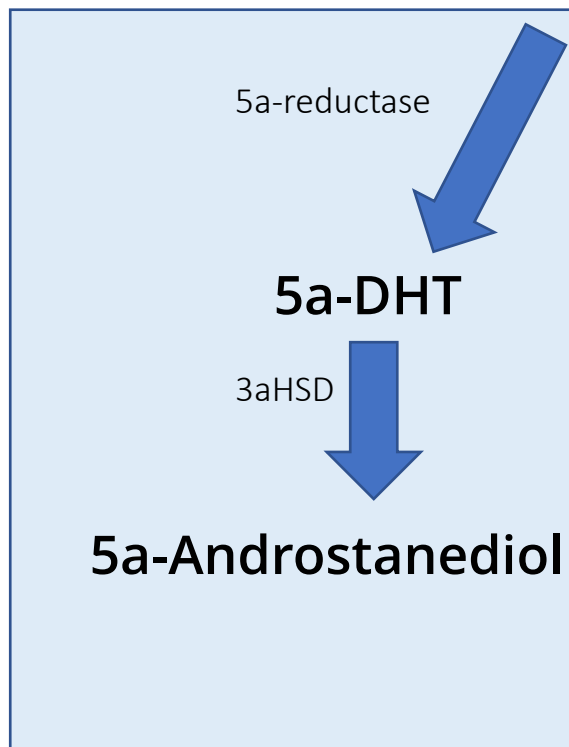
# Testosterone urine metabolites



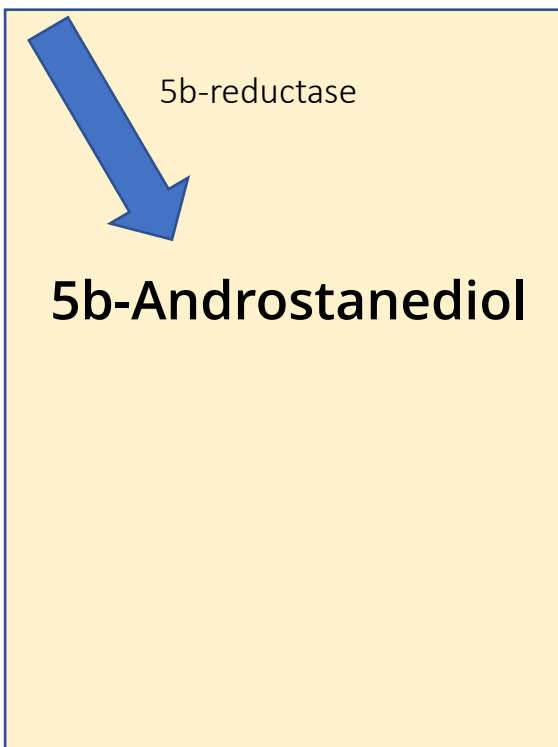
“alpha male”



Alpha pathway



More potent



Beta pathway

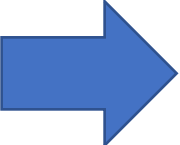
Less potent

# Evaluating *tissue* androgen activity

## Progesterone and Breast Cancer

[Britton Trabert](#),<sup>1</sup> [Mark E Sherman](#),<sup>2</sup> [Nagarajan Kannan](#),<sup>3</sup> and [Frank Z Stanczyk](#)<sup>4</sup>

potent. In women, however, levels of circulating DHT are often below assay detection, and do not reflect peripheral 5 $\alpha$ -reductase activity ([170](#)). Rather, androsterone glucuronide (ADT-G), a distal metabolite of DHT, together with androstanediol glucuronide (found as 2 isomers: 5 $\alpha$ -androsterone-3 $\alpha$ ,17 $\beta$  diol-3-glucuronide (3 $\alpha$ -diol-3G) and 5 $\alpha$ -androsterone-3 $\alpha$ ,17 $\beta$  diol-17-glucuronide (3 $\alpha$ -diol-17G)), have been shown to reflect total tissue-level androgenic activity better than the proandrogens (eg, testosterone, androstenedione, etc.) ([170](#), [171](#)). Additional research is necessary



In target tissues, testosterone is activated to 5 $\alpha$ -DHT by the enzyme 5 $\alpha$ -reductase. 5 $\alpha$ -DHT is 3x more potent than testosterone and is made and metabolized locally in the tissues to 5 $\alpha$ -androstanediol. Therefore, *urinary* 5 $\alpha$ -androstanediol may be a better marker of *tissue* 5 $\alpha$ -DHT activity than *urinary* 5 $\alpha$ -DHT. Androsterone can additionally be used to evaluate tissue androgen activity.

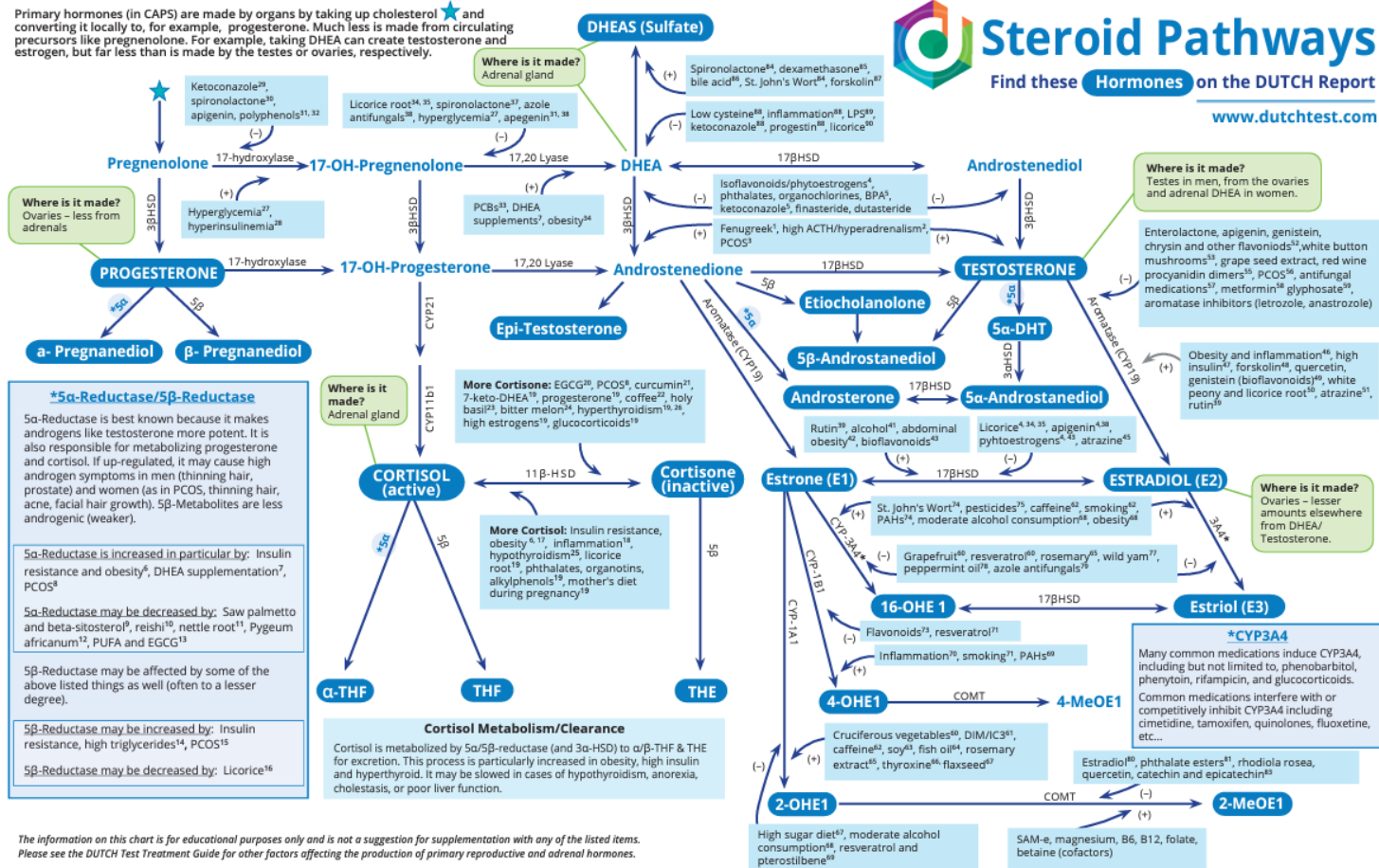


# Androgen Potency

- DHEA is NOT a hormone, but a prohormone
- DHEA can be metabolized into etiocholanolone and androsterone or converted into testosterone and estrogen in target tissues.
- Testosterone is metabolized into 5a-DHT and 5a-androstenediol in target tissues and into 5b-androstenediol by the liver.
- 5a-DHT is 4x more potent than testosterone
- Evaluate androgen activity in the tissue by looking at 5a-androstenediol & androsterone.
- 5b-androstenediol does not correlate with classic androgen symptoms due to the low androgenic potential of beta metabolites.

# DUTCH Steroid Pathways Chart

Primary hormones (in CAPS) are made by organs by taking up cholesterol and converting it locally to, for example, progesterone. Much less is made from circulating precursors like pregnenolone. For example, taking DHEA can create testosterone and estrogen, but far less than is made by the testes or ovaries, respectively.



<https://dutchtest.com/resource/steroid-pathway/>



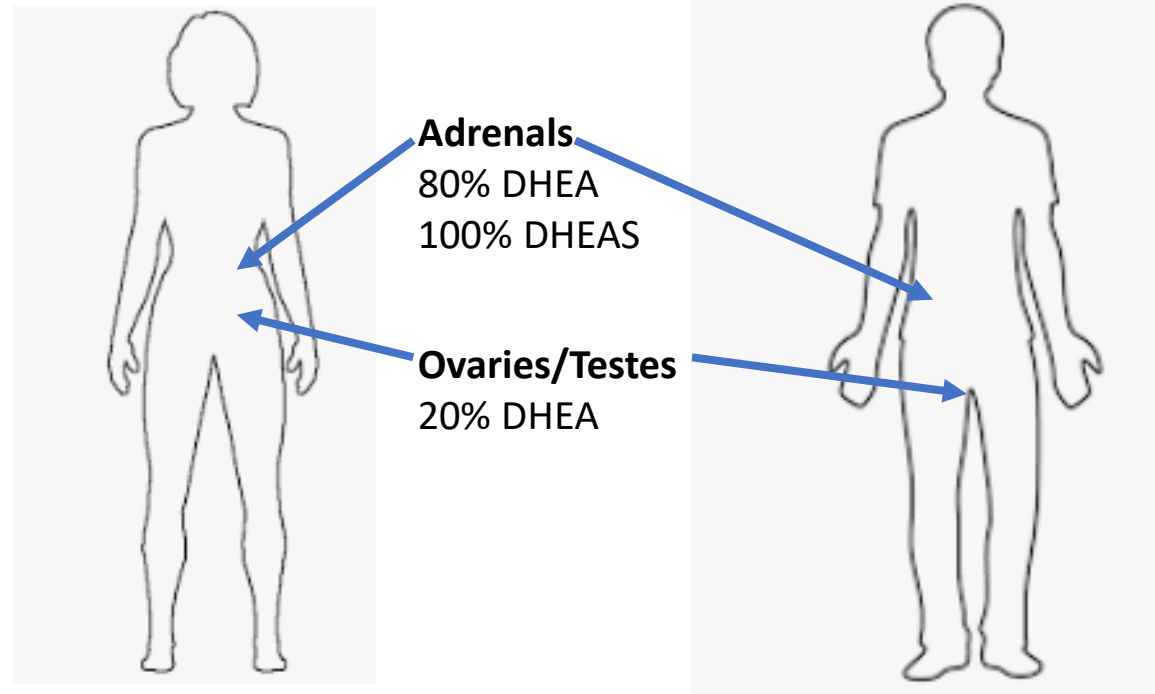
# Key Points

- We can evaluate androgens in both the serum (blood) and urine.
- Alpha metabolites are generally more potent androgens than beta metabolites.
- Evaluate androgen activity in the tissue by looking at 5a-androstanediol & androsterone.
- DHEA can influence testosterone metabolite levels and testosterone can influence etiocholanolone and androsterone levels.

# Where is DHEA made?

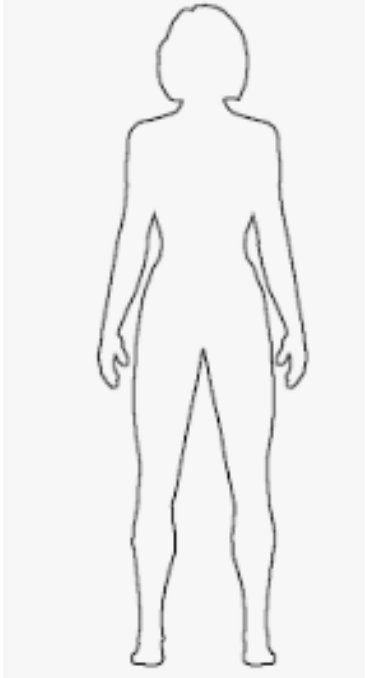
## DHEA Production in Cycling Females\* & Males

\*Most of a postmenopausal female's DHEA is derived from the adrenal glands.



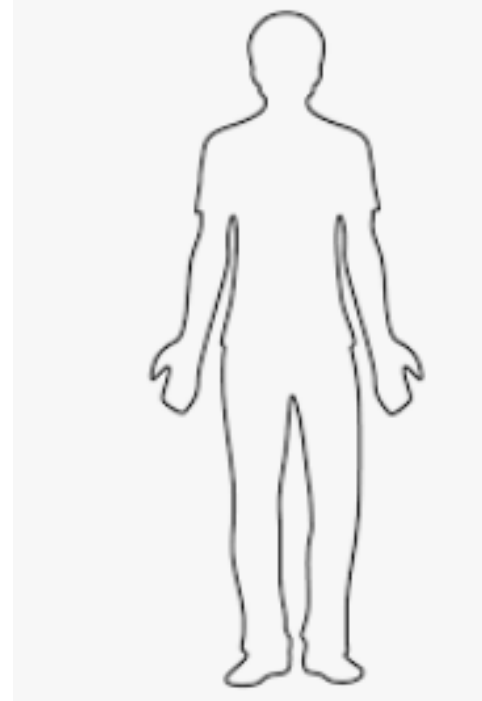
# Where is testosterone made?

## Cycling Females\*



- 25% ovaries
- 25% adrenals
- 50% fat tissue (converted from androstenedione)

## Men



- 95% testes
- 5% adrenals

\*Most of a postmenopausal woman's testosterone is derived from the adrenal glands.



# Why might a female have low androgens?

Good Question! Let's explore reasons why a female may have lower androgens:

## Low DHEA

- Age – naturally declines with aging
- HPA axis dysfunction
- Inflammation (inflammation lowers sulfation so DHEA higher but DHEA-S lower)
- SULT2A1 problems (higher DHEA but lower DHEA-S)
- Medications (glucocorticosteroids, opioids, Pulmicort inhaler, Metformin/Glucophage)

## Low Testosterone

- Low ovarian/adrenal output
- Low precursors (DHEA, androstenedione)
- Poor hypothalamic/pituitary communication
- Surgically removed ovaries
- Age
- Decreased blood flow to the glands
- Diabetes
- Elevated SHBG (decreased free T)
- Medications (glucocorticosteroids, opioids, accutane)
- Zinc deficiency

<https://dutchtest.com/wp-content/uploads/2020/04/Treatment-Guide-Booklet-REF040220.pdf>



# Why might males have low androgens?

Good Question! Let's explore reasons why a male may have lower androgens:

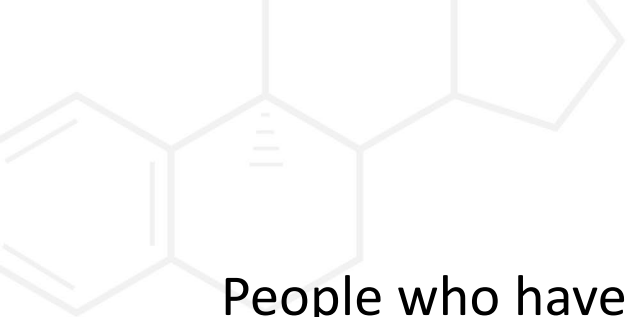
## Low DHEA

- Age – naturally declines with aging
- HPA axis dysfunction
- Inflammation (inflammation lowers sulfation so DHEA higher but DHEA-S lower)
- SULT2A1 problems (higher DHEA but lower DHEA-S)
- Medications (glucocorticosteroids, opioids, Pulmicort inhaler, Metformin/Glucophage)

## Low Testosterone

- Medications (performance steroids, glucocorticosteroids, opioids, Accutane, anti-androgen therapy)
- Recent testosterone supplementation
- Zinc deficiency
- Environmental exposure
- Regular THC use
- Alcohol
- Age
- Sleep disturbance
- Obesity
- Hypothyroidism
- Diabetes
- Increased aromatization
- Hyperprolactinemia
- Elevated SHBG
- Leptin and leptin receptor mutation
- Isolated or combined pituitary or hypothalamic disease
- Hypogonadism/removal of testicle
- Testicular infection
- Space occupying lesion to pituitary or hypothalamus
- Infarction affection pituitary or hypothalamus
- Decreased blood flow to the glands
- Autoimmune anti-Scc antibodies - Leydig cell specific
- Radiation to the groin area, chemo at-large
- Traumatic Brain Injury

<https://dutchtest.com/wp-content/uploads/2020/04/Treatment-Guide-Booklet-REF040220.pdf>



# UGT Deletion

People who have a UGT genetic deletion won't metabolize a lot of their testosterone (and 5a-DHT and 5b-androstanediol) into the major forms that urine tests measure (mainly glucuronidated metabolites). **Thus, genetic variants in the UGT2B17 enzyme reduce these urinary hormone levels without affecting serum levels.**

For this reason, low and very low urinary testosterone levels should be confirmed with serum testing before treatment. Serum testing should include total testosterone, free testosterone, either calculated (needs SHBG and albumin) or measured by equilibrium dialysis.

Epi-testosterone is made by the testes in about the same concentration as testosterone. Epi-testosterone is not androgenic but is included on the DUTCH test because it may be helpful when assessing the validity of the urinary testosterone result. If epi-testosterone is much higher than testosterone, 5a-DHT, and 5b-androstanediol, it suggests that the UGT deletion may be present.

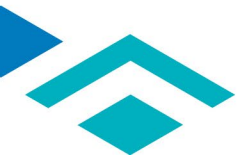


# Key Points

- Most DHEA comes from the adrenals in BOTH males and females.
- 95% of testosterone comes from the testes in males.
- Both the ovaries and the adrenals greatly contribute to testosterone in females.
- There are MANY reasons that a female or male might have androgen deficiency or androgen excess. Proper workup is essential.
- Due to the possibility of the UGT deletion, always confirm low testosterone in the serum (blood).



# Case Study



# Example of LOW androgens: Bob

Bob, 56 years old, has **LOW** androgens. He's overweight, struggles with fatigue and brain fog and finds it difficult to gain muscle mass. He has high cholesterol and diabetes. He loves fishing.

| Low Testosterone      |
|-----------------------|
| <u>Symptoms</u>       |
| Belly Fat             |
| Bone Loss             |
| Low Energy            |
| Low Sex Drive         |
| Low Muscle Mass       |
| Mood Issues/Brain Fog |
| Gynecomastia          |
| Erectile Dysfunction  |

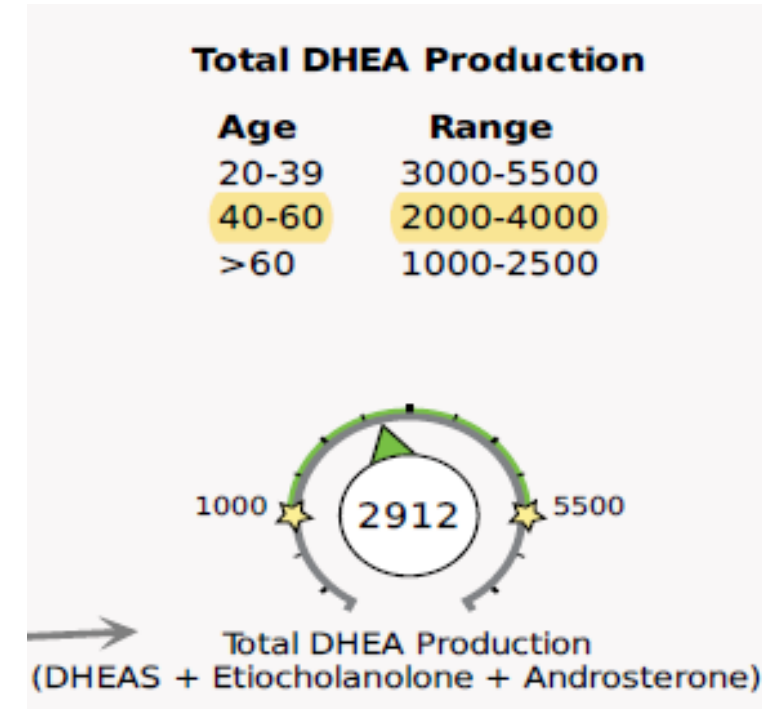
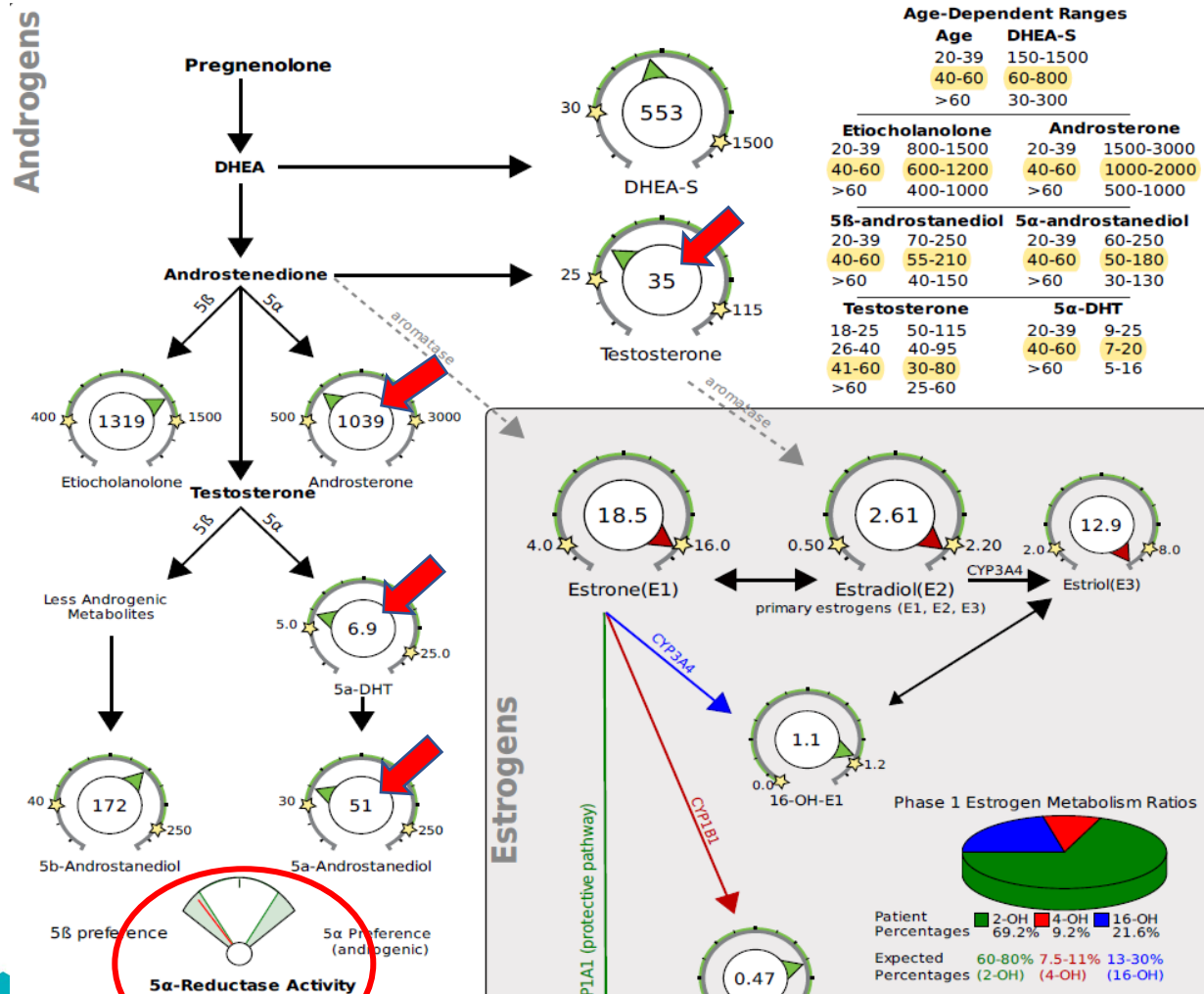
## Bob's Symptoms:

- Fatigue
- Brain fog
- Difficulty putting on muscle mass



# Bob's DUTCH results

Bob, 56 years old, has **LOW** androgens and **HIGH** estrogen for his age.

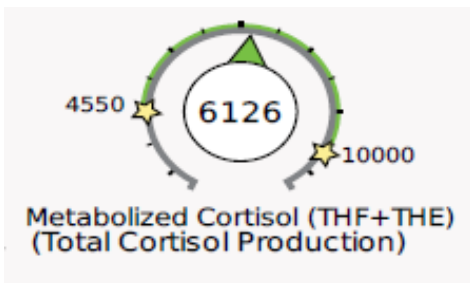


# Why does Bob have low androgens?

Good Question! Let's explore reasons why a man may have lower androgens:

## Low DHEA

- Age – naturally declines with aging
- HPA axis dysfunction
- Inflammation (inflammation lowers sulfation so DHEA higher but DHEA-S lower)
- SULT2A1 problems (higher DHEA but lower DHEA-S)
- Medications (glucocorticosteroids, opioids, Pulmicort inhaler, Metformin/Glucophage)



## Low Testosterone

- Medications (performance steroids, glucocorticosteroids, opioids, Accutane, anti-androgen therapy)
- Recent testosterone supplementation
- Zinc deficiency
- Environmental exposure
- Regular THC use
- Alcohol
- Age
- Sleep disturbance
- Obesity
- Hypothyroidism
- Diabetes
- Increased aromatization
- Hyperprolactinemia
- Elevated SHBG
- Leptin and leptin receptor mutation
- Isolated or combined pituitary or hypothalamic disease
- Hypogonadism/removal of testicle
- Testicular infection
- Space occupying lesion to pituitary or hypothalamus
- Infarction affection pituitary or hypothalamus
- Decreased blood flow to the glands
- Autoimmune anti-Scc antibodies - Leydig cell specific
- Radiation to the groin area, chemo at-large
- Traumatic Brain Injury



# So, what should Bob do?



What can Bob do to improve his fatigue, brain fog, and help him put on muscle mass?

The basics:

- Regulate blood sugars
- Weight reduction
- Slow/block aromatization
  - Chrysin, EGCG, white button mushrooms, weight reduction, lower inflammation, lower stress, regulate blood sugars, etc.



What's a fisherman to do?





# References

Institute of Medicine (US) Committee on Understanding the Biology of Sex and Gender Differences; Wizemann TM, Pardue ML, editors. Exploring the Biological Contributions to Human Health: Does Sex Matter? Washington (DC): National Academies Press (US); 2001. 3, Sex Begins in the Womb. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK222286/>

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