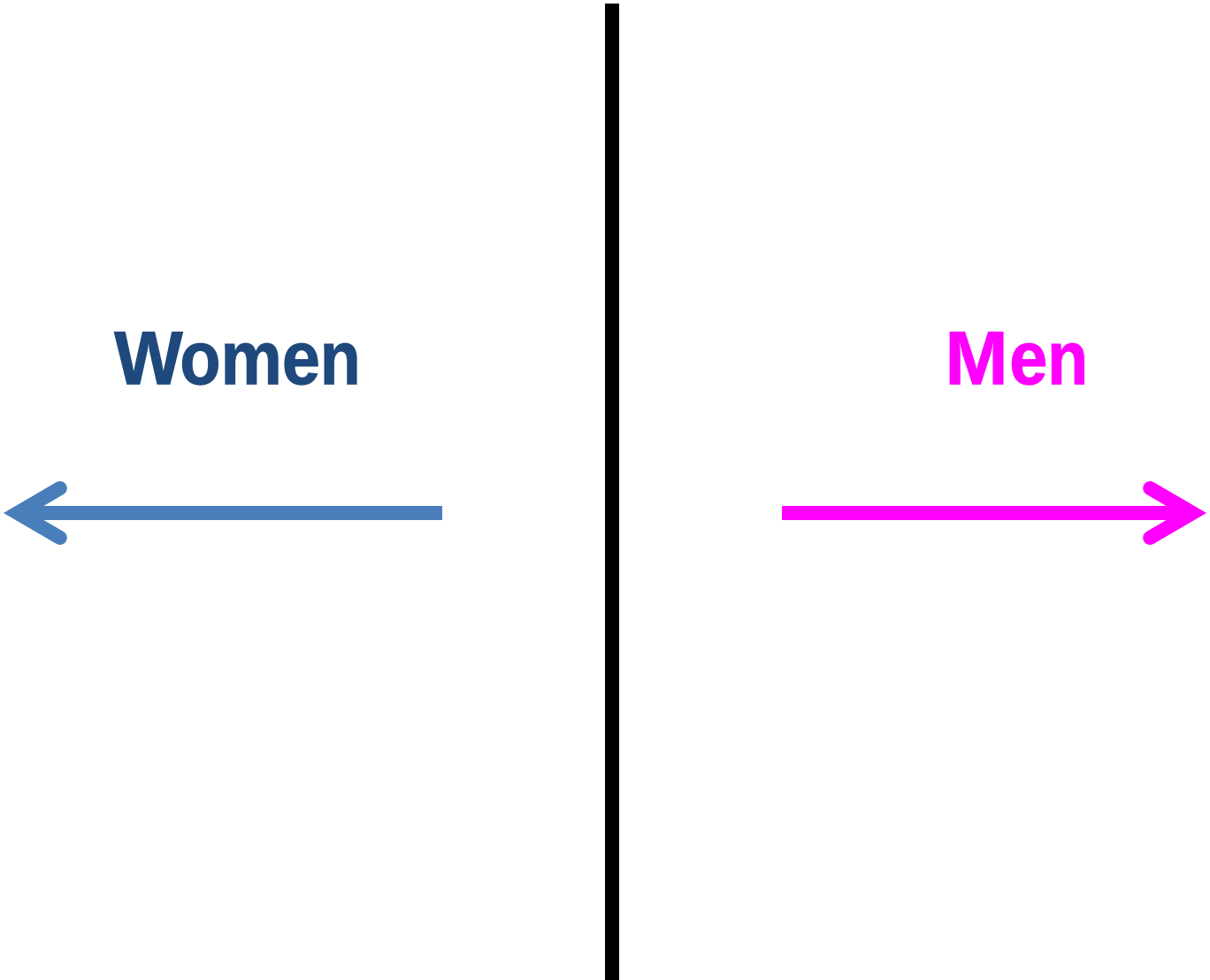
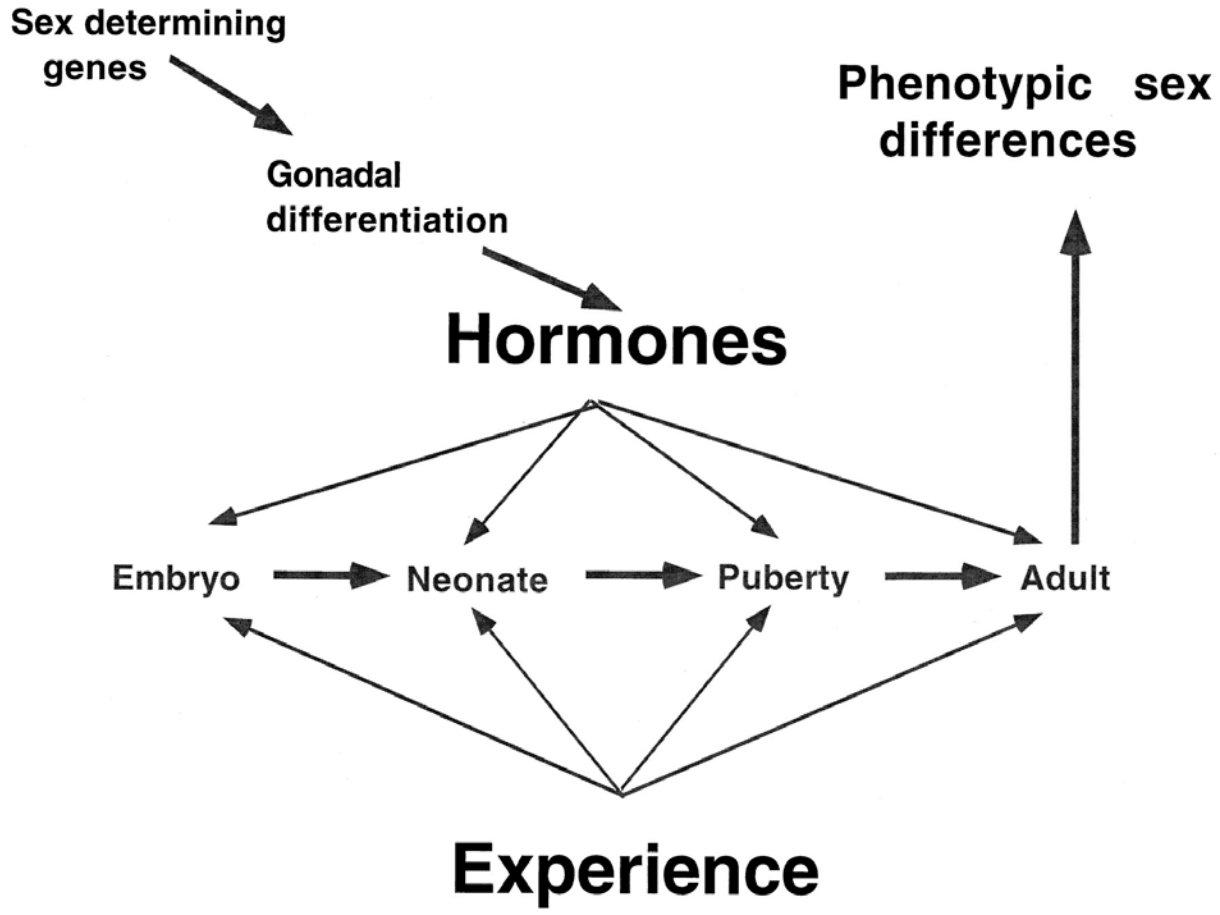
Please Take Seats by Gender as Shown
Leave Three Seats Empty in the Middle



Sexual Differentiation & Development

Neal G. Simon, Ph.D.
Professor
Dept. of Biological Sciences

Signaling Cascade & Events Leading to Phenotypic Sex Differences



Divide into Groups of 4 – 5

Prepare a List of 4 Behavioral/Psychological Characteristics that Differentiate the Sexes

Sexual Differentiation

1. Chromosomal Sex : XX, XY

2. Gonadal Sex: Ovaries, Testis

3. Hormonal Sex: Androgens, Estrogens, & Progestins (mostly about T)

4. Brain Differentiation: Masculinization

5. Gender Identity: Male, Female

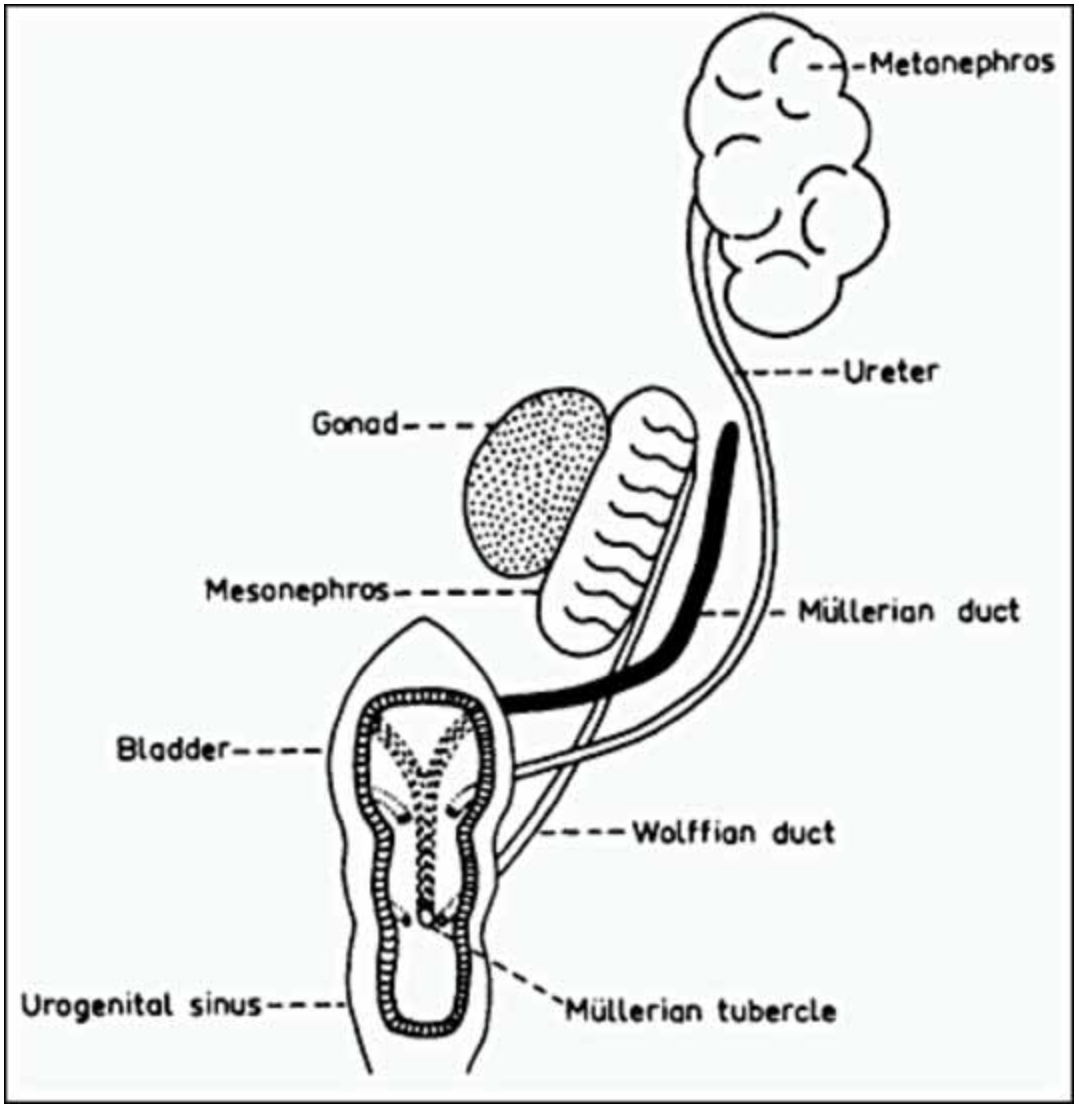
6. Psychosexual Development: Male, Female, Heterosexual , Homosexual, Transexual

7. Sexual & Sexually Dimorphic Behavior

Sexual Differentiation

Undifferentiated Reproductive Tract

Both Wolffian and Müllerian ducts are present. Müllerian ducts open in the urogenital sinus at the level of the Müllerian tubercle between the orifices of the Wolffian duct

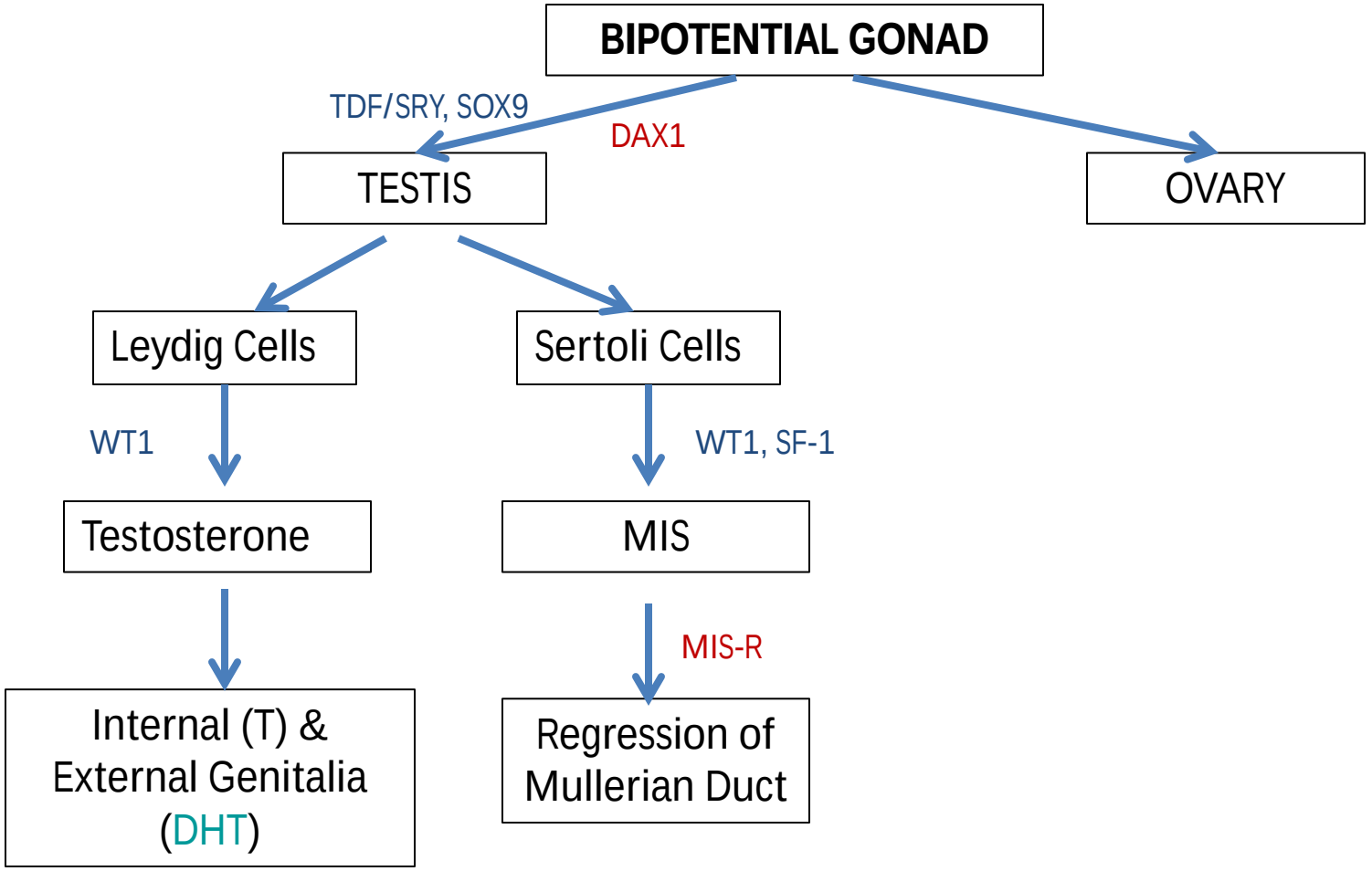


Mullerian Duct: uterus, fallopian tubes, and upper vagina

Wolfian Duct: epididymis, vas deferens, seminal vesicles

Key Genes in Gonadal Differentiation

TDF/SRY (sex determining region of the Y chromosome) is a testis determining factor on the short arm of the Y chromosome. **SOX9** gene is also important in male sexual differentiation. **DAX1,** an orphan member of a nuclear hormone receptor family located on the X chromosome, interacts with steroidogenic factor 1 (**SF-1**). Other genes involved in male gonadal differentiation include the tumor-suppressor gene **WT1** (Wilms' tumor 1), and the Müllerian inhibiting substance gene **(MIS)** and its receptor, **MIS-R**.

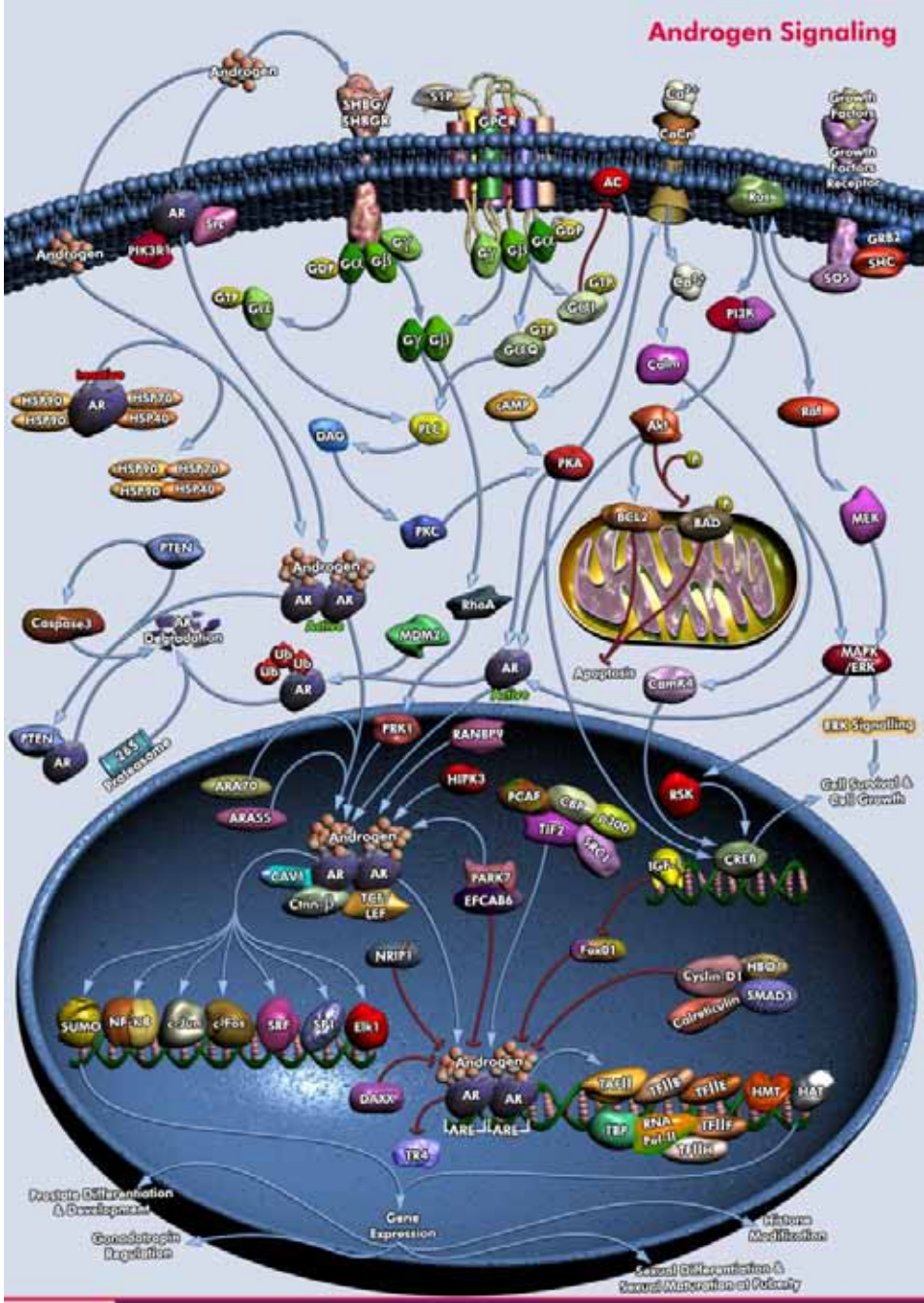


•The appropriate regulation of androgen activity is necessary for a range of developmental and physiological processes, particularly male sexual development and maturation.

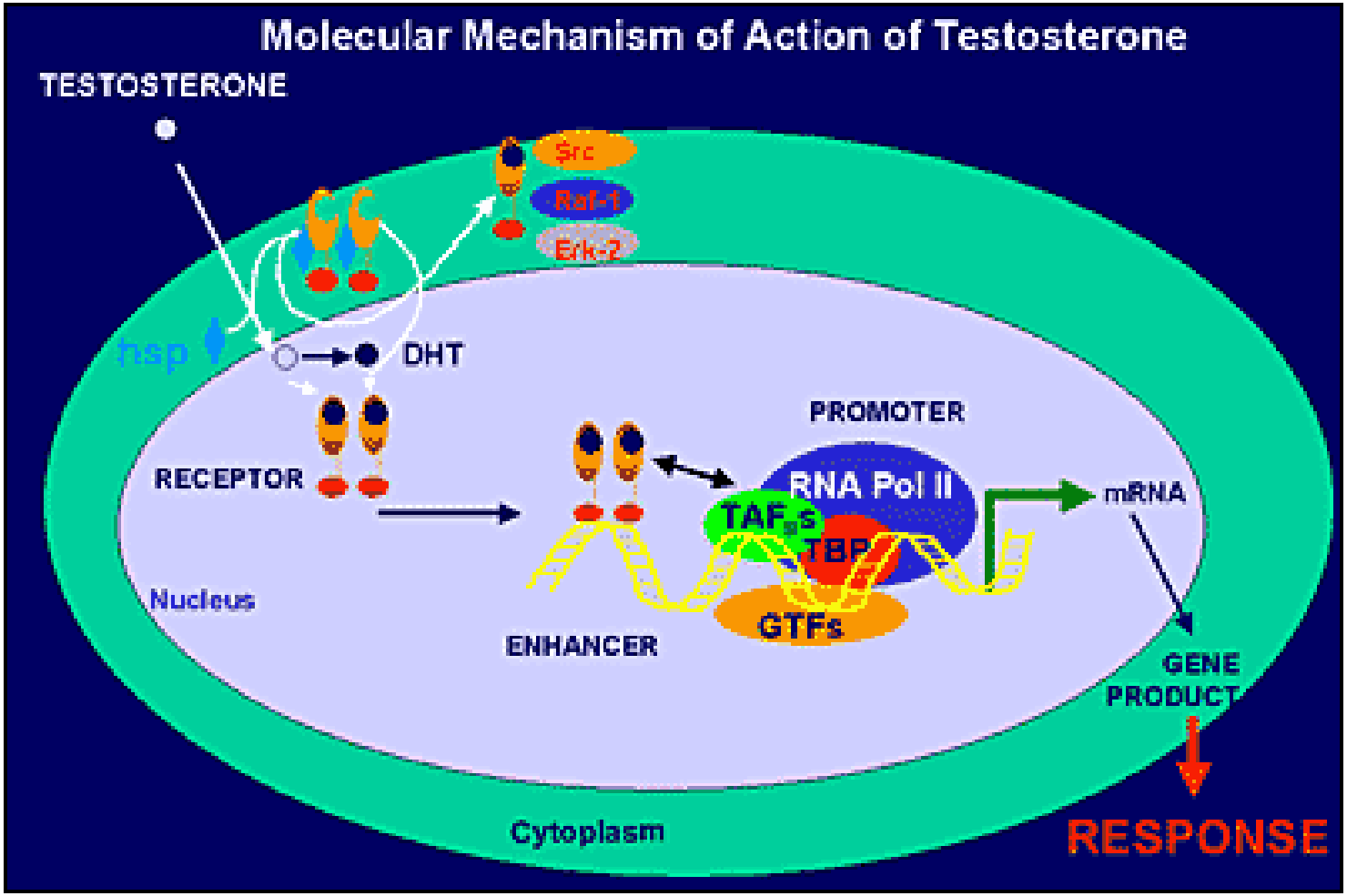
• Androgen ablation therapy is often combined with treatment with nonsteroidal antiandrogens, such as hydroxyflutamide, to block residual adrenal androgen action.

• Androgen Replacement Therapy has been in use for over 60 years to treat patients with male hypogonadal disorders and/or failure of sexual development.

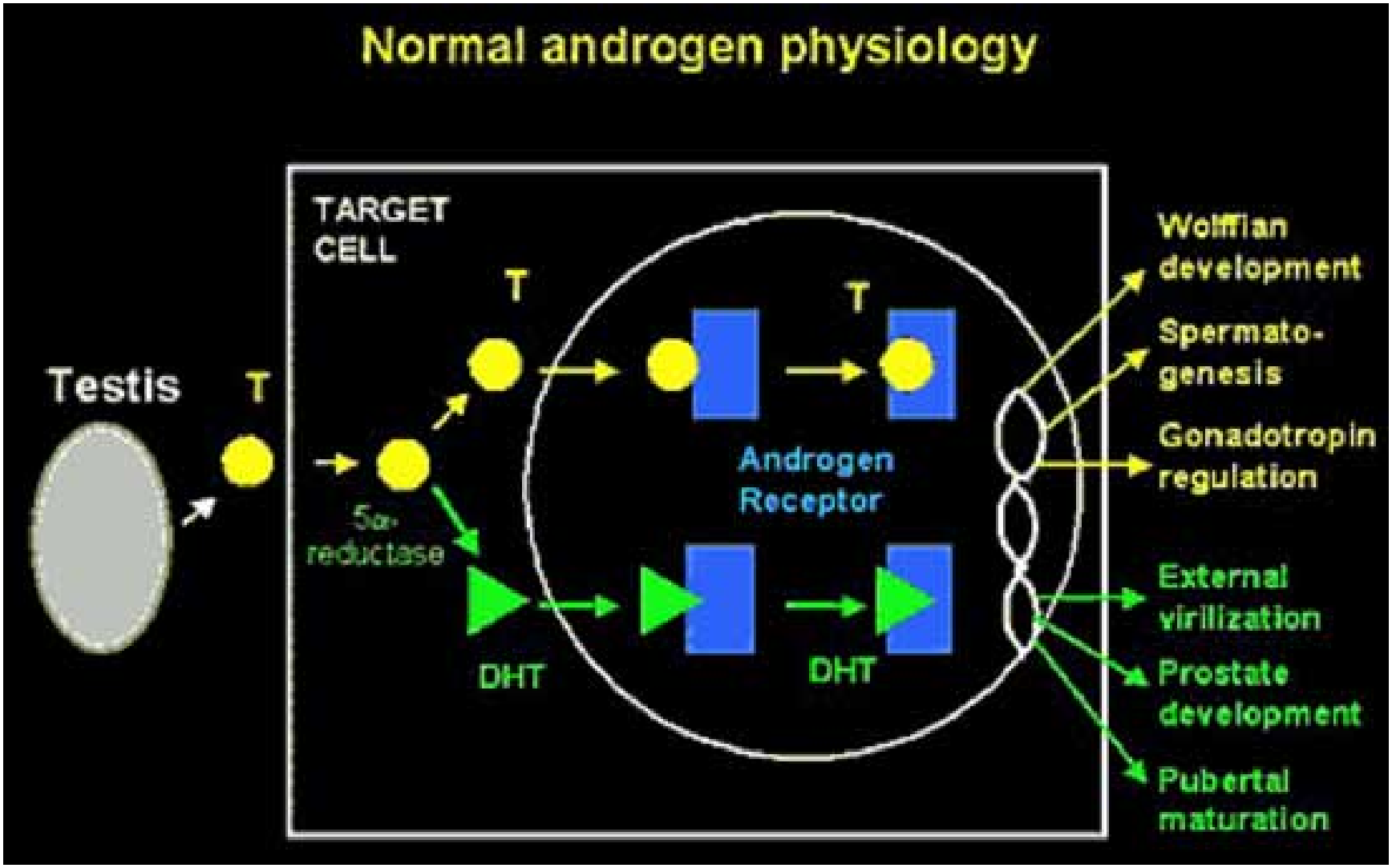
• The last decade has witnessed a wider therapeutic role of androgens for non-classical indications. These include male contraception and depressive states frequently associated with a variety of chronic systemic conditions such as physiological aging.



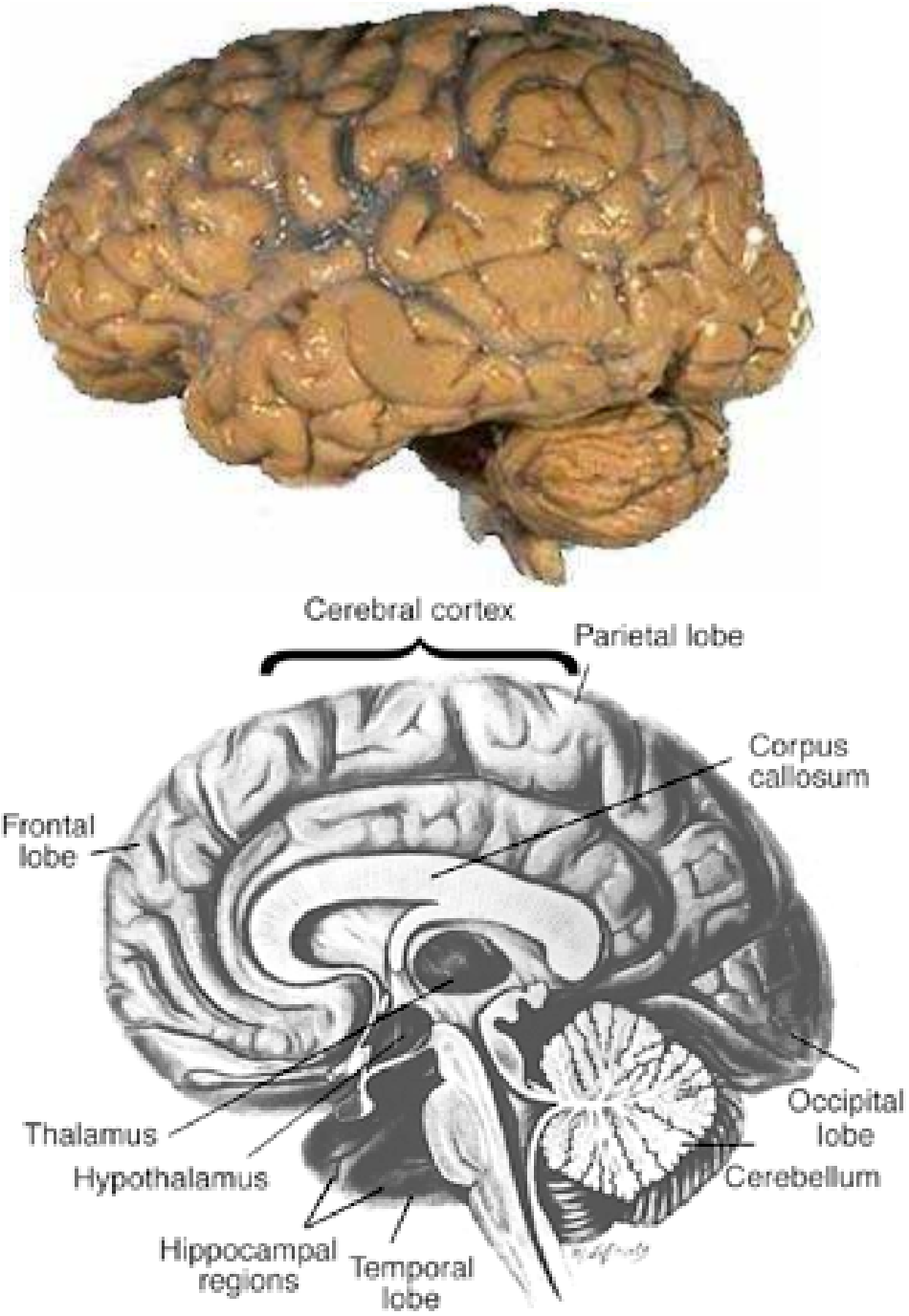
Cellular Events Mediating Androgen Signaling



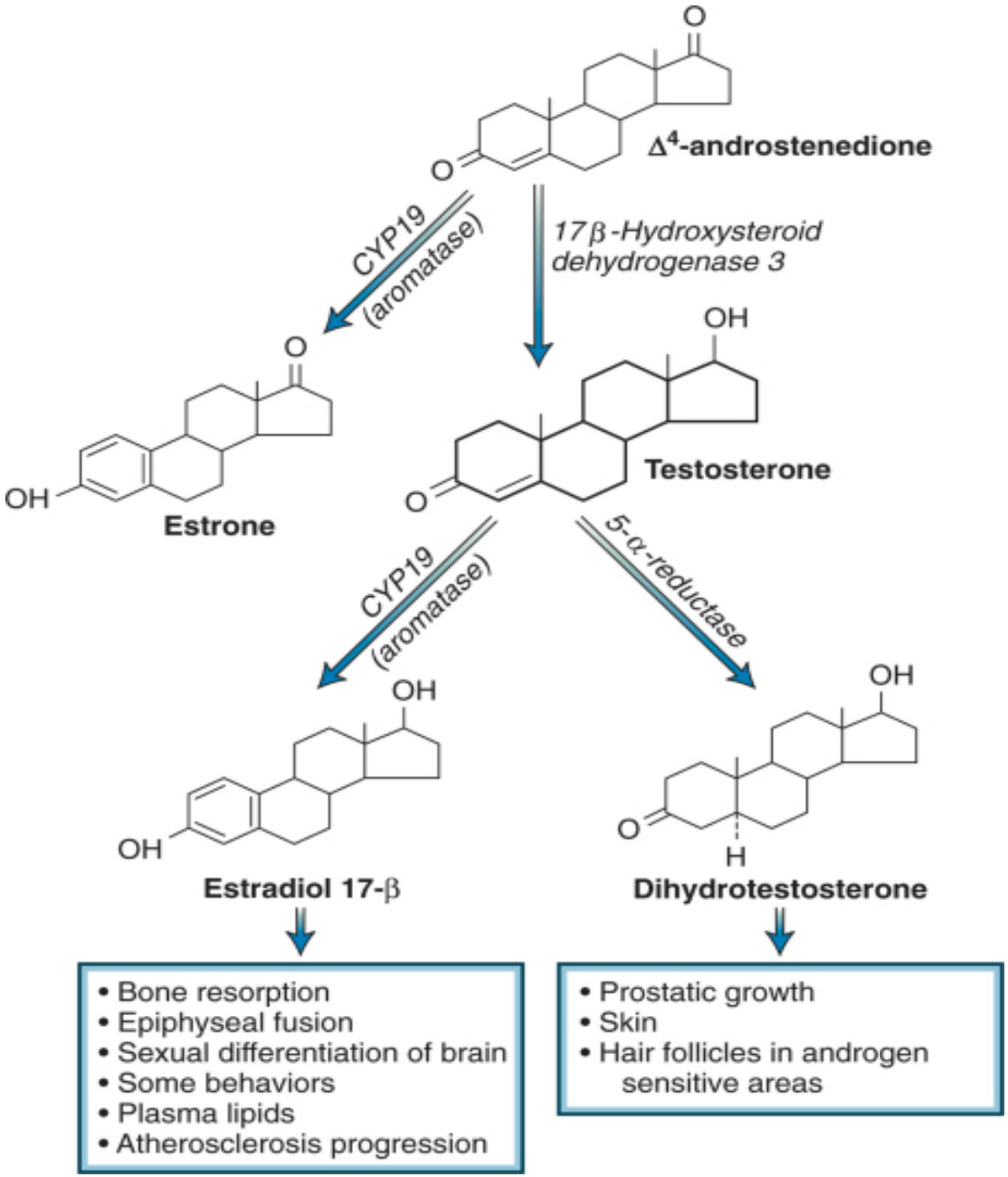
Core Functions of Testosterone and Dihydrotestosterone in Males

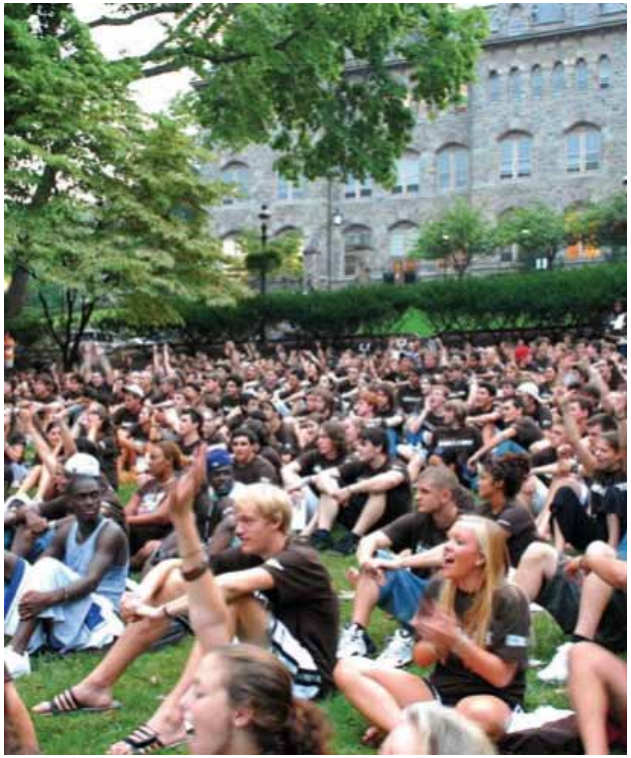


The Human Brain: A Major Target for Sexual Differentiation

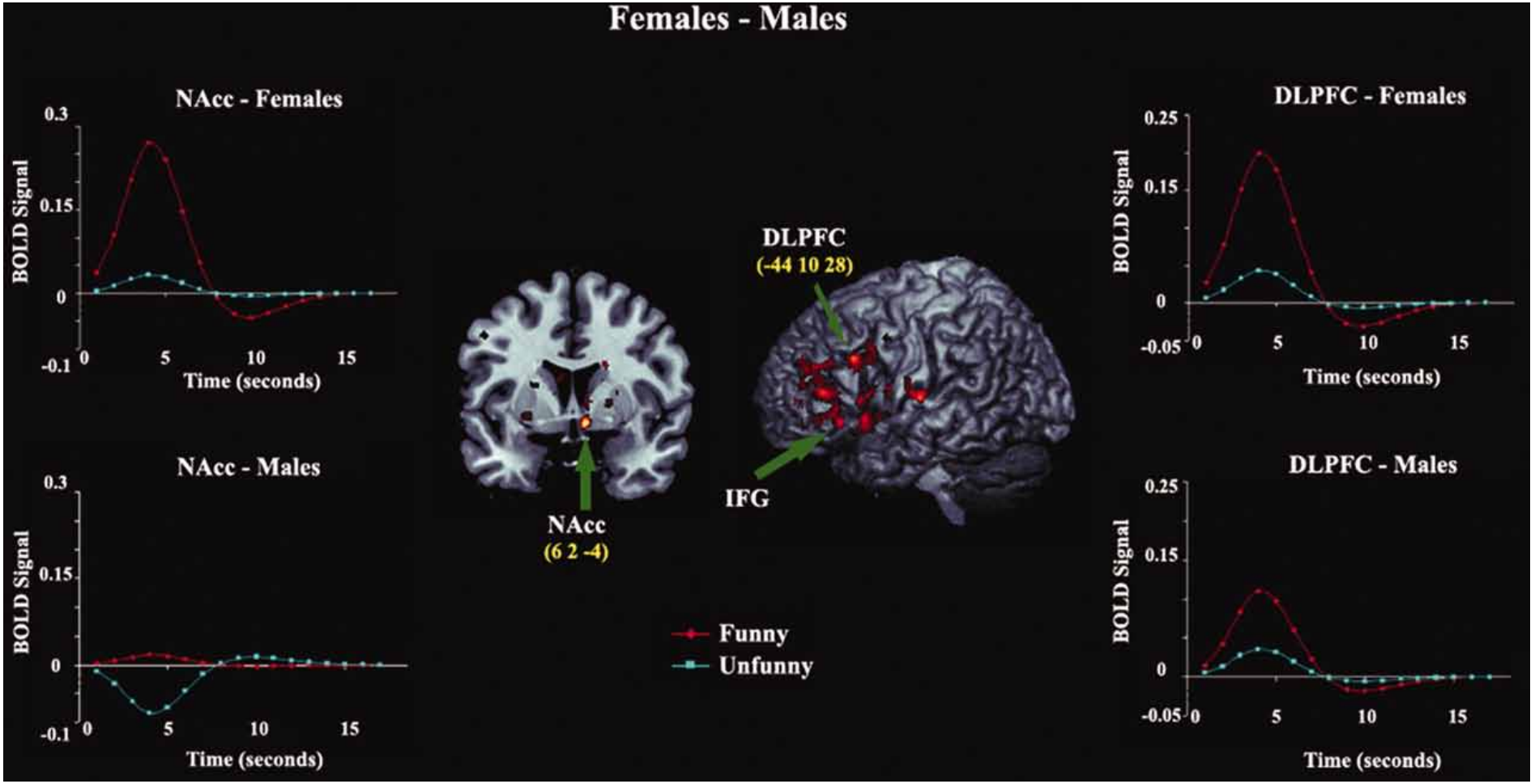


Testosterone: Aromatization to Estrogens





Female - Male activation: Time-series Analysis of NAcc and DLPFC



Female - male comparison shows greater female activation in the DLPFC, IFG, and MFG (BA 45, 46, and 47), as well as the NAcc. Averaged time-series analysis for funny vs. unfunny activity in a 10-voxel subcluster of the NAcc (stereotaxic coordinates, 6, 2, -4; $P < 0.0001$) reveals strong female activation during funny stimuli and little activity during unfunny events. Males show low activation during funny stimuli and deactivation during unfunny events.

Azim E et al. PNAS 2005;102:16496-16501

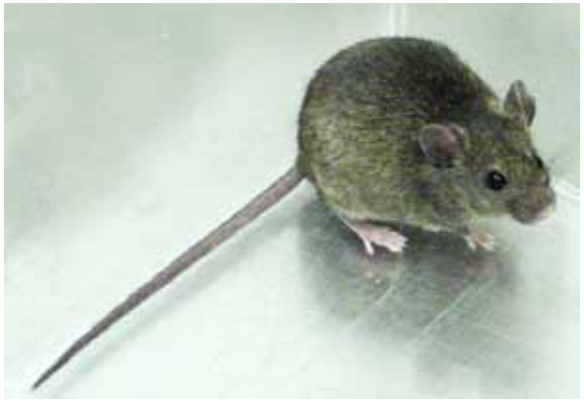
PNAS

Aggression: Hormonal Regulation

Definitions

Ø Conspecific Aggression

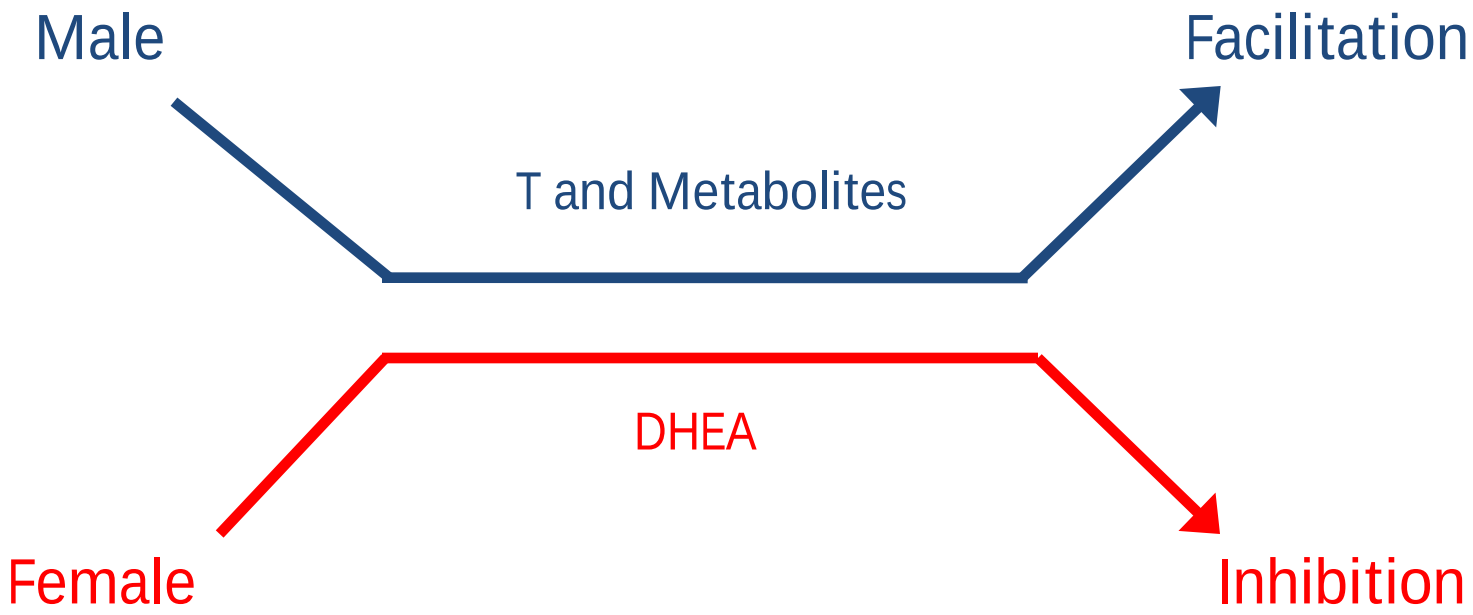
- Part of reproduction
- Establishment of dominance status
- Access to Resources



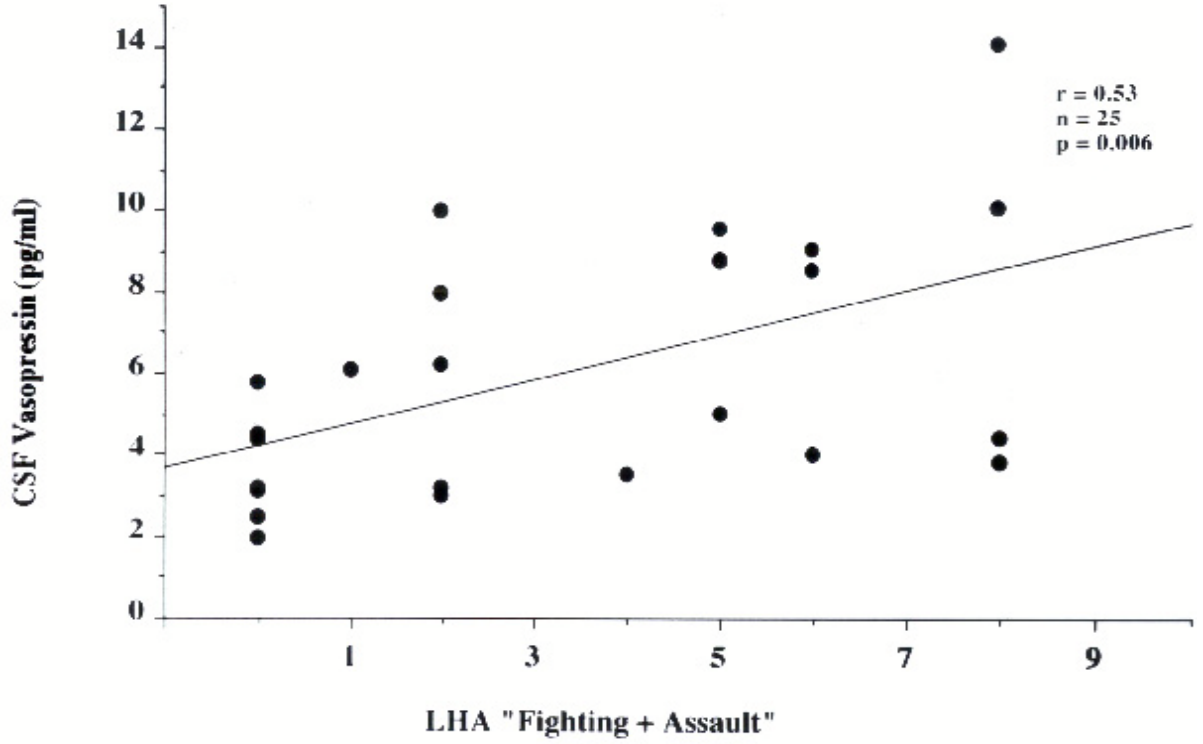
Ø Violence/Inappropriate Aggression

- Intent to harm and cause injury
- Assault, murder

Sex Differences

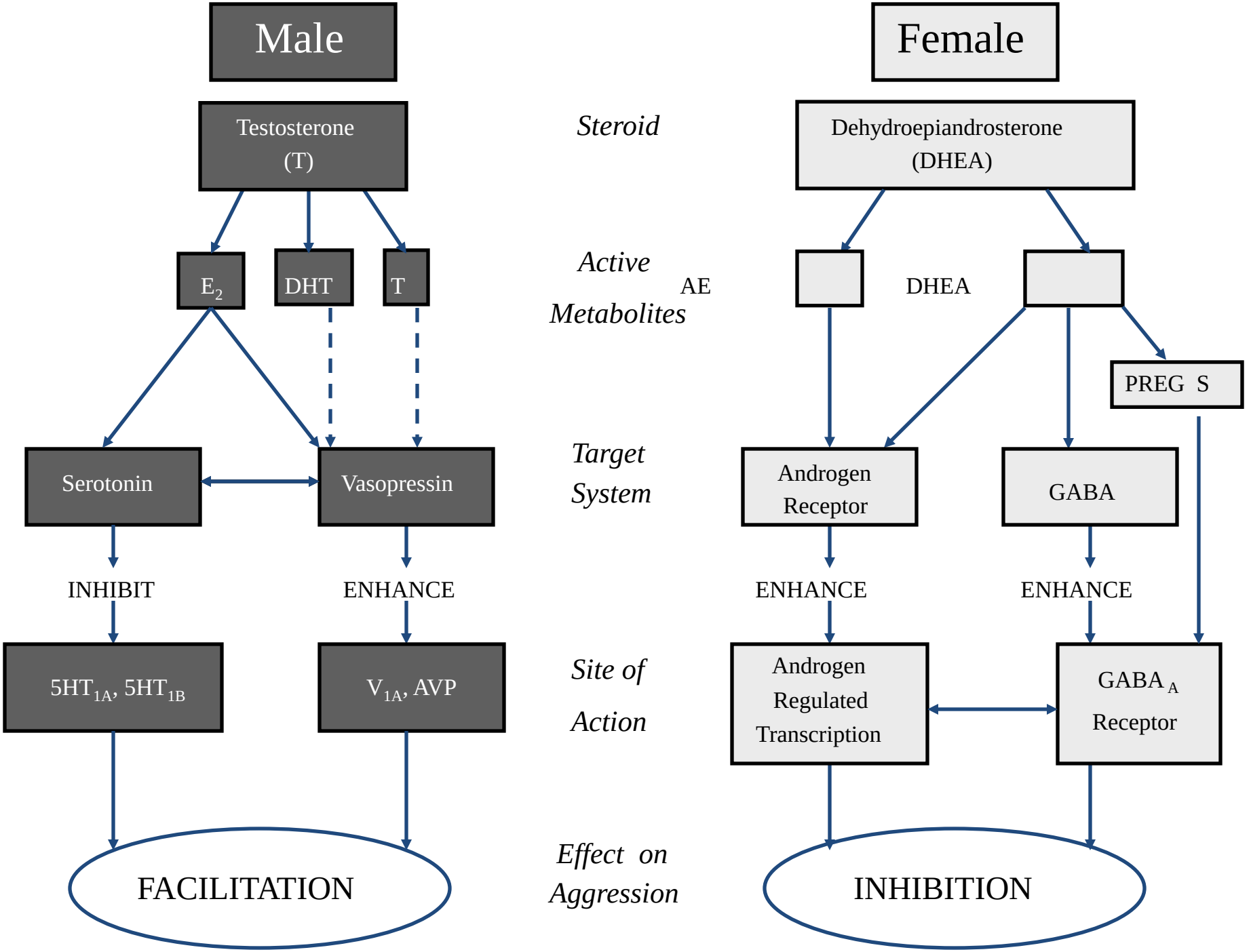


Patients with Violent Personalities Have Blunted Serotonin Activity and Elevated CSF Vasopressin



- Patients with history of “fighting & assault” show weak prolactin response to fenfluramine challenge.
- Prolactin levels are negatively correlated with CSF vasopressin levels.

Coccaro et al., 1998


Male
Female
Testosterone (T)
Dehydroepiandrosterone (DHEA)
Steroid
Active Metabolites
E2
DHT
T
AE
DHEA
PREG S
Target System
Serotonin
Vasopressin
Androgen Receptor
GABA
INHIBIT
ENHANCE
ENHANCE
ENHANCE
Site of Action
5HT1A, 5HT1B
V1A, AVP
Androgen Regulated Transcription
GABA A Receptor
Effect on Aggression
FACILITATION
INHIBITION

Disorders of Sexual Differentiation: Accidental & Biological

Case Studies

1. **Traumatic Genital Loss: Male**

2. **Ambiguous Sex: Female or Male?**

Case 1: Traumatic Genital Loss

The patient was born on Aug. 22, 1965, 12 minutes before his identical twin brother. Both babies were healthy and developed normally until they were seven months old, when they were discovered to have a condition called phimosis, a defect in the foreskin of the penis that makes urination difficult.

The parents were told that the problem was easily remedied with circumcision. During the procedure at the hospital, a doctor who did not usually perform such operations was assigned to the Reimer babies. The physician used an electric cautery machine with a sharp cutting needle to sever the foreskin.

But something went terribly awry. Exactly where the error lay "in the machine, or in the user" was never determined. What quickly became clear was that baby had been irreparably maimed.

As Nature Made Him

By John Colapinto

http://www.npr.org/templates/story/story.php?storyId=1894187

Intersex Conditions

A. Inadequate Androgen

- 5-alpha reductase deficiency
- Androgen Insensitivity Syndrome (AIS)
- Partial Androgen Insensitivity Syndrome (PAIS)
- Gonadal dysgenesis (partial & complete)
- Aphallia

B. Excess Androgen

- Congenital Adrenal Hyperplasia (CAH)
- Progestin Induced Virilization

C. Others

- Klinefelter Syndrome (47, XXY)
- Turner Syndrome (45, X)
- Hermaphroditism

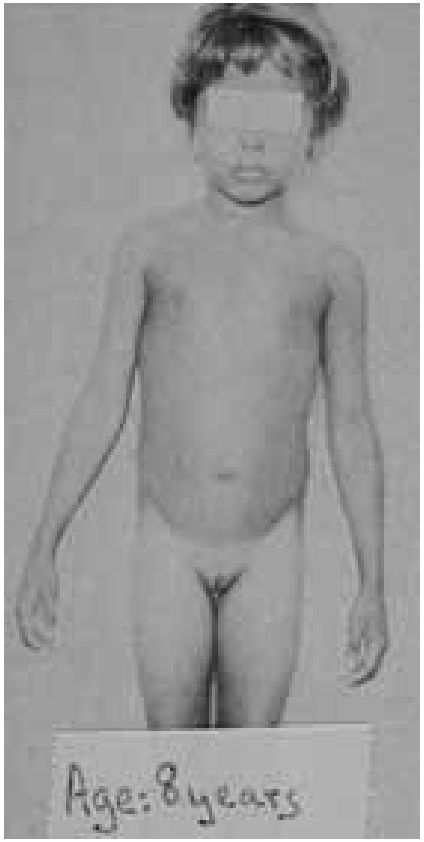
Guevedoces: Partial Androgen Insensitivity

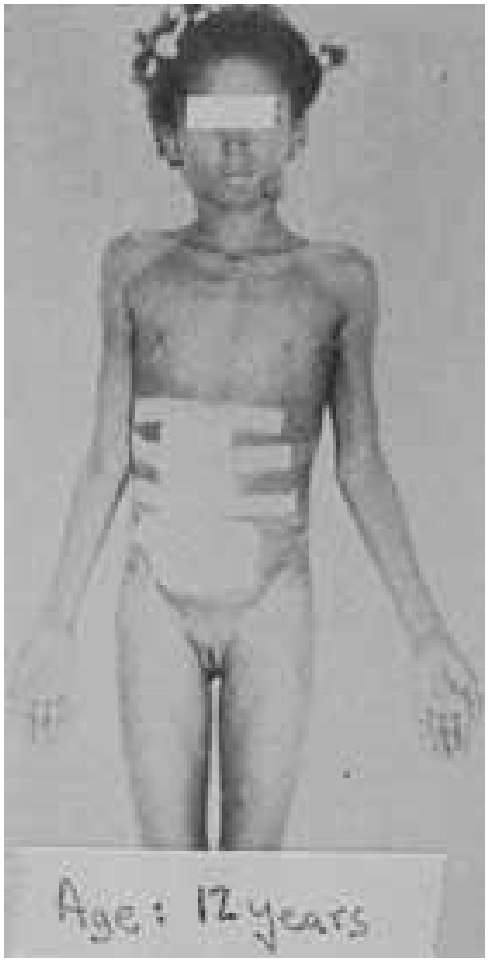
In an isolated village of the southwestern Dominican Republic, 2% of the live births in the 1970's were guevedoces (actually male pseudohermaphrodites).

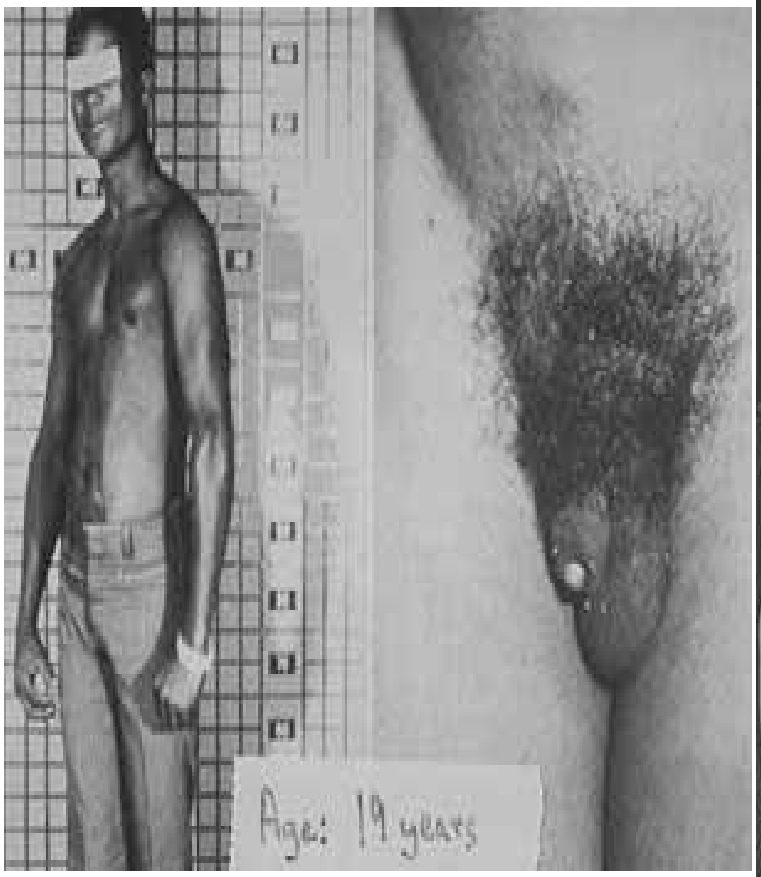
Imperato-McGinley et al, 1974

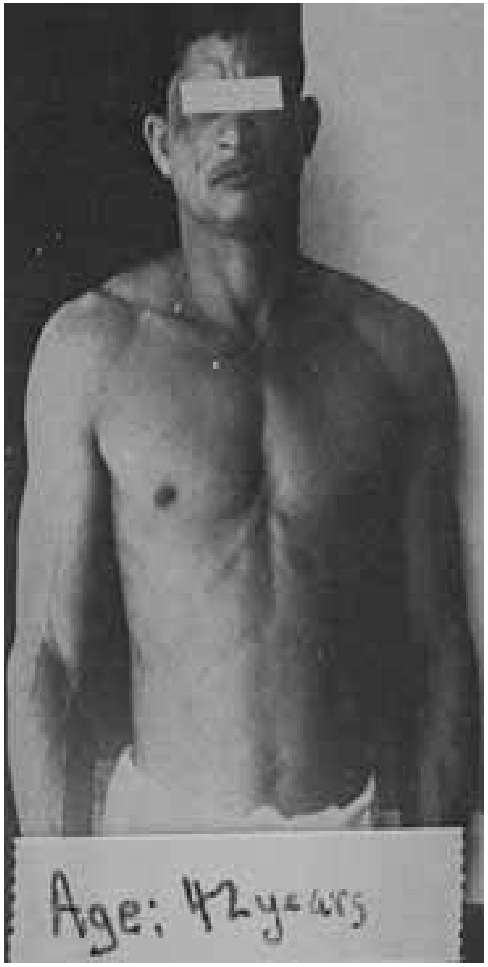

AGE: 18 months


AGE: 4 years


Age: 8 years


Age: 12 years

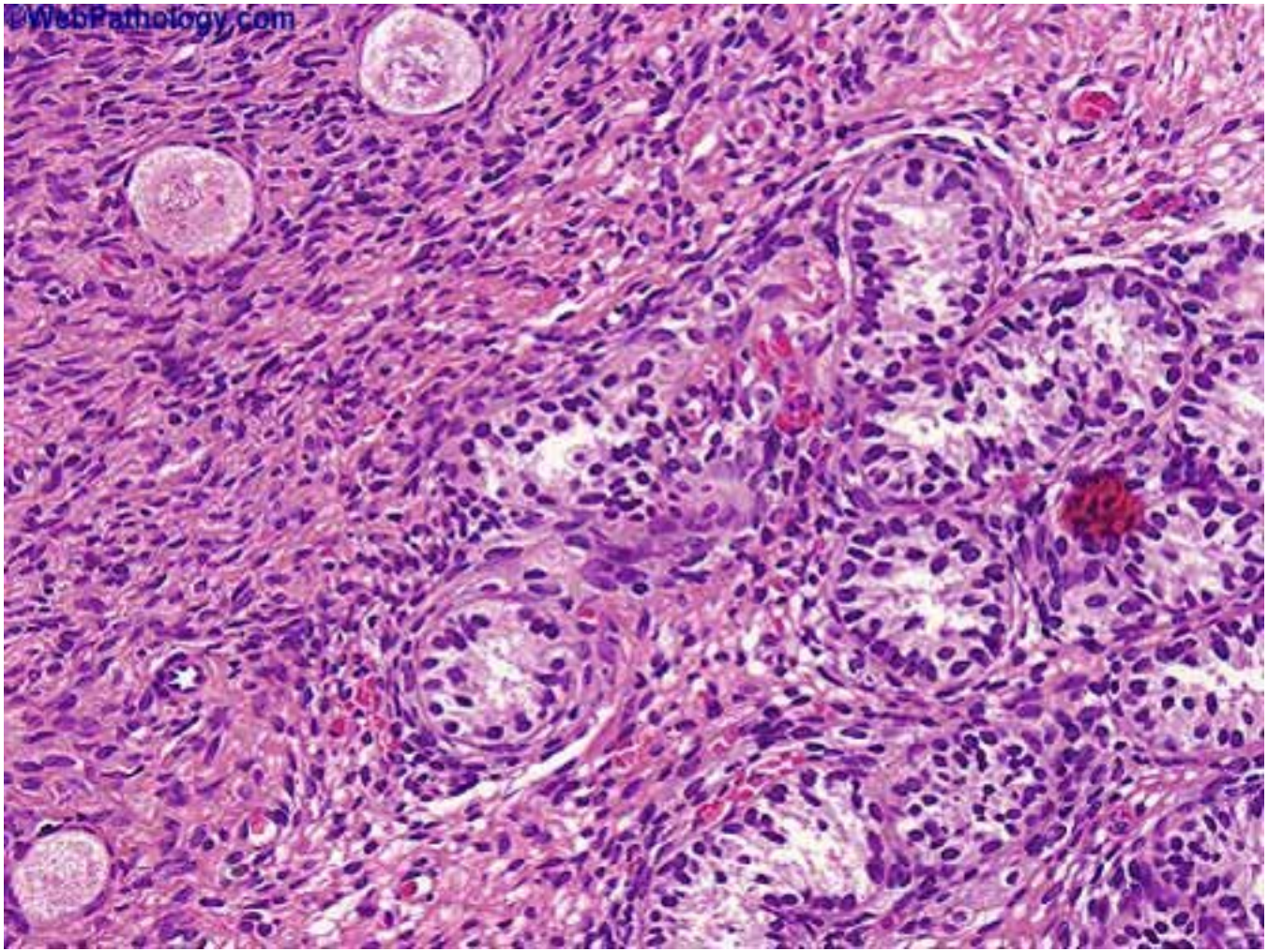

Age: 19 years


Age: 42 years

Translational Impact

- Ø Rethinking of “rules & models” for sexual differentiation
- Ø Anti-androgen Therapy
- Ø Androgen Replacement

True Hermaphroditism: Both Ovarian and Testicular Cells are present in Gonadal Tissue (Ovotestis)



Three ovarian follicles are seen on the left and numerous small seminiferous tubules with immature sertoli cells are seen on the right.

Webpathology.com

Thank you for your time and attention