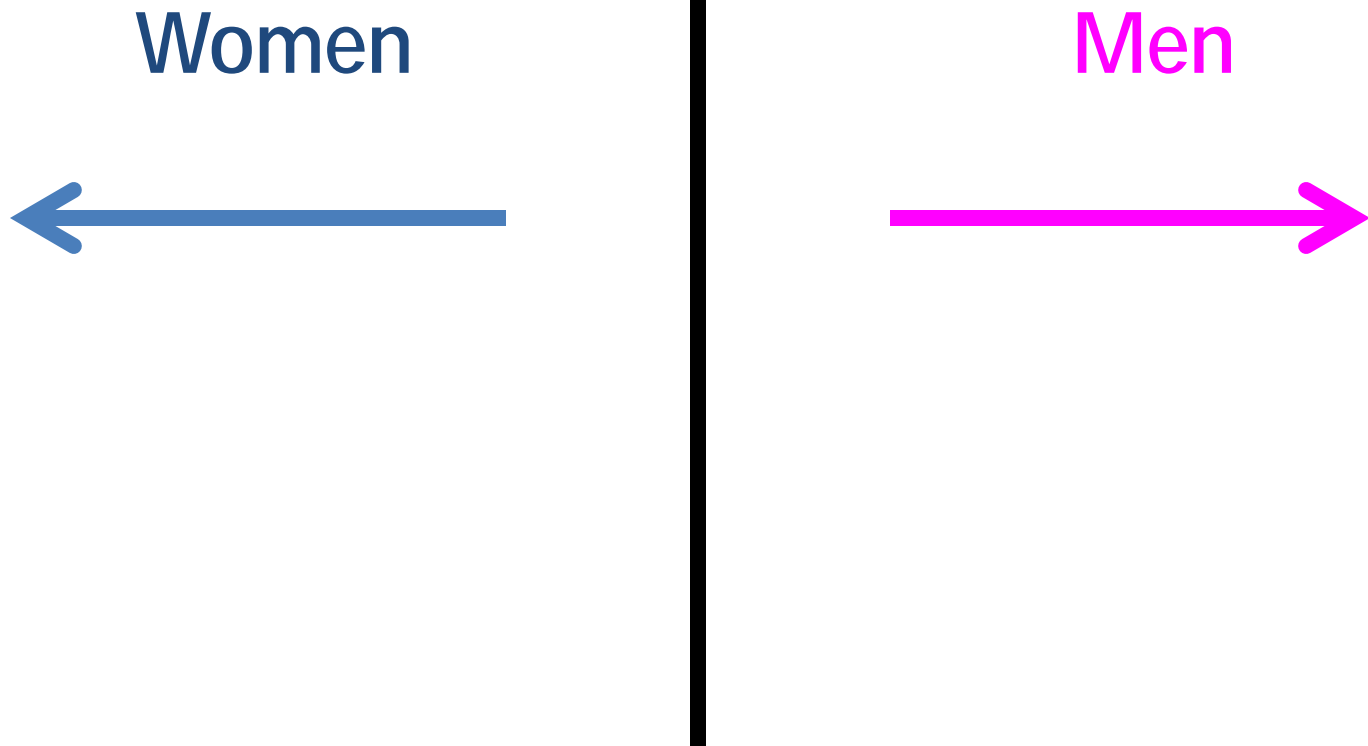


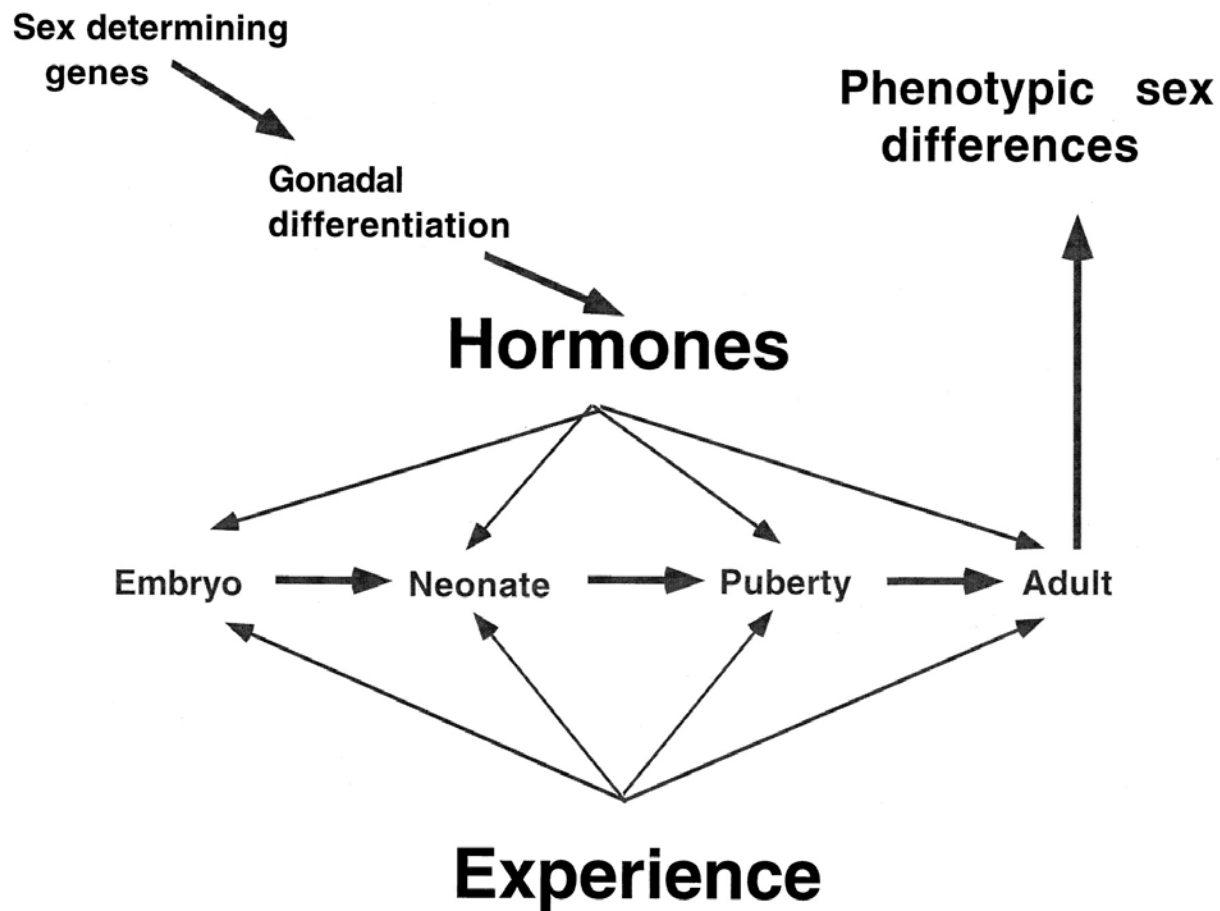
Please Take Seats by Gender as Shown
Leave Three Seats Empty in the Middle



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**

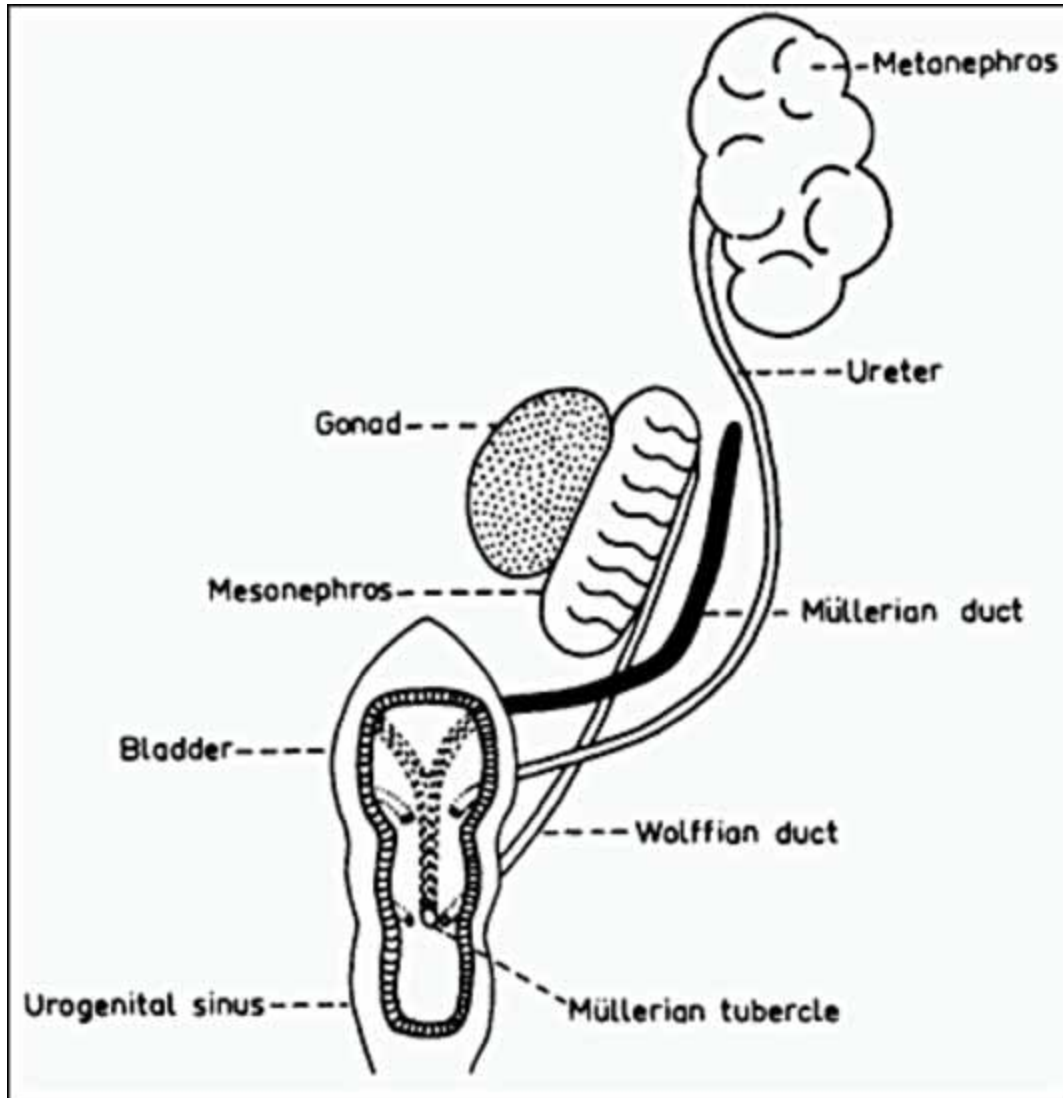
Sexual Differentiation

- 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

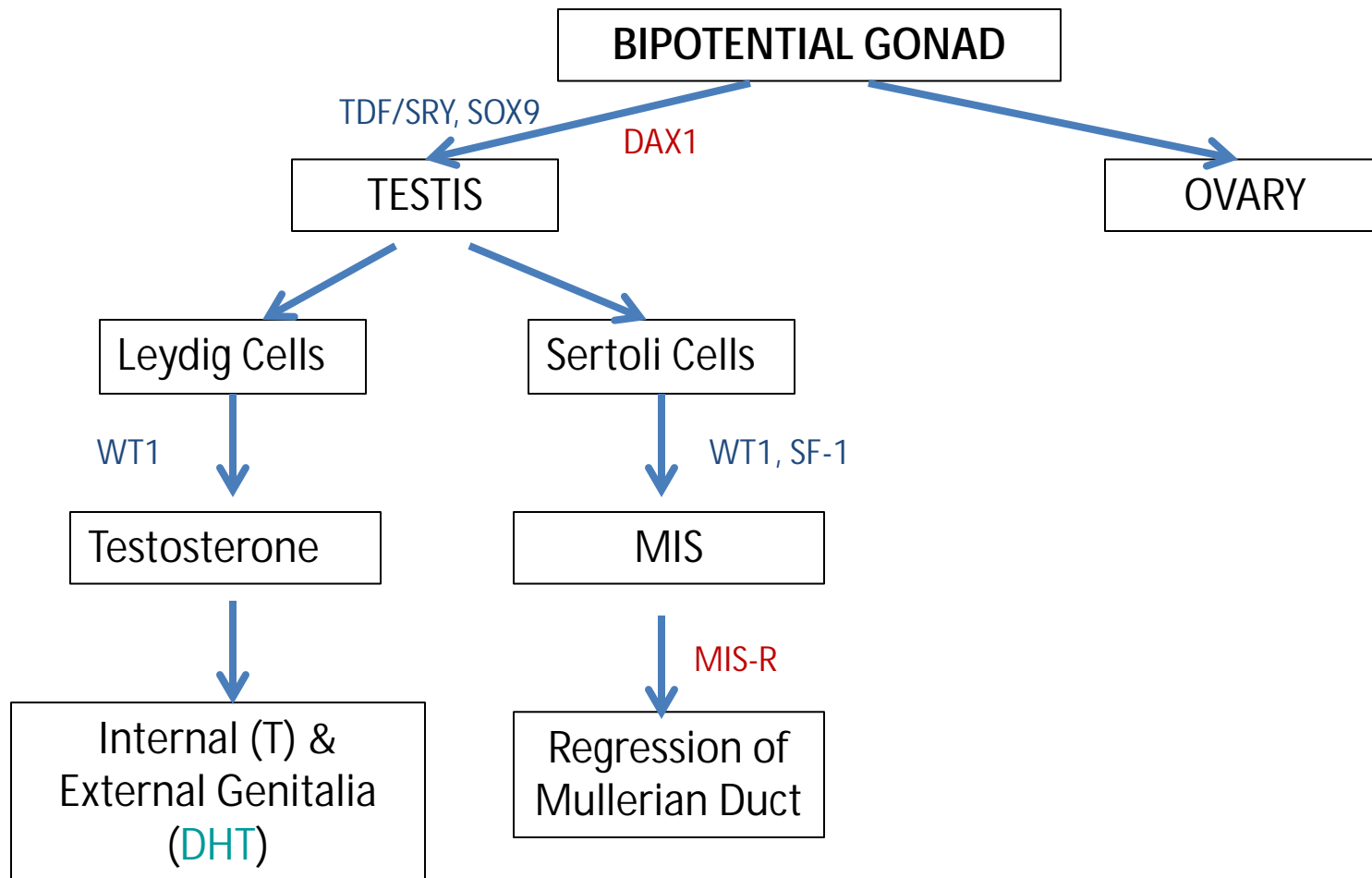


Müllerian Duct: uterus, fallopian tubes, and upper vagina

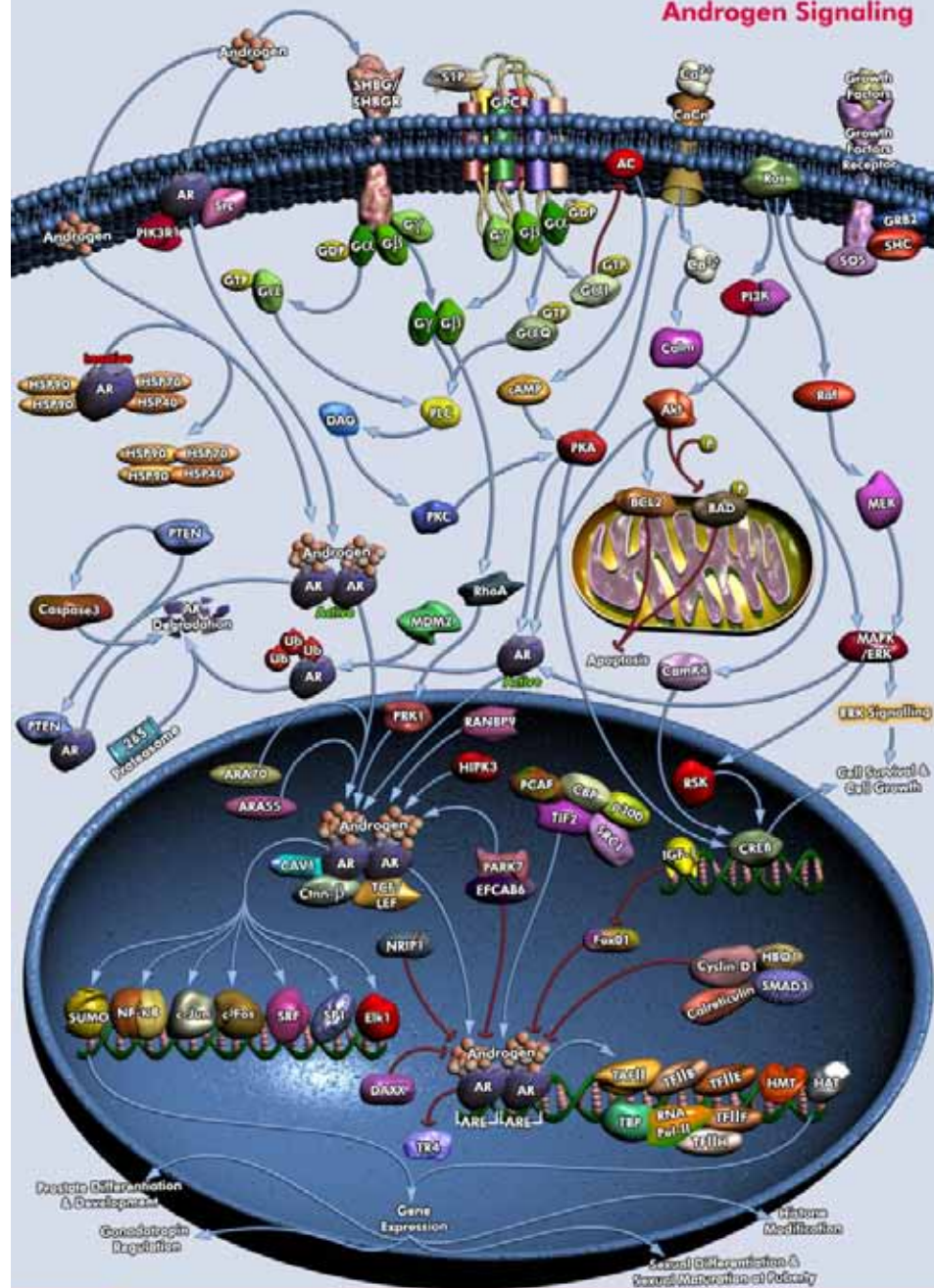
Wolffian Duct: epididymis, vas deferens, seminal vesicles

Key Genes in Gonadal Differentiation

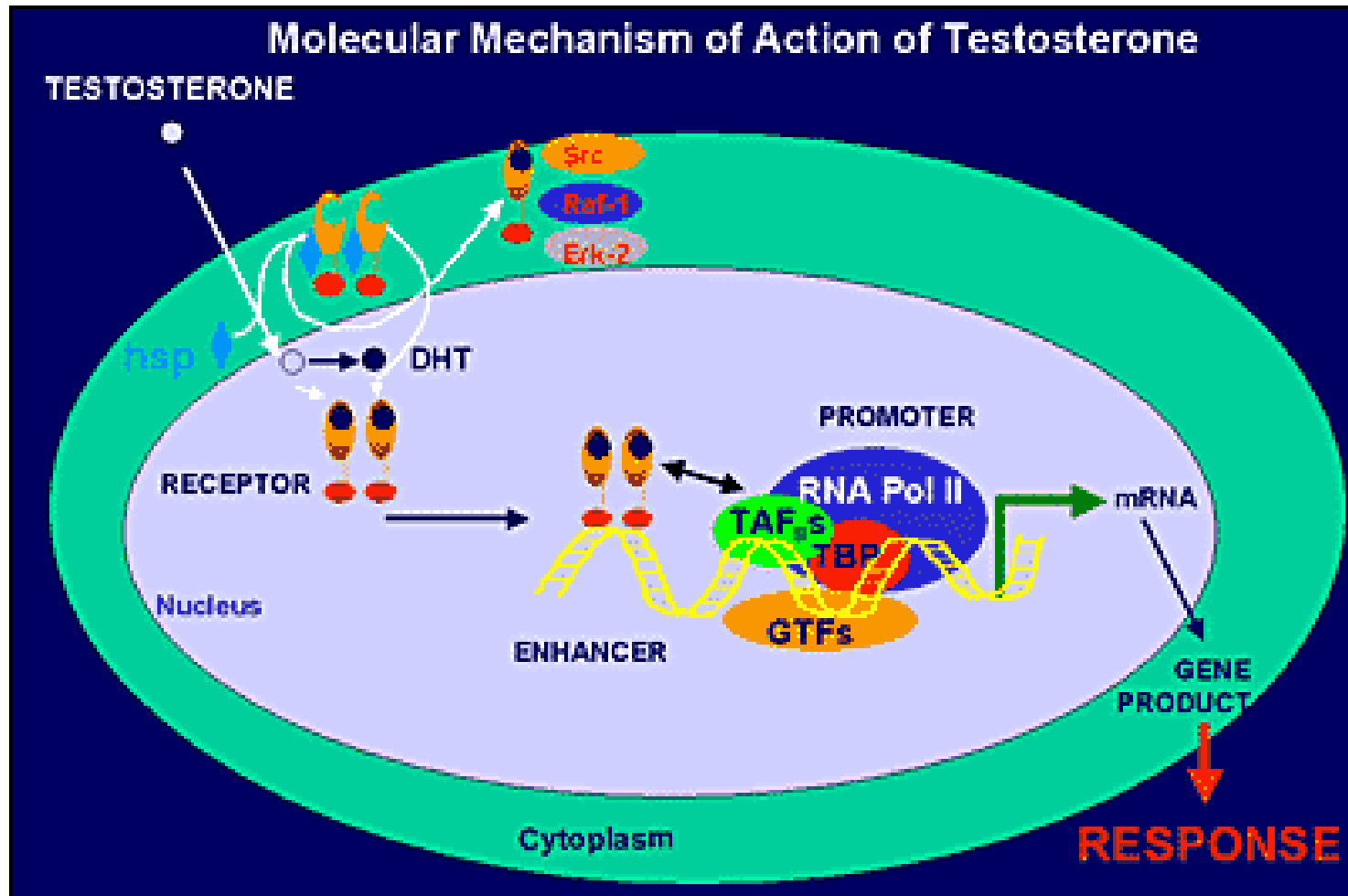
TDF/SRY (sex determining region of the Y chromosome) is a testis determining factor on the short arm of the Y chromosome. **SOX9** gene is also important in male sexual differentiation. **DAX1**, an orphan member of a nuclear hormone receptor family located on the X chromosome, interacts with steroidogenic 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**.



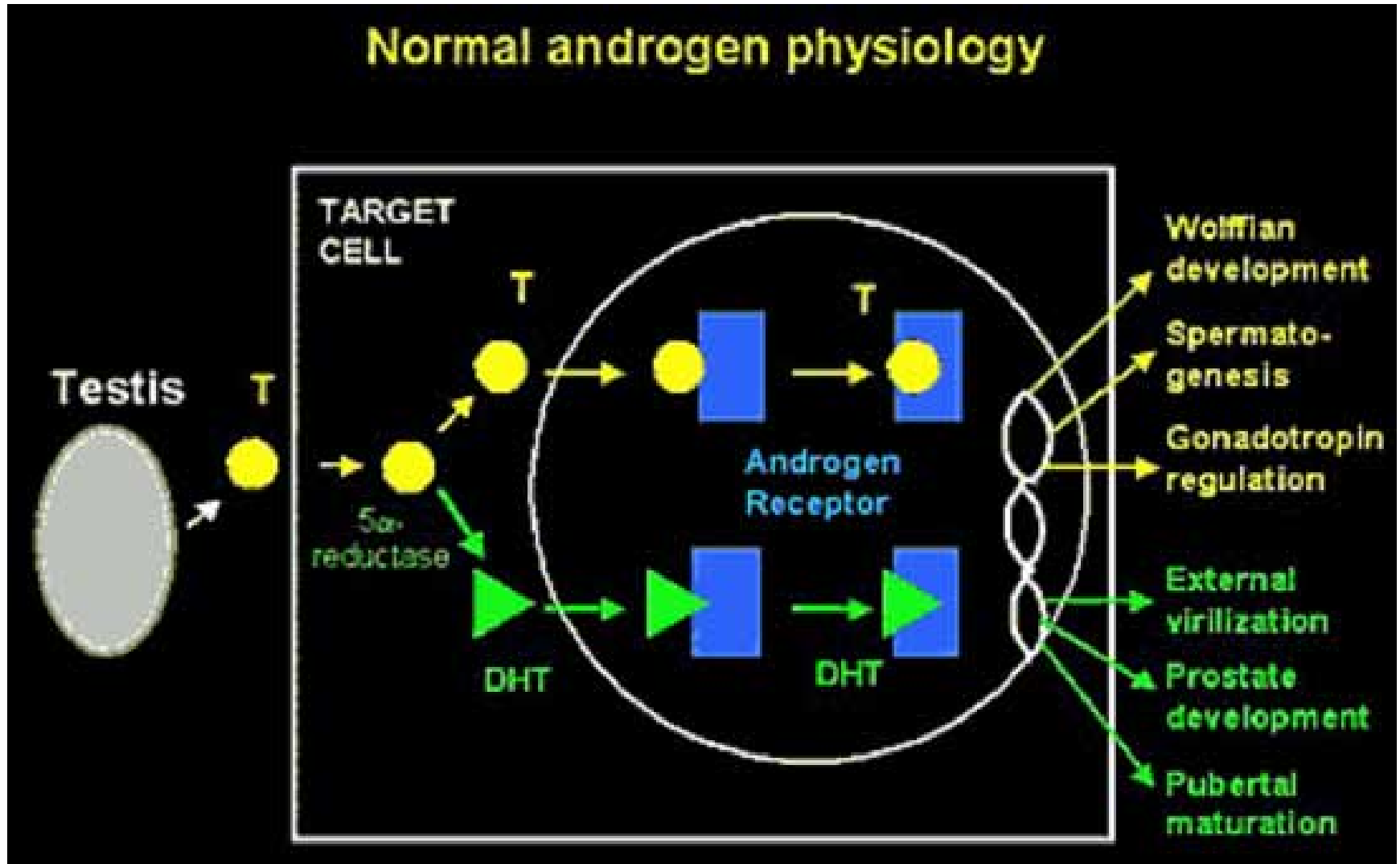
- The appropriate regulation of androgen activity is necessary for a range of developmental and physiological processes, particularly male sexual development and maturation.
- Androgen ablation therapy is often combined with treatment with nonsteroidal antiandrogens, such as hydroxyflutamide, to block 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.



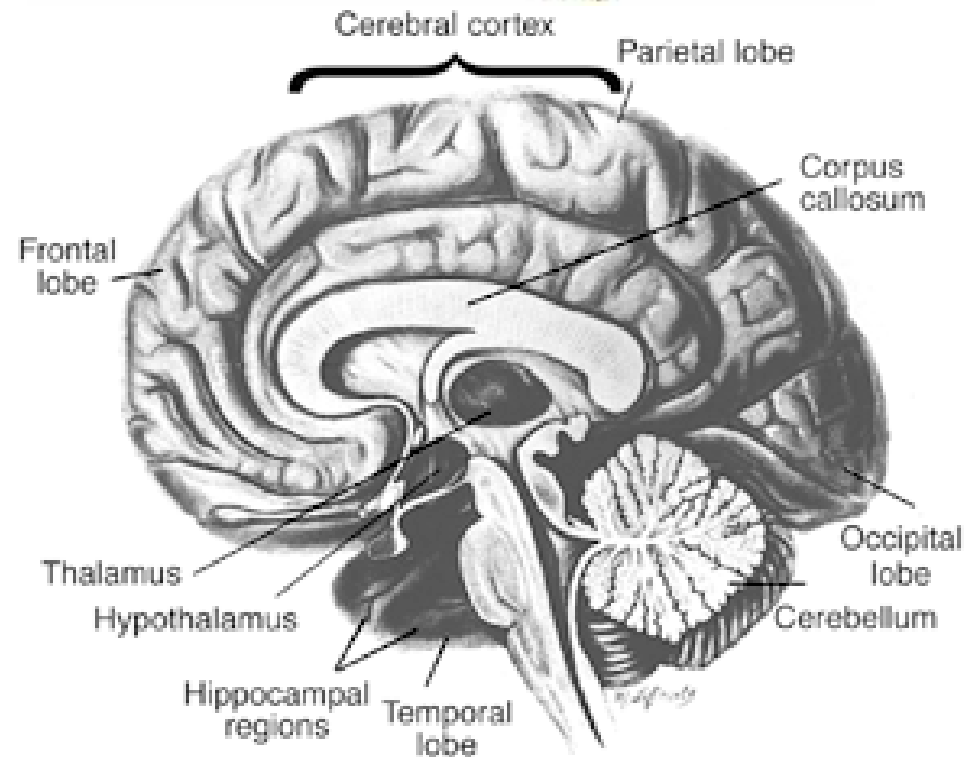
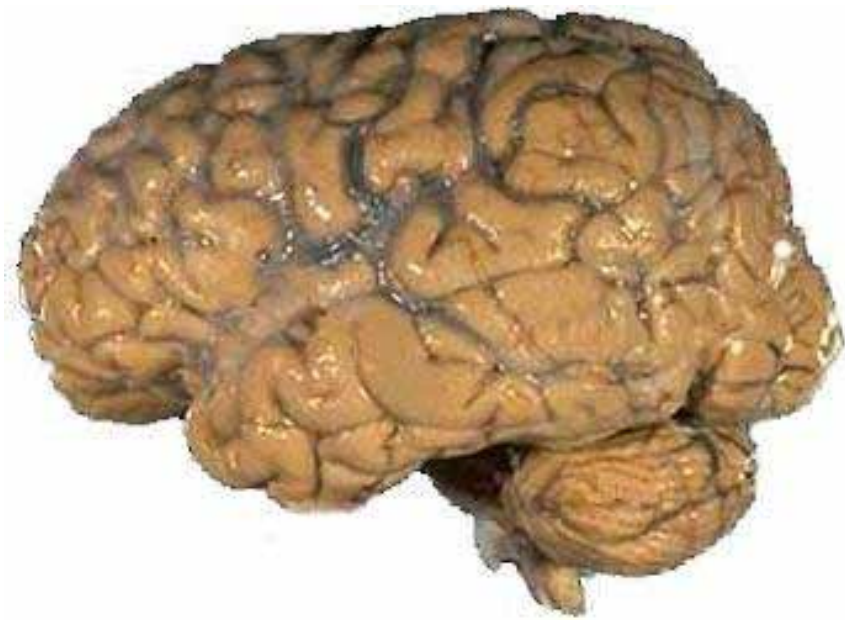
Cellular Events Mediating Androgen Signaling



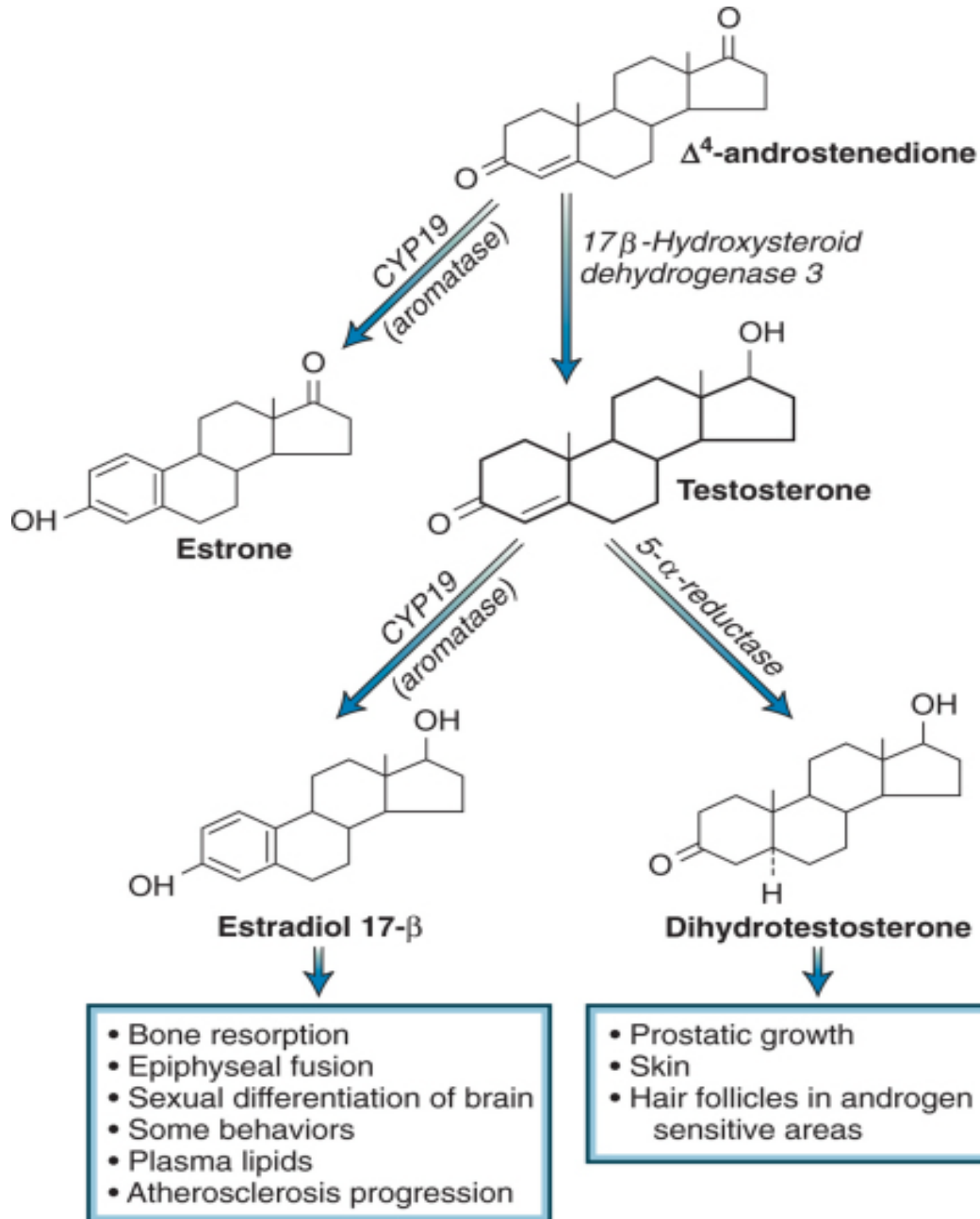
Core Functions of Testosterone and Dihydrotestosterone in Males



The Human Brain: A Major Target for Sexual Differentiation



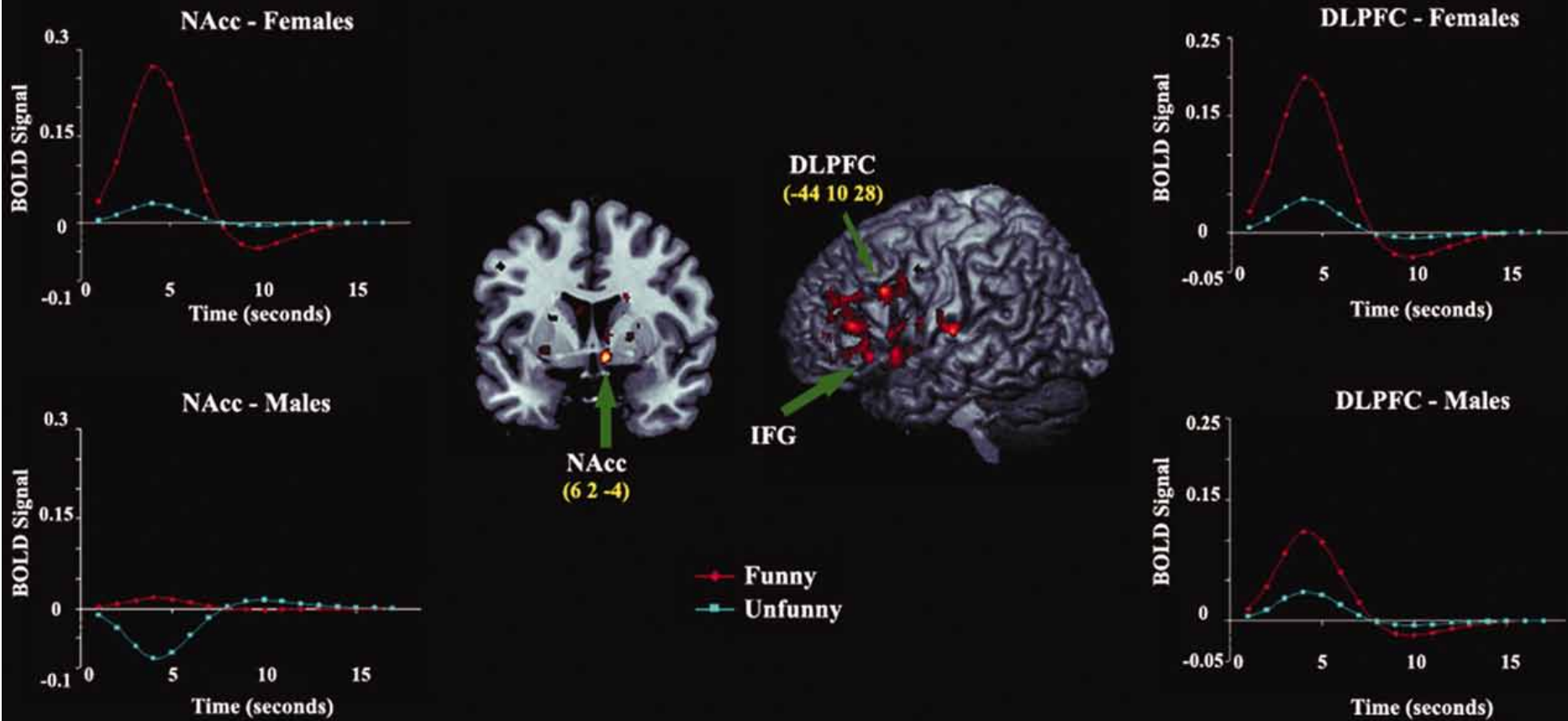
Testosterone: Aromatization to Estrogens





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

Females - Males



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.

Aggression: Hormonal Regulation

Definitions

∅ Conspecific Aggression

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



∅ Violence/Inappropriate Aggression

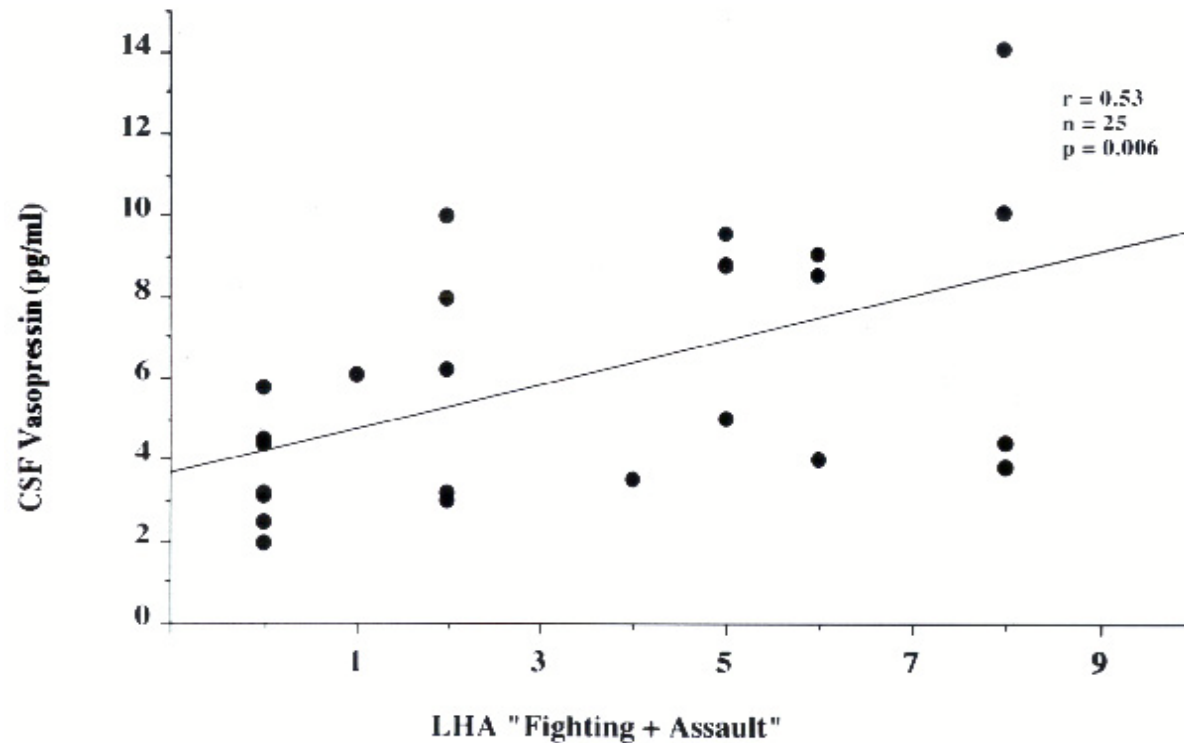
- Intent to harm and cause injury
- Assault, murder



Sex Differences

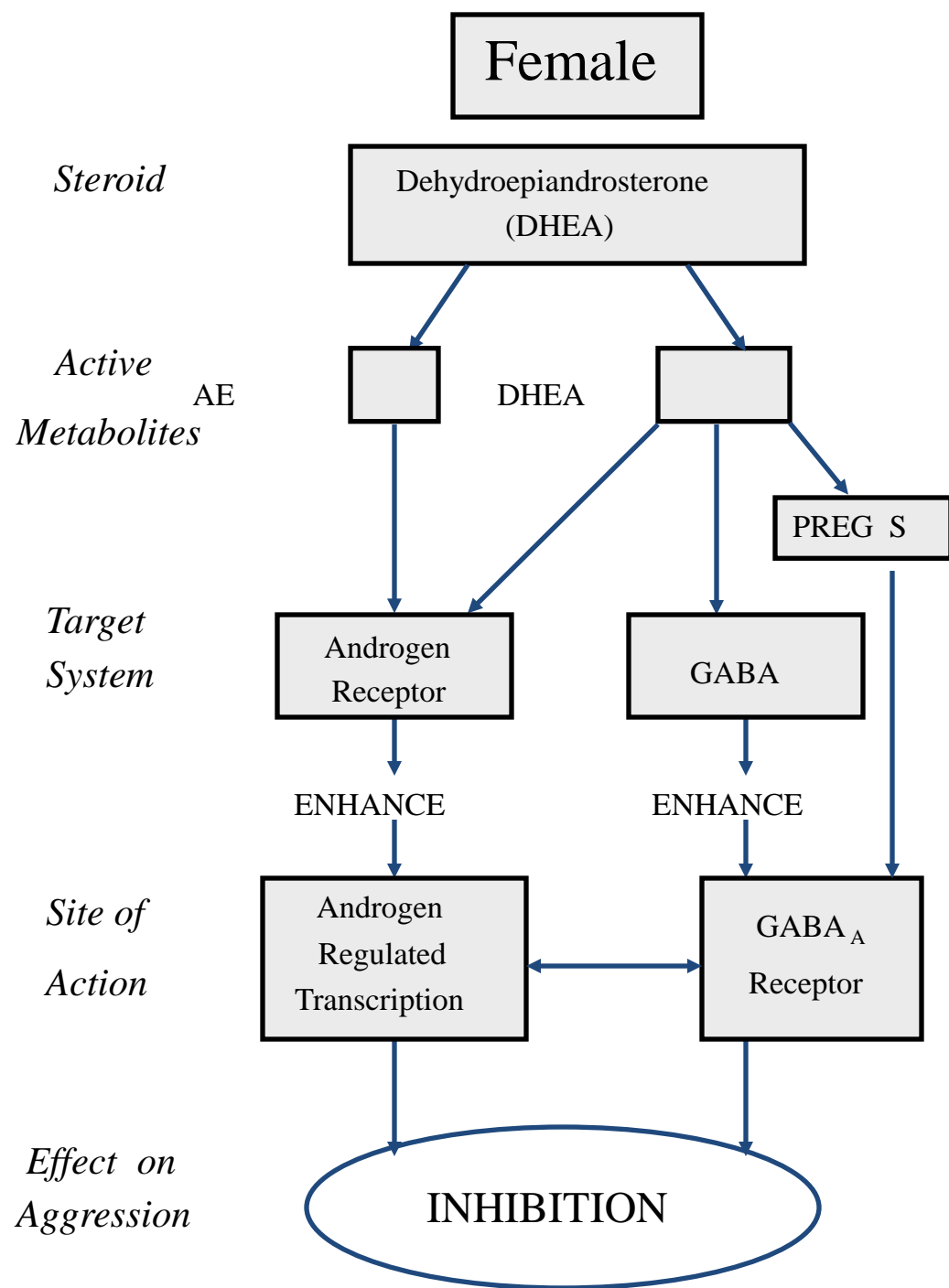
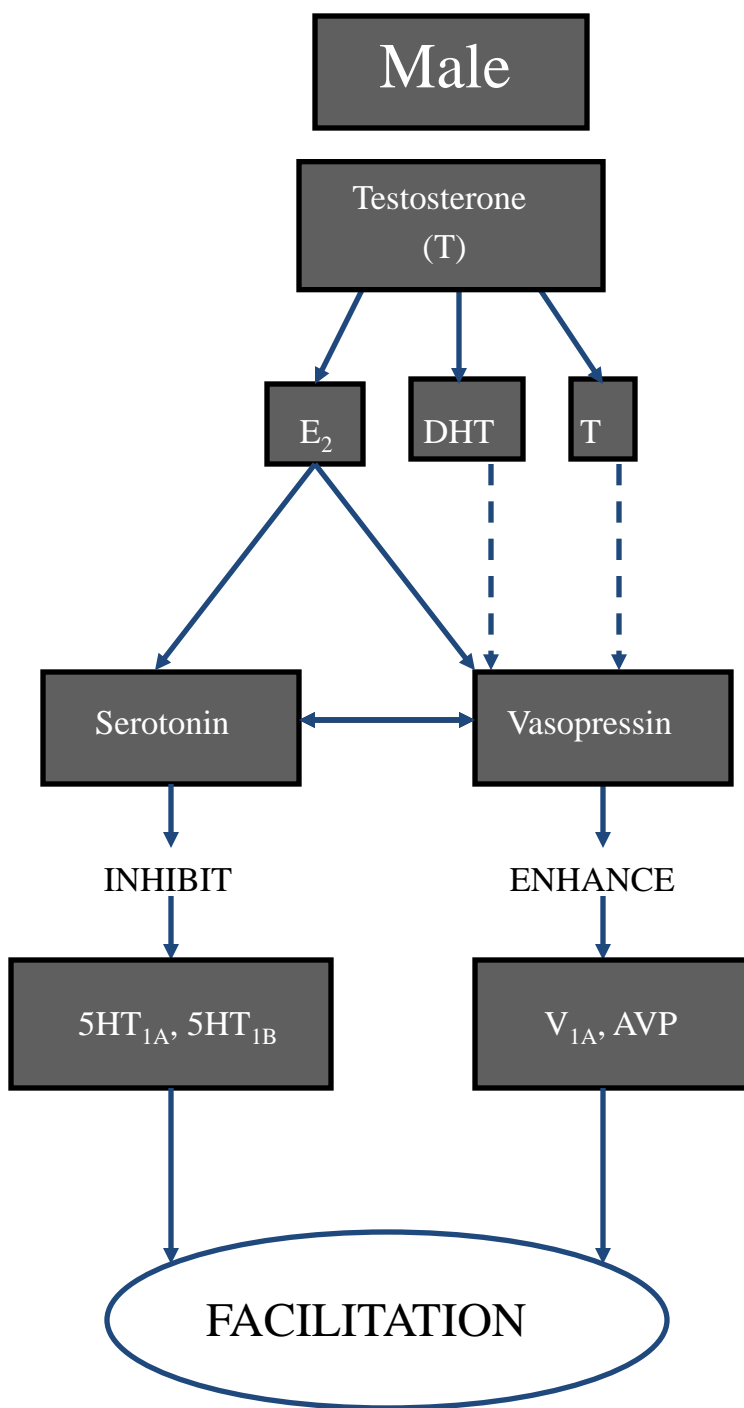


Patients with Violent Personalities Have Blunted Serotonin Activity and Elevated CSF Vasopressin



§ Patients with history of “fighting & assault” show weak prolactin response to fenfluramine challenge.

§ Prolactin levels are negatively correlated with CSF vasopressin levels.



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



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

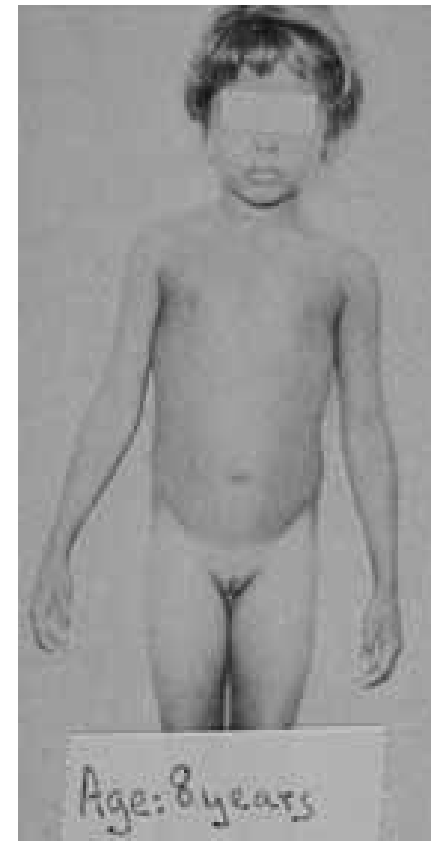
Klinefelter Syndrome (47, XXY)

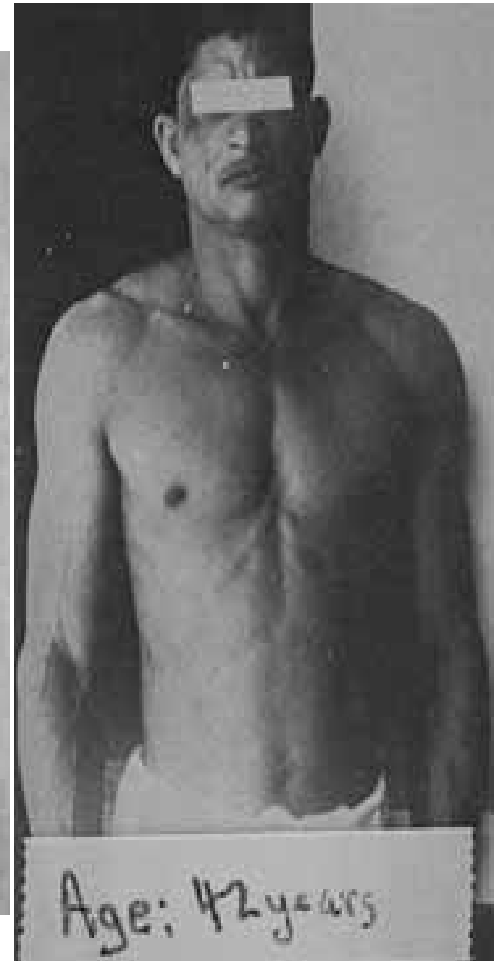
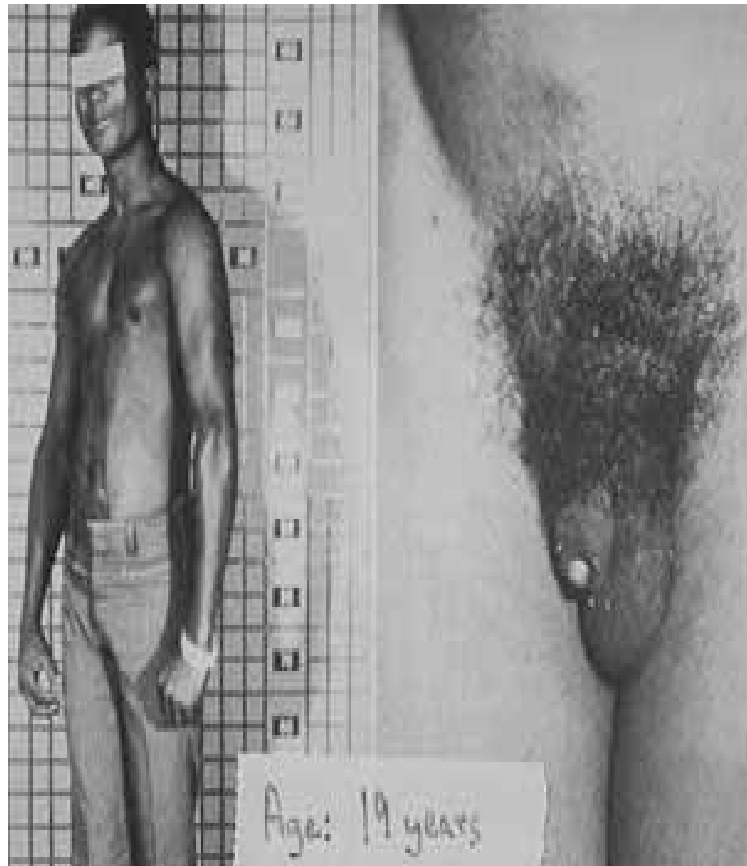
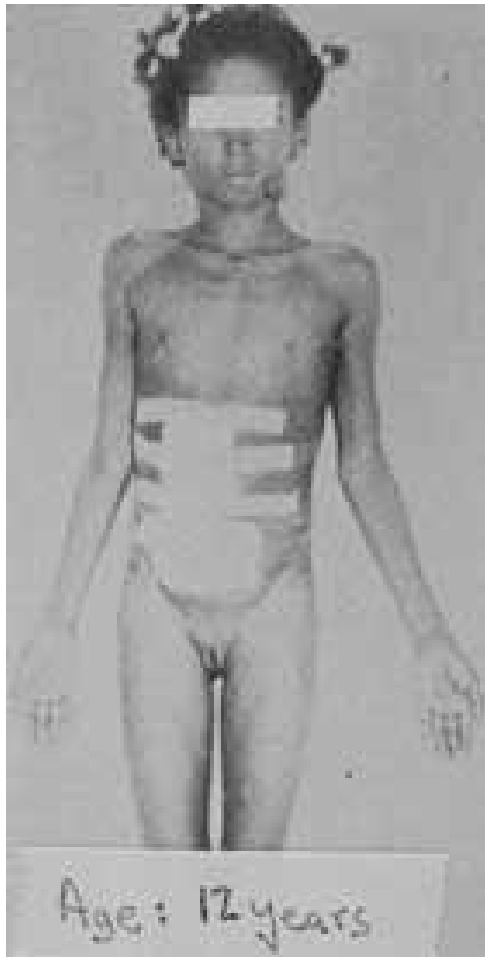
Turner Syndrome (45, X)

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).



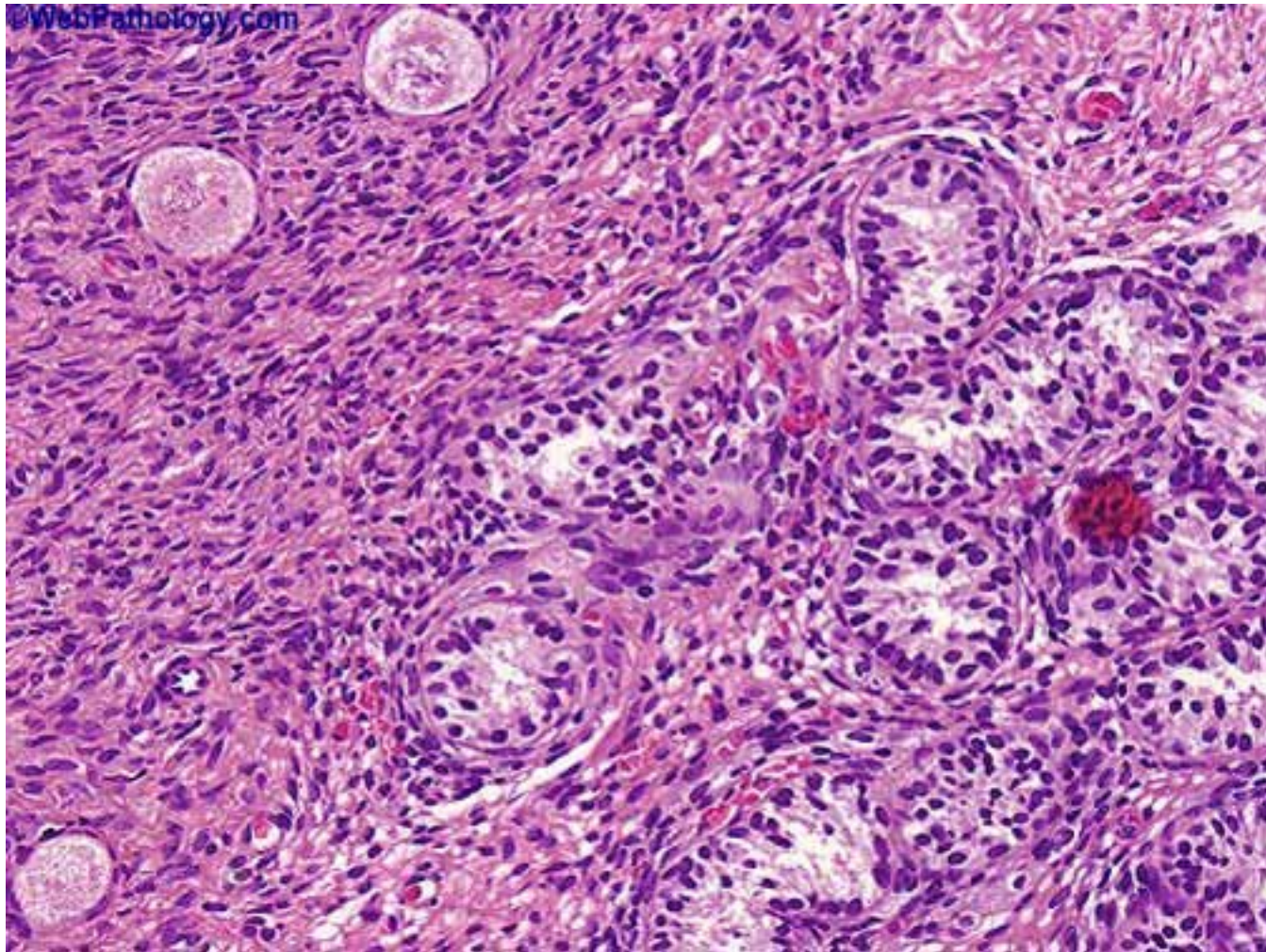


Translational Impact

- 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.

Thank you for your time and attention