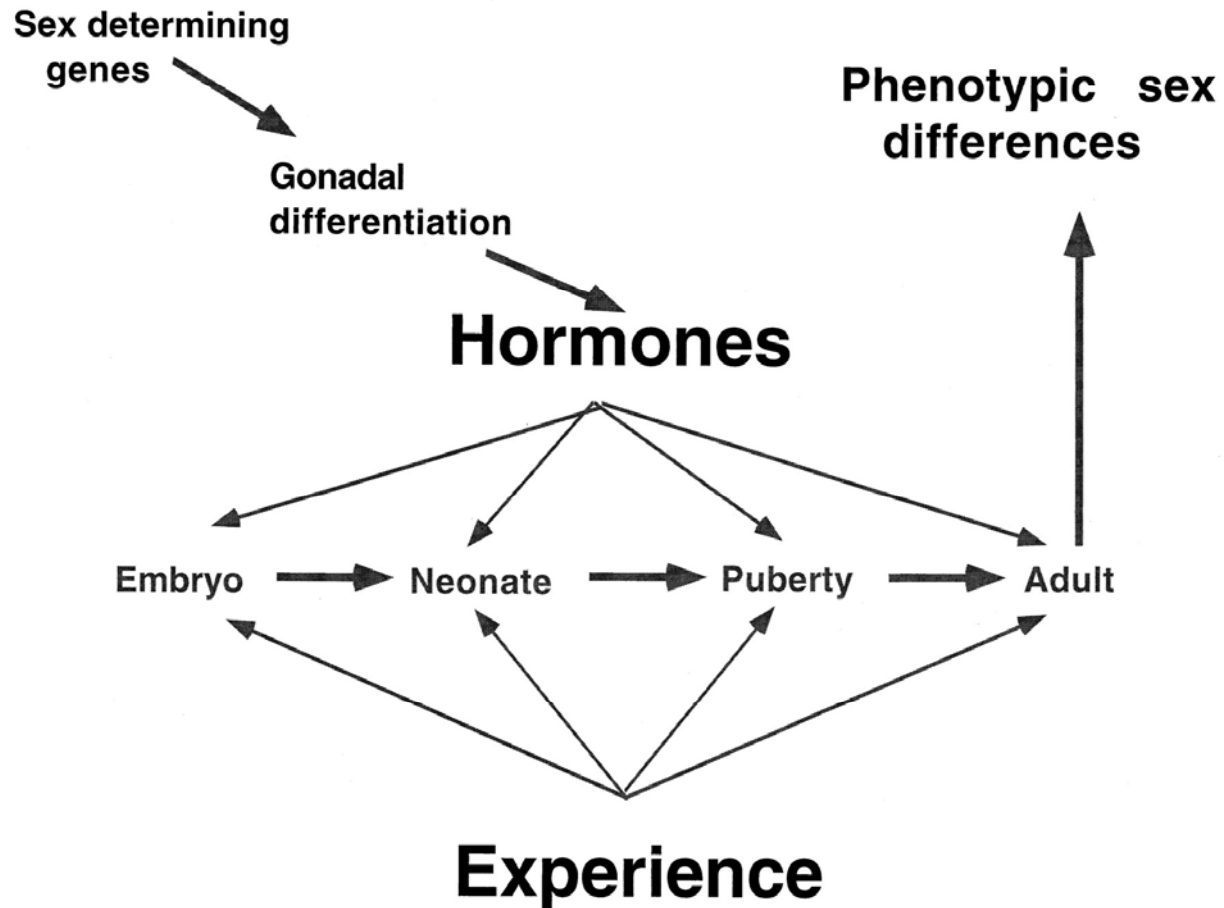


# **Sexual Differentiation & Development**

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# Signaling Cascade & Events Leading to Phenotypic Sex Differences



# Sexual Differentiation

1. Chromosomal Sex
2. Gonadal Sex
3. Hormonal Sex
4. Brain Differentiation
5. Gender Identity
6. Psychosexual Development
7. Sexual Behavior

# Models

## ➤ Non-primate

- Organization-Activation
- Sensitization

## ➤ Humans

- Biology
- Socialization

# 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>

## **Case 2: Ambiguous Sex: Female or Male?**

August 2009. By now, most of you will be aware that a female 800m sensation has been disqualified on the grounds that the IAAF had conducted tests on her to establish her sex, and that she might be male . This latest report is the climax of rumors that have been doing the rounds ever since the 18-year set the world's fastest time of 1:56.72 in a low key meeting in Mauritius recently.

In the days after her 1:56 time, it was widely reported/speculated that the athlete was cleared by testing done by her national federation. In the last few days, it has emerged that she was in fact tested, twice, by her provincial athletics federation, who are claiming that the tests showed nothing unusual.

The competitor is therefore in a terrible situation. The latest reports are saying that the testing, was conducted, but that there are no grounds for disqualification and that the test results will take weeks to release and so she will run tonight.



# Caster Semenya

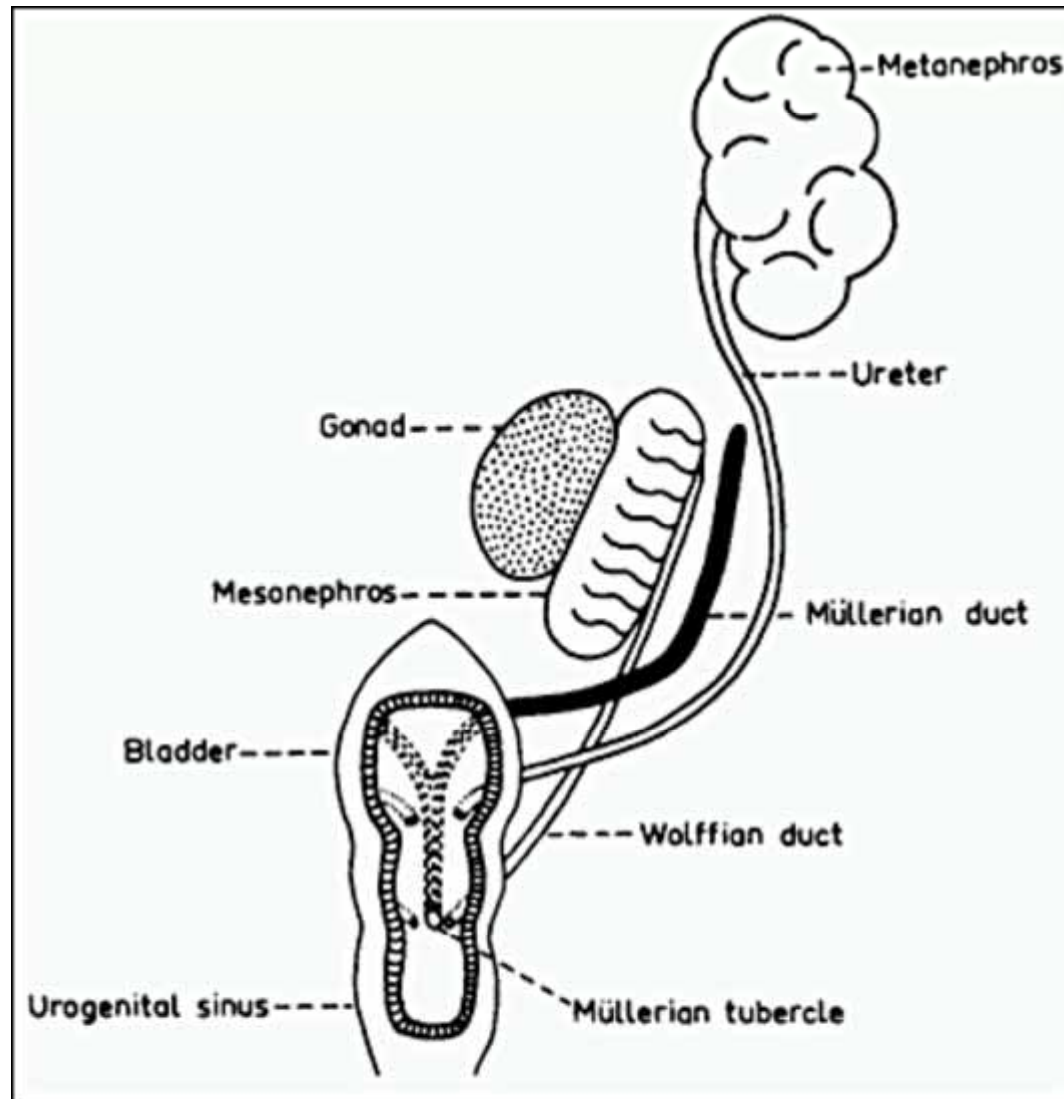


# Sexual Differentiation

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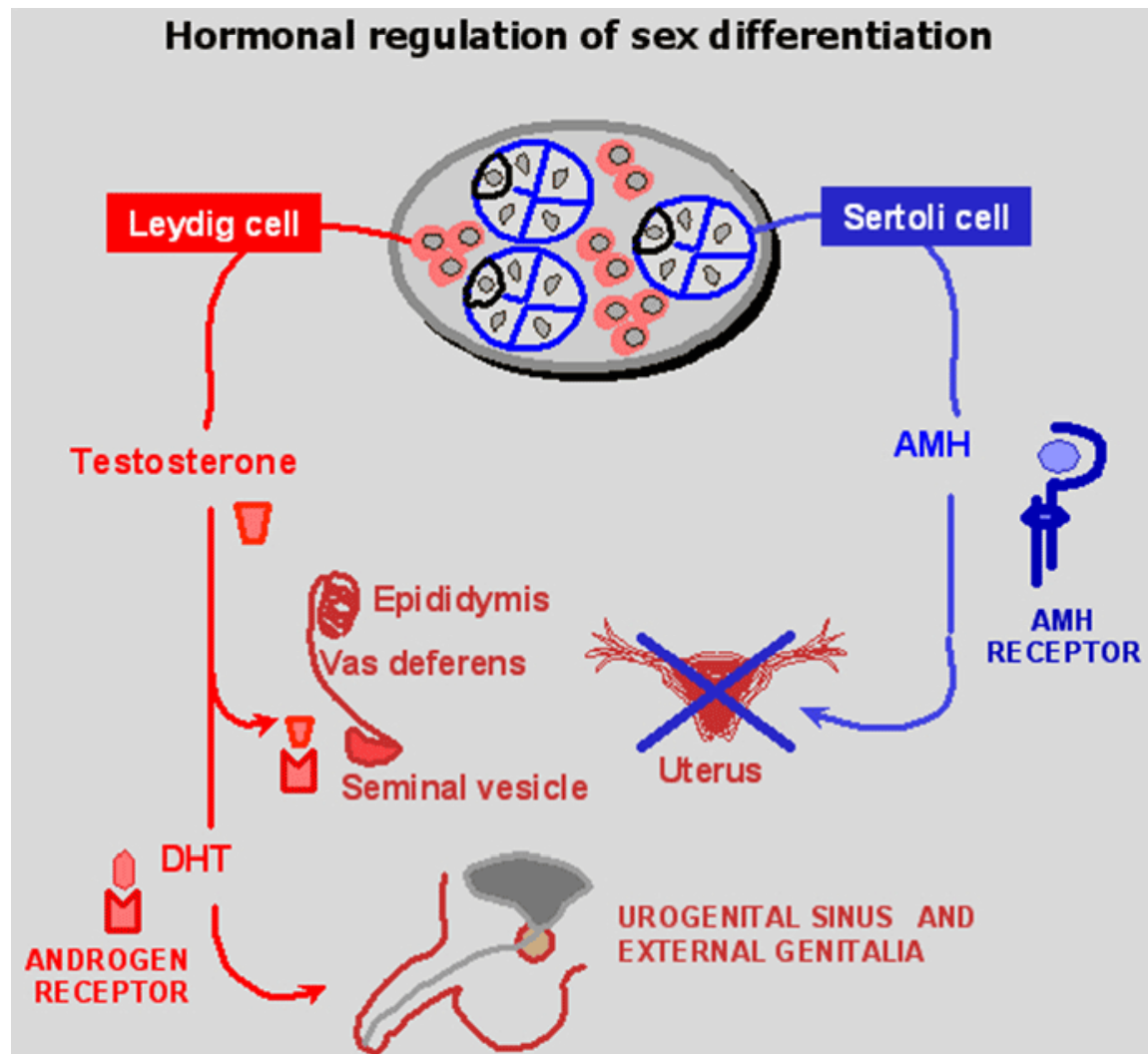
# **Sexual Differentiation**

**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**

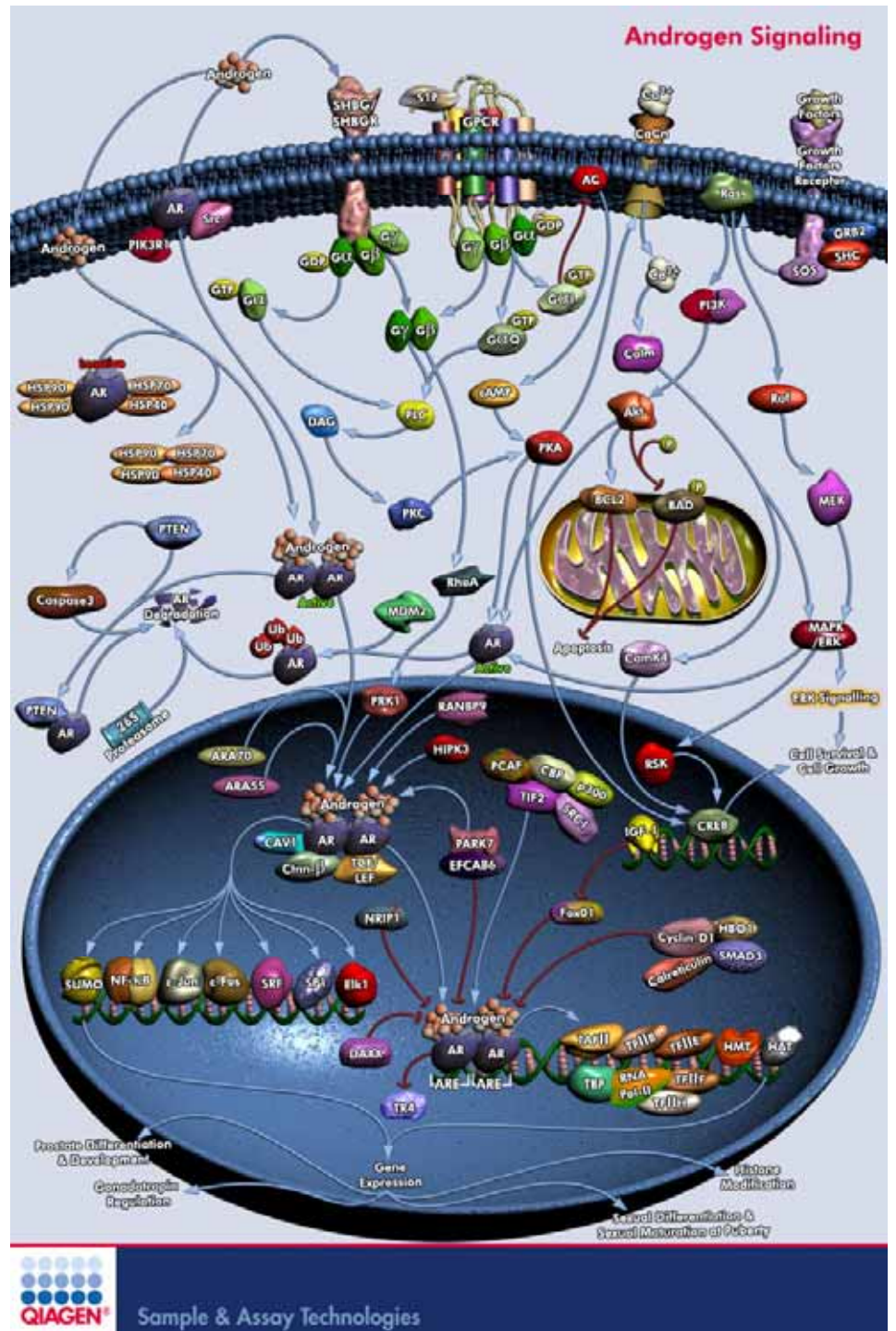


## Hormonal Control of Male Reproductive Tract Differentiation

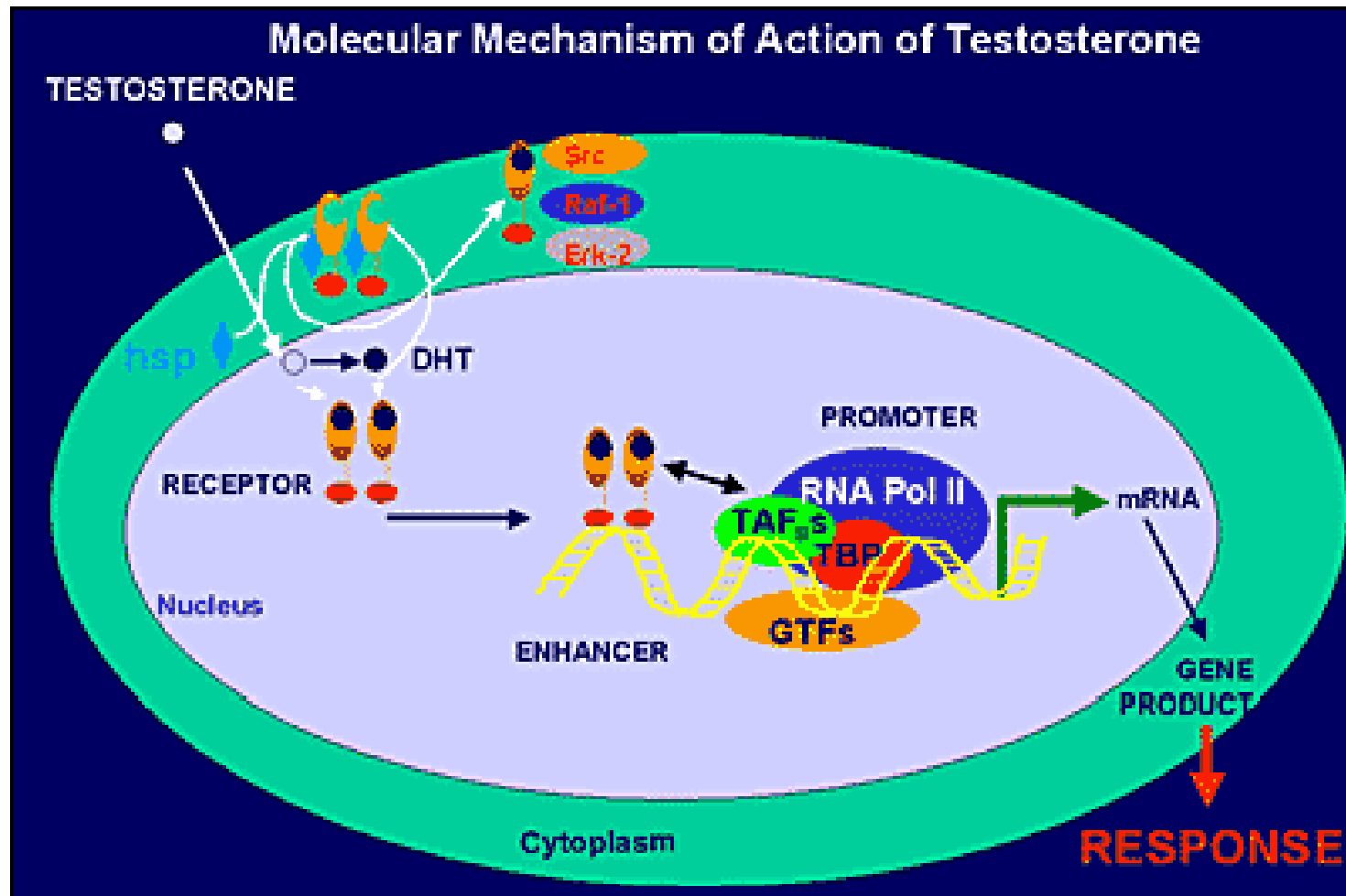
Wolffian ducts are maintained by testosterone (T) produced by Leydig cells. Müllerian ducts regress under the influence of AMH produced by fetal Sertoli cells, acting through the AMH receptor. The urogenital sinus and external genitalia are virilized by dihydrotestosterone (DHT), resulting from the reduction of testosterone by the enzyme  $5\alpha$ -reductase (not shown). T and DHT act through the androgen receptor



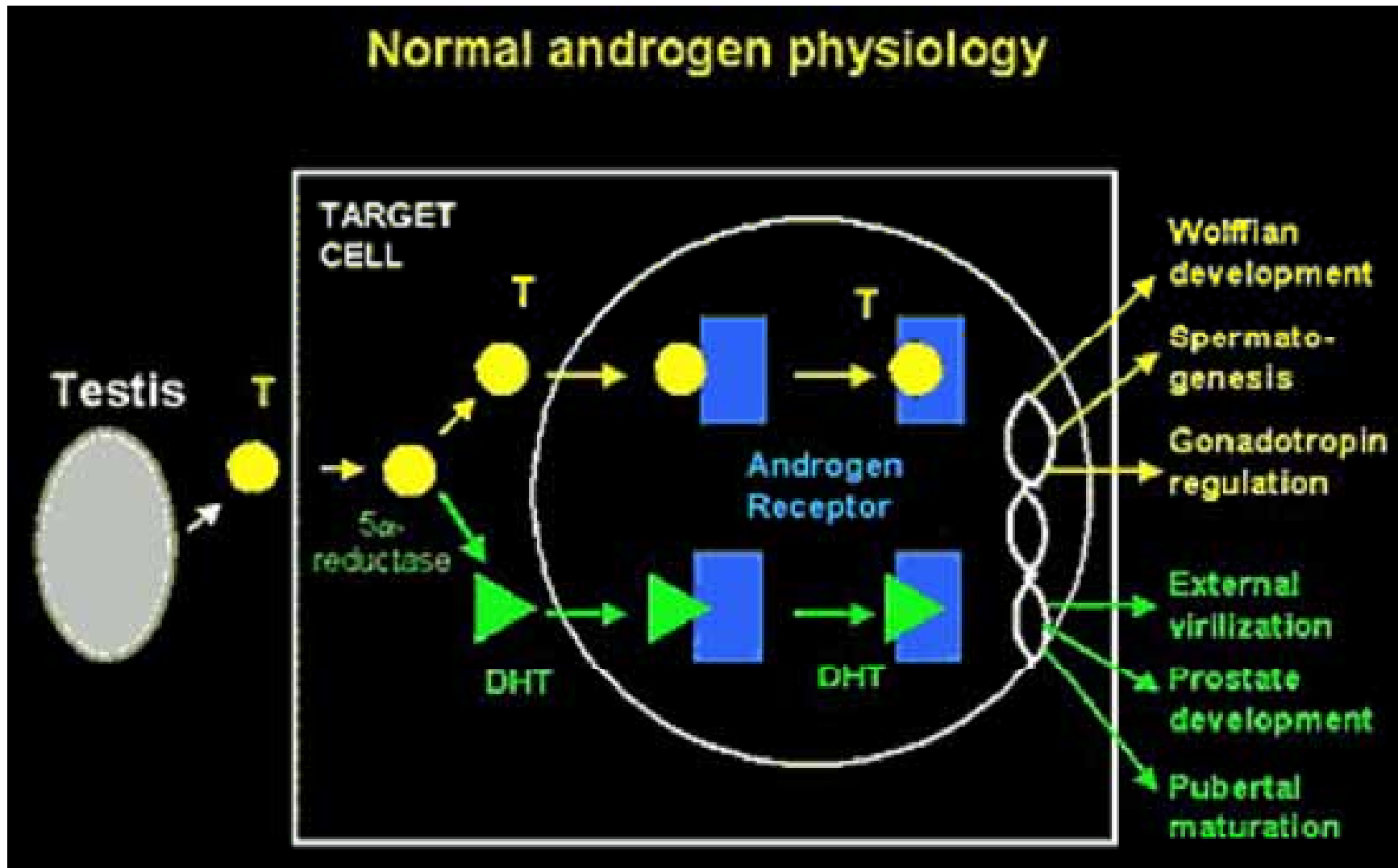
- The appropriate regulation of androgen activity is necessary for a range of developmental and physiological processes, particularly male sexual development and maturation.
- Excessive production of adrenal androgens can cause premature puberty in young boys and their hypersecretion in females, may produce a masculine pattern of body hair and cessation of menstruation.
- 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 nonclassical 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

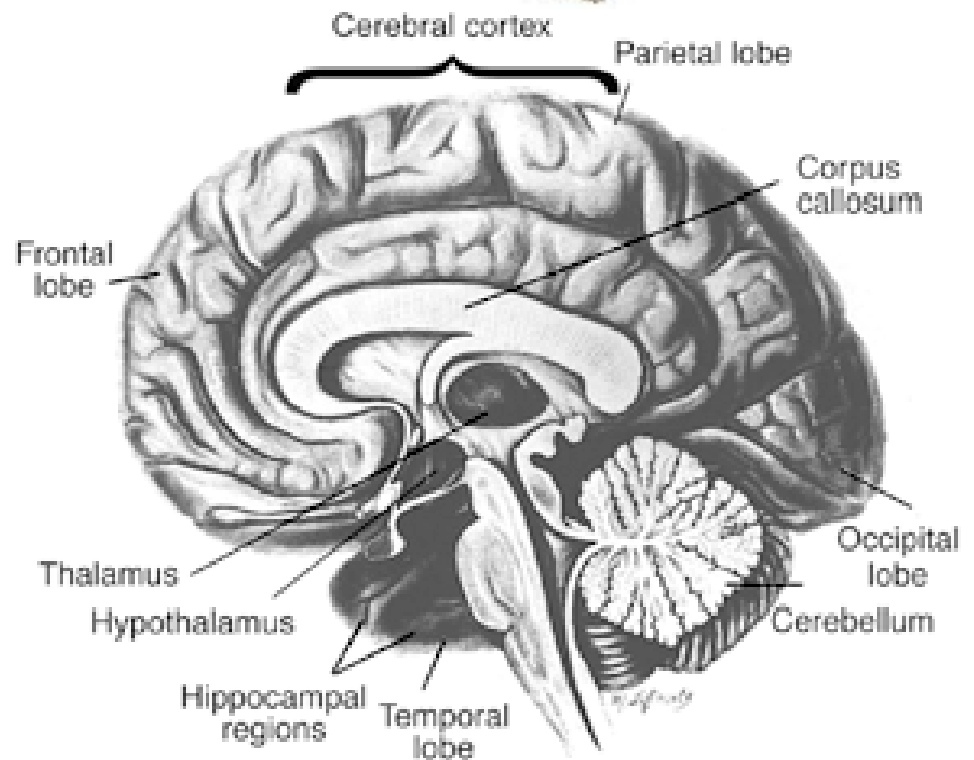
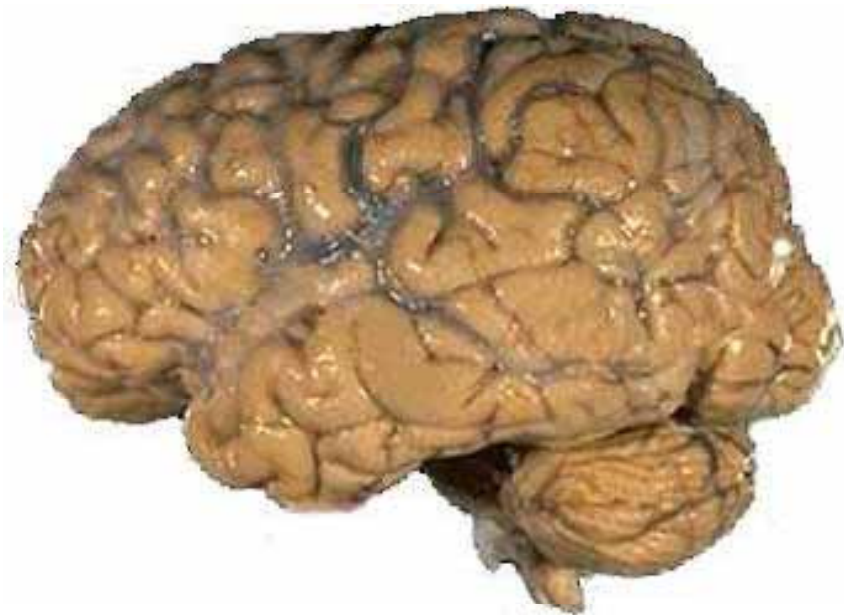


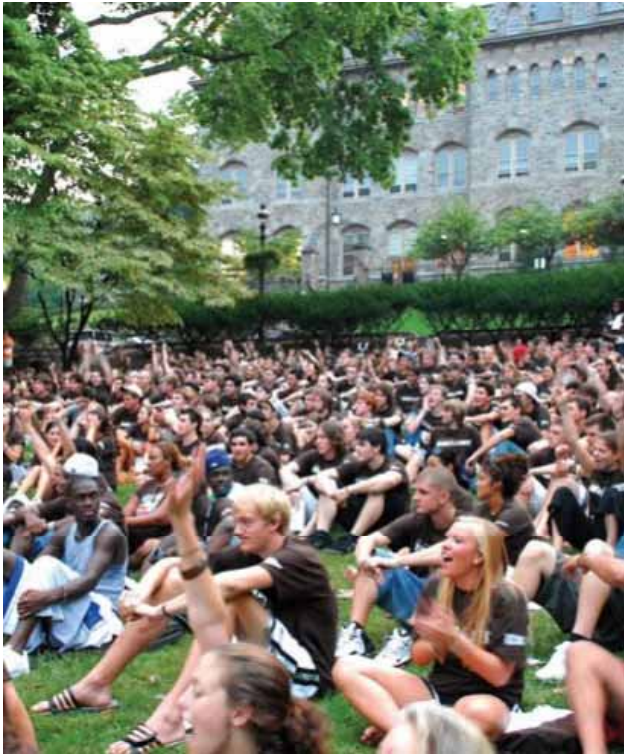
# Core Functions of Testosterone and Dihydrotestosterone in Males



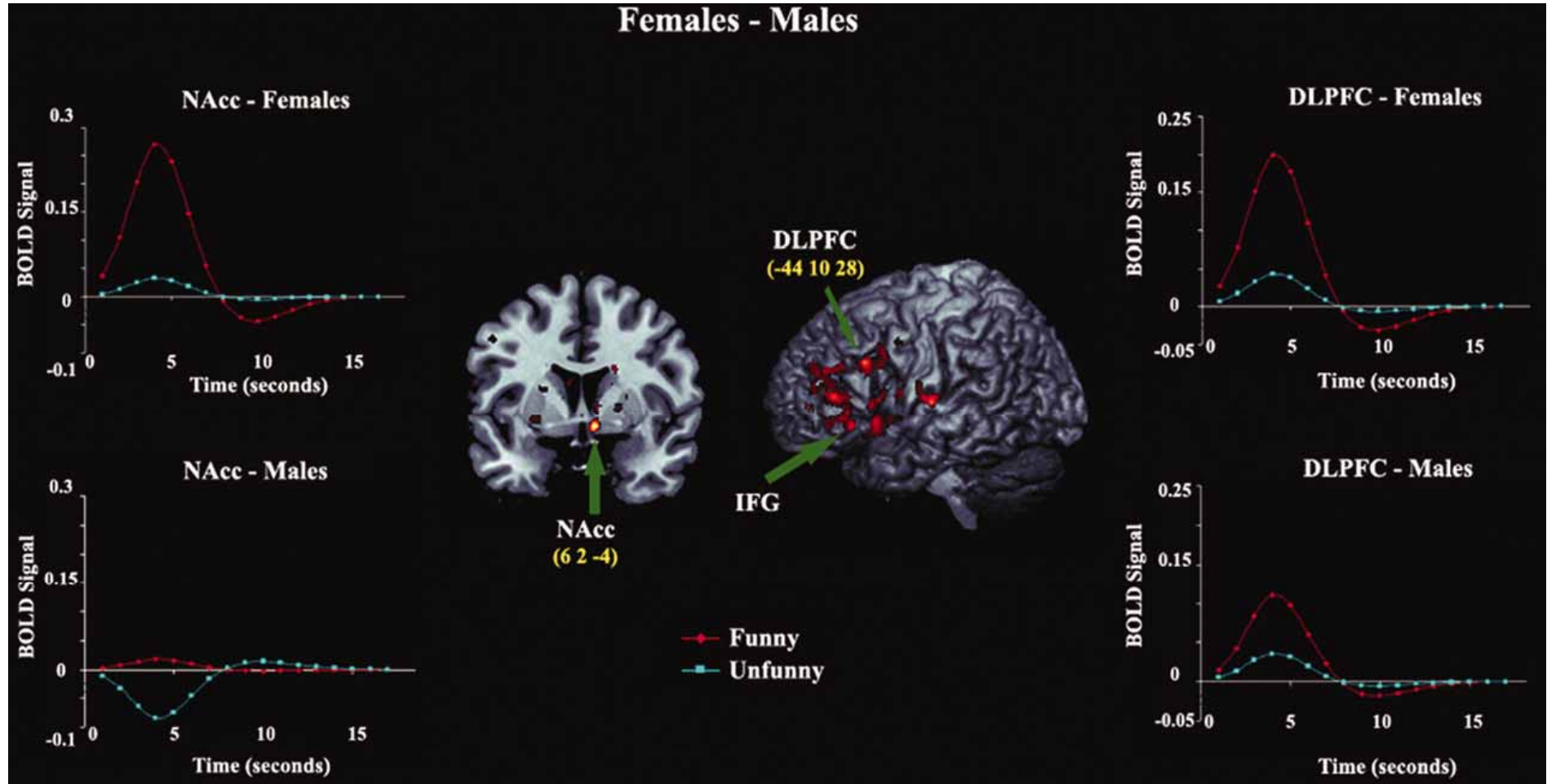


# The Human Brain: A Major Target for Sexual Differentiation





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



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.

# **Disorders of Sexual Differentiation**

# Intersex Conditions

5-alpha reductase deficiency

Androgen Insensitivity Syndrome (AIS)

Partial Androgen Insensitivity Syndrome (PAIS)

Aphallia

Congenital Adrenal Hyperplasia (CAH)

Progestin Induced Virilization

Swyer Syndrome

Gonadal dysgenesis (partial & complete)

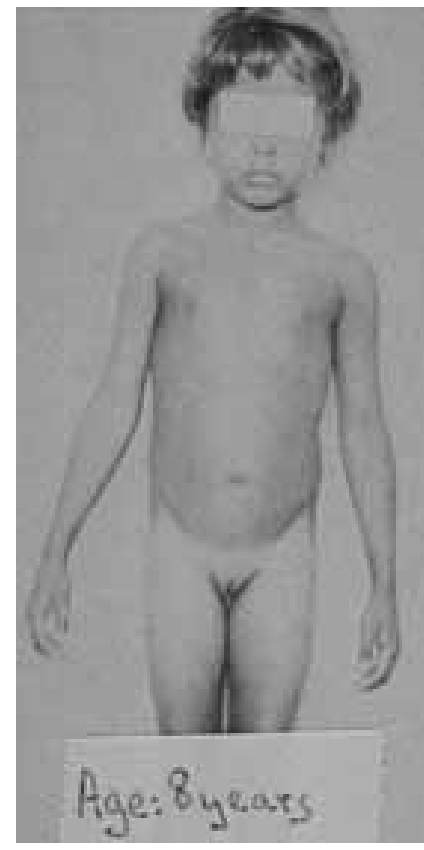
Klinefelter Syndrome

Turner Syndrome

Hermaphroditism

## **Guevedoces: Partial Androgen Insensitivity**

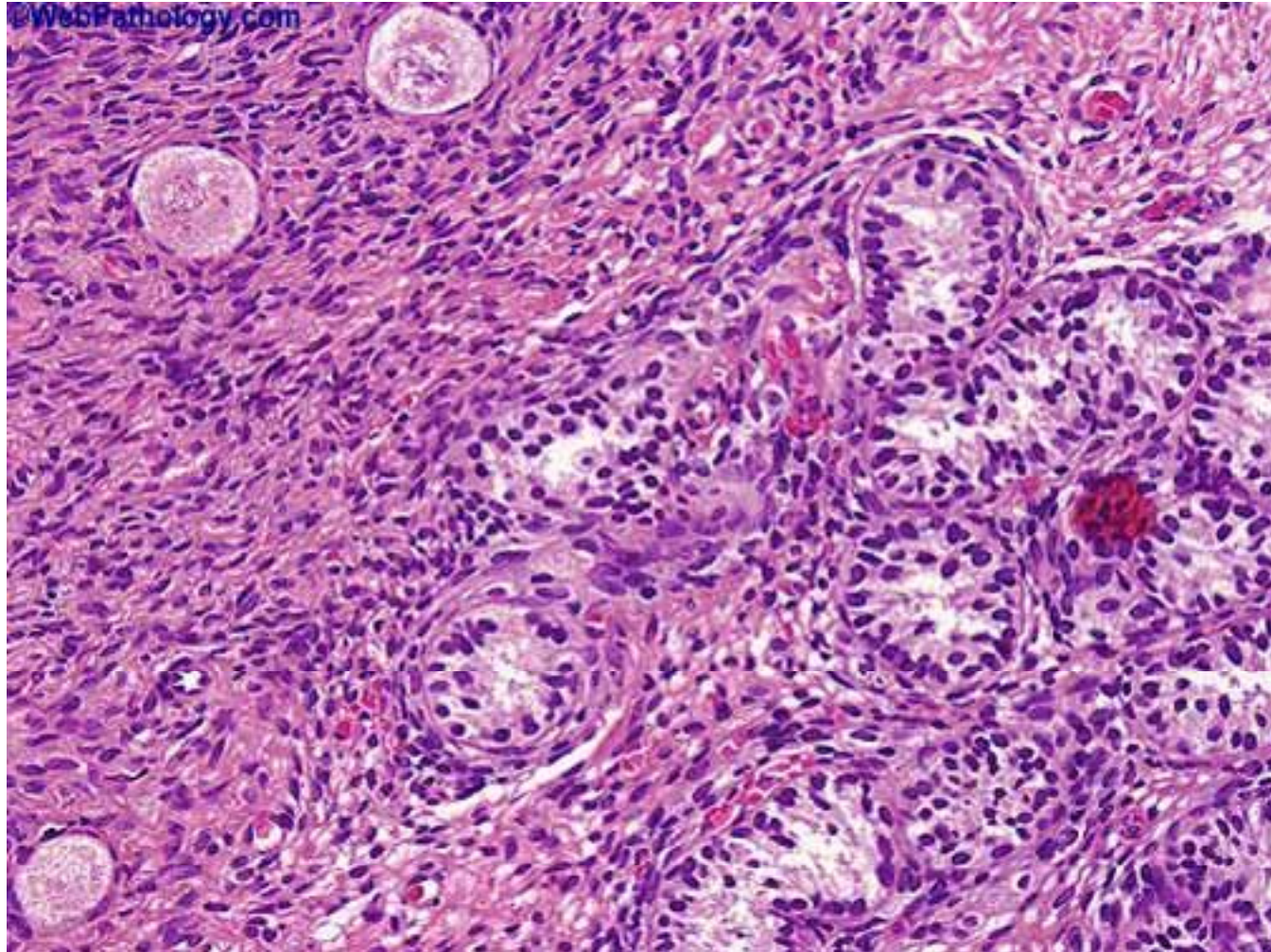
In an isolated village of the southwestern Dominican Republic, 2% of the live births were in the 1970's, guevedoces (actually male pseudohermaphrodites). These children appeared to be girls at birth, but at puberty these 'girls' sprout muscles, testes, and a penis. For the rest of their lives they are men in nearly all respects (see photograph 6 below). Imperato-McGinley et al, 1974







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



**Thank you for your time and attention**