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

Women

Men
Sexual Differentiation & Development

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Signaling Cascade & Events Leading to Phenotypic Sex Differences

Sex determining genes → Gonadal differentiation → Hormones

Embryo → Neonate → Puberty → Adult

Phenotypic sex differences → Experience
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

Normal androgen physiology

Testis → Testosterone (T) → 5α-reductase → Dihydrotestosterone (DHT) → Androgen Receptor → Various effects:
- Wolffian development
- Spermatogenesis
- Gonadotropin regulation
- External virilization
- Prostate development
- Pubertal maturation
The Human Brain: A Major Target for Sexual Differentiation
Testosterone: Aromatization to Estrogens

- Estradiol 17-β:
  - Bone resorption
  - Epiphyseal fusion
  - Sexual differentiation of brain
  - Some behaviors
  - Plasma lipids
  - Atherosclerosis progression

- Dihydrotestosterone:
  - Prostatic growth
  - Skin
  - Hair follicles in androgen sensitive areas
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

Male

Facilitation

T and Metabolites

DHEA

Female

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

Prolactin levels are negatively correlated with CSF vasopressin levels.

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

- Testosterone (T)
- Androgen Receptor
- GABA Target System
- Testosterone (T)
- Steroid
- Dehydroepiandrosterone (DHEA)
- Active Metabolites
- Androgen Regulated Transcription Site of Action
- 5HT1A, 5HT1B, V1A, AVP
- Serotonin
- Vasopressin
- INHIBIT
- ENHANCE

Female

- Androgen Receptor
- GABA Receptor
- Enzyme (AE)
- Dehydroepiandrosterone (DHEA)
- PREG S
- Steroid
- ENHANCE
- ENHANCE

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.
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
Translational Impact

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