Biological Origins of Sexual Orientation & Gender Identity

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The published findings from embryology, endocrinology, genetics, epigenetics, anatomy, pediatrics, psychiatry, gynecology, urology, audiology, orthopedics, and neurobiology, will be presented, confirming that sexual orientation and gender identity are biologically conferred on all humans during gestation.

Conclusions

- Boys and girls come from the same one tissue during pregnancy,
- Under the influence of variable enzymes and hormones, the fetus develops and later expresses along a spectrum of sexually dimorphic differences:
  - Anatomy (e.g.: brain, bones, genitals, larynx.)
  - Physiology (e.g.: play, skills, voice, ambulation, orientation, identity)
- Naturally occurring, experimental, and clinical embryonic endocrine conditions are strongly correlated with orientation and identity.

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Biological origins of sexual orientation and gender identity: Impact on health☆

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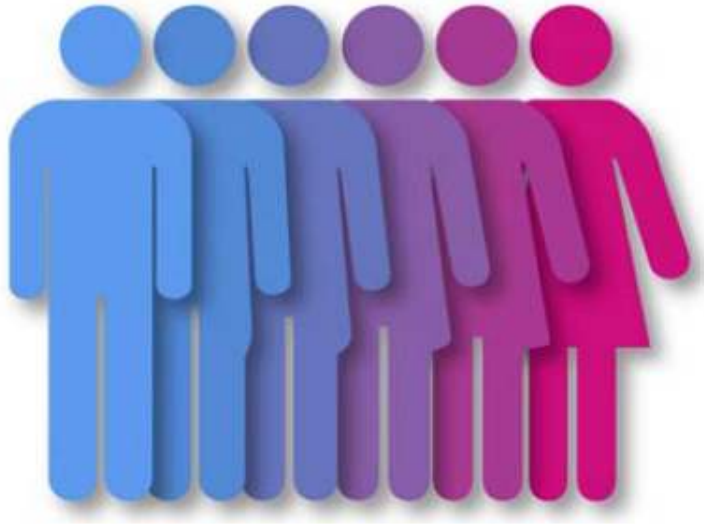
HIGHLIGHTS

- Sexual orientation is biologically conferred in the first trimester of pregnancy.
- Gender identity is biologically conferred during the middle trimester of pregnancy.
- Health risks are conferred by the social stigma of minority status.
- Gynecologic Oncologists can provide quality care to these minority individuals.

GRAPHICAL ABSTRACT



Naturally occurring,
experimental,
and clinical embryonic endocrine conditions
are strongly correlated
with orientation and identity.

Sexual behavior in other vertebrates

- 450 species of mammals and birds:
  - repeated homosexual activity, mounting behavior to orgasm,
  - mutual masturbation, oral sex.
  - all ages, both genders.
  - lifelong relationships,
  - in presence of opposite sex.
- Previously unreported, or as “practice for real sex.”
- Gene pool preserved when families do not overpopulate and when relatives help raise other’s children.

Bagemihl B. Biological Exuberance: Animal Homosexuality and Natural Diversity: St. Martin’s Press; 1999.

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Homosexual Behaviour in Animals

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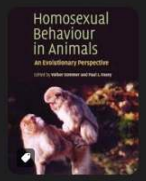

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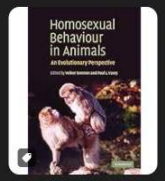

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The Washington Post
Yes, those cuddling lions ...


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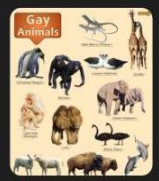
An alternate hypothesis for same-sex ...



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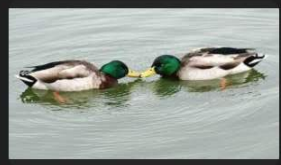
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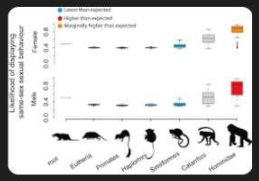

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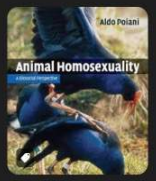

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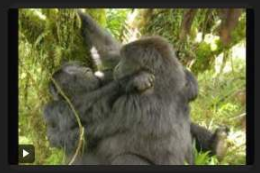
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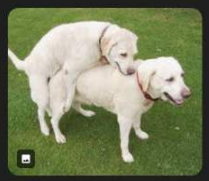
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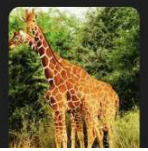
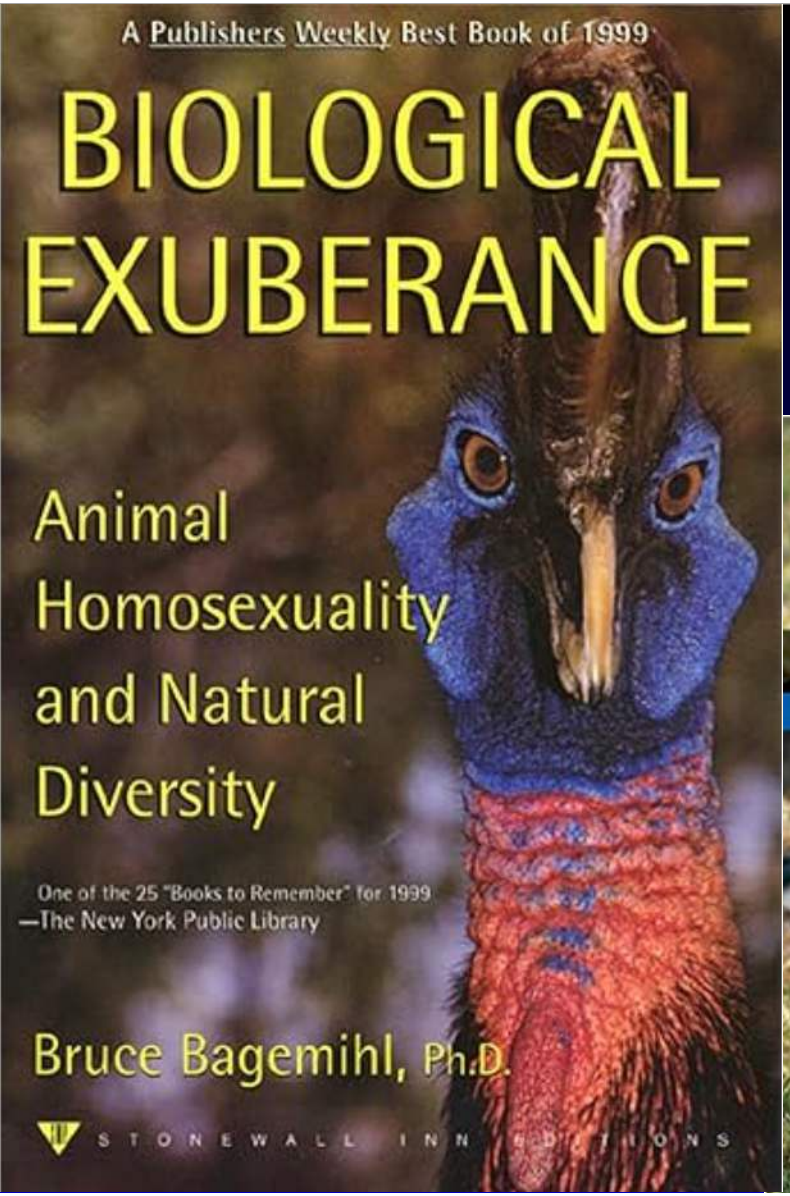
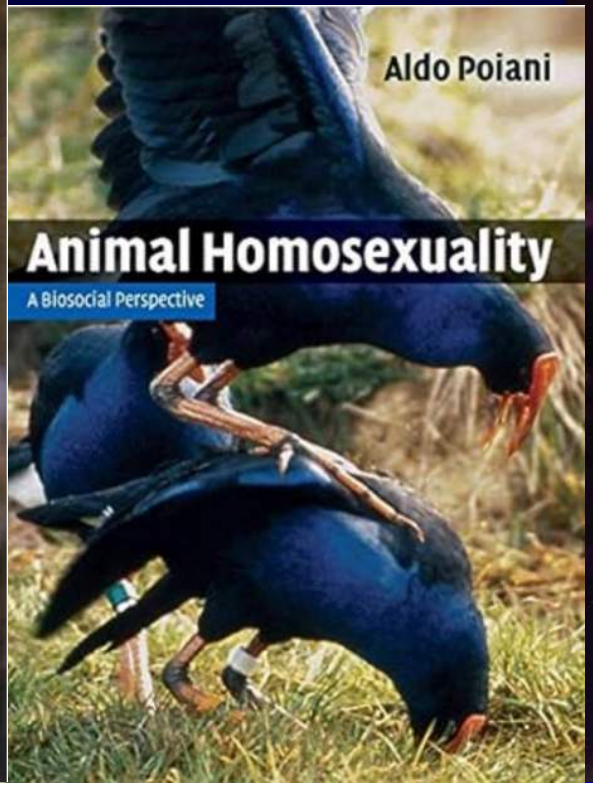



A Publishers Weekly Best Book of 1999
BIOLOGICAL EXUBERANCE
Animal Homosexuality and Natural Diversity
One of the 25 "Books to Remember" for 1999
—The New York Public Library
Bruce Bagemihl, Ph.D.
STONEWALL INN EDITIONS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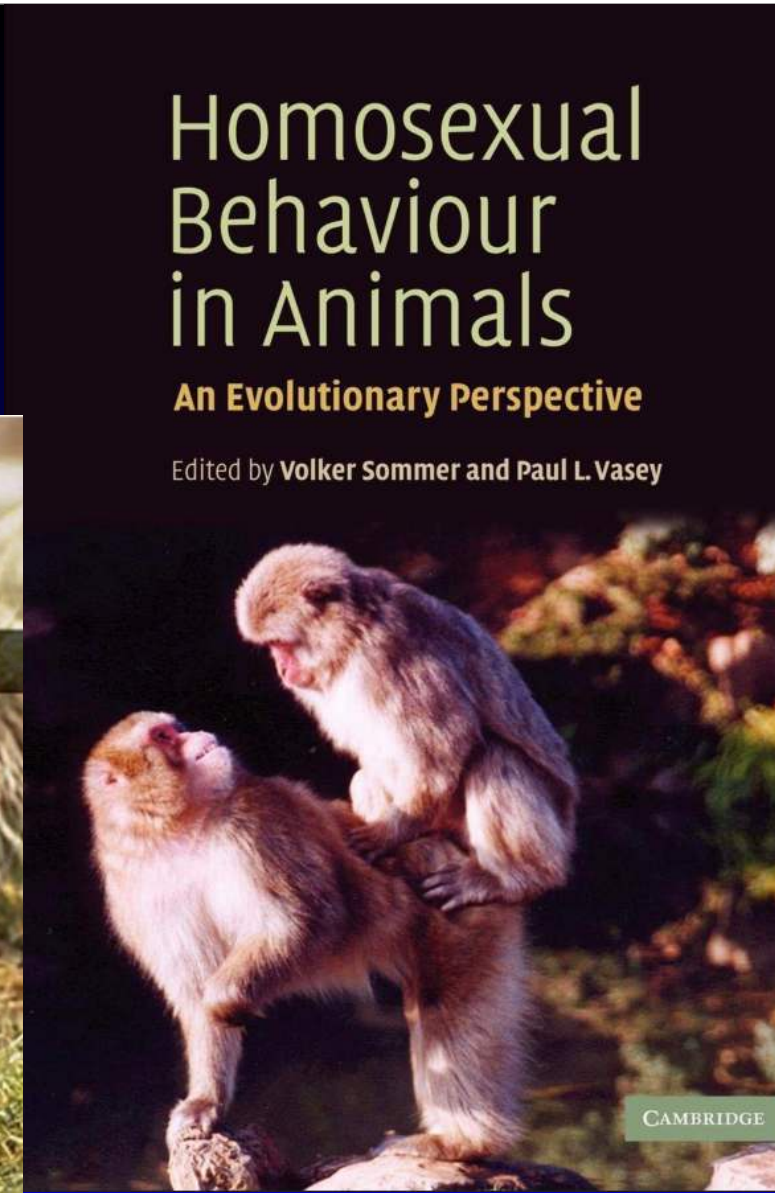
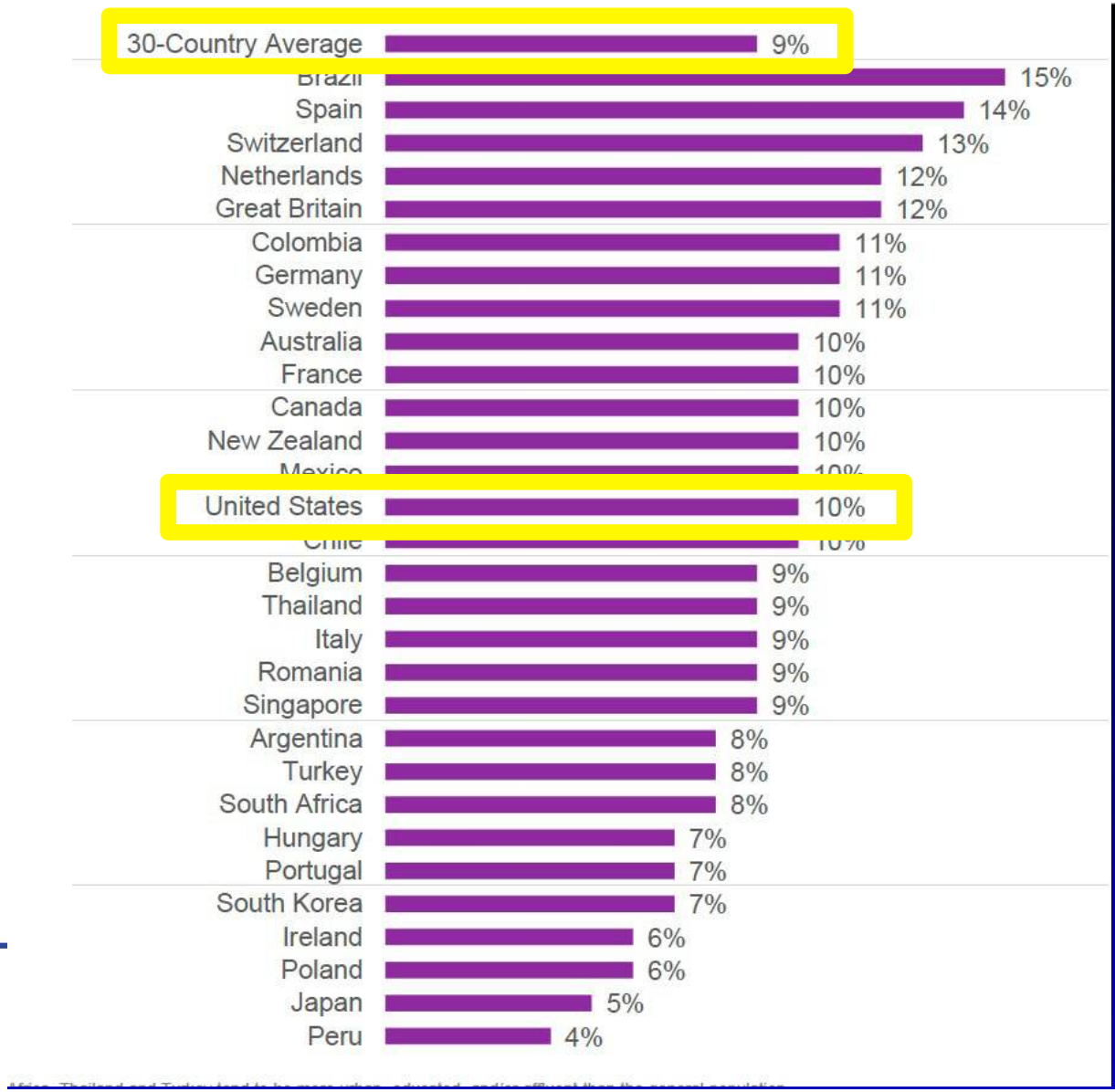
Animal Homosexuality
A Biosocial Perspective


Homosexual Behaviour in Animals
An Evolutionary Perspective
Edited by Volker Sommer and Paul L. Vasey
CAMBRIDGE

Net % of LGBT+ Adults By Country

Any of:

- Lesbian/gay/homosexual
- Bisexual
- Pansexual/omnisexual
- Asexual
- Transgender
- Non-binary/gender non-conforming/gender-fluid
- Other than male or female



About Ipsos

Ipsos is the third largest market research company in the world, present in 90 markets and employing more than 18,000 people.

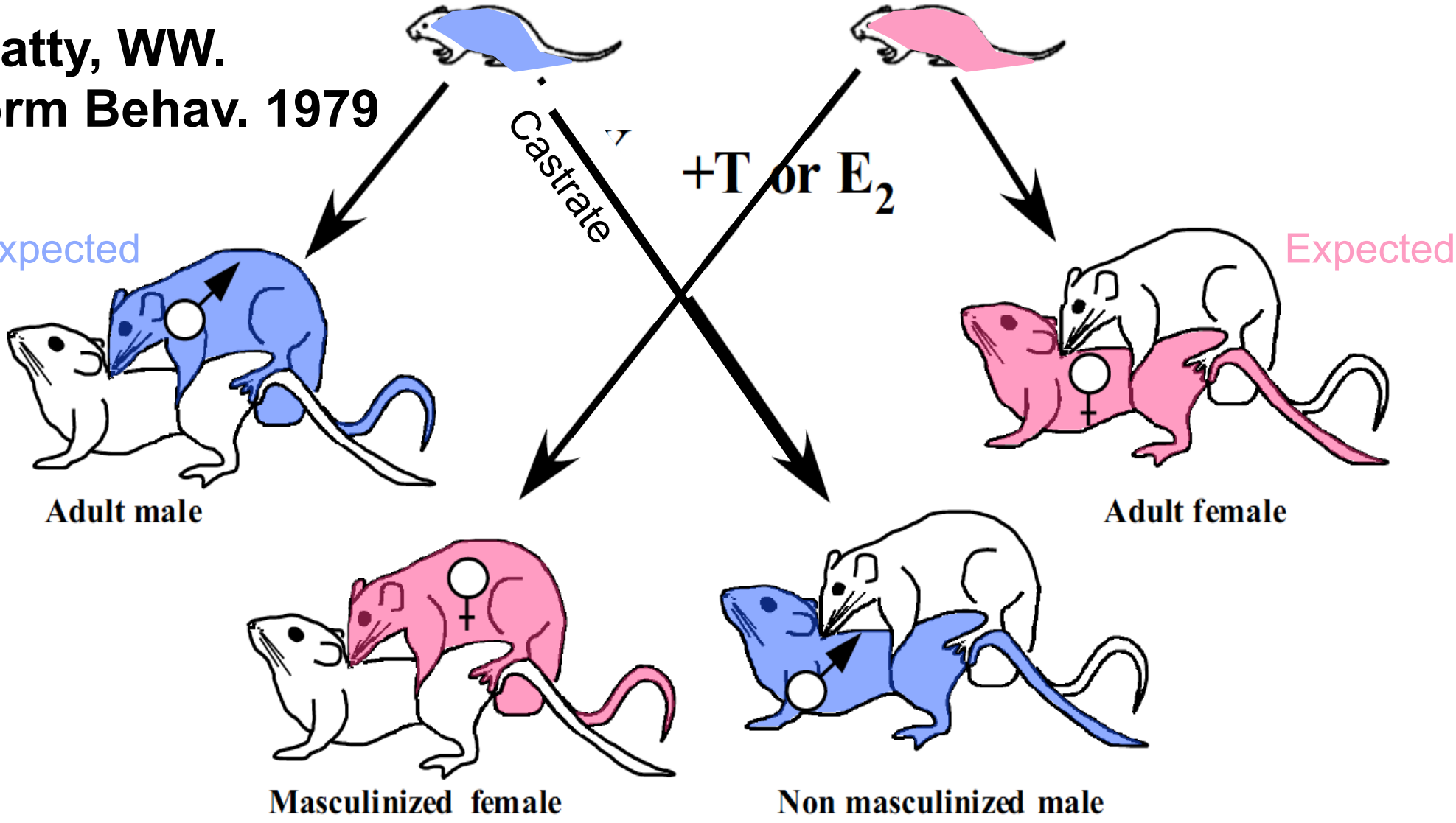
Naturally occurring,
experimental,
and clinical embryonic endocrine conditions
are strongly correlated
with orientation and identity.

1959: "Organization" (hormone effect during gestation)

- Injected pregnant mother pigs with testosterone. Among the female offspring,
  - Masculinized genitalia.
  - At puberty:
    - More mounting behavior than controls.
    - Would not do lordotic presentation like controls.
- Organizational effect is lifelong, and stronger than later activational effect.

» Phoenix, CH, et al. *Endocrinology. 1959.*
» Goy, RW, et al. *J Reprod Fertil. 1963.*

Beatty, WW.
Horm Behav. 1979



Balthazart, *Endocrinology*, 152, 8, 2011, 2937–2947

Organization by sex steroid hormones in monkeys

- Testosterone has a direct effect on the brain, and, once converted into estrogens by aromatase, may also act on developing neurons.
- Experimental androgen levels during prenatal and neonatal development permanently influence sex dimorphic features:
  - Play behavior- males higher activity levels
  - Aggression - males more.
  - Learning skills.

» Beatty, WW. Horm Behav. 1979.

Prenatal administration of aromatase inhibitors (AI) in rodents affects organization

- AI's prevent formation of testosterone in fetus.
  - Male offspring preferred sexually active males, over receptive female.
  - They do lordosis with other males, but also some male-typical behavior with females.
- Confirms the hypothesis that human sexual orientation is underlined by changes in the endocrine milieu during gestation.
  - Olivera-Hernandez, Advances in Neurobiology, January 2015

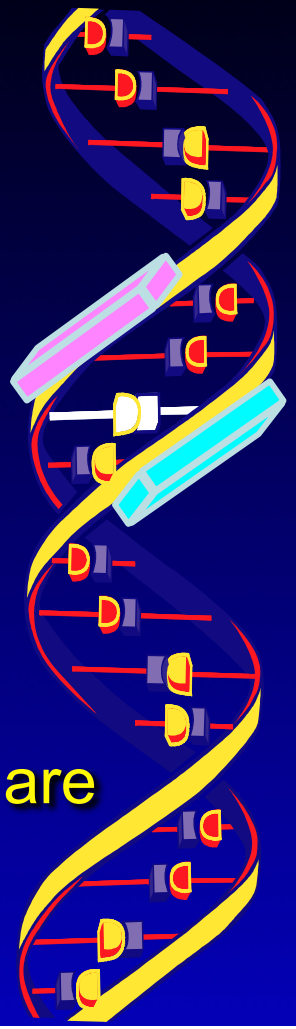
But what about humans?

Gene expression: genomic determination

- DNA makes a codon. (letters we learn).
- Codons make a gene. (words we use).
- Genes makes a protein. (sentences we construct).
- Proteins build the body. (essays we write).

- Epigenetics: Which of two genes express. (publication).

- Among 25,000 genes in humans, 2% code for proteins. Rest are controlling expression: epigenetics.

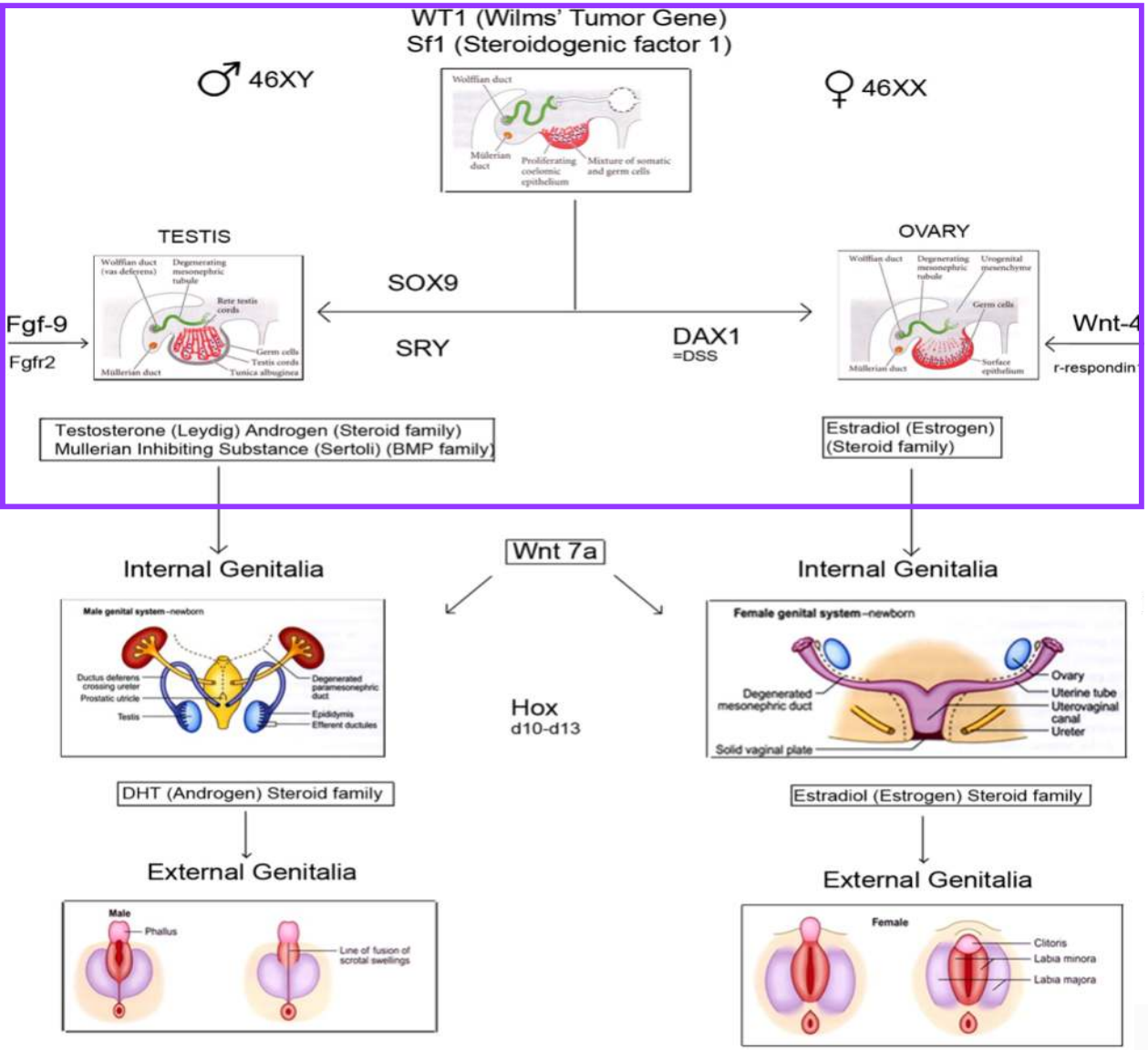


Prenatal chemistry and embryology:

- Determination: Genes make many proteins that instruct the formation of gonads.
- Differentiation: Gonads develop into an ovary or testis.
- Organization: Ovary or testis secrete hormones that engender the brain and body in “masculine”/“feminine” directions.
-
- Activation: Post-natal hormones (eg puberty, adult supplementation—no effect on orientation, identity)

Phoenix, CH, et al. *Endocrinology. 1959.*

Goy, RW, et al. *J Reprod Fertil. 1963.*

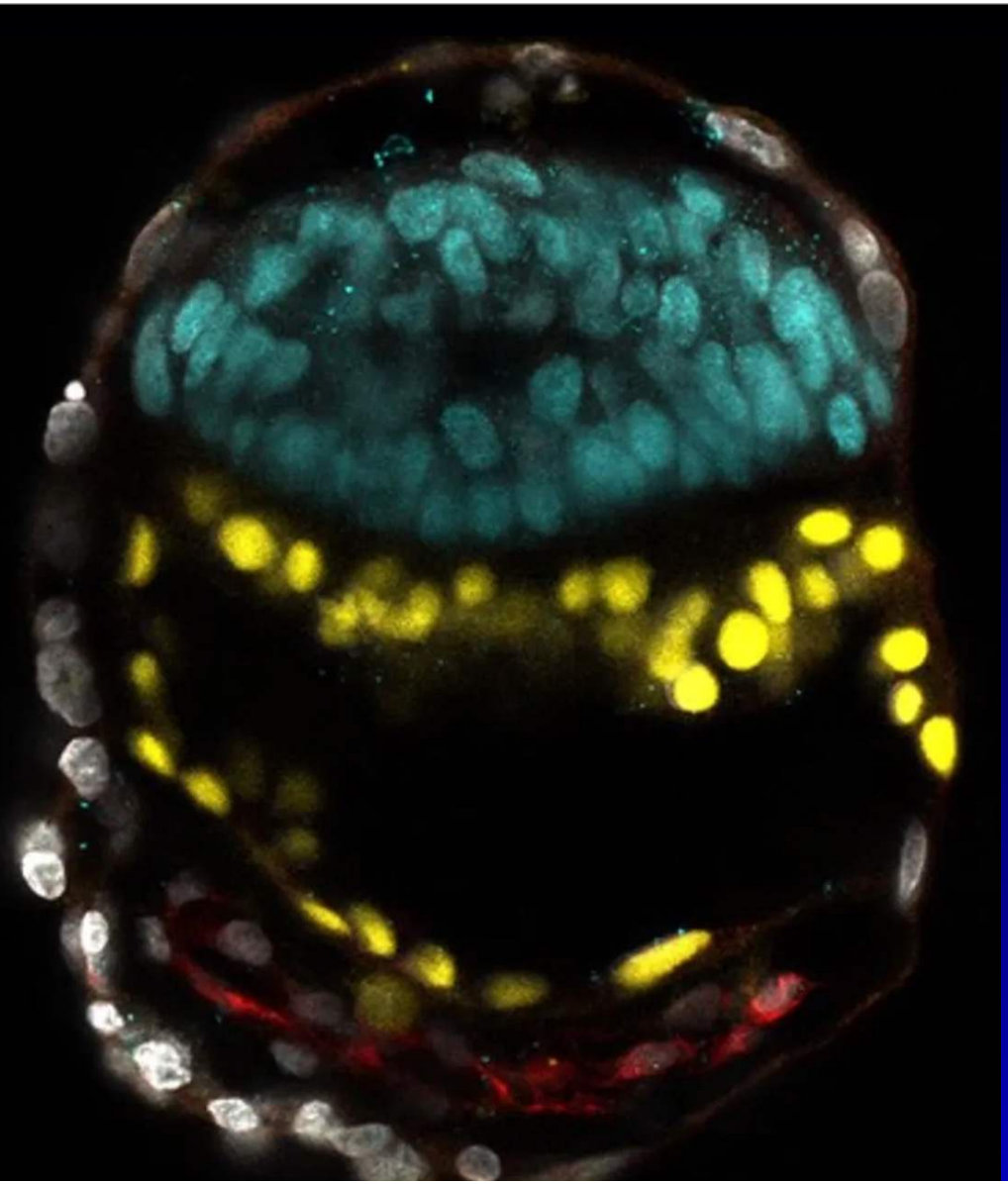


DETERMINATION(1-3 wks)

DIFFERENTIATION(4 wks)

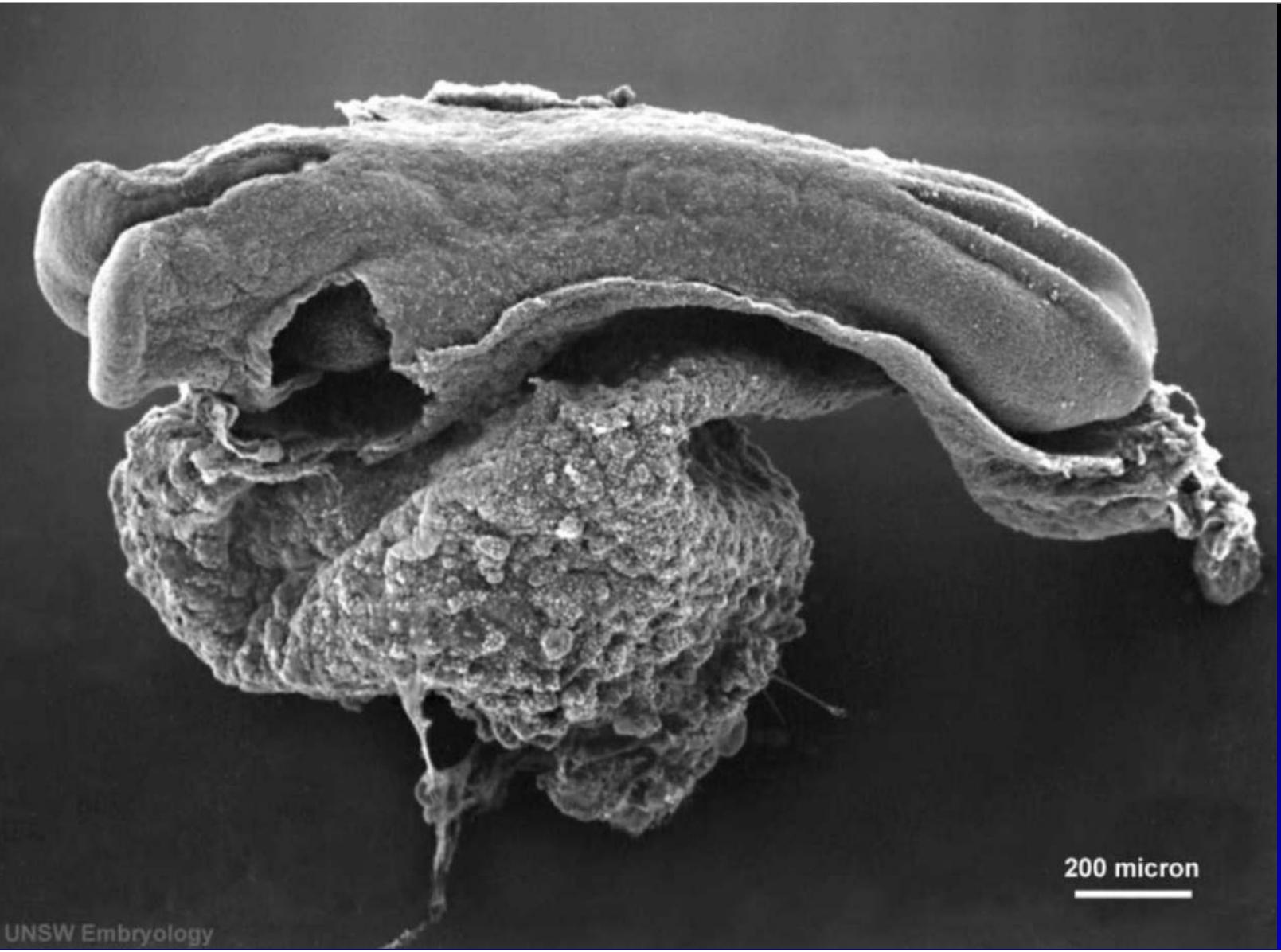
ORGANIZATION(6-9 wks)

ACTIVATION (puberty)



Week 1embryo

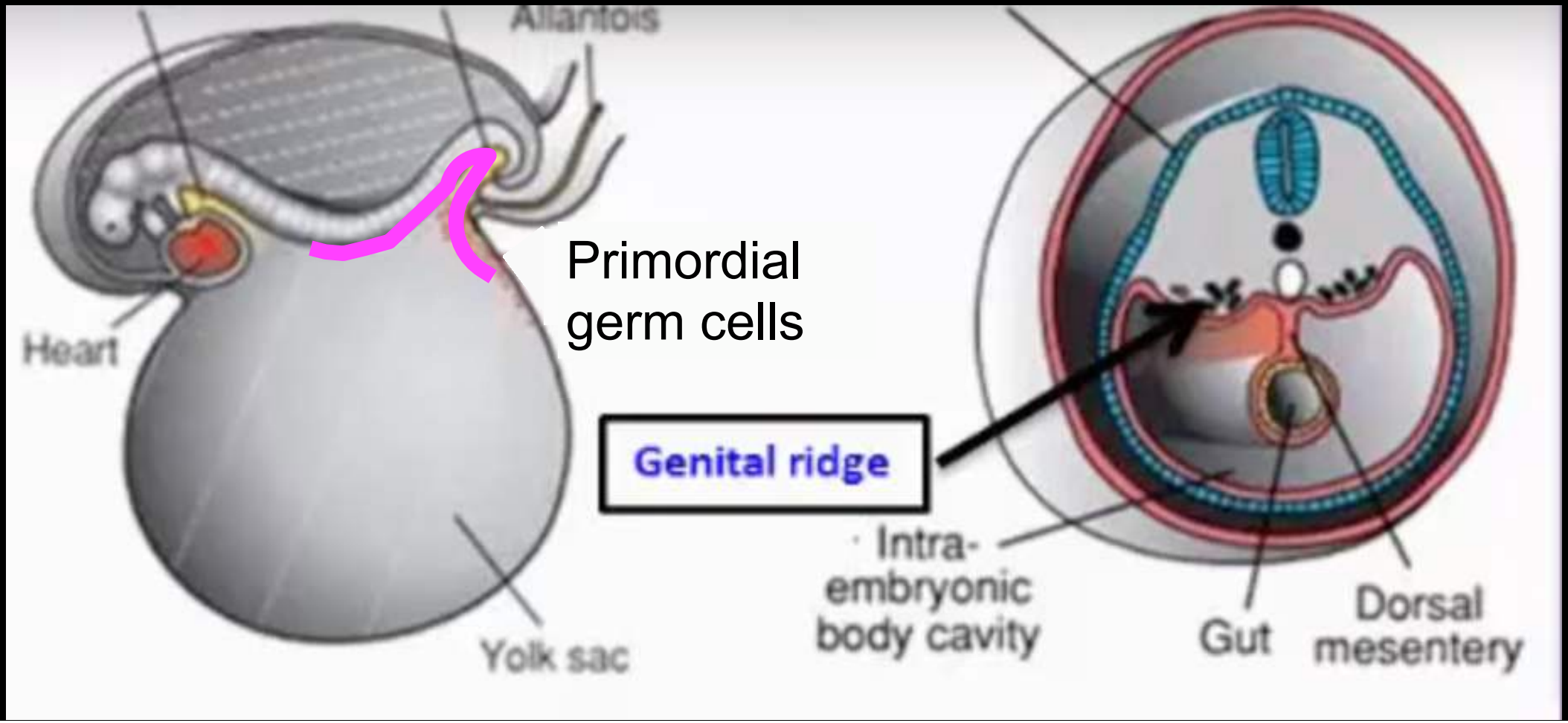
- Three major tissue structures:
  - epiblast (cyan) forms fetus.
  - yolk sac (yellow), absorbed.
  - extra-embryonic mesoderm (red), and trophoblast layer (white) forms placenta.
- Oldak, B., Wildschutz, E., Bondarenko, V. et al. Complete human day 14 post-implantation embryo models from naive ES cells. Nature 622, 562–573 (2023). https://doi.org/10.1038/s41586-023-06604-5

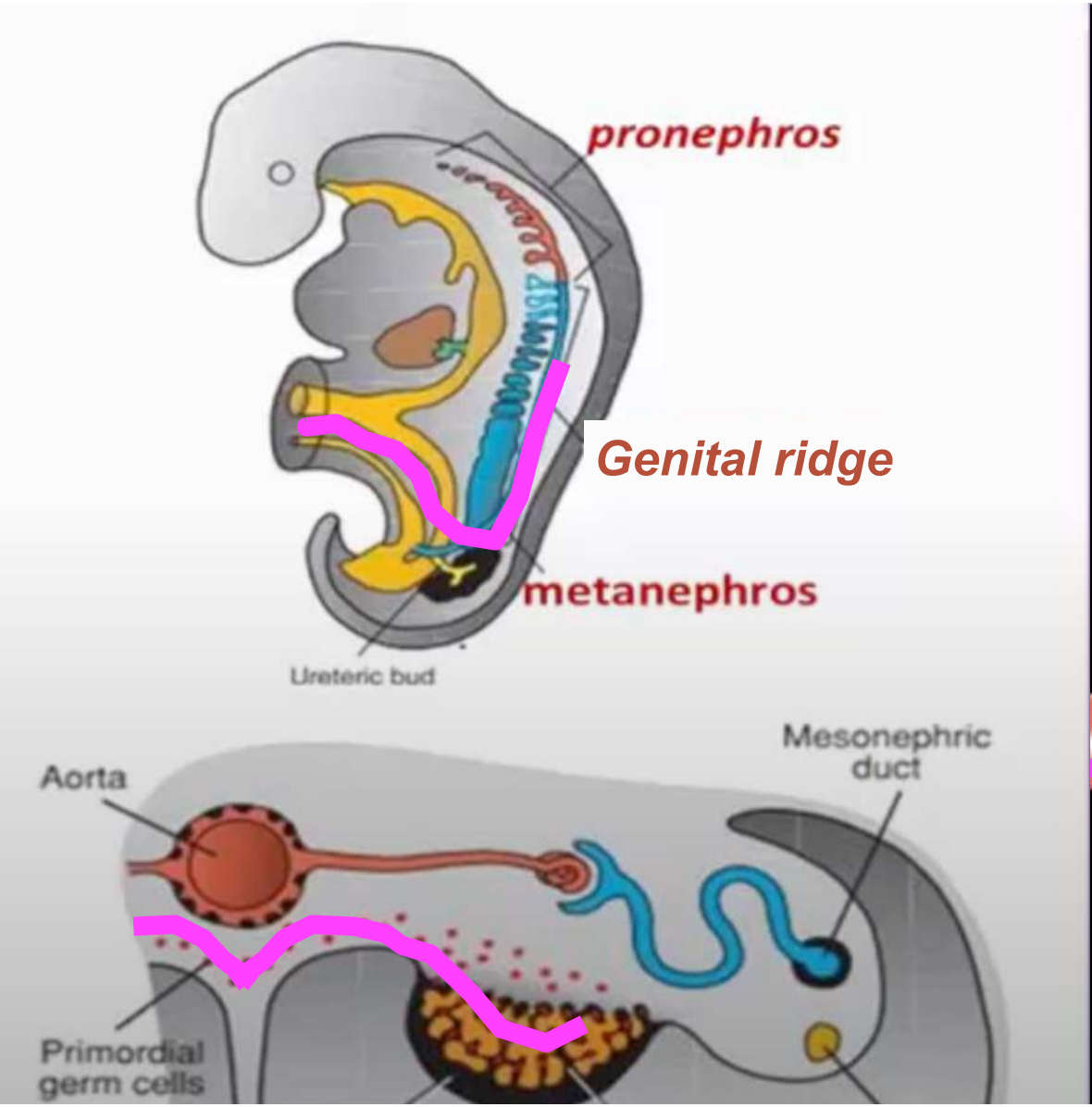


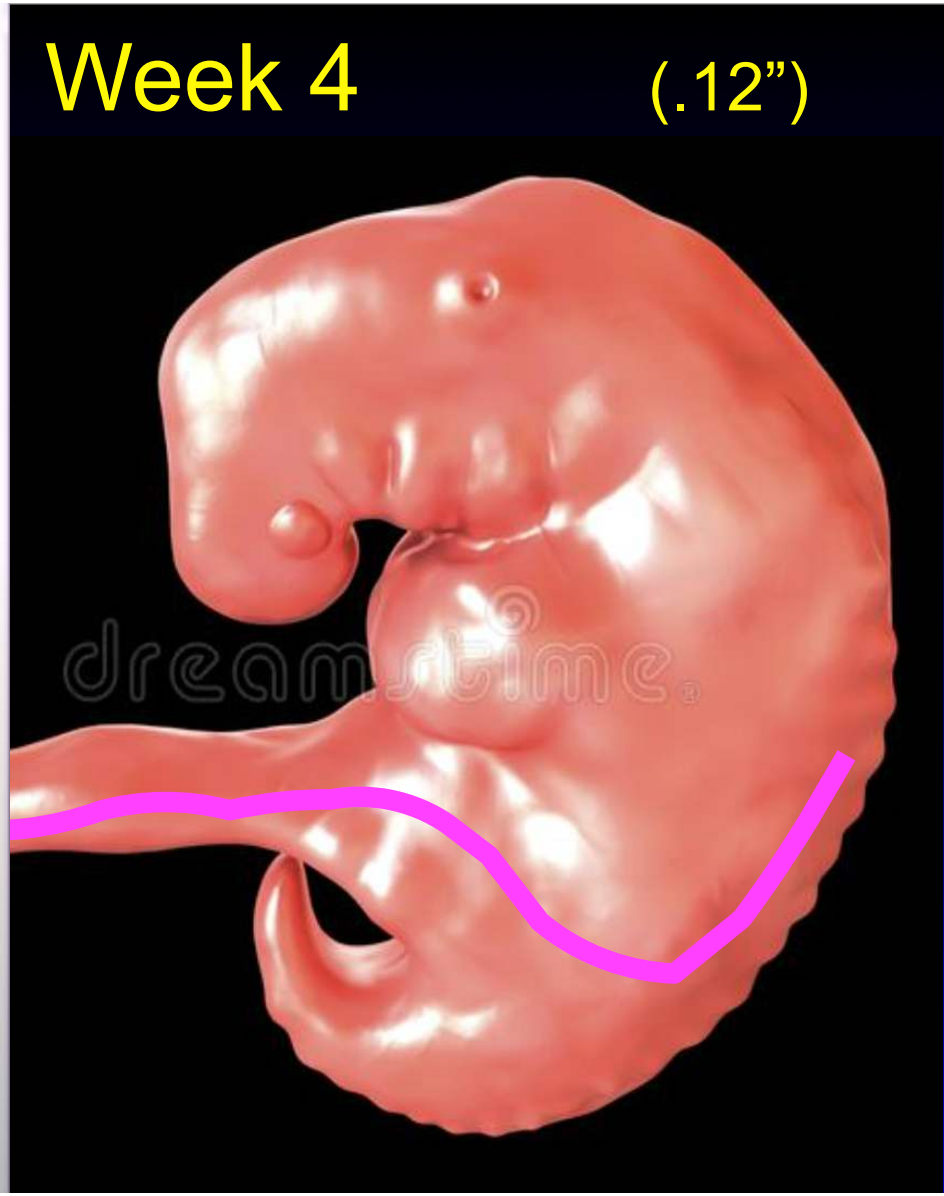
Week 3

- Spinal cord begins as fold of skin.
- Yolk sac shrinks as placenta implants and develops blood supply

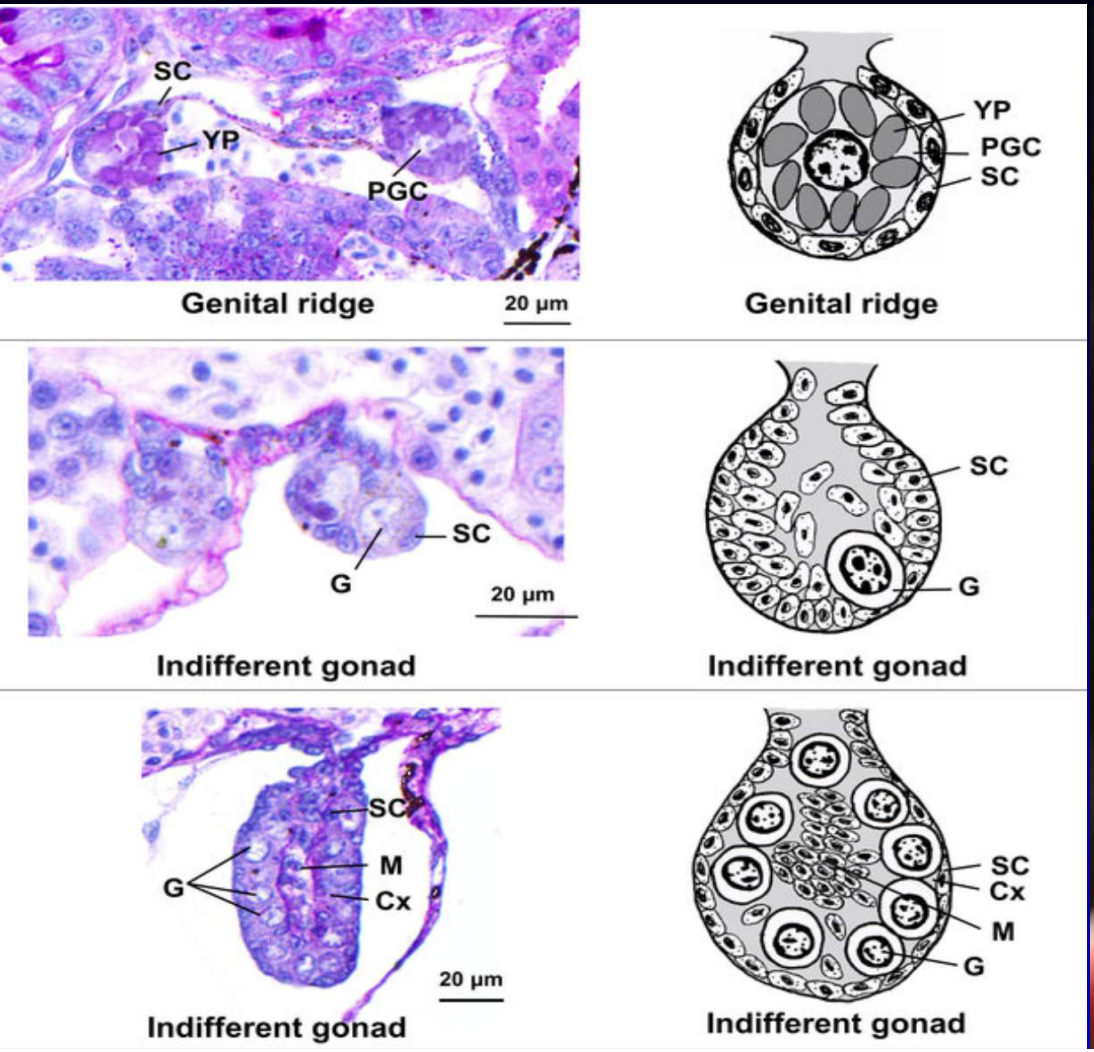
Week 2 embryo




pronephros
Genital ridge
metanephros
Ureteric bud
Aorta
Mesonephric duct
Primordial germ cells


Week 4
(.12”)

- The **genital ridge** is formed, provide somatic cells to the gonad.

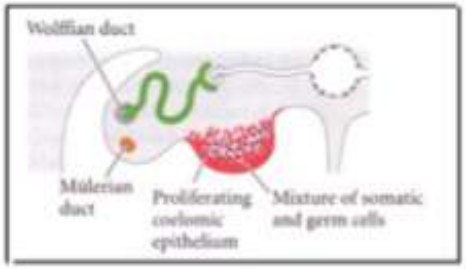


DETERMINATION

(1-3 weeks)

WT1 (Wilms' Tumor Gene)
Sf1 (Steroidogenic factor 1)

♂ 46XY

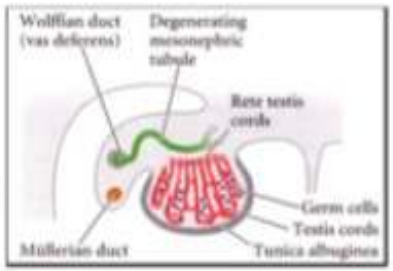


♀ 46XX

DIFFERENTIATION

(4-9 weeks)

TESTIS



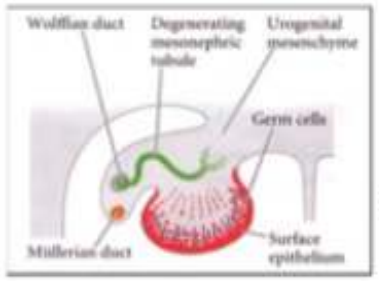
Fgf-9 → Fgfr2

SOX9

SRY

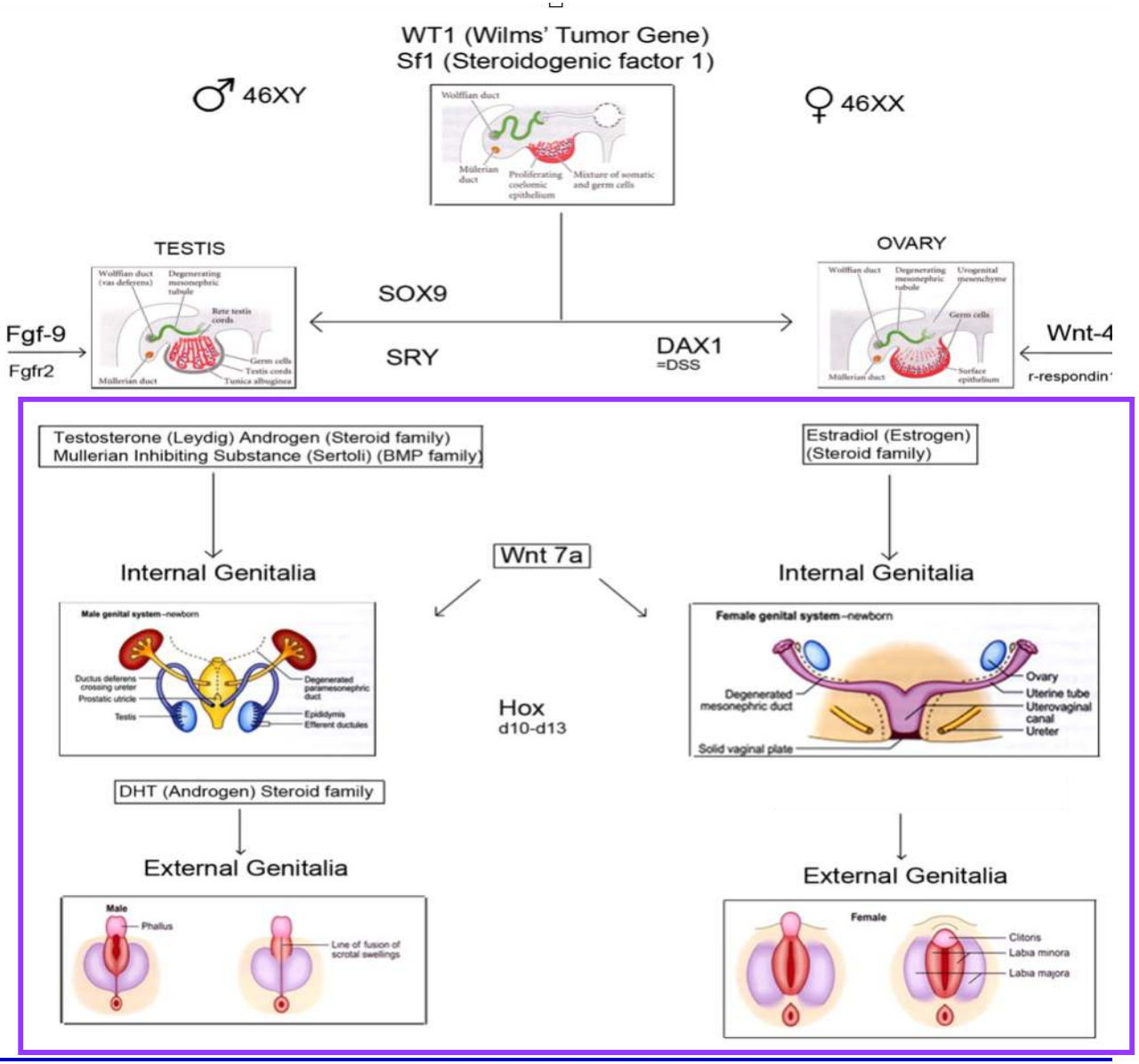
DAX1
=DSS

OVARY



Wnt-4 ← r-respondin1

Testosterone (Leydig) Androgen (Steroid family)
Mullerian Inhibiting Substance (Sertoli) (BMP family)



DETERMINATION (1-3 wks)

DIFFERENTIATION (4 wks)

ORGANIZATION (6-12 wks)

ACTIVATION (puberty)

ORGANIZATION

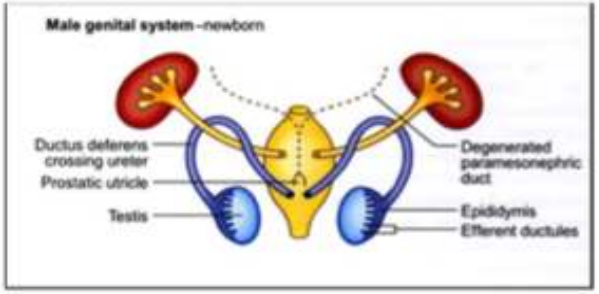
(6-12 weeks)

Testosterone (Leydig) Androgen (Steroid family)
Mullerian Inhibiting Substance (Sertoli) (BMP family)

Estradiol (Estrogen) (Steroid family)

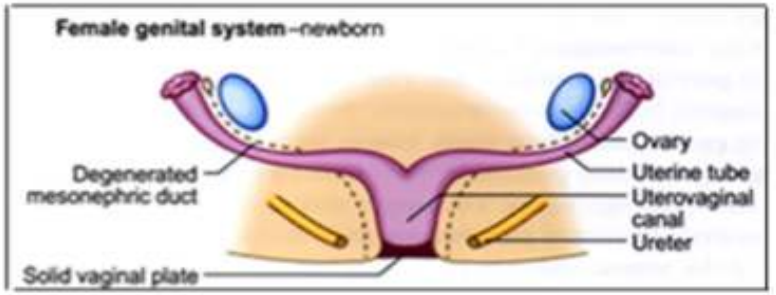
Wnt 7a

Internal Genitalia



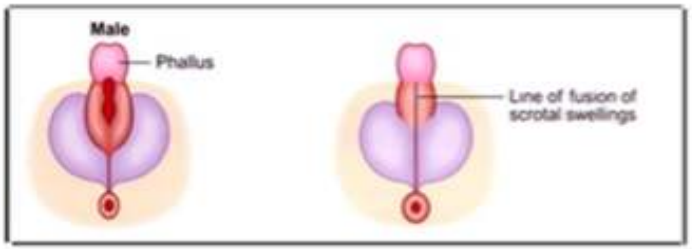
Hox
d10-d13

Internal Genitalia

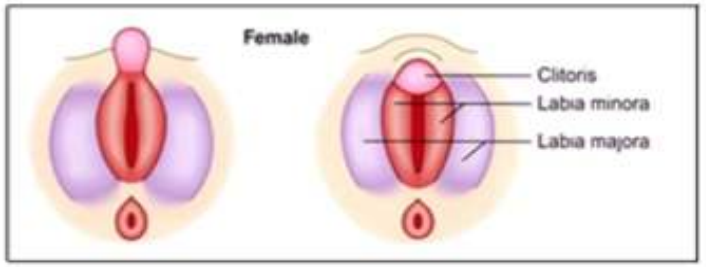


DHT (Androgen) Steroid family

External Genitalia



External Genitalia



Differentiation of ovaries, week 6

- If no or delayed SRY secretion, genital ridge differentiates into ovaries, secrete only trace estrogen.
  - Brain, body female-typical, androphilic.
  - Uterus, tubes and upper vagina form.
  - Genital tubercle (clitoris) enlarges until 84 days.

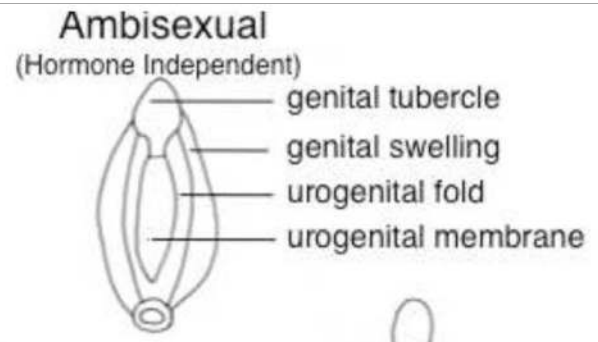
Piprek, RP,
J Appl Genet, 2009

Differentiation of testes. week 6

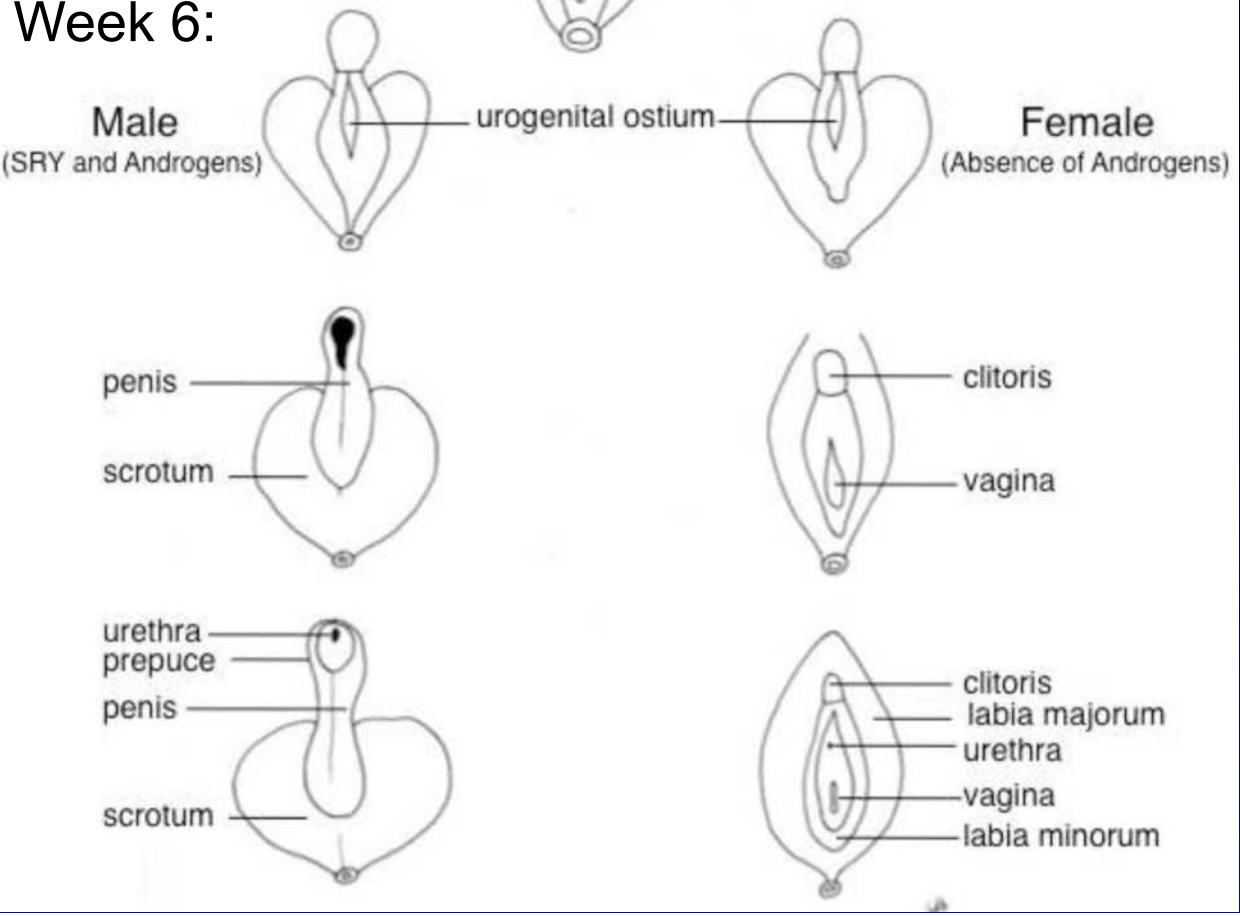
- If Sry or excess Sox9 secreted before day 42, genital ridge differentiates into testis and <u>secretes testosterone:</u>
  - Brain and body male-typical, gynephilic
  - Anti-Müllerian Hormone (AMH) prevents female ducts.
  - Genital tubercle (phallus) grows beyond 84 days.

Piprek, RP,
J Appl Genet, 2009

Week 5:

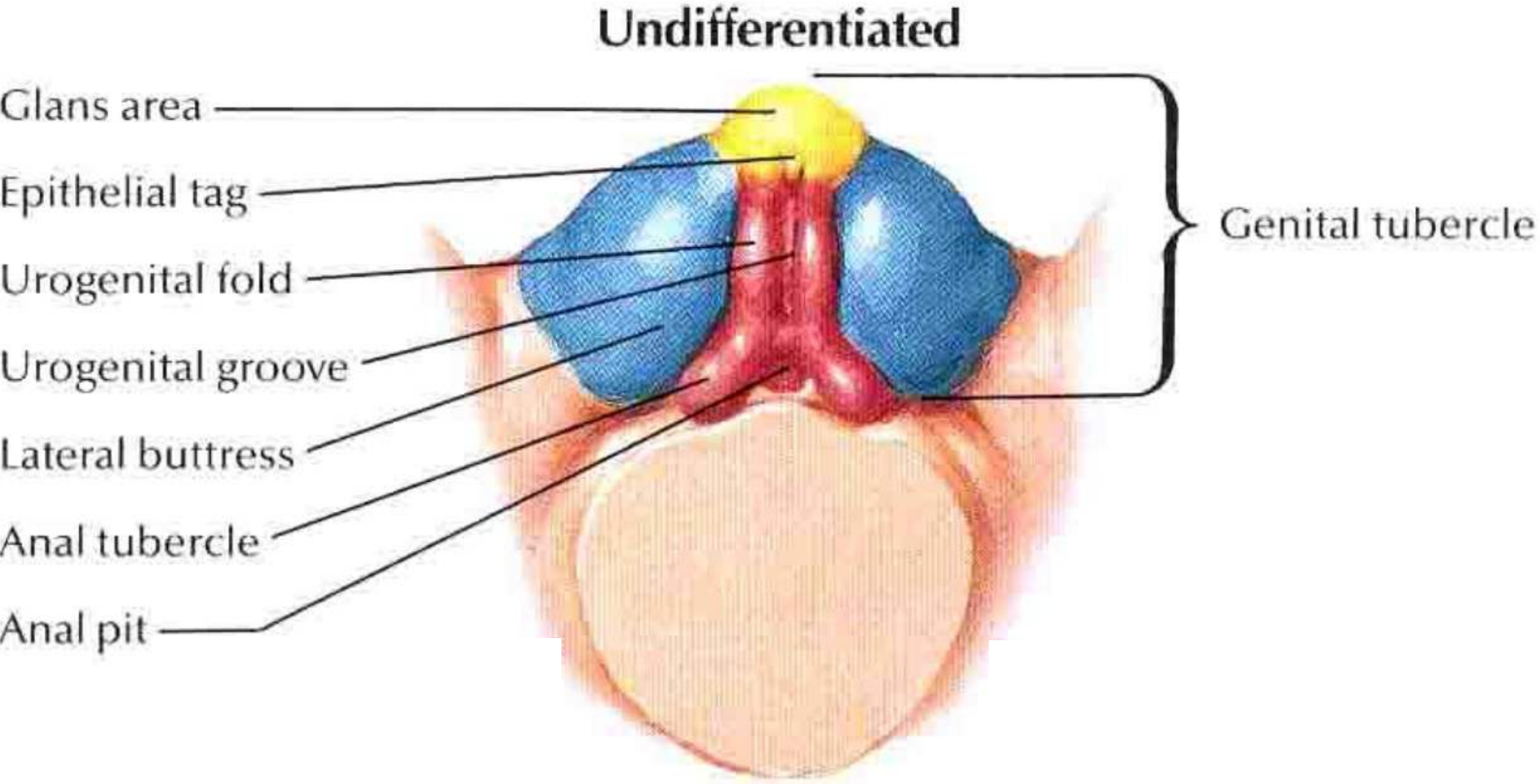


Week 6:

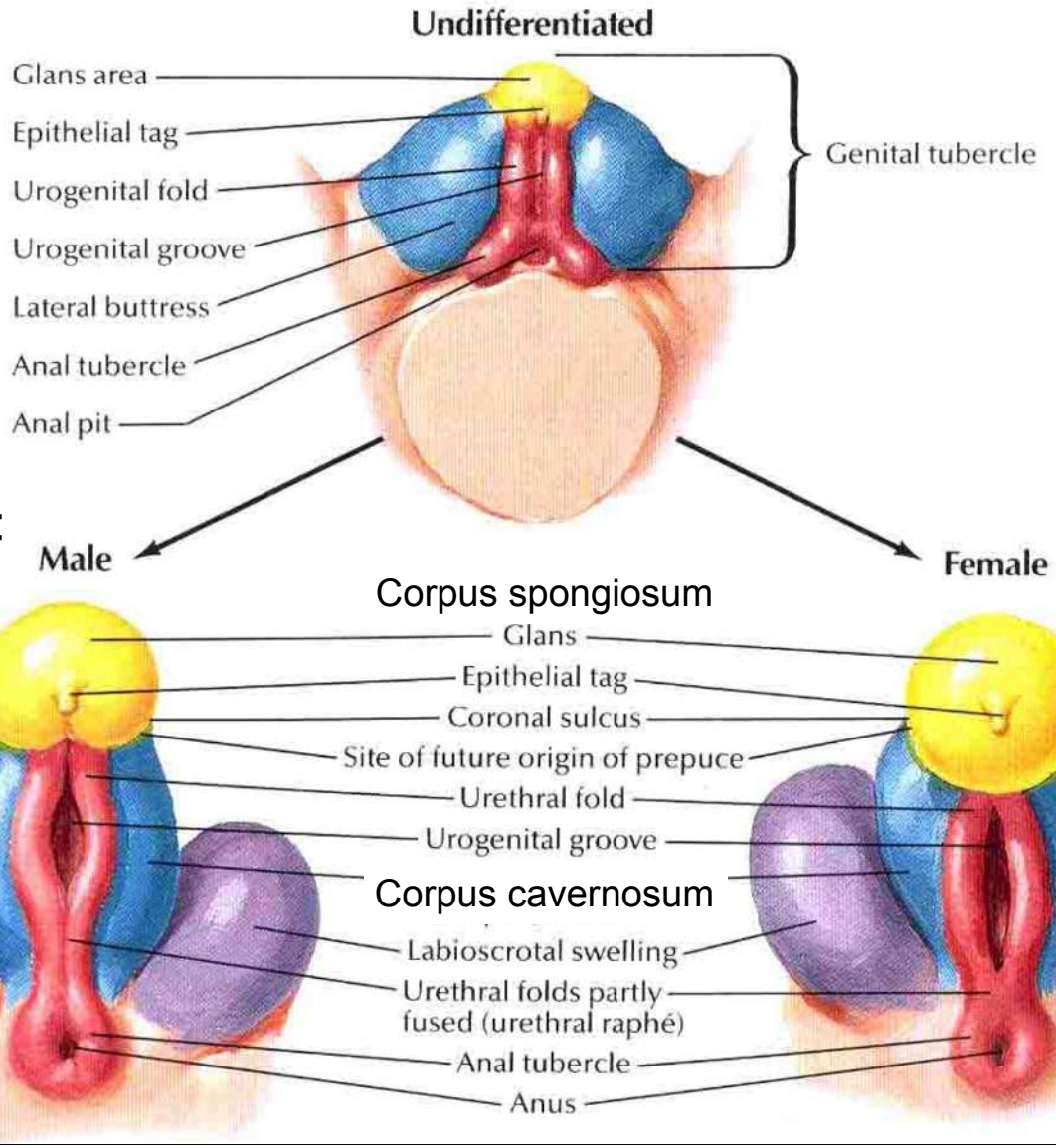


- Cells pile up in the midline of the perineum, forming the genital tubercle, through a hormone-independent process, from gestational weeks 8 and 12.
  - If testosterone present, the genital tubercle (penis) elongates, fusing in the underside midline, converting the urethral groove into a urethra. The labioscrotal folds fuse in the midline to form the scrotum.
  - Absent hormones, the labia majora stay separate and the genital tubercle (clitoris) stops growing at week 12.

Week 5:

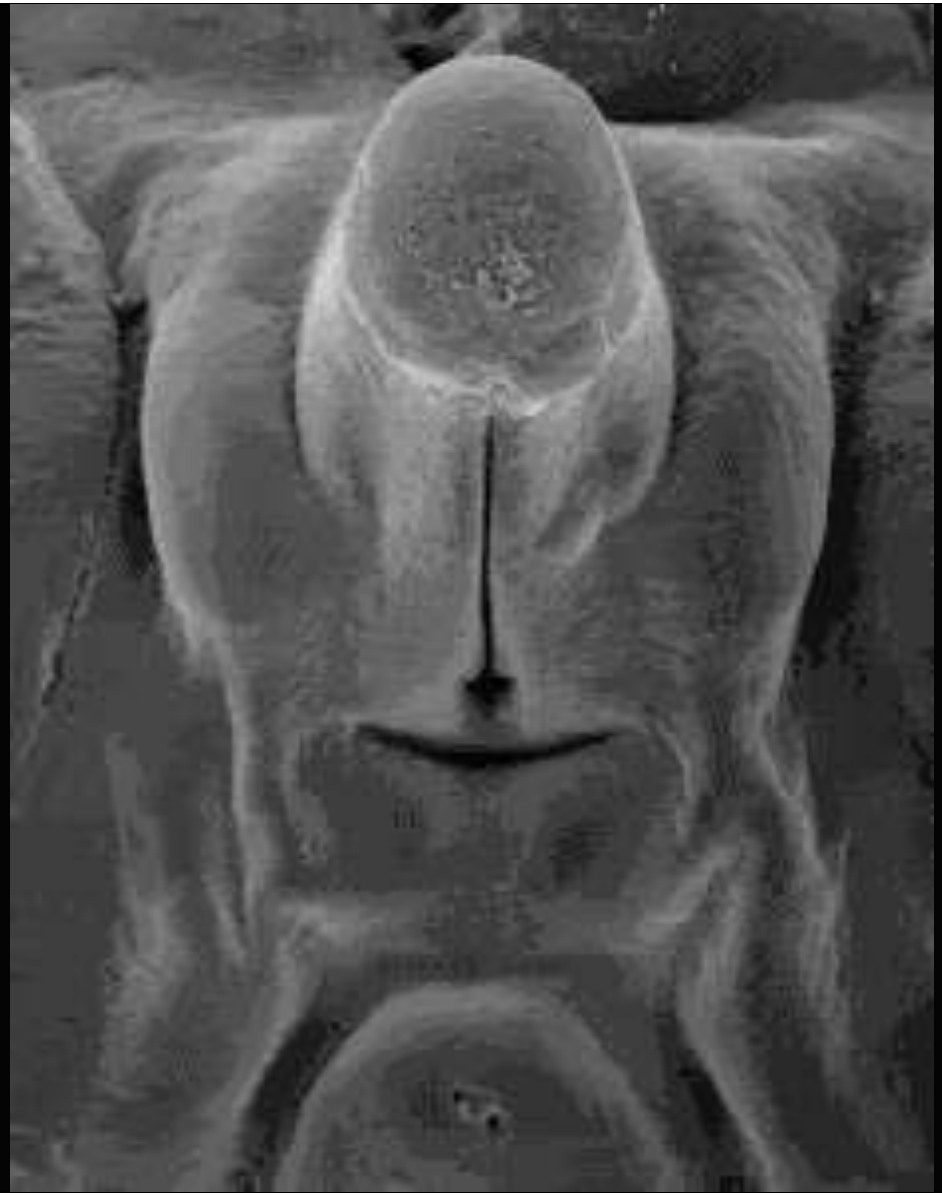

Undifferentiated
Glans area
Epithelial tag
Urogenital fold
Urogenital groove
Lateral buttress
Anal tubercle
Anal pit
Genital tubercle

Week 5:

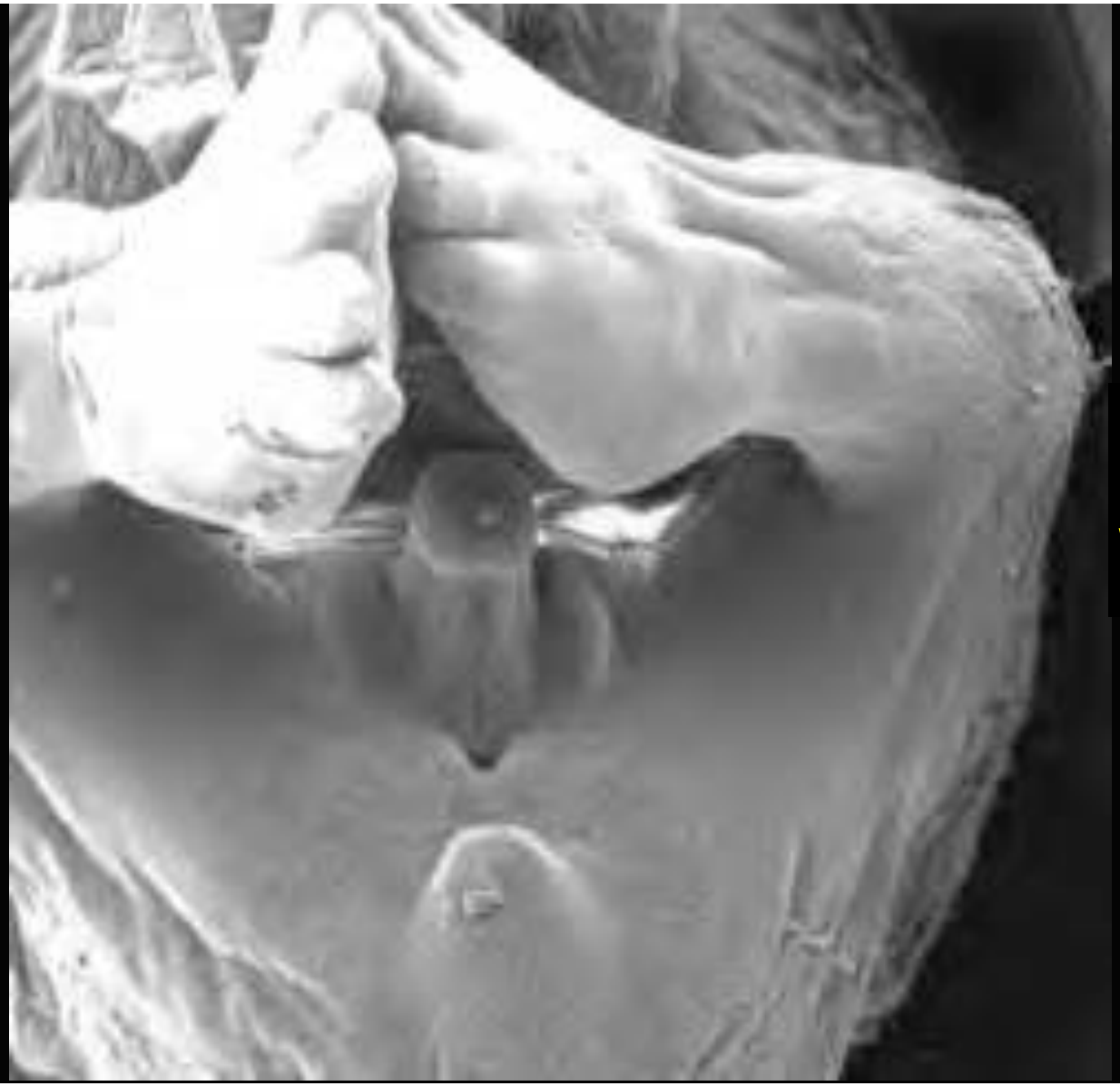


Weeks 6 to12:

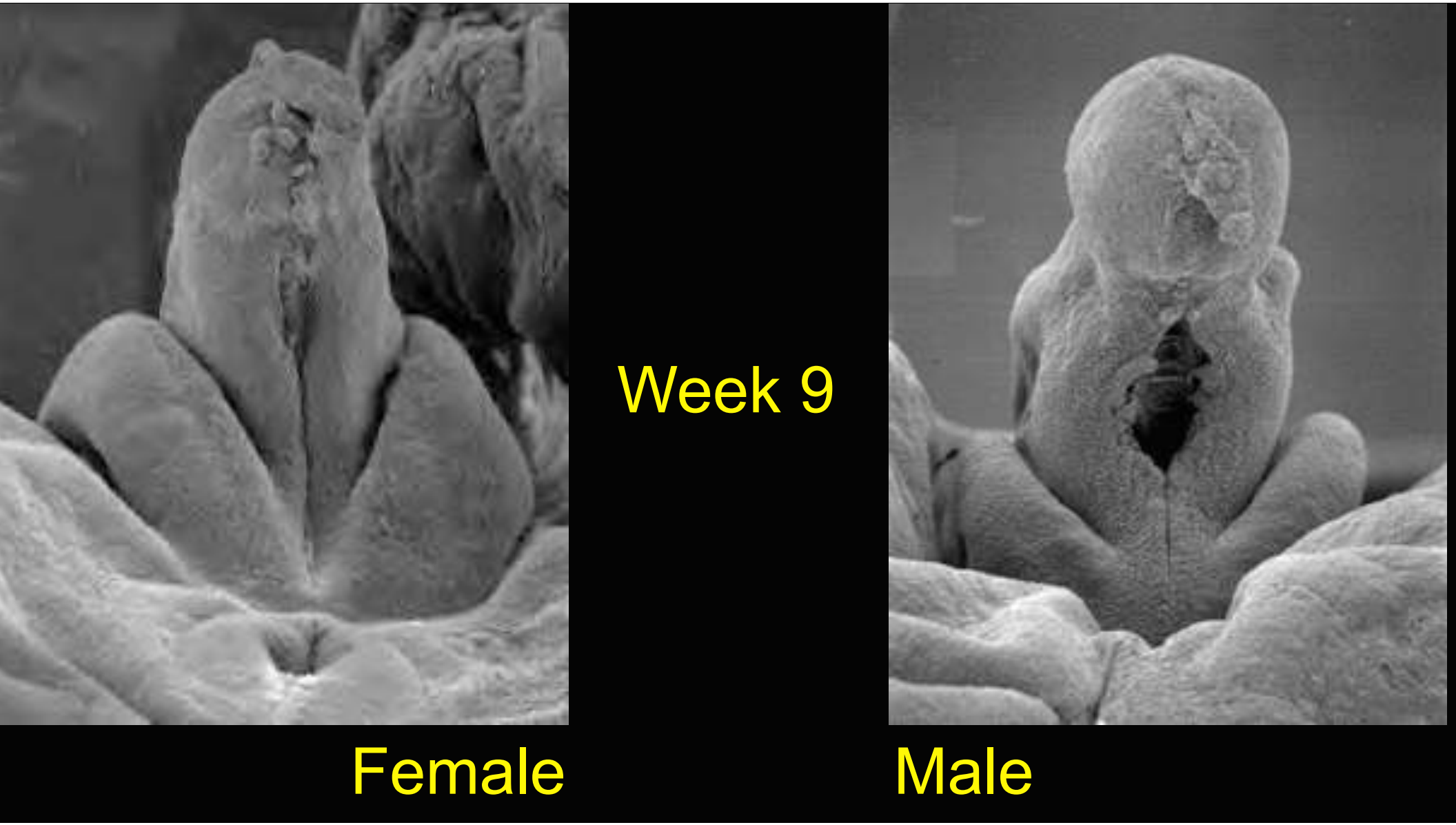
Week 7



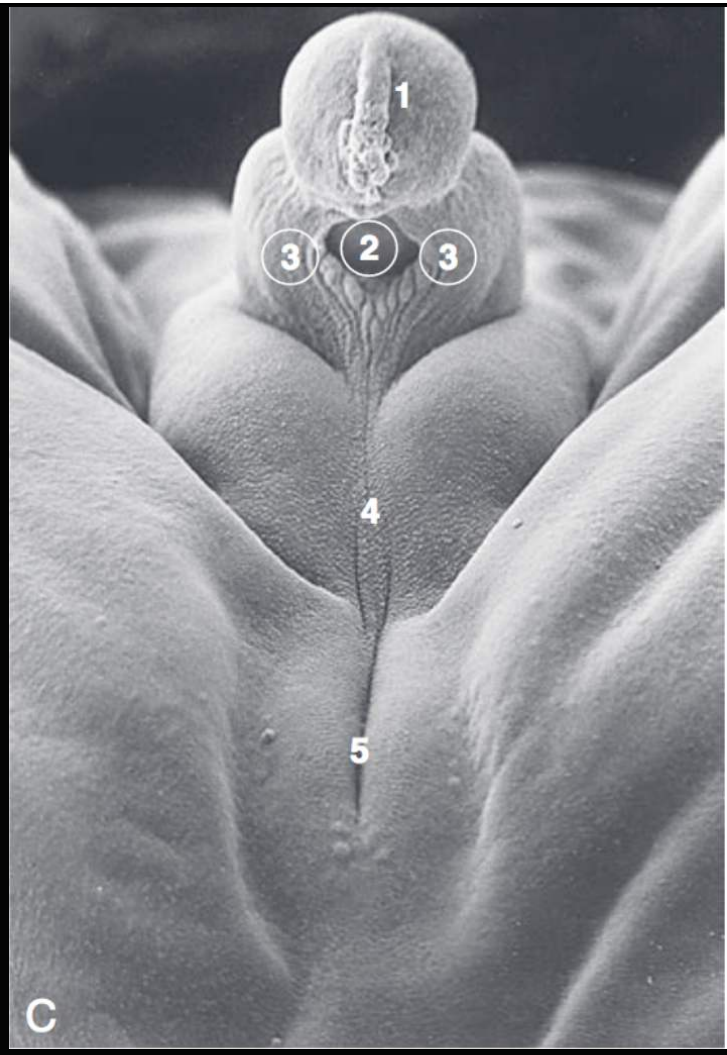
Week 7.5



Week 8


Week 9
Female
Male

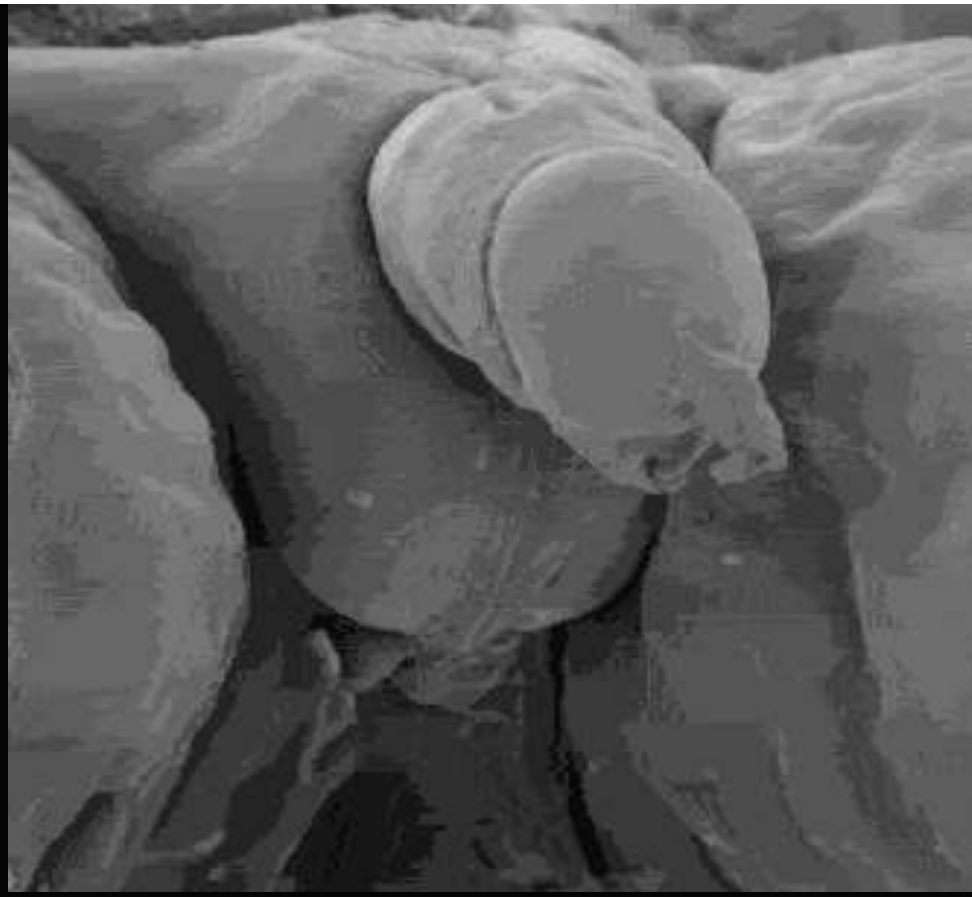
Week 10



Female

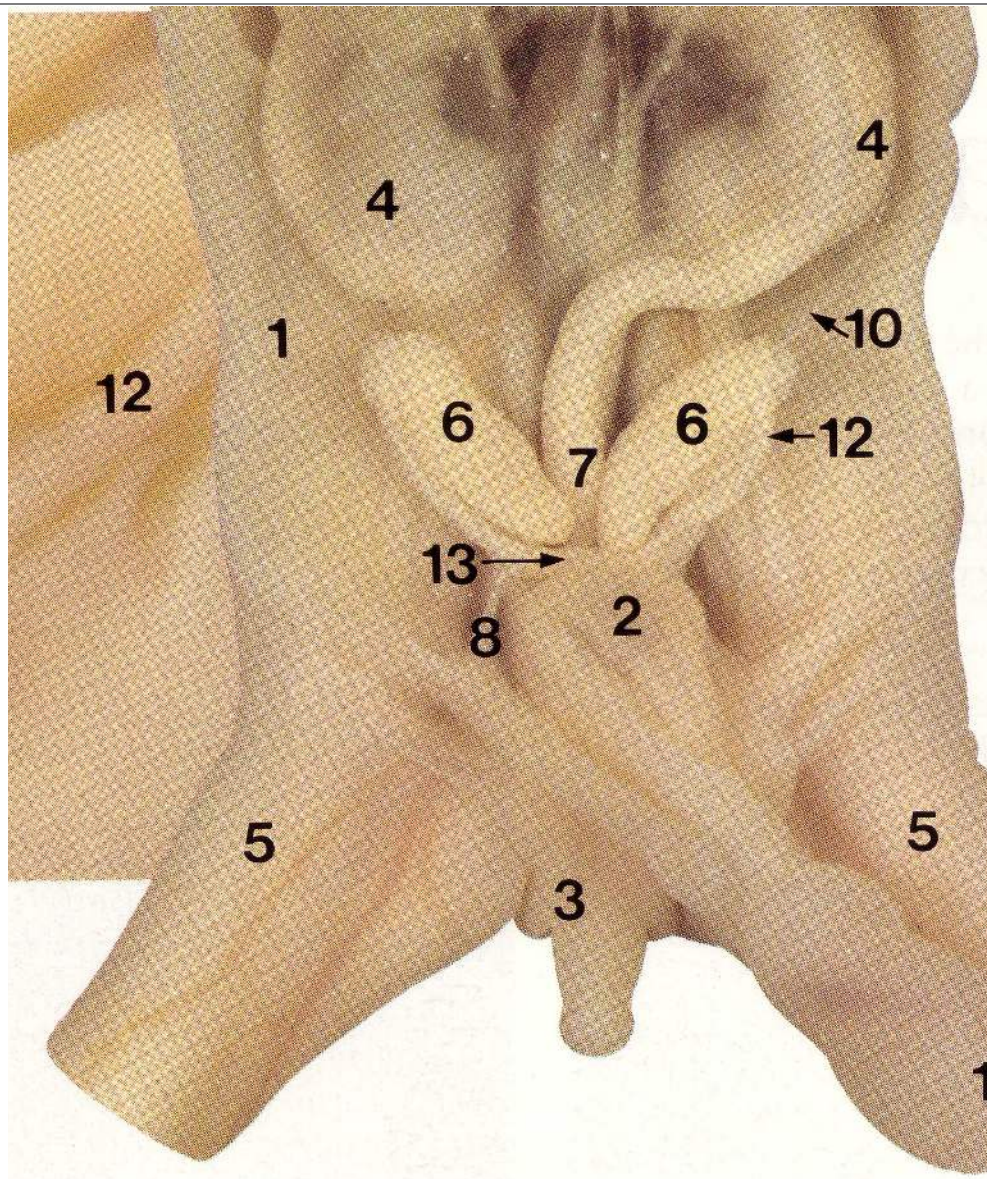
Male

Week 11



Female

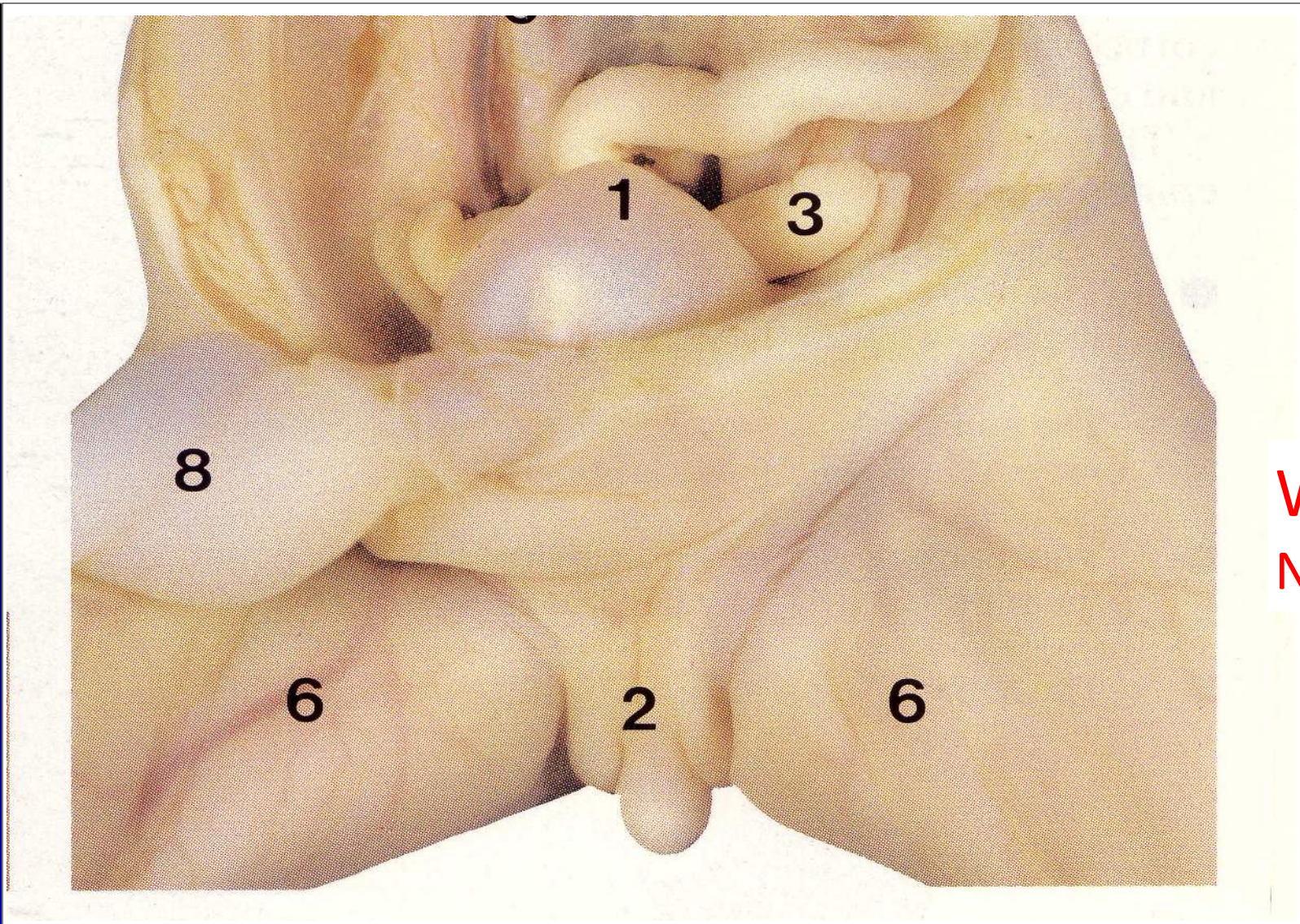
Male



1. abdomen
2. bladder
3. external genitalia
4. kidney
5. leg
6. ovary
7. rectum
8. round ligament of the uterus
9. suprarenal gland
10. suspensory ligament
11. umbilical cord
12. uterine tube
13. uterovaginal primordium

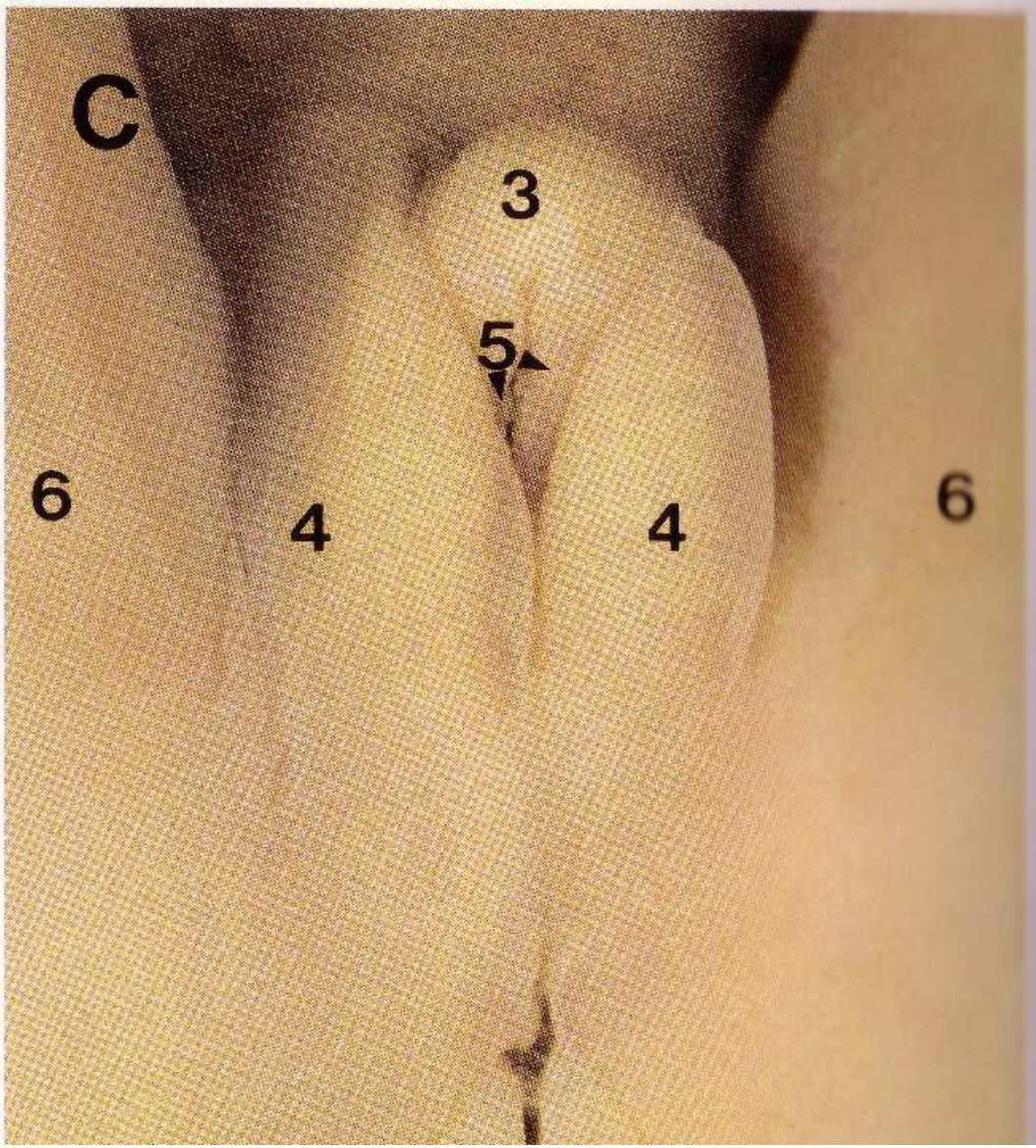
Week 9

Normal Female



Week 14

Normal Female



- Week 17 Normal Female

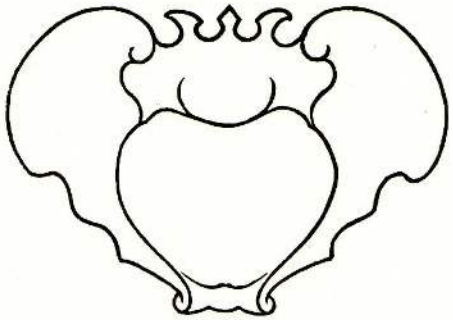
- The human penis and clitoris develop from the ambisexual genital tubercle.
- The neurovascular anatomy is similar in both the developing human penis and clitoris.
    - Baskin L, et al, Differentiation. 2018 Sep-Oct;103:74-85.

A TOPOGRAPHICAL HAND ATLAS

HUMAN SEX ANATOMY

by

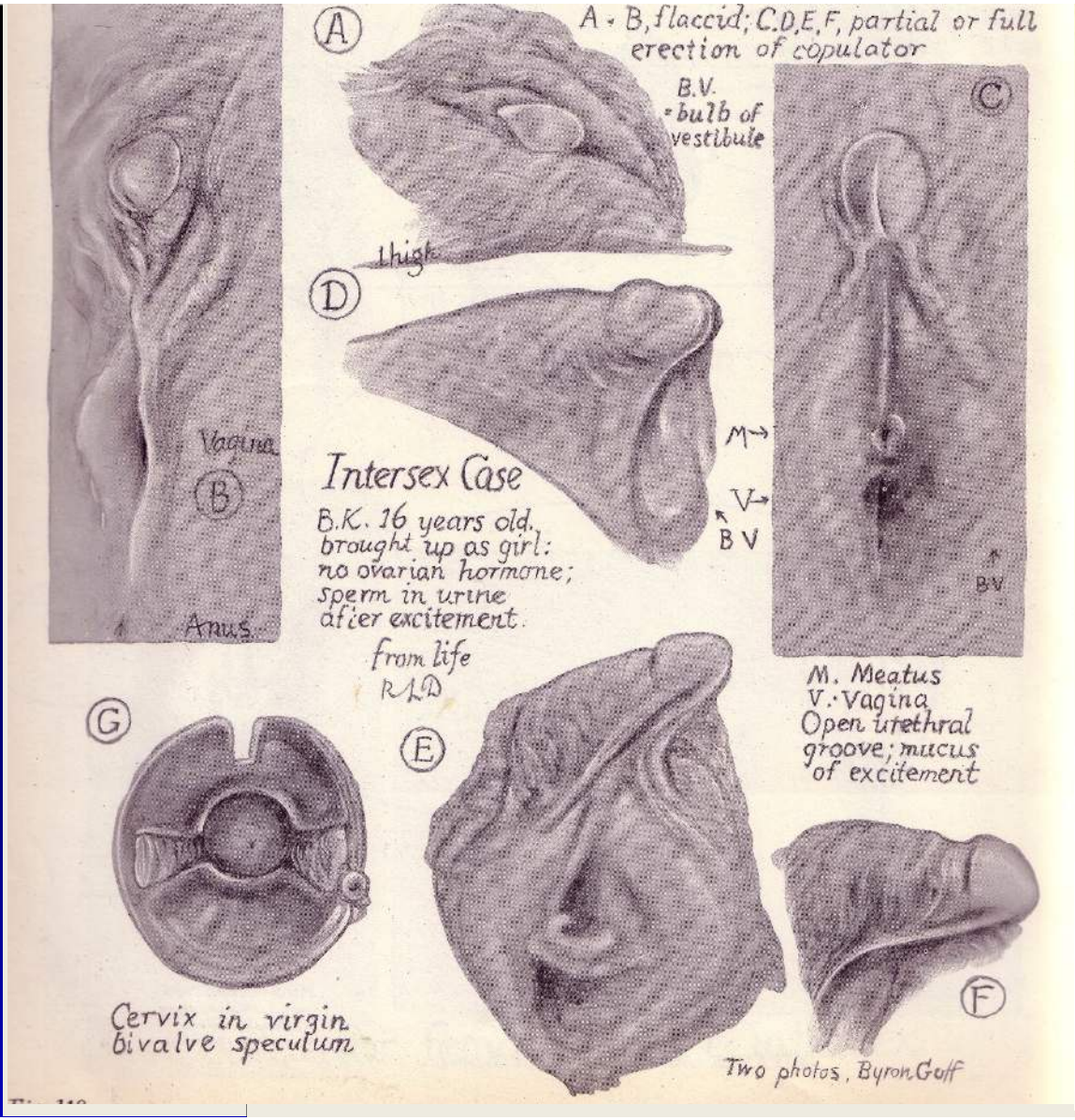
ROBERT LATOU DICKINSON
M.D., F.A.C.S.



SECOND EDITION

BALTIMORE
THE WILLIAMS & WILKINS COMPANY
1949

- 1949


A
A - B, flaccid; C.D.E.F, partial or full erection of copulator
B.V. = bulb of vestibule
Thigh
C
D
Vagina
B
Anus
M→
V→
↖ B V
B.V
Intersex Case
B.K. 16 years old, brought up as girl: no ovarian hormone; sperm in urine after excitement.
from life
R.L.D
M. Meatus
V. Vagina
Open urethral groove; mucus of excitement
G
E
F
Cervix in virgin bivalve speculum
Two photos, Byron Goff

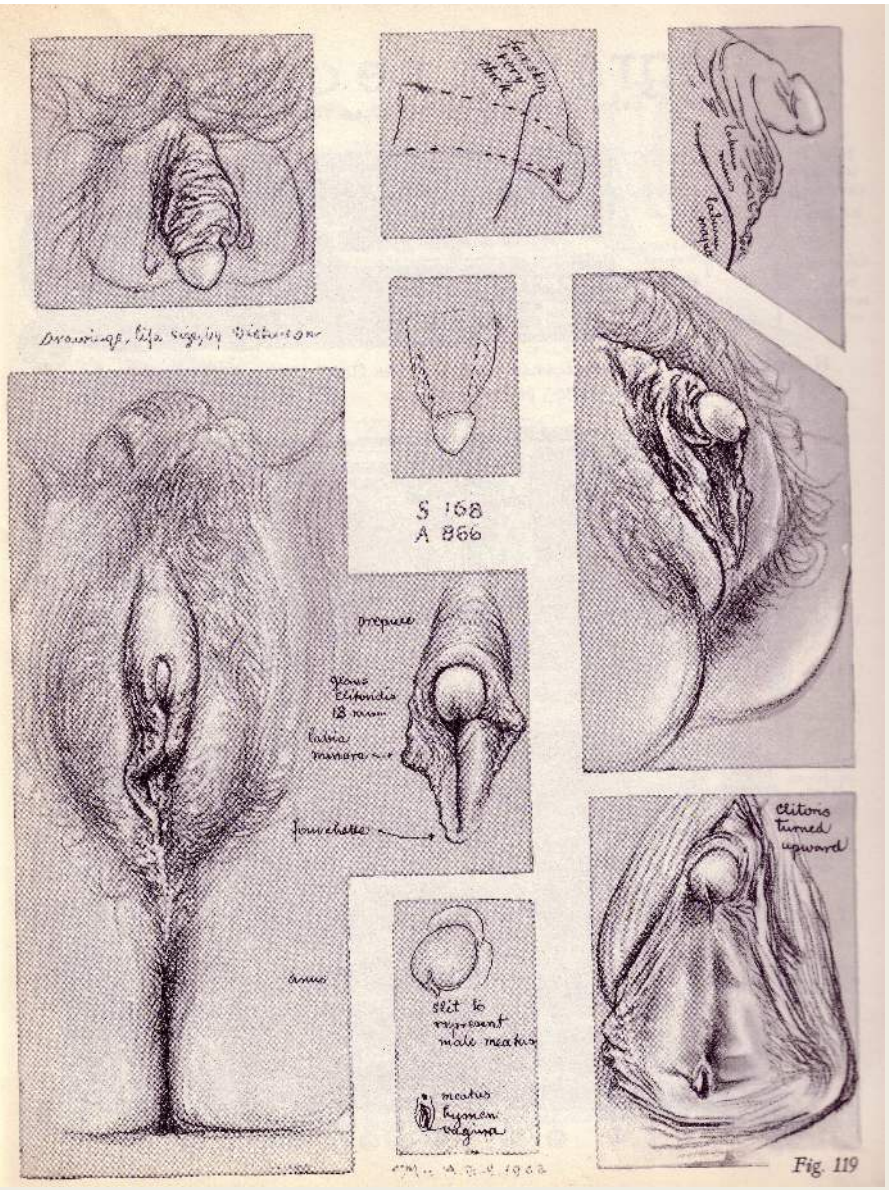
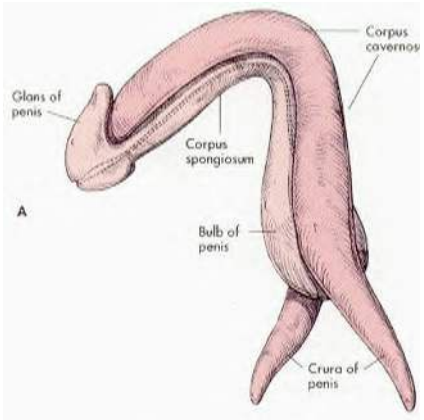
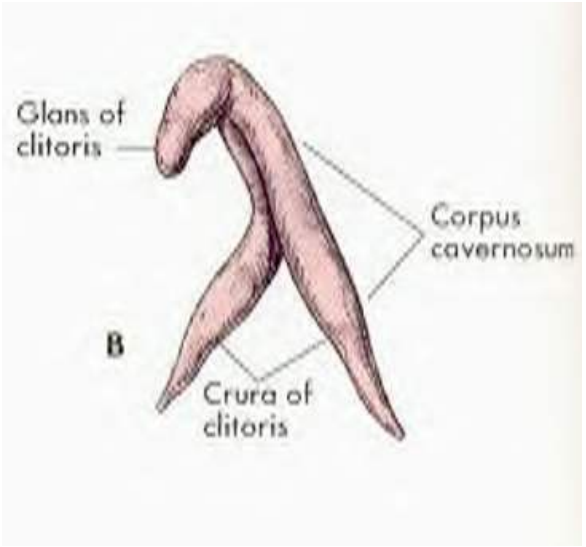

Drawings, life size, by Dickinson
S 168
A 866
prepuce
glans clitoridis 18 mm
labia minora
fourchette
anus
slit to represent male meatus
meatus
hymen
vagina
clitoris turned upward

Fig. 119

If no testosterone secreted during gestation, growth stops at week 12

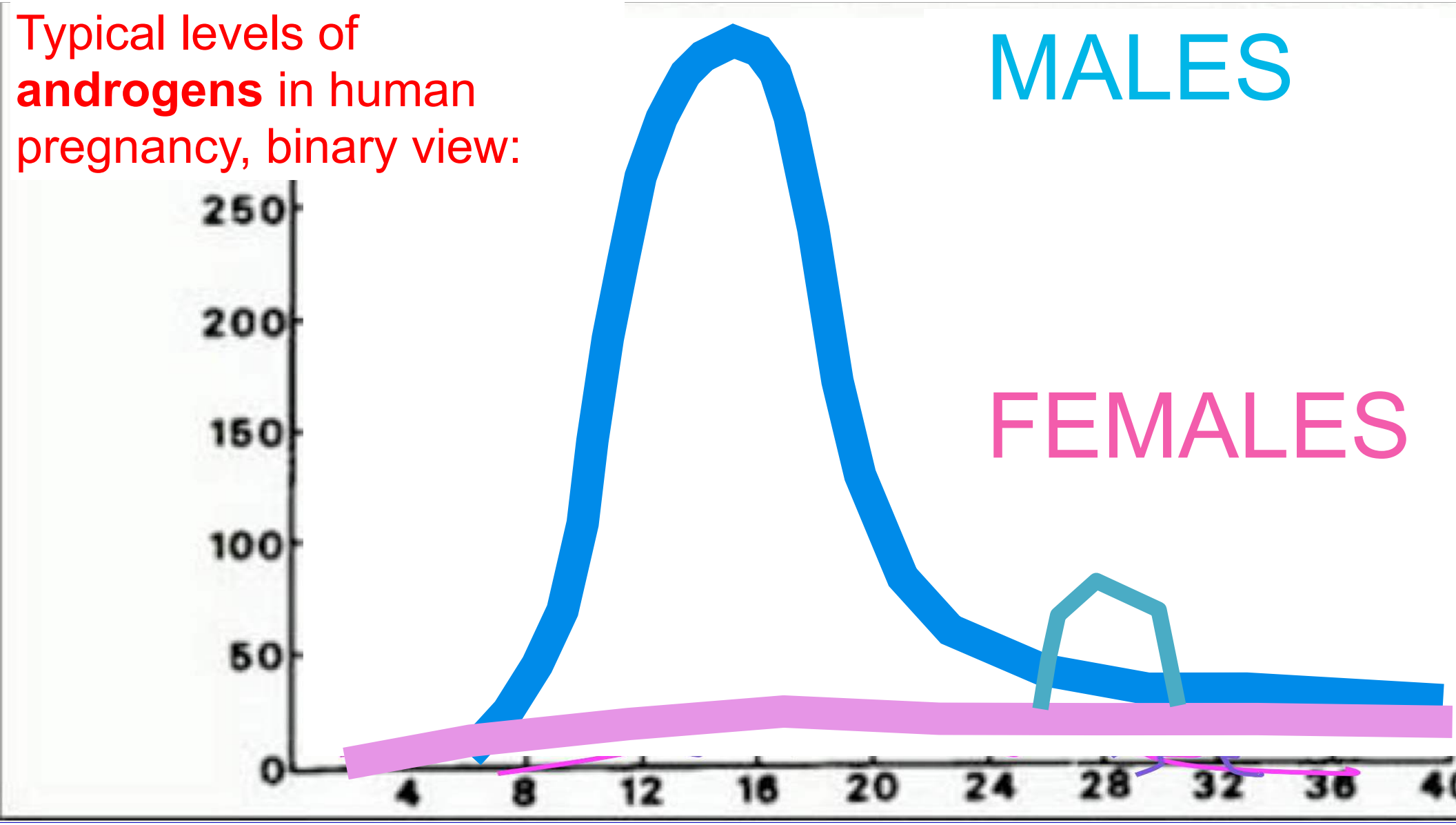




Both at week 12

If testosterone secreted during gestation, growth continues.

Typical levels of **androgens** in human pregnancy, binary view:



Two testosterone surges affect male fetuses.

- First trimester stimulates genital growth and brain effects.
- Second trimester surge further masculinizes the male brain.
- These two processes are independent, explaining transsexualism.
- “All the genetic, postmortem, and in vivo scanning observations support the neurobiological theory about the origin of gender dissonance, i.e., sizes of brain structures, neuron numbers, molecular composition, functions, and connectivity of brain structures that determine our gender identity or sexual orientation.”
- “There is no evidence that one’s postnatal social environment plays a crucial role in the development of gender identity or sexual orientation.”

- Swaab, D., et al (2022). Sexual Differentiation of the Human Brain in Relation to Gender-Identity, Sexual Orientation, and Neuropsychiatric Disorders. In: Pfaff, D.W., et al (eds) Neuroscience in the 21st Century. Springer, Cham.

Binary view of Sexual Humanity

Gender - identity

Man — Woman

Orientation - attraction

To women — To men

Social sex role - cultural norm

Masculine — Feminine

Biological sex - genital anatomy

Penis, scrotum — Clitoris, labia

Anatomy/physiology: Somatic, Neural

Androgenized — Feminized

The Binary view of sexual dimorphism

- Most typically, a male fetus secretes testosterone in the first trimester.
- Their external genitals are male-like and the genital tubercle enlarges after 12 weeks to form a penis.
- They identify as male, exhibit boy-like play patterns, develop masculine visuospatial abilities, bone structures and body motion, vocal range, math abilities, and an orientation toward women.

- Most typically, a female fetus secretes little or no testosterone.
- Their external genitals remain female-like and the genital tubercle stops enlarging after 12 weeks.
- They identify as female, exhibit girl-like play patterns, develop feminine bone structures and body motion, and exhibit increased empathy, verbal fluency, and a sexual orientation toward men.

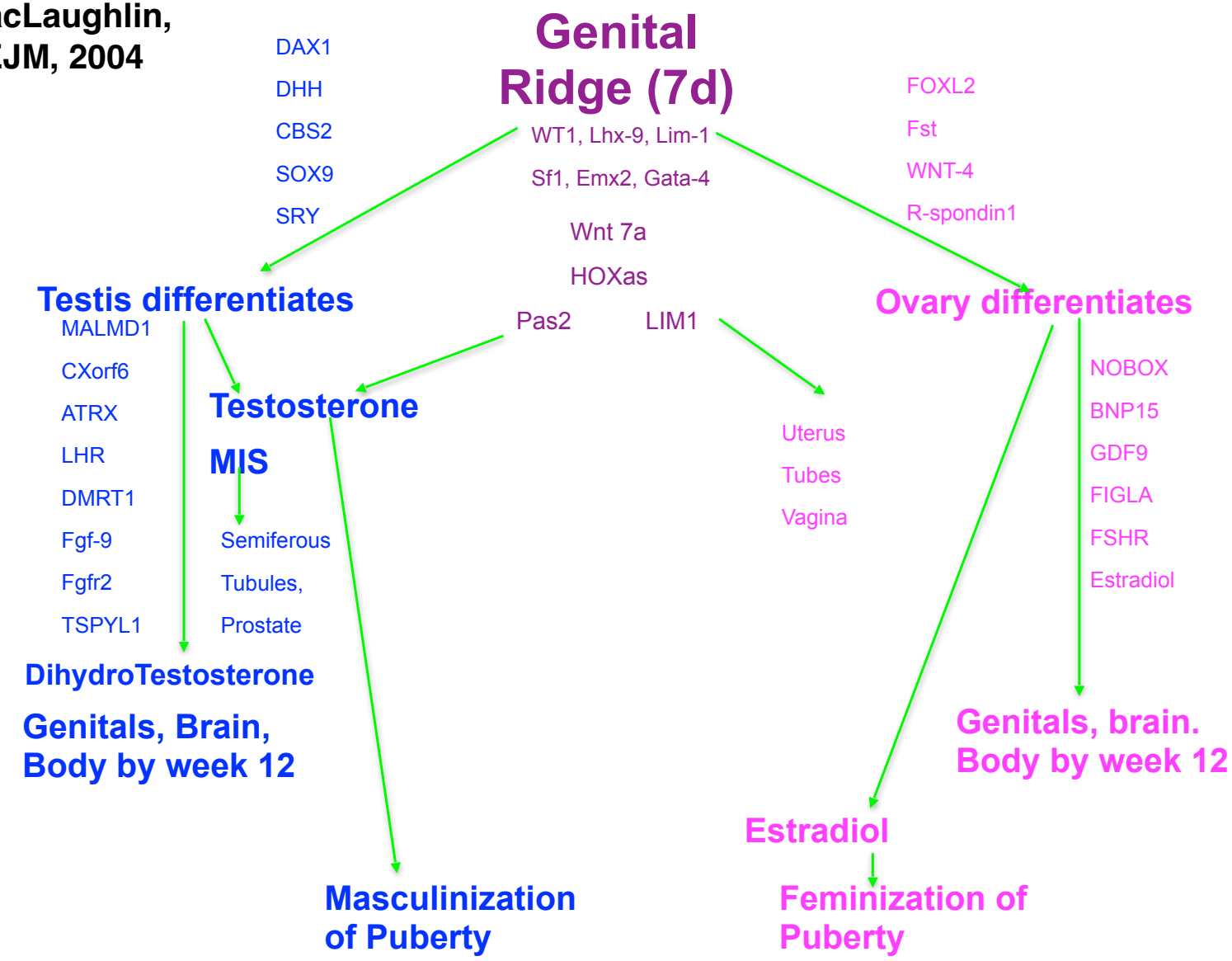
Organization: variable testosterone levels during gestation

- Testosterone levels in cord blood is typically 9x higher in males compared to females. (Abramovich, 1974)

- Testosterone levels in amniotic fluid correlate with sexually differentiated human play preferences between boys and girls, increasing effect with increasing age, and not moderated by social/cultural factors.
  - Boys prefer male-typical toys and aggressive play.
  - Girls prefer female-typical toys and play, over gender-atypical toys.

Davis, & Hines, (2020). How large are gender differences in toy preferences? A systematic review and meta-analysis of toy preference research. *Archives of Sexual Behavior, 49*(2), 373–394.

MacLaughlin, NEJM, 2004



DETERMINATION
Genes instruct gonads

DIFFERENTIATION
Gonads become Ov / Tes

ORGANIZATION
Ov / Tes instruct body/brain

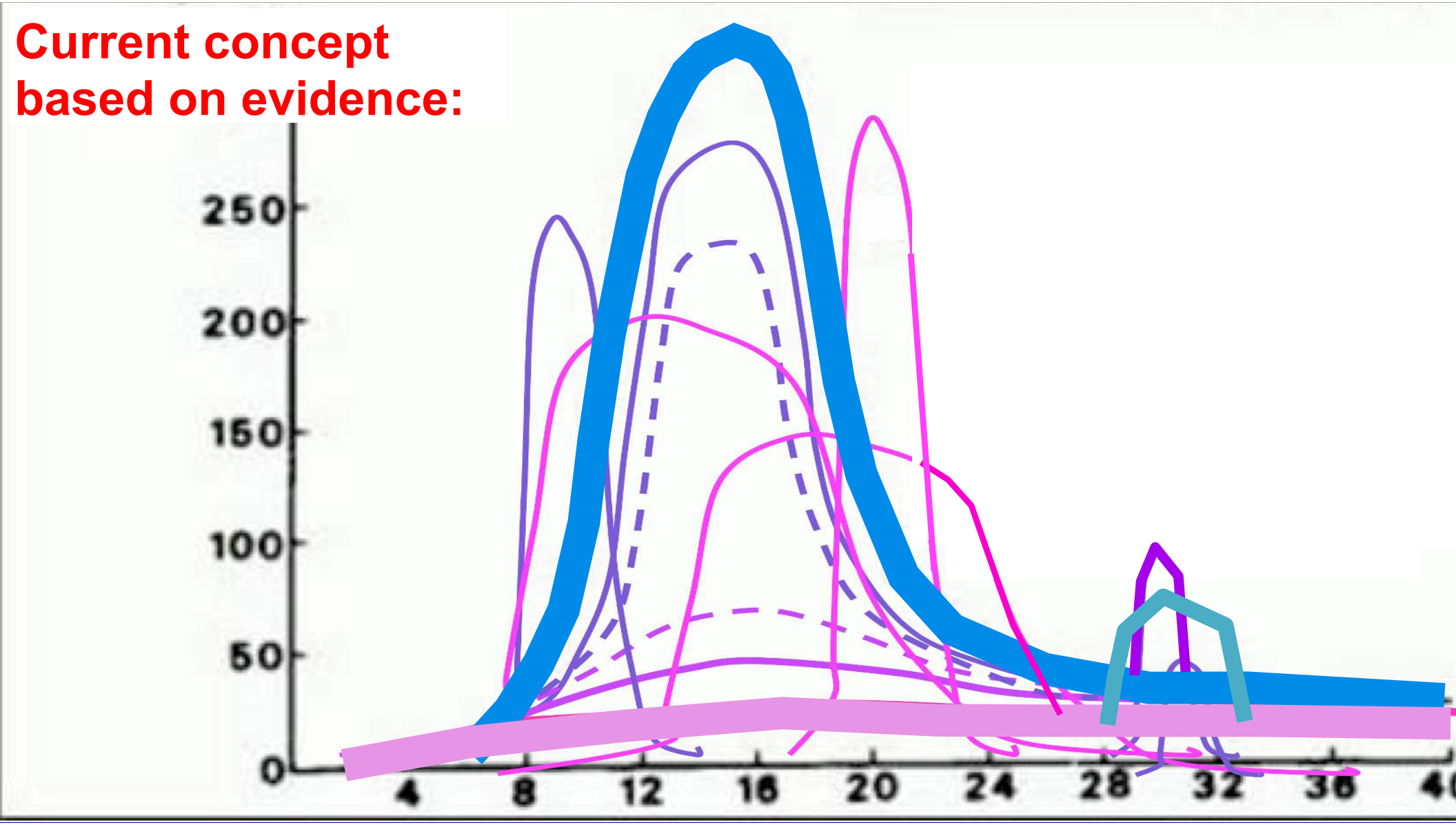
ACTIVATION
Hormones activate body

32 predictors for sexually dimorphic traits, so far

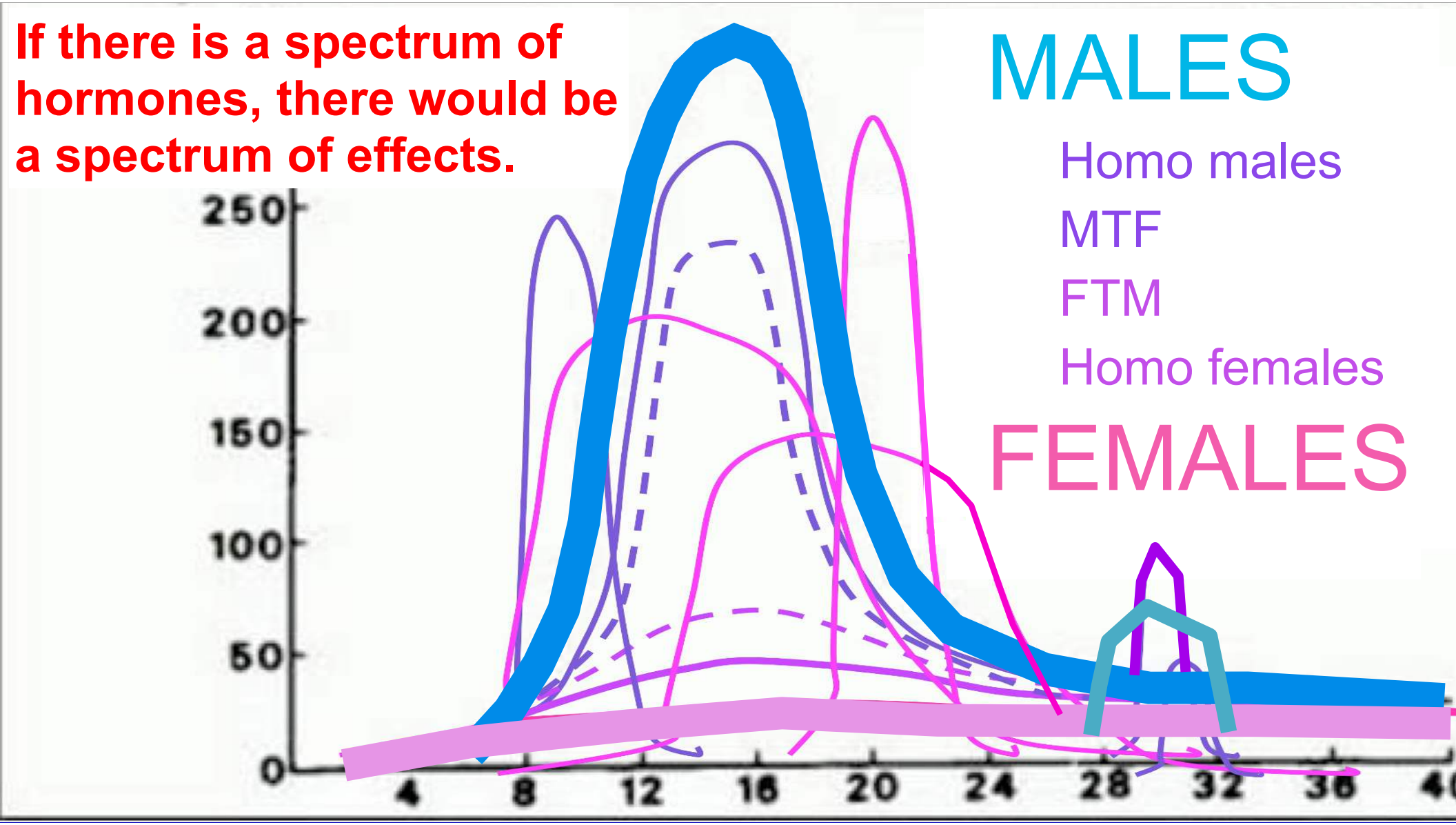
- For example, each of 32 chemicals can be high, normal, low, absent.
- There are 4^{32}, or 1,852,020,188,851,841 possible outcomes of sexually dimorphic traits: a spectrum.

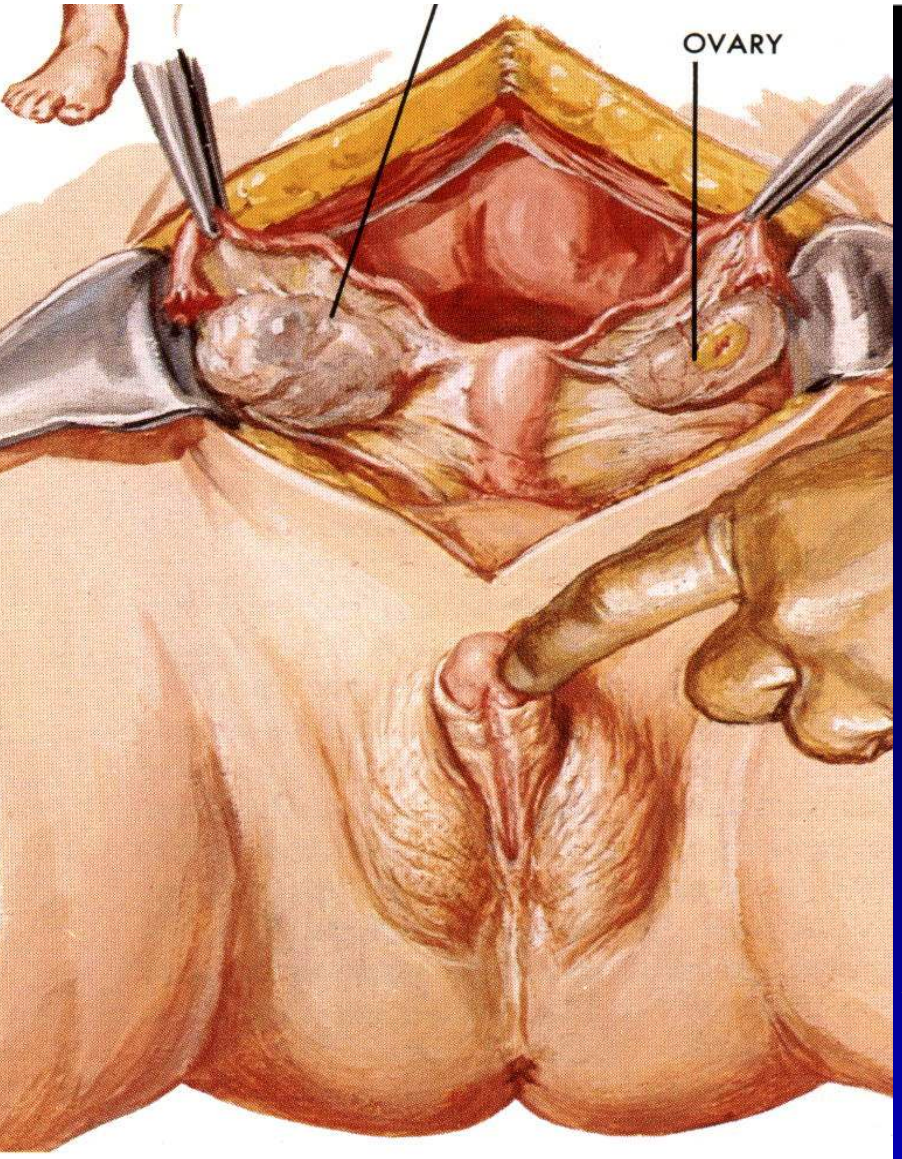
Probability of multiple events https://www.storyofmathematics.com/probability-of-multiple-events/

Current concept based on evidence:



If there is a spectrum of hormones, there would be a spectrum of effects.



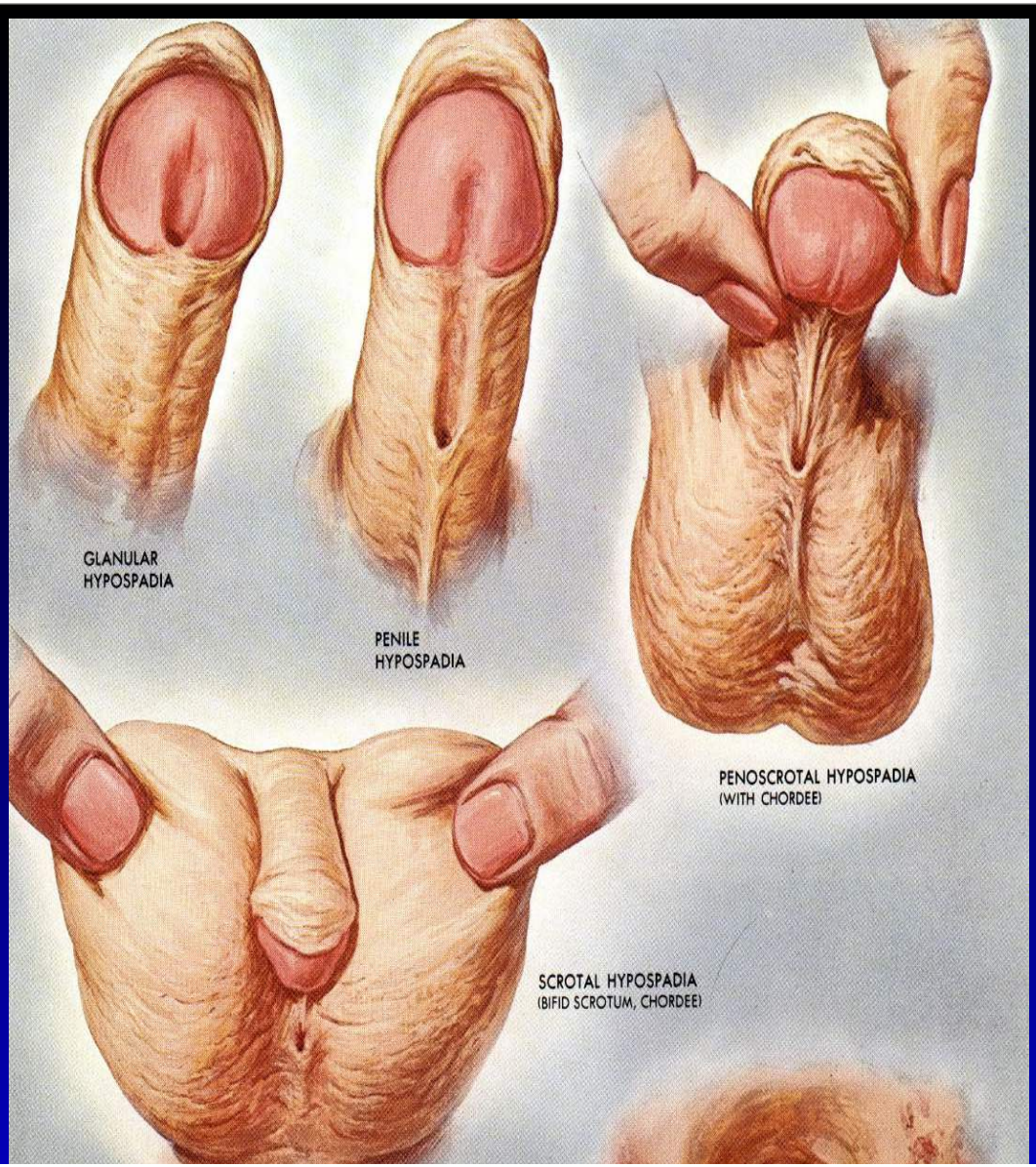


Organization of XX

Under “extra” testosterone influence:

- A clitoris can keep growing.
- The uterus may remain small.
- The brain may be androgenized.
- Identity: cis, non-binary or trans.
- Orientation: Bi, gynephilic

Adrenals, stress, medications, OCP’s. DES, environmental hormones.



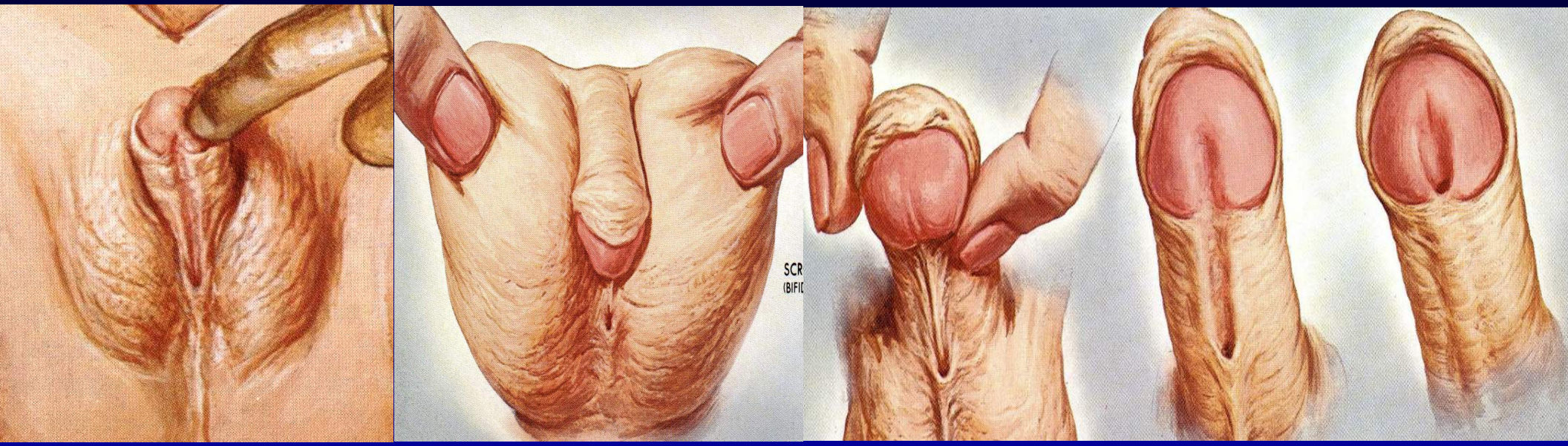
Organization of XY

Under “less” testosterone influence:

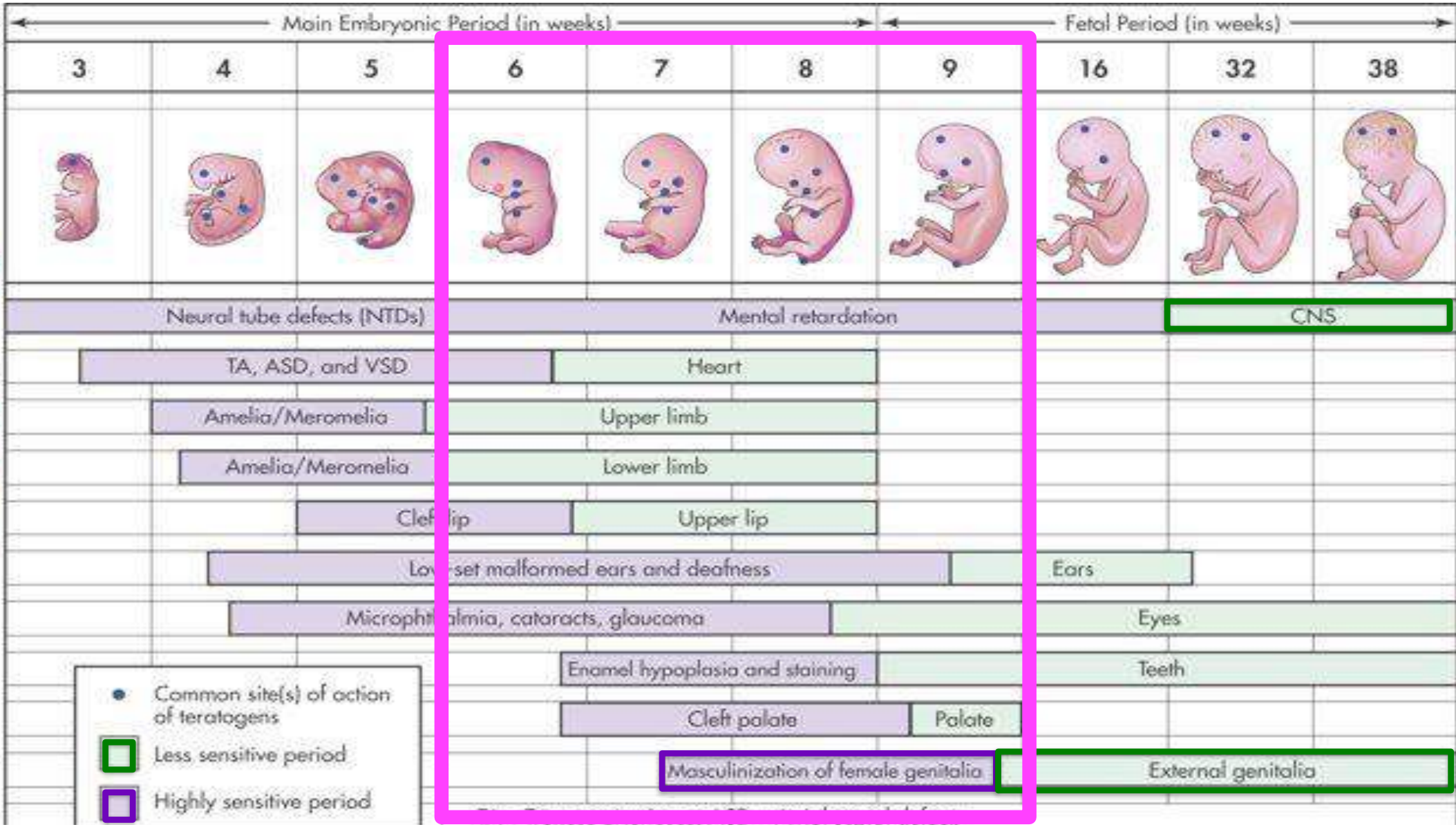
- A phallus can stop growing.
- Urethra may not complete.
- Testes may not descend.
- Brain may be less androgenized
  - Identity: cis, non-binary or trans.
  - Orientation: Gay, Bisexual

Genetics, maternal PCOS, environmental hormones, more brothers,

Organization:
Spectrum of genital development



Diversity of Sexual Differentiation (DSD's)

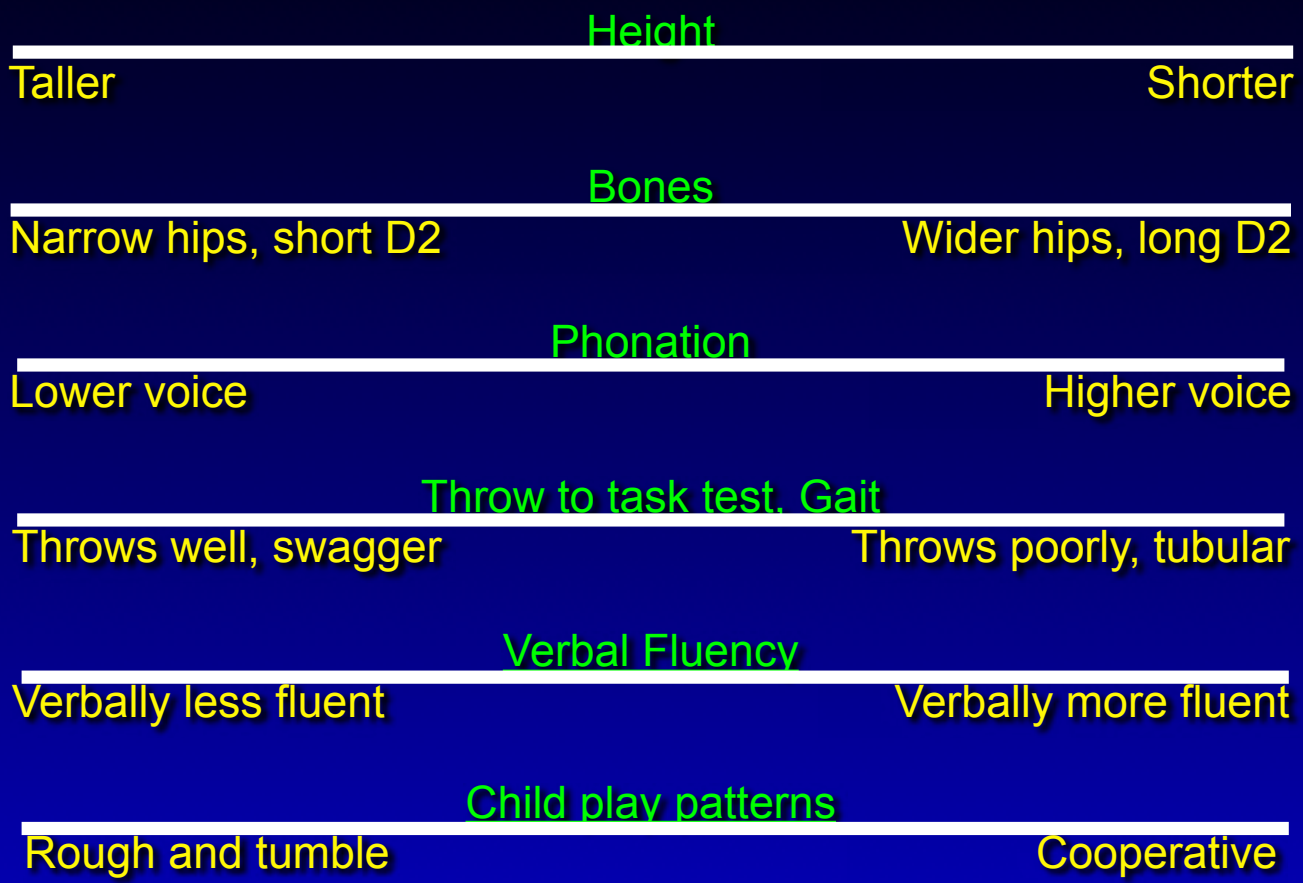

Main Embryonic Period (in weeks)
Fetal Period (in weeks)
3
4
5
6
7
8
9
16
32
38
Neural tube defects (NTDs)
Mental retardation
CNS
TA, ASD, and VSD
Heart
Amelia/Meromelia
Upper limb
Amelia/Meromelia
Lower limb
Upper lip
Ears
Eyes
Enamel hypoplasia and staining
Teeth
Cleft palate
Palate
Masculinization of female genitalia
External genitalia
Common site(s) of action of teratogens
Less sensitive period
Highly sensitive period

Sexually “dimorphic traits”:
Characteristics organized by sex hormones *in utero*

- Physical anatomy:
  - Genital size and appearance, breasts, body hair, vocal chords.
  - Somatic: bones, height, pelvic bone, digit length larynx.
  - Neural: Hypothalamus, INAH, corpus calosum

- Physical function:
  - Child play styles, running, throwing, walking, voice.
  - Gender Identity, orientation, hearing, verbal fluency, articulation, grammar, visuospatial skills.

Prenatal androgens **organize** many other sexually dimorphic features

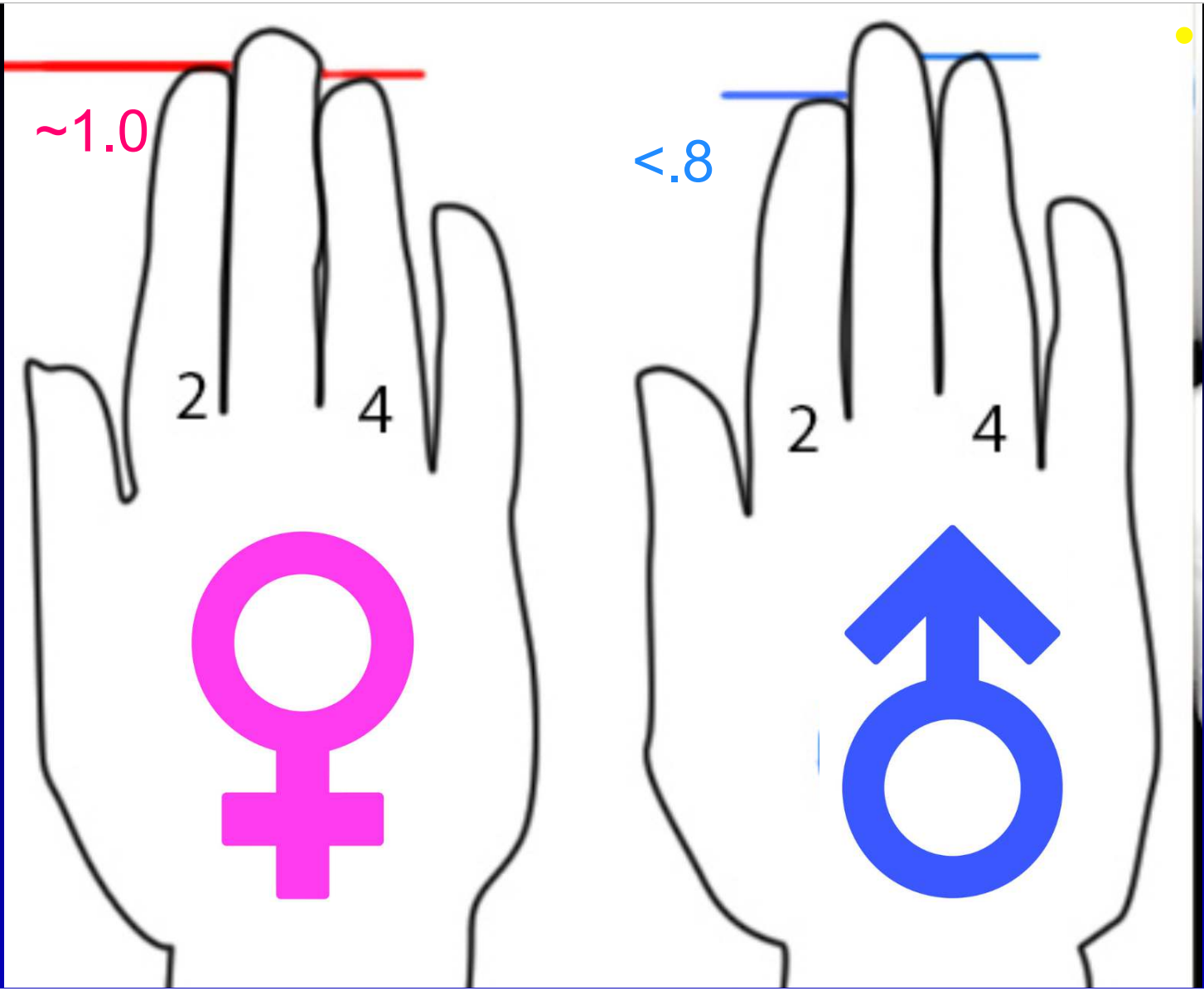



• Men are typically taller

Pelvic bone spectrum

Male pelvis:
Narrower, heart-shaped

Female pelvis:
Wider sub-pubic angle



- 2D/4D digit ratio

Men have shorter index fingers than their ring fingers.

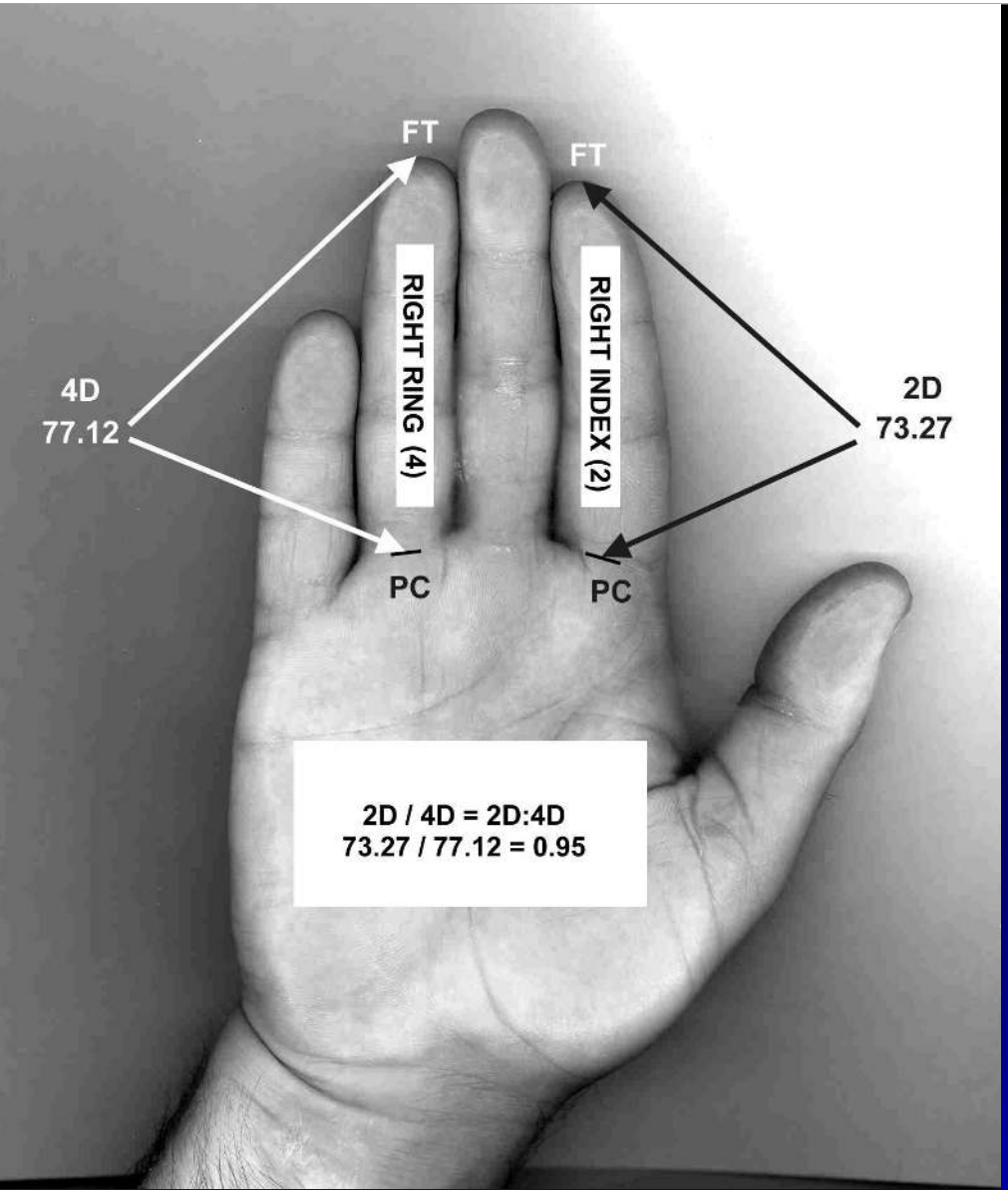
Ratio is lower

Women have longer index fingers than their ring fingers.

Ratio is higher

Organization effects: Digits

- 2D/4D digit ratio is biologically conferred as a dimorphic trait:
- Constant since birth.
- Not influenced by adult hormone levels.



Prenatal androgens shorten index finger

- A lower, masculinized 2D:4D ratio is seen in lesbians, and female-to-male transsexuals.

  Manning JT, et al Digit Ratio (2D:4D; Right-Left 2D:4D) and Multiple Phenotypes for Same-Sex Attraction: The BBC Internet Study Revisited. Arch Sex Behav. 2024 Jan;53(1):213-222.

  Leinung, M.C.,The Biologic Basis of Transgender Identity: 2D:4D Finger Length Ratios Implicate A Role for Prenatal Androgen Activity, AACE Endocrine Practice,Volume 23, Issue 6, P669-671, June 2017

- A higher, feminized 2D:4D ratio is noted in gay men and male-to-female transsexuals.

  Lupu DC, et al, In support of 2D:4D: More data exploring its conflicting results on handedness, sexual orientation and sex differences. PLoS One. 2023 Aug 22;18(8)

  Siegmann EM, et al, Digit ratio (2D:4D) and transgender identity: new original data and a meta-analysis. Sci Rep. 2020 Nov 9;10(1)

Prenatal androgens organize all sexually dimorphic features on a spectrum

- Lesbians tend to have more male-typical features such as spatial and visuospatial skills, less body dissatisfaction and lower rates of eating disorder, lower voice pitch, greater athletic and throwing skills, possibly lower pain thresholds, more ambidexterity or left-handedness compared with heterosexual women.

- Gay males tend to have more feminine-typical traits such as fluid body movement, self-objectification, eating disorders, letter and verbal fluency, body dissatisfaction, speech patterns, and fingerprint patterns compared with heterosexual men.

  - Burke SM, et al. J Psychiatry Neurosci. 2016
  - *Xu Y, et al Neurosci Biobehav Rev. 2017*
  - *Hall JA, Arch Sex Behav 1995.*
  - Rahman, Q, et al. *Hippocampus. 2008*
  - Rahman, Q, et al. *Neuropsychology. 2003*

Organization effects: Phonation

- Laryngeal anatomy is is biologically conferred as a dimorphic trait.

  Hamdan Aet al. *Ear, Nose & Throat Journal*. 2020

- Distinctive phonetic variations biologically conferred as a dimorphic trait.
- Detection of masculinity and femininity from audio samples possible.
- Gay men and Lesbian/bisexual women sounded less gender-typical than heterosexual samples.

  Munson, B. (2007). Lang Speech 50(Pt 1): 125-142.

Organization effects: Gait

- Gait is biologically conferred as a dimorphic trait:
  - Males typically have "tubular moving with shoulder swagger"
  - Females typically have "hourglass body moving with hip sway"

- Computer-generated gender-typical or -atypical animations of walk were accurately correlated with orientations.

Kozlowski, et al. *Perception & Psychophysics* **21**, 575–580 (1977).

Johnson, et al. (2007). J Pers Soc Psychol 93(3): 321-334.

Organization effects: Audiology

- Click-evoked otoacoustic emissions (CEOAEs) are echo-like sounds that are produced by the inner ear in response to click-stimuli and OAEs are masculinized by prenatal exposure to androgens late in gestation.
  - Males hear lower pitched sounds than females.

- Prenatal androgens affect both non-heterosexuality and the auditory system.
  - Adult Lesbians' CEOAE were masculinized.
  - Trans-girls' CEOAE were feminized.

- McFadden, D, Sexual Orientation and the Auditory System, Frontiers in Neuroendocrinology February 2011, 32(2):201-13
- Burke SM, et al, Postnatal Effects of Sex Hormones on Click-Evoked Otoacoustic Emissions: A Study of Adolescents with Gender Dysphoria. Arch Sex Behav. 2020 Feb;49(2):455-465.

Childhood dimorphism

- The 2D:4D ratio correlates with gender role play, aggression-proneness, preferred toy types of children.
  - Körner LM, et al,. Arch Sex Behav. 2020 Oct;49(7):2715-2724.

- Playing with gender-atypical toys/games/clothes, tomboy or sissy.
- Desiring gender-atypical careers,
- Gender identity confusion in adolescence (esp if Trans).
- Negative reaction to breast development, menarche, genital anatomy (70% for Trans).

  - Whitam, Arch Sex Behav 1991. Phillips, Arch Sex Behav 1995. Ehrhardt, Arch Sex Behav 1979. Antoszewski, Acta Chir Plast 1998.
  -

Prenatal brain organization from hormone exposure (Henley et al., 2011).

- The sexually dimorphic nucleus of the preoptic area (SDN-POA) of the anterior hypothalamus shows sex differences in structure in a number of sheep mice and rats.
  - Grady et al., 1965; He et al., 2018; Henley et al., 2011; Rhees., 1990; Roselli., 2004).
- The third interstitial nucleus of the anterior hypothalamus (INAH-3)—differs in size and cell number between heterosexual and homosexual men.
  - LeVay, 1991; Byne et al., 2001).
- Male and female homosexuals have elevated non-righthandedness relative to heterosexual men and women
  - Lalumiere et al., 2000),

Organization effects: Brain anatomy

- Brain anatomy is biologically conferred as a dimorphic trait. Several cortical and subcortical brain regions.
  - Heterosexual males had larger thalamus and pre-central gyrus, smaller putamen than homosexual men.

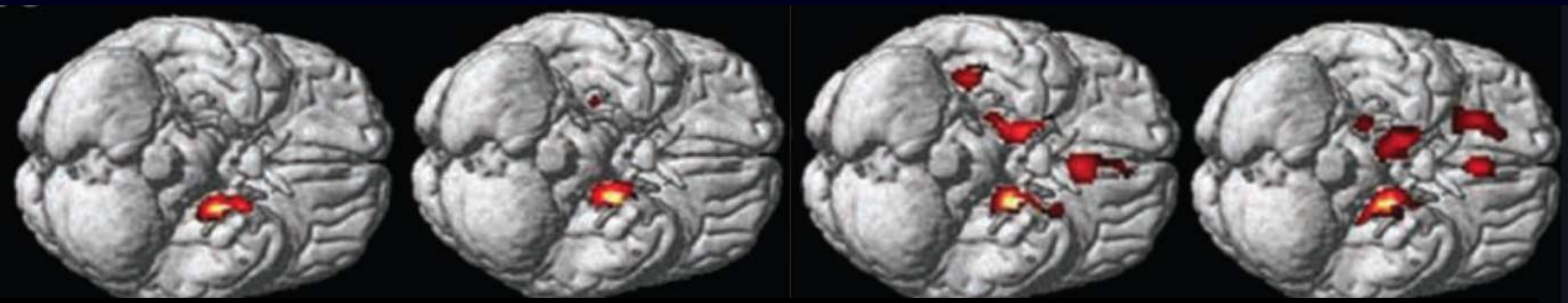
Male

Female

  - Hetero females smaller putamen, larger pre-central gyrus than lesbians.

Votinov, M., et al. . Sci Rep 11, (2021).

Organization effects:
Brain anatomy



Hetero males Homo females Hetero females Homo males

Cerebral responses to putative pheromones and objects of sexual attraction were recently found by PET scan to differ between homo- and heterosexual subjects. These results suggest a linkage to neurobiological entities.

Savic, I, et al. *Proc Natl Acad Sci U S A. 2008.*

Organization effects: neurocognitive and physiologic abilities

- Female face causes greater reaction in thalamus and medial prefrontal cortex of heterosexual men and homosexual women.
  » Kranz et al, Current Biology, 2006
- Lesbians prefer female pheromones over male scents, like heterosexual men, and their brains are activated by female scents similarly to men.
  » Berglund, H. *Proc Natl Acad Sci U S A. 2006*.
- EEG patterns of HM men more like female pattern.
  » Alexander JE, et al. Int J Psychophysiol 1993.
- Differentiation manifests itself on a continuum leading to a variety of patterns of sexual orientation and identity, and by extension, preferred partner characteristics.
  » Muscarella, F, et al. *Neuro Endocrinol Lett. 2004*

Transgender brain anatomy resembles identified gender

- Anterior commissure - cognitive abilities and language.
  - » Allen, LS, et al. Proc Natl Acad Sci U S A. 1992
- Suprachaismatic nucleus.
  - » Swaab, DF. Gynecol Endocrinol. 2004
- Cerebral and amygdala.
  - » Savic, I, et al. Proc Natl Acad Sci U S A. 2008.
- Bed nucleus of the stria terminalis (BSTc)
  - » Kruijver, FP. J Clin Endocrinol Metab. 2000
  - » Chung, WC, et al. J Neurosci. 2002
- Interstitial nucleus of the anterior hypothalamus, INAH-3.
  - » Byne et al., 2001;
  - » Levay, S. Science. 1991

Two testosterone surges affect male fetuses.

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Organization XY males
Prenatal hormonal Organization: permanent

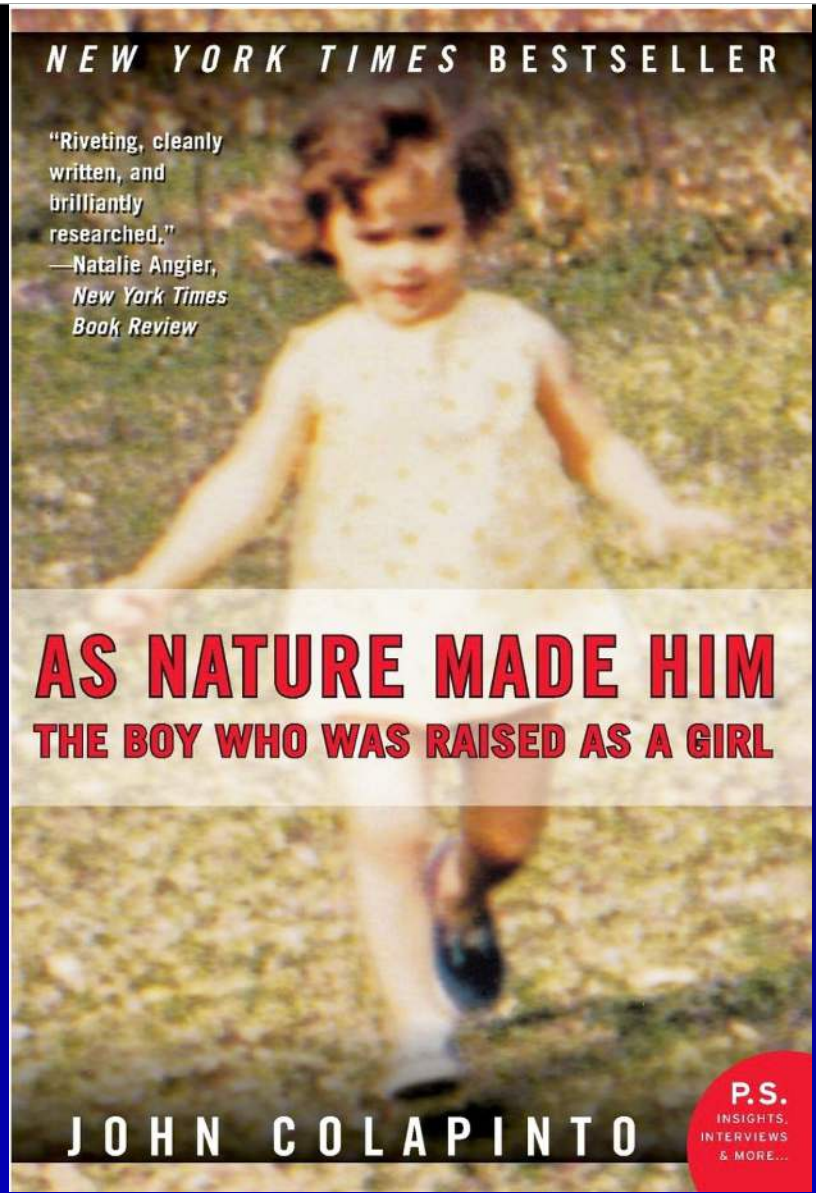
- 46 XY male infants, normal testes:
  - Ablatio penis - injury at circumcision
  - Cloacal exstrophy - congenitally open bladder, usually abnormal external genitalia, open “rectoperineum.”

- Testes removed, raised as girls. Surveyed at age 14+ and older,
  - 29/39 reassigned themselves as men.
  - 31/39 are with women life-partners.

– Mustanski, BS. Annu Rev Sex Res. 2002
– Bradley et al., 1998;
– Diamond and Sigmundson, 1997;
– Reiner and Gearhart, 2004; Reiner and Kropp, 2004)

As Nature Made Him: David Reimer's story

- In 1965, John Money, a Johns Hopkins psychologist, convinced the parents of a twin boy with *ablatio penis* from a circumcision error to raise him as a girl.
- Money constructed female genitalia, prescribed hormone treatments, and psychological counseling.
- He used the case as evidence to support his theory that gender identity is malleable, and primarily learned, not biological.
- The child's uninjured brother developed normally.
- The child struggled with the assigned gender identity and eventually, when finally informed of his medical history, made the decision to live as a male.



NonBinary Individuals

- The existence of gender variance is widely documented both historically and cross-culturally.
- It can be defined as “any type of trans identity that is not always male or female.” It is [also] where people feel they are a mixture of male and female, and dis-identify with rigid gender binaries, and in some cases, as a direct challenge to the social institutions that perpetuate binaries.
    - Monro S. Non-binary and genderqueer: An overview of the field. Int J Transgend. 2019 Jan 21;20(2-3):126-131

Transgender treatments normalize life:

- Lief (1993). "Orgasm in the postoperative transsexual." Arch Sex Behav
- Miach (2000). "Utility of the MMPI-2 in assessing gender dysphoric patients." J Pers Assess
- Rehman (1999). "The reported sex and surgery satisfactions of 28 postoperative male-to- female transsexual patients." Arch Sex Behav
- Tsoi (1993). "Follow-up study of transsexuals after sex-reassignment surgery." Singapore Med J
- van Kesteren (1997). "Mortality and morbidity in transsexual subjects treated with cross-sex hormones." Clin Endocrinol (Oxf)
- Bodlund (1996). "Transsexualism--general outcome and prognostic factors: a five-year follow-up study of nineteen transsexuals in the process of changing sex." Arch Sex Behav

Transgender treatments normalize life:

- Cohen-Kettenis (1997). "Sex reassignment of adolescent transsexuals: follow-up." J Am Ac Child Adolesc Psychiatry
- De Sutter (2001). "Gender reassignment and assisted reproduction: present and future reproductive options for transsexual people." Hum Reprod
- Gallarda (1997). "[The transsexualism syndrome: clinical aspects and therapeutic prospects]." Encephale
- Haraldsen (2000). "Symptom profiles of gender dysphoric patients of transsexual type compared to patients with 10personality disorders / healthy adults." Acta Psychiatr Scand
- Hepp (2002). "[Treatment follow-up of transsexual patients. A catamnestic study]." Nervena
- Michel (2002). "The transsexual: what about the future?" Eur Psychiatry.

We get that it is the first trimester milieu of hormones and chemicals.

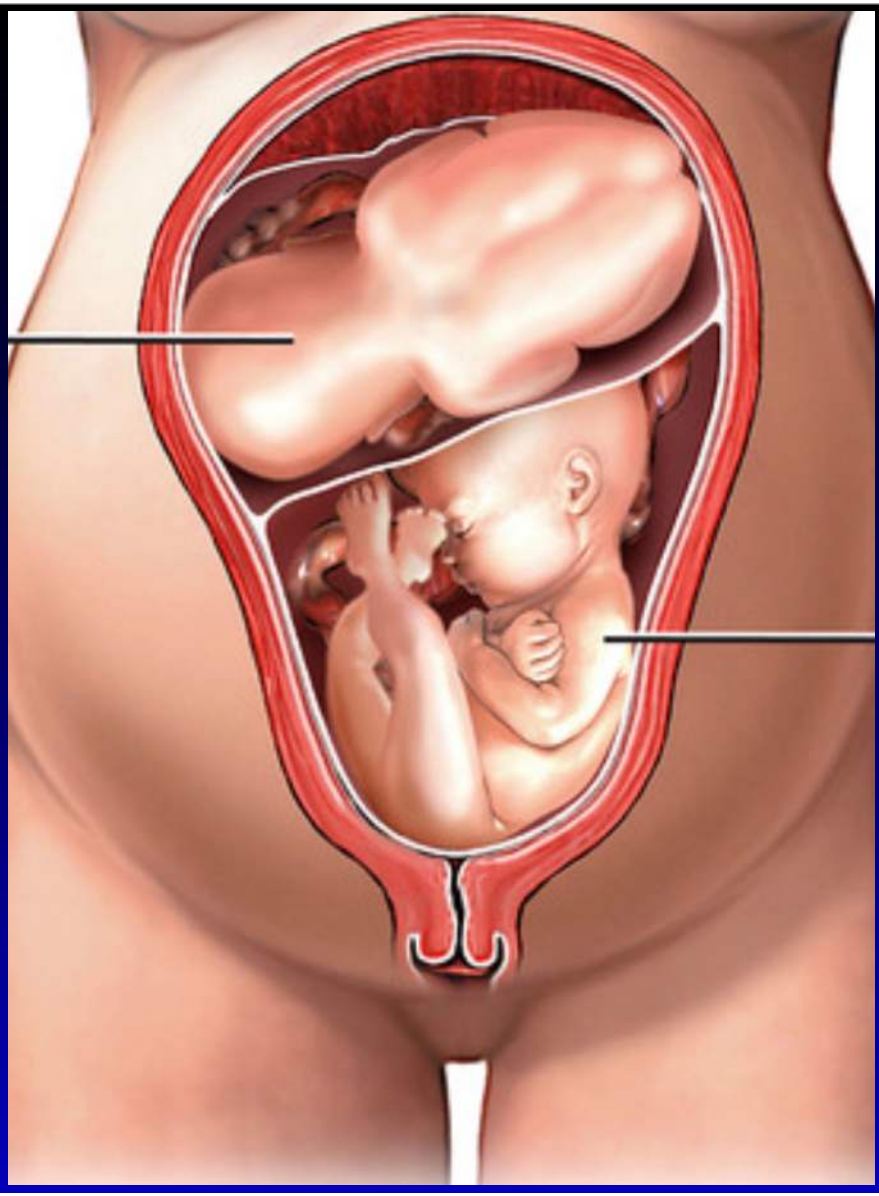
But….

What causes those “variances” of prenatal hormones?

XX females: with male co-twin

- 18-19th century Finnish civil records. (Pre-birth control, pro-marriage)

- Female co-twins of males were:
  - 25% less likely to have children than female-female twins,
  - less likely to marry at all, even if the male twin died within three months of birth.
    - Lummaa, V,. Proc Natl Acad Sci 2007.



XX females: with male co-twin

- Female children who had male co-twins compared with those who had female co-twins had masculinized:
  - Pattern of childplay.
  - Bone structures: 2D:4D is low
  - Brain structure
  - Disordered eating.
  - Cerebral lateralization.
- Normal serum testosterone levels.

Cohen-Bendahan, *Psychoneuroendocrinology. 2004*.
van Anders, SM, et al. *Horm Behav. 2006*
Culbert, KM, et al. *Arch Gen Psychiatry. 2008*
Peper, JS, et al. *Eur J Endocrinol. 2009*

Genetics: concordance in identical twins

	Males:	Females:	Both:
• Monozygotic twins:	52%	48%	32%
• Dizygotic:	22%		13%
• Non-twin:	9%	14%	9%
• Adopted:	11%	6%	

Bailey et al. Arch Gen Psychiatry. 1991;48(12):1089-96
Bailey et al. Arch Gen Psychiatry. 1993;50(3):217-23.
Kendler, Am J Psychiatry. 2000, 157(11).

- Genes, SNIP's on Chromo# 4, 7, 8, 10, 11, 13, 14 implicated. More study needed.

Bogaert, Horm and Beh, 119, March 2020

- Genome-Wide Association Study did not identify any genetic loci reaching genome-wide significance at $p < 5 \times 10\text{-}8$ among 47,748 men or women.

Drabant et al, 2012, 23andMe, Inc, Mountain View, CA

XY males with male co-twin Epigenetics or fraternal explains

- Epigenetics: chemicals bind to DNA modulate gene expression.
- Gay male co-twins have higher 2D:4D than their heterosexual male co-twins, confirming that the digit effect was not genetic, since they are identical, but likely epigenetic, resulting in disparate internal prenatal hormonal milieus.
- Epigenetic modifications in five genome regions contribute to the non-binary, "spectrum" effect of sexually dimorphic traits and orientations.

Morgan, CP et al, Biol. Sex Differ. 2017.

Rice, U. Et al, Mol. Ecol. 2016.

Ngun et al. 2015; cited in Balter, 2015

XY males: Fraternal Birth Order

- Numerous studies confirm that having more older brothers increases the probability of homosexuality in later-born males.
  - Cells (or fragments,Y-linked membrane proteins (NLGN4Y and PCDH11Y) from male fetuses enter the maternal blood inducing antibody formation.
  - NLGN4Y binds with neurexins to form synapses.
  - Progressive immunization by subsequent male gestations induces more antibodies.
  - These antibodies block male-differentiation by binding to male-specific molecules on the surface of neurons and preventing these neurons from 'wiring-up' in a fully male-typical pattern.

Dean and Dresbach, 2006

Blanchard Ray, 2020, Proc. R. Soc. B.

Boggaert et al 2018

XY males: Fraternal Birth Order

- Men who did not identify as gay but who anonymously reported homosexual feelings by survey, had a greater mean number of older brothers than did those who reported no secret homosexual feelings.
  - » McConaghy et al Fraternal birth order and ratio of heterosexual/ homosexual feelings in women and men. *J Homosex. 2006.*

XY males: 5AR Defect

- 5α-reductase (5AR) is an enzyme that transforms weaker DHT to stronger testosterone (T) in the prostate, seminal vesicles, and brain.
- 33 known 5AR mutations blocking T convertion to DHT.
- Family lines with recurring 5AR mutations in Dominican Republic, Papua New Guinea, Turkey, and Egypt.

XY males: 5AR Defect

- Boys have ambiguous or female-typical genitals, usually raised as a girl, with male-typical play patterns, and male gender identity as child. . . . . but…..
- At puberty, (surging levels of androgens) their bodies and genitals then masculinize and testes descend.

- Often unrecognized until long after surgical reduction of their phallus into a clitoris, a practice now discouraged.

XY males: Androgen Insensitivity Syndrome:

- AIS is a mutation of androgen receptors that prevents recognition of T, and subsequent androgenization.
- Normal blood levels of T are ignored.
- Genitals: female 7%, clitoromegaly 49%, indeterminate 32%.
- 72% assigned female, 12% transition at puberty.
- Usually psychosocially female, oriented toward men, and have a higher, (feminized) 2D:4D digit ratio.

Maimoun et al (2011) The Journal of clinical endocrinology and metabolism.

Genetics: "XY males. Xq28"

- Increased rates of same-sex orientation were found in the maternal uncles and male cousins.
- 33/40 gay brothers share Xq28, suggesting that at least diversity of male sexual orientation is genetic.

  Hamer, DH. Science. 1993
- Hu confirmed Hamers work:
  - 22 brothers discordant for orientation.
  - 67% brothers concordant for orientation.

  Hu, S Nat.Genet. 1995

- A recent meta-analysis of all data available concluded that Xq28 has a significant but certainly not exclusive role in male sexual orientation.

46 XX: variance in SRY, or DAX-1, Ad4BP/SF-1, WT1, GATA4, WNT4, FGF9 and RSPO1.

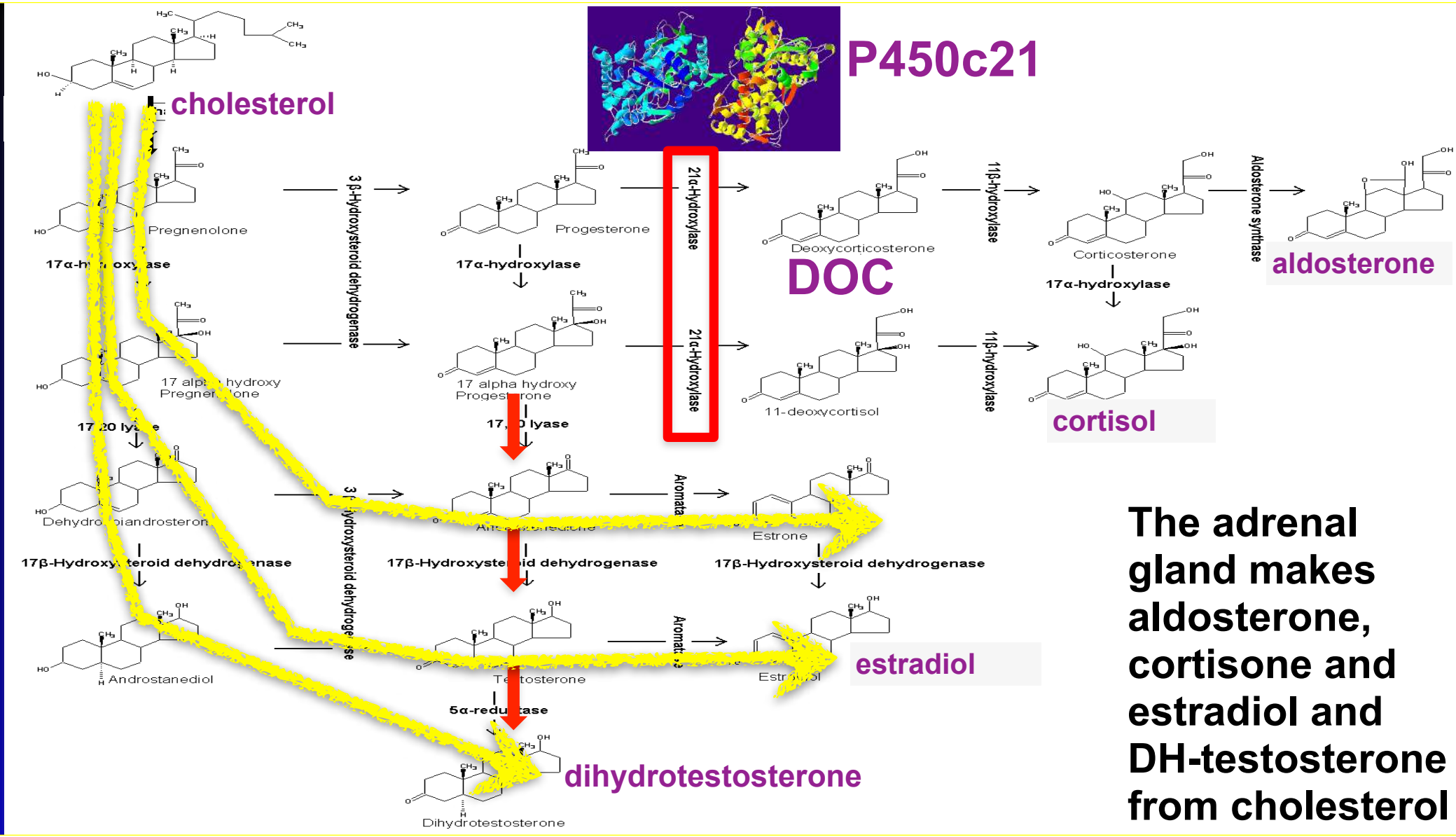
- Currently, the genetic cause of less than 50% of DSD individuals has been solved and oligogenic disease has been proposed.
- Each gene affects genital anatomy, gender identity to some extent even with variations in others.
- Three genital phenotypes:
  - Female internal and external
  - Ambiguous external genitals,
  - Male with normal penile length, infertility.
- Other features:
  - microrchidism and Gynecomastia, short stature
  - female pubic hair distribution, decreased facial hair
    - Camats N, et al Oligogenic Origin of Differences of Sex Development in Humans. Int J Mol Sci. 2020

Organization XX females: CAH

- Congenital Adrenal Hyperplasia (CAH): 1:15,000 babies with insufficient enzyme in adrenal.
- Buildup of unprocessed androgenizing chemical released into fetal blood.
  - Classical – starts during gestation.
  - Simple virilizing (SV): mild disorders of sexual differentiation (DSD's).
  - Salt-Wasting (SW): life-threatening vomiting, dehydration soon after delivery, with moderate-severe DSD's.
- Among all types: More bisexuals, lesbians and FTM's.

Meyer-Bahlburg HF, et al

Arch Sex Behav. 2008.



The adrenal gland makes aldosterone, cortisone and estradiol and DH-testosterone from cholesterol

Organization XX females: CAH

- Unprocessed excess androgens can masculinize brain / bones / genitals /behavior:
  - Larger clitoris, ambiguous genitals.
  - Narrow pelvis, shorter index finger.
  - Childhood play behavior – more aggressive.
  - Adult sexual orientation – up to 50% are lesbian.
  - Adult gender identity – some become transsexual FTM.

Meyer-Bahlburg HF, et al Arch Sex Behav. 2008.
Pasterski, V, et al. Horm Behav. 2007.
Hines, M, et al. J Sex Res. 2004.
Pasterski, V, et al. Horm Behav. 2007

Organization XX females: CAH

20 publications of 471 women with CAH and 237 controls.

	CONTROLS	CAH
Bisexual/Lesbian imagery	0-20%	15-50%
Lesbian partners	2-4%	17-36%

Meyer-Bahlburg, et al Arch Sex Behav. 2008.

Organization XX females: CAH

- The reported rate of gender dysphoria in CAH females exceeds that in the general population (5% vs. 0.002–0.003%).
  - Dessens et al, Arch. Sex. Behav. 2005.
- Factors influencing gender in later gestation:
  - compounds that change the levels of these hormones, such as anticonvulsants (DPH and Phenytoin).
    - Dessens, AB, et al. Arch Sex Behav. 1999.

Organization XX females: CAH

- Female-to-Male transsexuals show:
  - 50% show CAH symptoms, compared with 13% of controls.
  - Higher androgens levels in serum (17OHP, OHPREG, DOC,)
  - PCOS and adrenocortical hyperresponsiveness to ACTH common.

Bosinski, HA, et al. *Psychoneuroendocrinology. 1997*

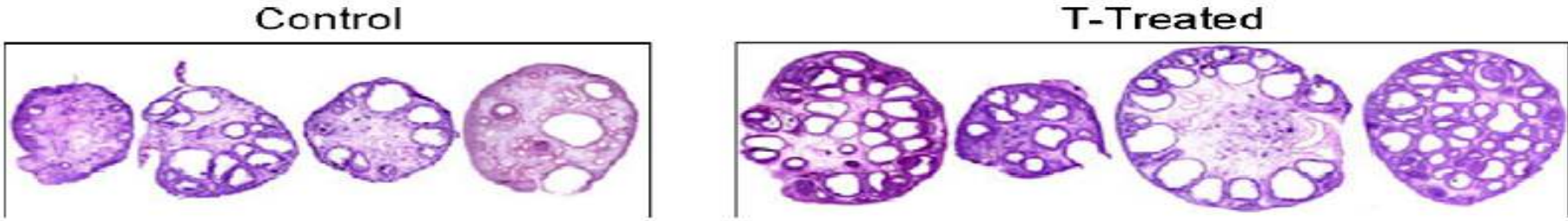
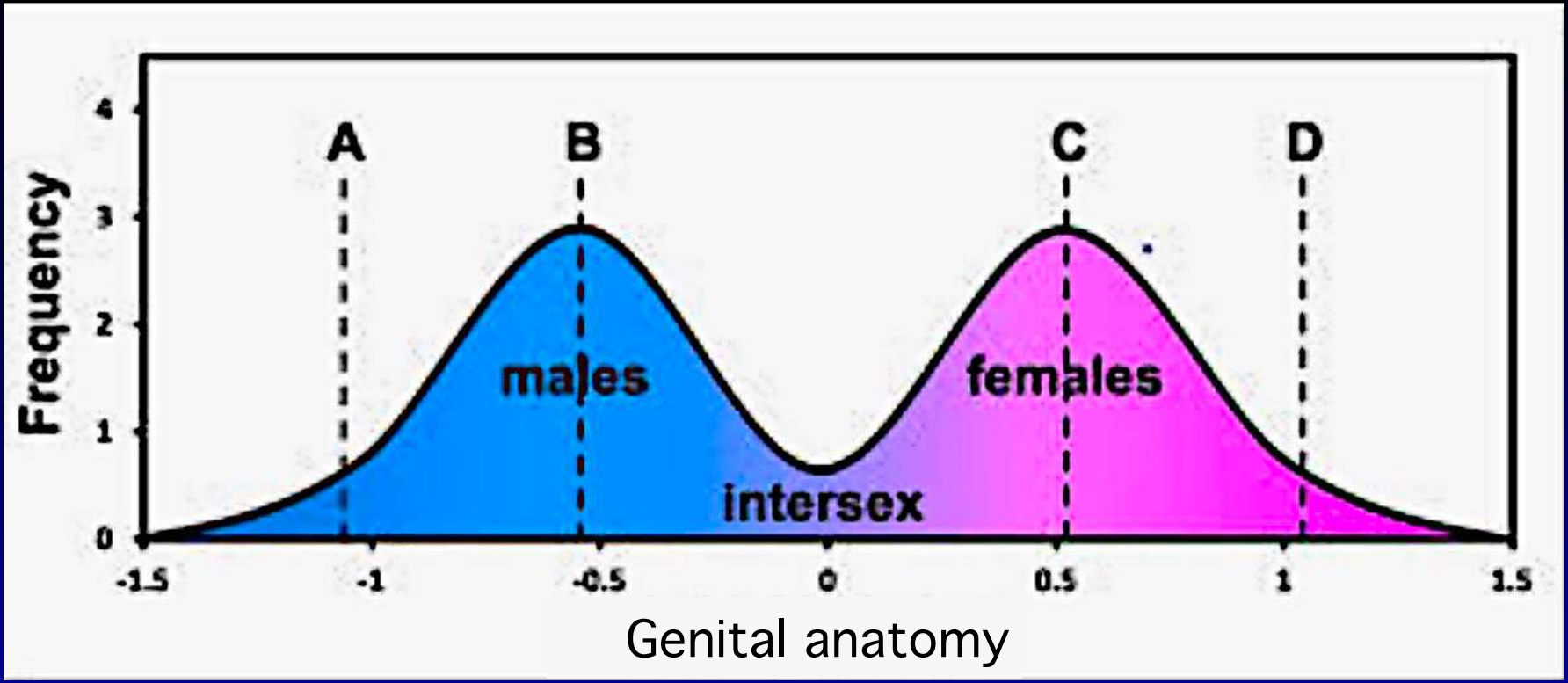


Fig. 7. Ovarian follicular morphology of control lambs and lambs treated prenatally with T or DHT
Note the larger size and multifollicular nature of the ovaries



Genital anatomy

Organization:
Xenoestrogens, diethylstilbesterol (DES)

- Fetal exposure to oral contraceptives, anticonvulsants (DPH and Phenytoin) can affect hormone levels and may be associated with MTF transsexualism:
  - Dessens, AB, et al. Arch Sex Behav. 1999.
  - Swaab, et al (2009). Functional neurology 24(1): 17-28.

- Fetal exposure to Diethylstilbestrol (DES) associated with 1.58% rate of MTF transsexualism.
  - Gaspari L, et al. Early Female Transgender Identity after Prenatal Exposure to Diethylstilbestrol: Report from a French National Diethylstilbestrol (DES) Cohort. Journal of Xenobiotics. 2024; 14(1):166-175.

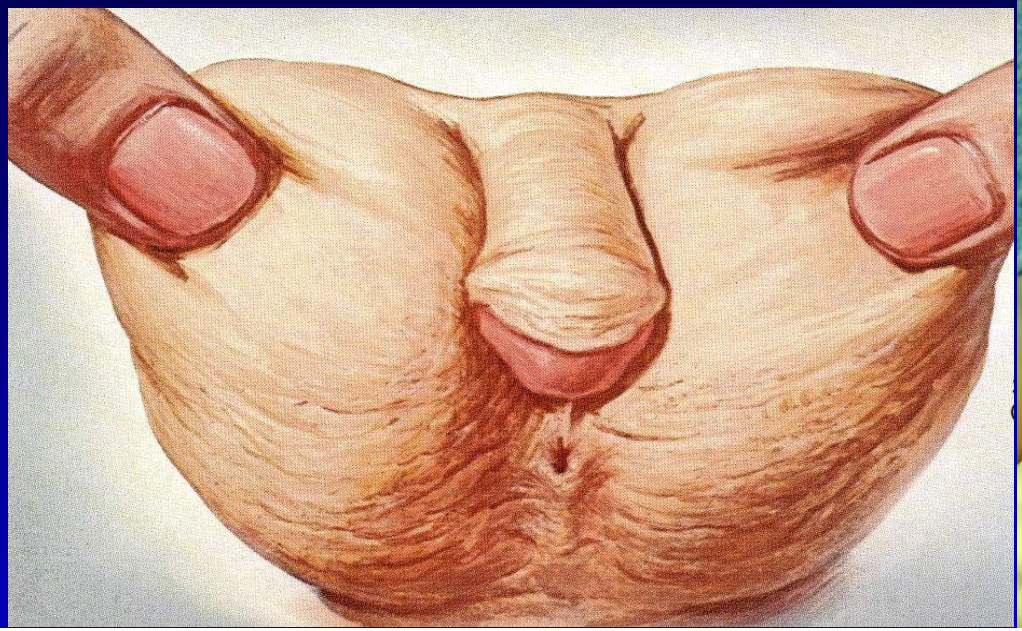
Organization:
Endocrine Disruptors

Found in plastics, personal care products, and pesticides, Phthalates, bisphenol A, pesticides, polychlorinated biphenyls and dioxins interfere with hormone signaling.

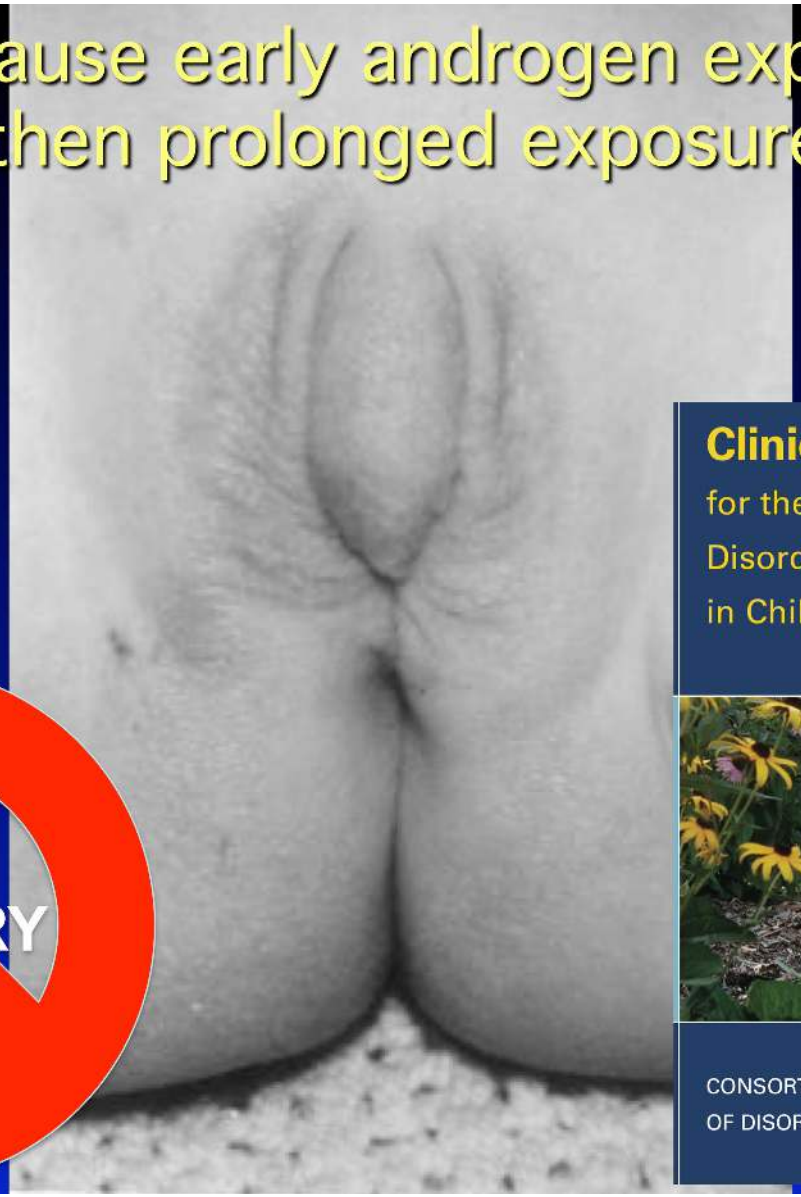
- **Female mammals:** alter fertility, hormone levels, follicle numbers and cyclicity, early puberty and reproductive aging, litter size and sex ratios in pups, ovarian cysts, adenomyosis, anogenital anatomy.
- **Male mammals:** alter sex steroid hormone levels, decrease sperm count, morphology and motility, cause early puberty and testes disease, and anogenital anatomy.

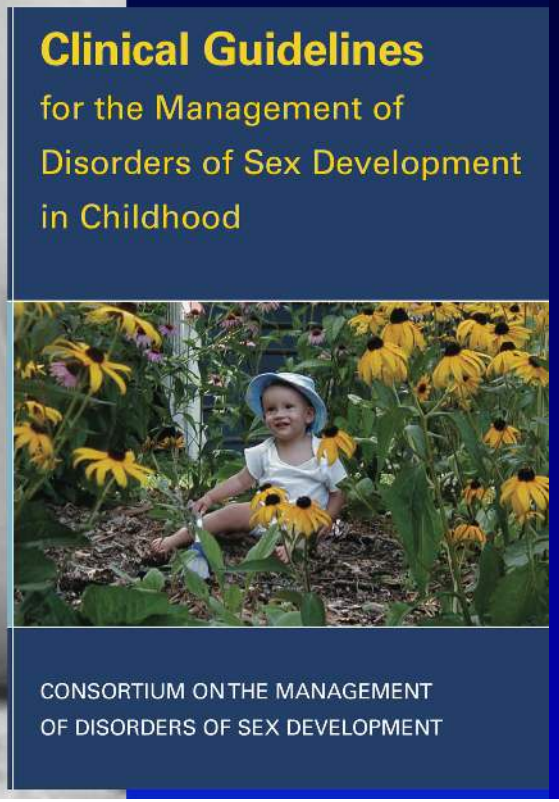
- Brehm E, Flaws JA. Transgenerational Effects of Endocrine-Disrupting Chemicals on Male and Female Reproduction. Endocrinology. 2019 Jun 1;160(6):1421-1435.

Diverse sexual development (DSD's) is the spectrum of anatomy that develops from the spectrum of proteins, enzymes and hormones that influence the genital growth.



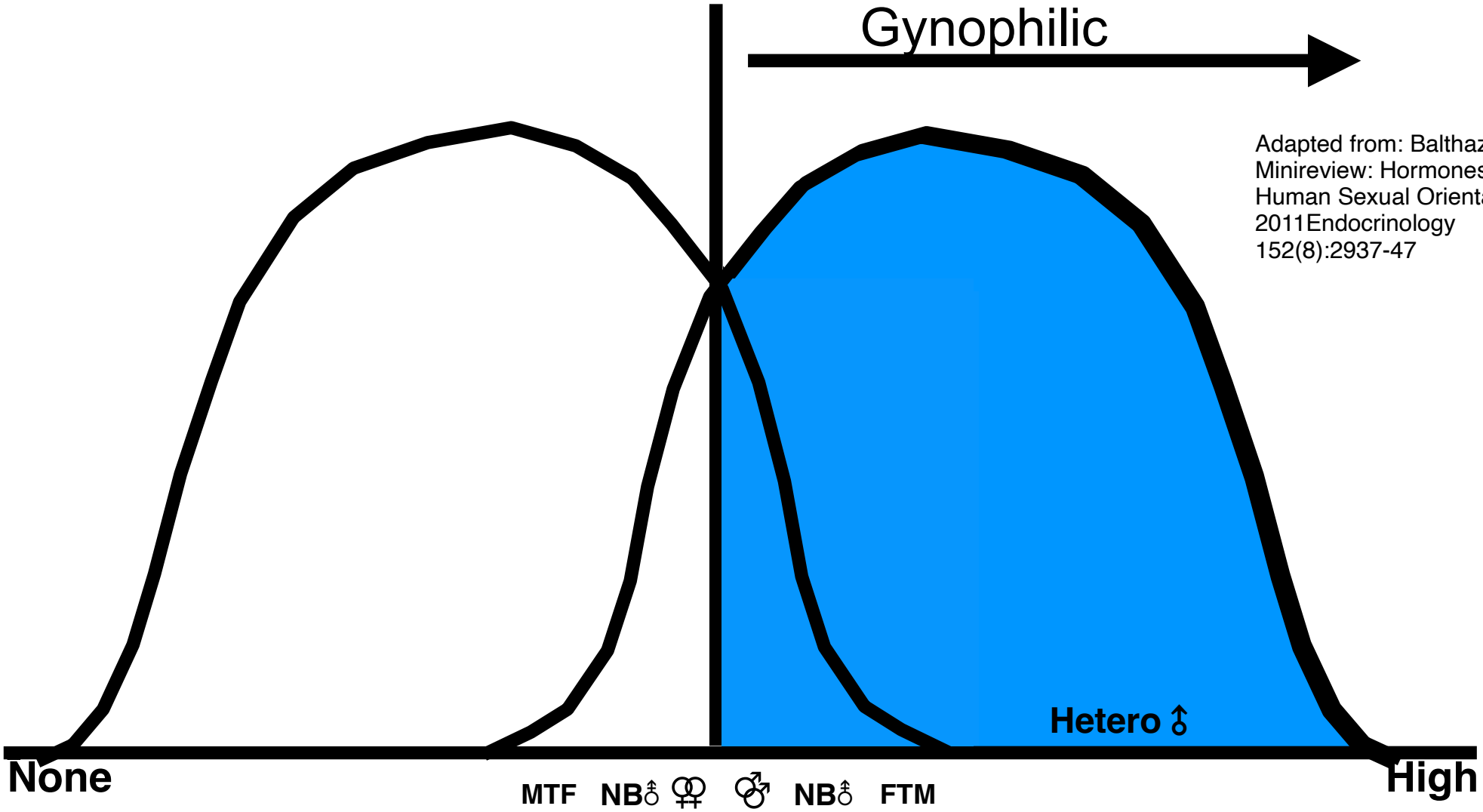
CAH can cause early androgen exposure to brain and then prolonged exposure to genitals





A theory of organization: relative prenatal androgen levels

PRENATAL ANDROGEN EFFECT	LOW 2%	LOWISH 1%	DECREASED 3%	90% AVERAGE	INCREASED 3%	HIGHISH 1%	HIGH 2%


Gynophilic
Adapted from: Balthazart, Minireview: Hormones and Human Sexual Orientation, 2011Endocrinology 152(8):2937-47
Hetero ⚥
None
MTF
NB⚧
⚢
⚣
NB⚧
FTM
High

“The book on social influences is not closed so much as it is blank.”

LeVay, S. (2011). "From mice to men: Biological factors in the development of sexuality." Frontiers in neuroendocrinology 32(2): 110-113.

“There is no proof that social environment after birth has an effect on gender identity or sexual orientation.”

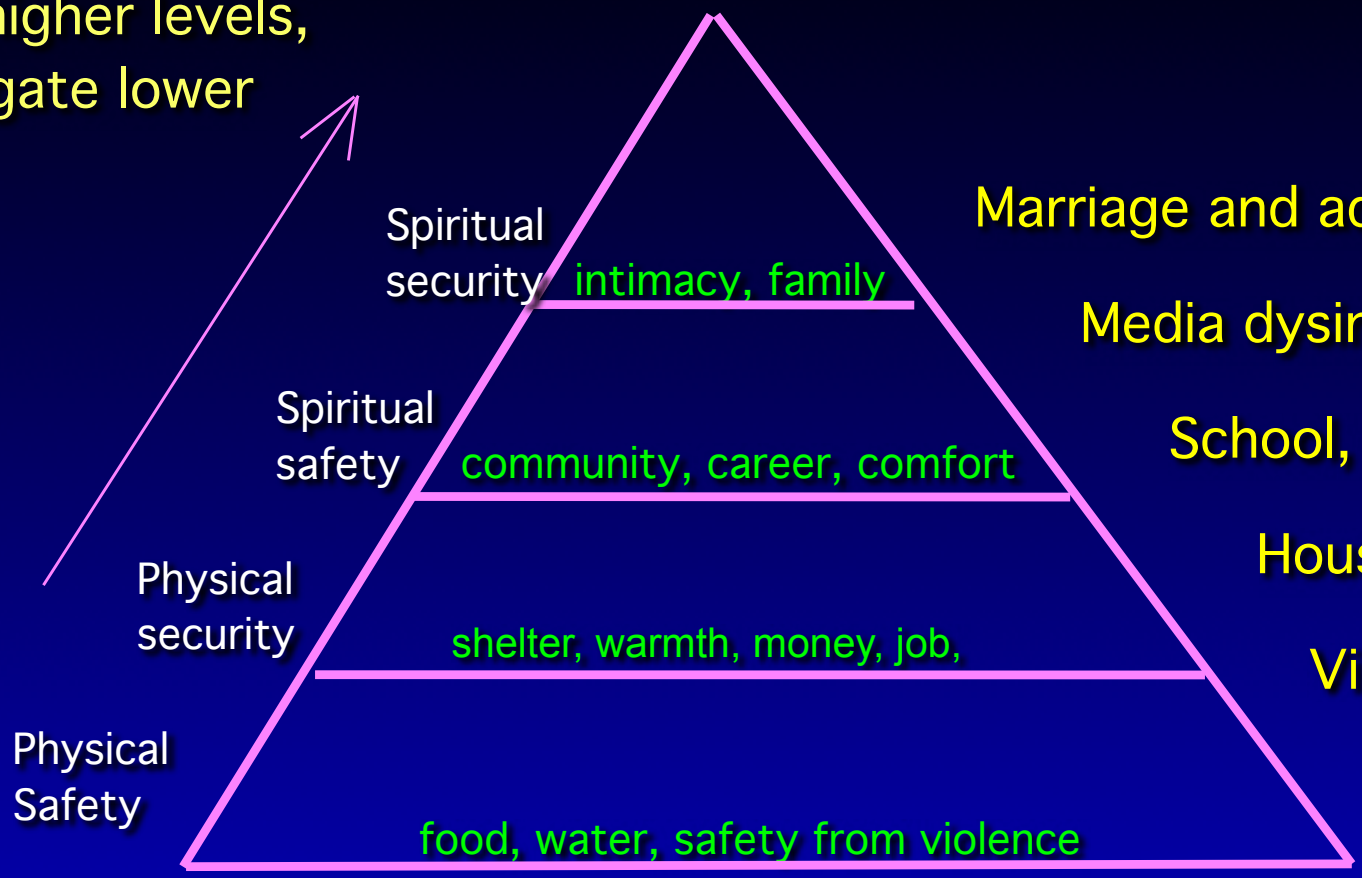
Swaab, D. F. and A. Garcia-Falgueras (2009). "Sexual differentiation of the human brain in relation to gender identity and sexual orientation." Functional neurology 24(1): 17-28.

Conclusions

- A unique orientation and gender identity will emerge in everyone, despite ubiquitous majority modeling: media, education, laws, families.
- No orientation or identity is inherently (genetically, biologically, socially) hazardous,
- Risk factors are conferred through the processes of legalized discrimination–
  - socialization of cisgender heterosexuals against others.
  - concomitant conditioning of minority individuals against themselves.

MASLOW'S HIERARCHY OF HUMAN NEED FULFILLMENT

To reach higher levels,
must navigate lower



Marriage and adoption laws

Media dysinformation

School, family disdain

Housing/job discrim.

Violence

Maslow AL. Motivation and Personality. New York: Harper & Row.; 1970.

Thank you!

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What do you want for members of your family?

Safety from violence and taunting.

Quality education that reflects humanity.

Job security.

Serve in military.

Marry their loved one.

Pay taxes equally.

Medicare benefits.

Financial and legal security for family (health insurance, social security, pension, will).

Orientation and identity are NOT sensitive subjects

- Everybody has one!
- Bring up the subject with colleagues and name yourself as an ally to LGBTI's, so you can educate them.
- Do not be afraid to talk to children about LGBTI's, even if you are not the parent.
- Remember: You are not talking about sex, but about love and identity. Children already know about LGBTI's. Affirm that LGBTI's are different, and deserving respect, and not bad.
- Be willing to tell a child that whatever identity they find for themselves, and whomever they ever love, that you will always love them.You may be saving the life of this or another child.

What you can do to help:

- Respect and use the pronouns that people use for themselves, and ask others to do so, even when LGBTI's are not around.
- Make yourself comfortable using the words "trans people", "transfolk" or "transgender brothers and sisters."
- Be willing to ask: "What pronoun may I use for you?" or, "Do you have affection to for men, women both or neither?"
- Use the term "orientation" and omit the word "sexual." Nobody wants to think about others having sex.
- Be willing to take a gentle and respectful stand when you hear ignorant or disrespectful comments about LGBTI's, even when they are not around.

Be an ally to **everyone**

- Listen to the messages of the LGBTQI community.
- Use non-binary addresses. e.g.: people, folk, everyone.
- Comedian: “Theydies and Gentlethems!”
- You will make mistakes: “Thank you for correcting me.” and move on!
- Show up. Speak out. For each and all of us.