



School of Medical Sciences - Anatomy

Reproductive Embryology

Royal Hospital for Women - Reproductive Medicine Seminar 2018



Dr Mark Lip



<https://embryology.med.unsw.edu.au>

Background

- Uterine Tube Biobank (Prof Ledger)
- Trophoblast differentiation
- Digital Embryology Consortium
- Kyoto Collection (eBook)
- Human SEM (eBook)
- UNSW Embryology








<https://human-embryology.org/>

<https://embryology.med.unsw.edu.au>

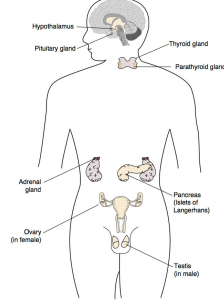
<https://itunes.apple.com/us/book/id1143922693>





Seminar Topics

Dr Rachael Rodgers - "Male and female reproductive/urogenital systems, breast, thyroid, adrenals, kidneys, hypothalamus and pituitary, it would be perfect."


http://tiny.cc/RHW_Embryo_Seminar_2018




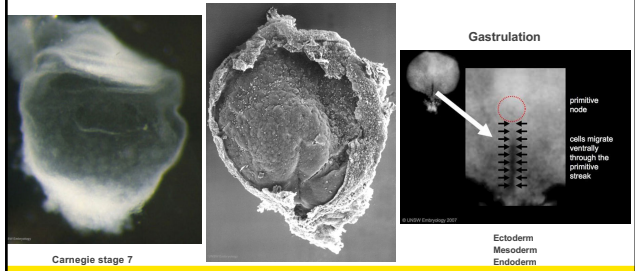
Urogenital - Timeline

Gestational Age (weeks)	Event	Fertilisation Age (weeks)
5	primordial germ cells (PGCs) migrate during gastrulation	3
6	intermediate mesoderm, pronephros primordium	4
7	mesonephros and mesonephric duct (Wolffian duct)	5
8	ureteric bud, metanephros, genital ridge	6 (35 days)
9	cloacal division, gonadal primordium - indifferent to first appearance of testis cords	7 (42 days)
10	paramesonephric duct (Müllerian duct), clear gonadal differentiation	8 (49 days)
11	paramesonephric duct fusion (female)	9 (56 days)
17	primary follicles (ovary)	15 (100 days)





Week 5 – PGC Formation



Gastrulation

primitive node

cells migrate ventrally through the primitive streak

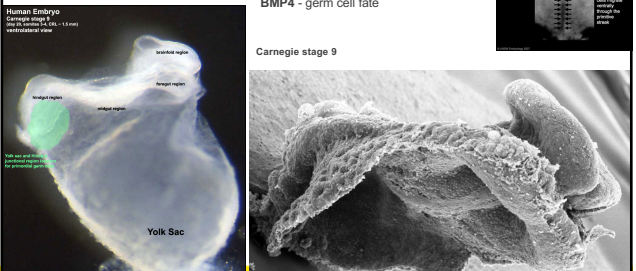
Ectoderm
Mesoderm
Endoderm

Carnegie stage 7

Remnant primitive streak cells - Sacrocaudal teratomas (most common solid tumor in newborn infants)

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Week 5 – PGC Early Location



BMP4 - germ cell fate

Carnegie stage 9

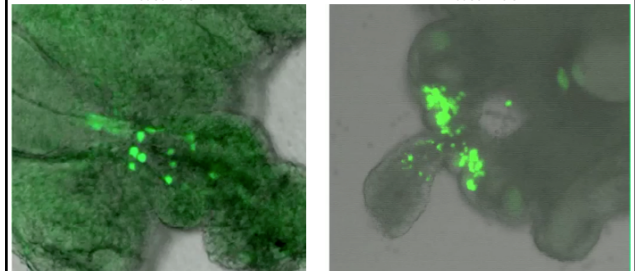
Yolk Sac

Human Embryo
Carnegie stage 9
day 25, weeks 5.5-6.5 - 1.5 mm
ventral view

primitive node
primitive streak
BMP4

Week 6 – PGC Migration – 3 phases

PGC



Mouse E9.5

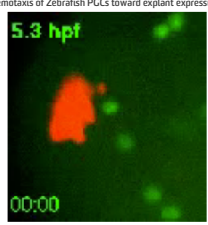
Mouse E10.5

Genomic features (PGCs) and labile cells differentiate into PGCs fetal life

Week 6 – PGC Migration

- Migration – Chemoattraction
 - **CXCR4** (C-X-C motif chemokine receptor 4)
 - expressed by PGCs
 - **SDF-1** (Stromal cell-derived factor 1)
 - **CXCL12**, C-X-C motif chemokine ligand 12
 - expressed in the genital ridges and surrounding mesenchyme
- Genome-wide DNA demethylation occurs during migration
- Male - form gonocytes undergo fetal mitosis

Chemotaxis of Zebrafish PGCs toward explant expressing SDF1a



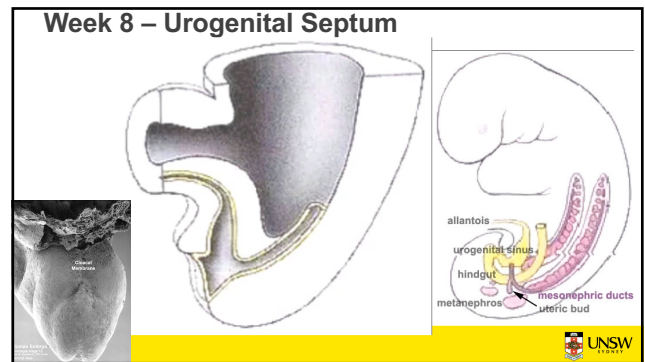
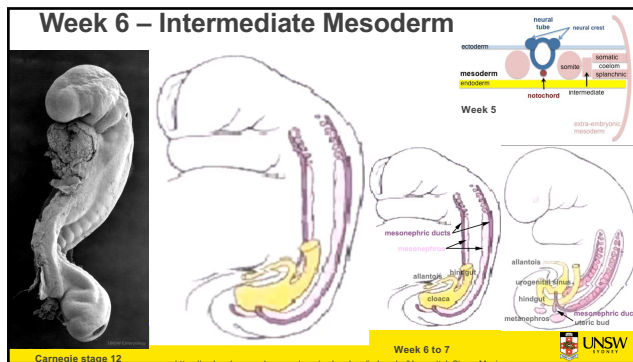
5.3 hpt

00:00

J Cell Sci. 2005 Sep 1;118(Pt 17):4027-38

OMIM - <https://www.omim.org>
HUGO Gene Nomenclature Committee - <https://www.genenames.org>

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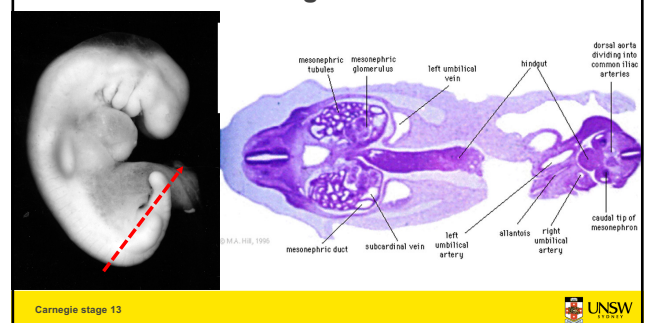


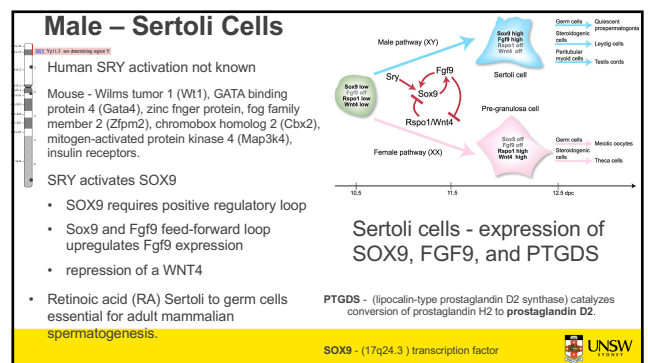
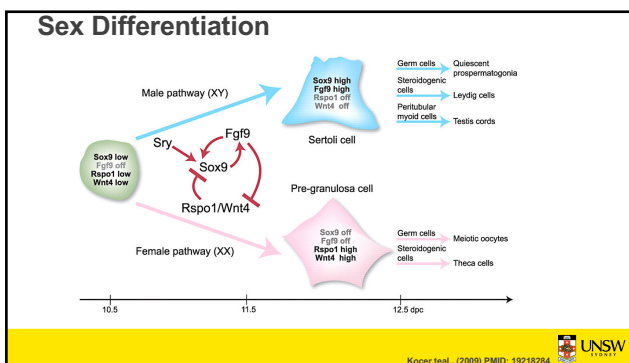
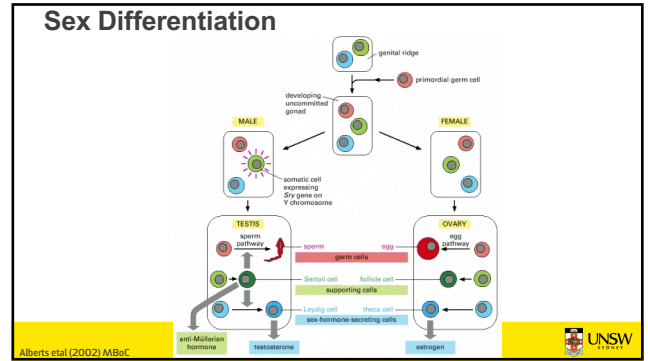
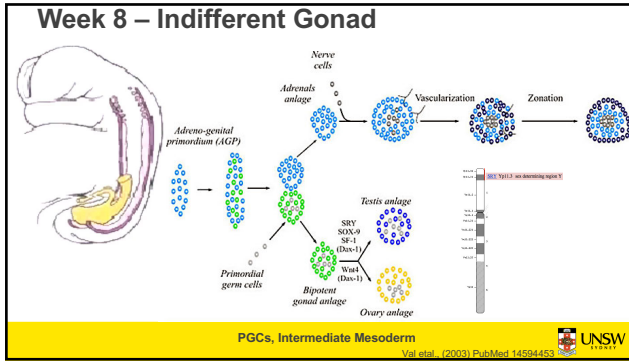
Genital Stages

1. Development of the indifferent gonad - (genital ridge) early embryo
2. Differentiation of gonad - (testis or ovary) late embryo, defining event in sexual differentiation
3. Differentiation of internal genital organs and ducts - late embryo to fetal
4. Differentiation of external genitalia – fetal
5. Development of secondary sexual characteristics - puberty



Week 7 – Genital Ridge





Female - Granulosa Cells

- Wnt4** secreted protein, inhibit testis-specific processes
- mesonephros migration of endothelial cells
- repress steroidogenesis by Sf1 or blocking recruitment of steroidogenic cell precursors
- RSPO1** secreted protein
 - agonist WNT4 signalling
- FOXL2** transcription factor
 - repress Sox9 by synergistic interaction with estrogen receptors α and β (ER- α - β)
 - postnatal follicle development and female fertility maintenance

Granulosa cells - WNT4, R-spondin (RSPO1), β -catenin, FOXL2, follistatin (FST)

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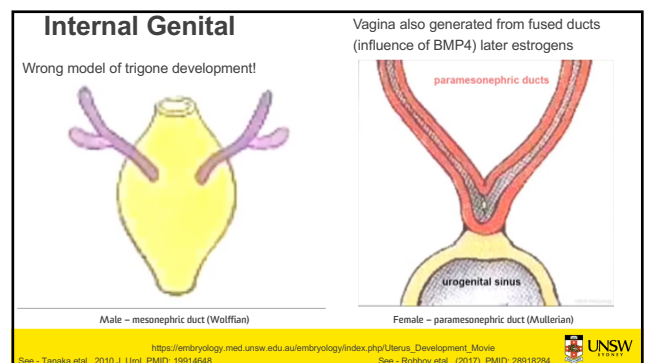
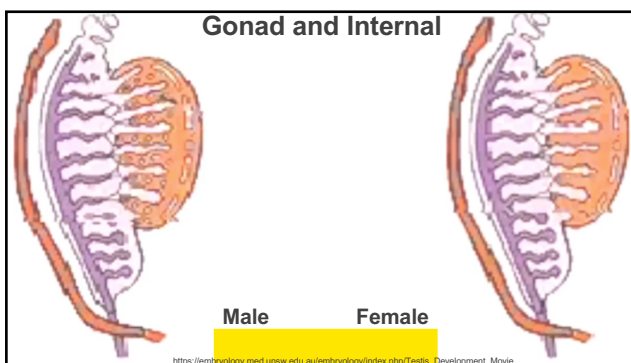
https://embryology.med.unsw.edu.au/embryology/index.php/Developmental_Signals_-_Wnt

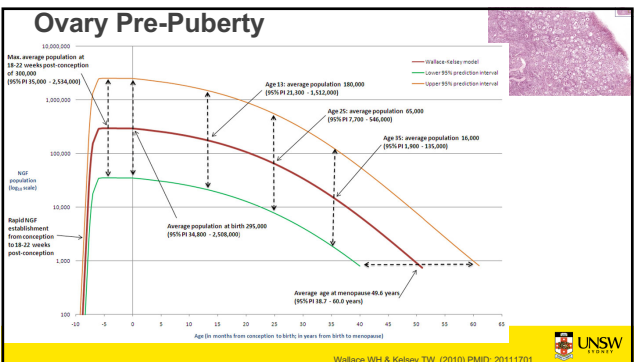
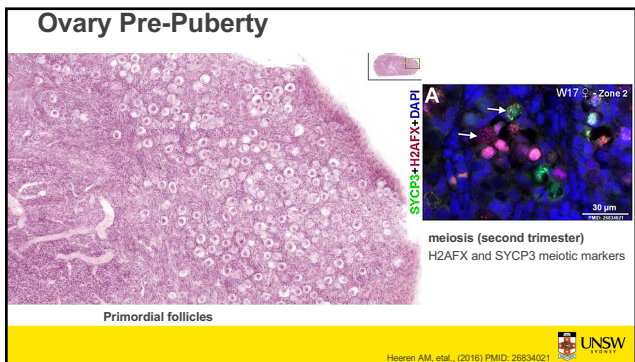
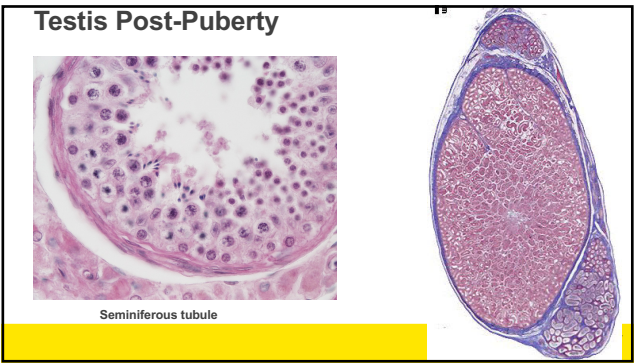
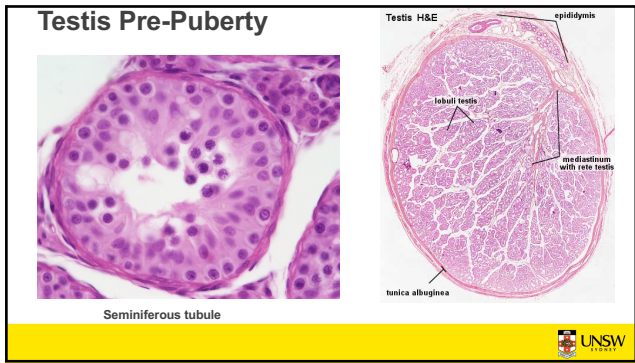
Mammalian Sexual Development Genes			
Gene (OMIM)	Protein Function	Gonad Phenotype of Null Mice	Human Syndrome
Bipotential gonad			
<i>Sox9</i>	Transcription factor	Blockage in genital ridge development	DuRoi's Syndrome, Frasier syndrome
<i>Sf1</i>	Nuclear receptor	Blockage in genital ridge development	Embryonic testicular regression syndrome
<i>Emx2</i>	Transcription factor	Blockage in genital ridge development	+
<i>Emx2</i>	Transcription factor	Gonadal dysgenesis	+
Testis-determining pathway			
<i>Sry</i>	Transcription factor	Reduced Sry levels, XY sex reversal	+
<i>Sry</i>	Transcription factor	XY sex reversal	XY sex reversal (SOX), XX sex reversal (SOX)
<i>Sox9</i>	Transcription factor	XY sex reversal	Campanacci dysplasia, XX sex reversal (SOX)
<i>Sox9</i>	Transcription factor	XY sex reversal in combination with partial loss of <i>Sox9</i> function	+
<i>Fgf9</i>	Signaling molecule	XY sex reversal	+
<i>Sox9</i>	Nuclear receptor	Impaired testis cord formation and spermatogenesis	Hypogonadism
<i>Pou4f1</i>	Transcription factor	XY sex reversal	+
<i>Sox9</i>	Signaling molecule	Impaired differentiation of Leydig and PM cells	XY gonadal dysgenesis
<i>Pou4f1</i>	Receptor	Reduction in mesonephric cell migration	+
<i>Pou4f1</i>	Enzyme	No phenotype	+
<i>Ahr</i>	Transcription factor	Abnormal testicular differentiation	X-linked isospermia with abnormal genitalia
<i>Ahr</i>	Helicase	NO	ATR syndrome
<i>Emx2</i>	Signaling factor	Blockage of testicular descent	Cryptorchidism
<i>Lgr6</i>	Receptor	Blockage of testicular descent	Cryptorchidism
<i>Hesx1</i>	Transcription factor	Blockage of testicular descent	Cryptorchidism
<i>Hesx1</i>	Transcription factor	Blockage of testicular descent	Cryptorchidism
<i>Mafk</i>	Receptor	No Müllerian duct degeneration	Persistent Müllerian duct syndrome
<i>Mafk</i>	Transcription factor	Dysgenesis of mesonephric tubules	+
<i>Lgr6</i>	Transcription factor	Aggression of Wolffian and Müllerian ducts	+
<i>Emx2</i>	Transcription factor	Loss of Sertoli and germ cells	XY female ^a
Ovary-determining pathway			
<i>Wnt4</i>	Signaling molecule	Müllerian duct agenesis, testosterone synthesis, and coelomic vessel formation	XY female (SOX)
<i>Foxl2</i>	Transcription factor	Primordial ovarian failure	BPES
<i>Sox9</i>	Nuclear receptor	XY sex reversal (SOX)	XY sex reversal (SOX)
<i>RSPO1</i>	Signaling molecule	XX sex reversal (SOX)	XX sex reversal (SOX)

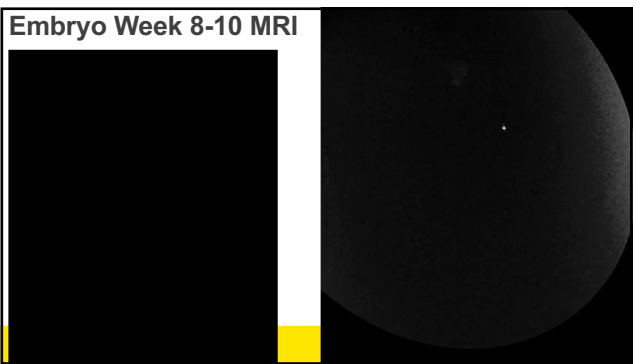
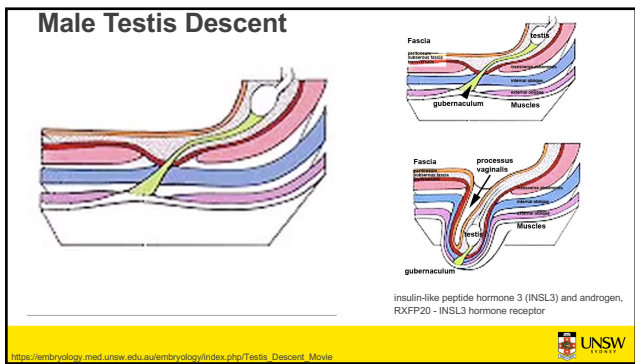
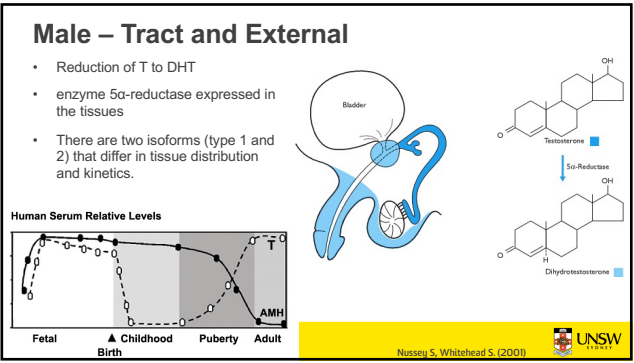
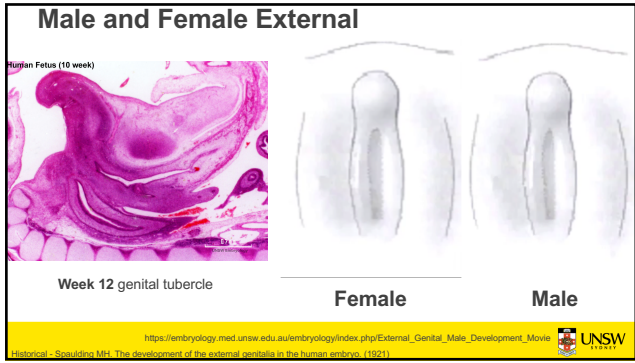
Table Legend: + BPES - Biparental gonadal dysgenesis syndrome

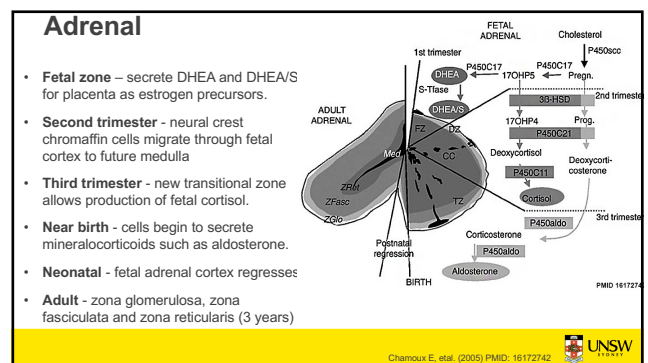
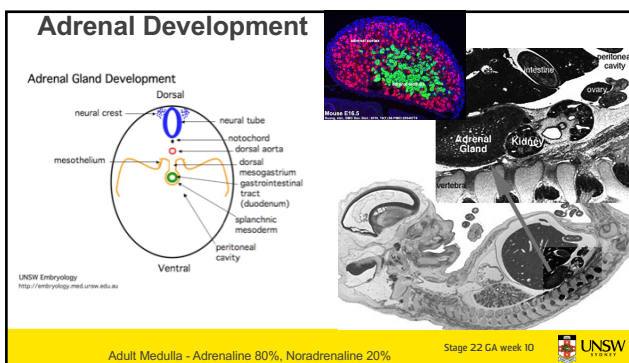
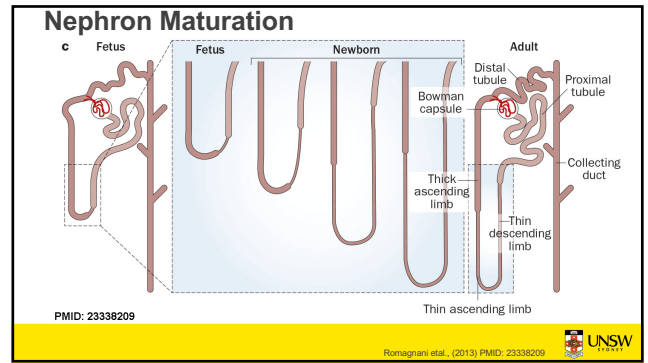
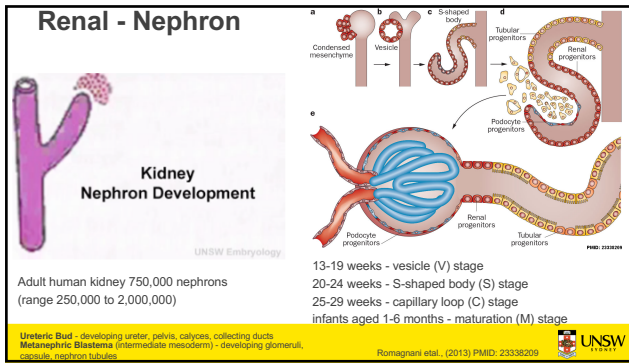
Modified from Mullerian Duct and Gonadal Development, 17323344

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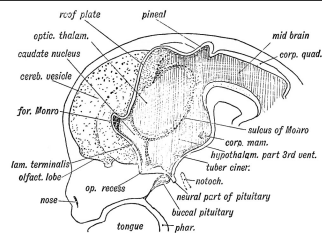






Hypothalamus

- Neuroectoderm - prosencephalon then rostral diencephalon after induction by the underlying prechordal plate.
 - Prosomeric model - hypothalamus and telencephalon are part of the secondary prosencephalon
- Sonic hedgehog (Shh) - initially expressed in prechordal plate, is essential for inductive process.
- ventro-lateral wall intermediate zone proliferation
- Mammillary bodies - form pea-sized swellings ventral wall of hypothalamus



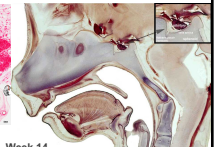
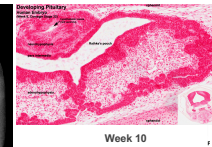
Neural swellings ventral wall of hypothalamus secondary vesicles" being replaced with gene expression model "prosomeres"



Pituitary

Development of the Hypophysis

- **Neuroectoderm**
 - prosencephalon, neurohypophysis
- **Ectoderm**
 - roof of stomodeum, Rathke's pouch, adenohypophysis

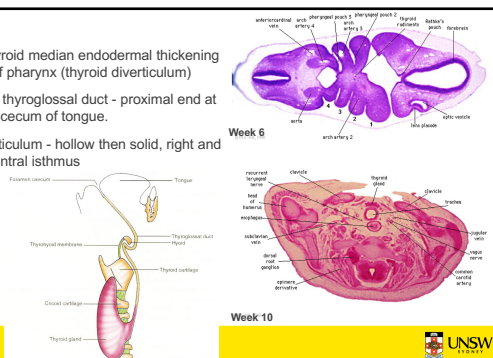


Week 7



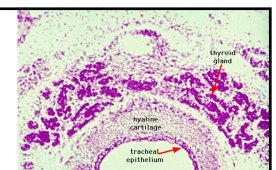
Thyroid

- **Week 6** - thyroid median endodermal thickening in the floor of pharynx (thyroid diverticulum)
- **Week 7-10** - thyroglossal duct - proximal end at the foramen cecum of tongue.
- thyroid diverticulum - hollow then solid, right and left lobes, central isthmus

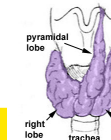


Thyroid

- **Week 13** - colloid appearance in thyroid follicles, iodine and thyroid hormone (TH) synthesis growth factors (insulin-like, epidermal) stimulates follicular growth
- Fetal TH - initial secreted biologically inactivated by modification
- late fetal secretion develops brown fat
- Iodine deficiency - during this period, leads to neurological defects (cretinism)
- Birth - TSH levels increase, thyroxine (T3) and T4 levels increase to 24 h, then 5-7 days postnatal decline to normal levels

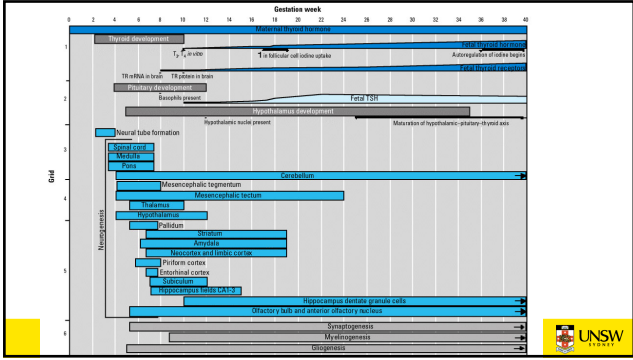


Week 10
Thyroid Pyramidal Lobe
(neck ventral view)



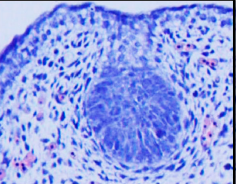
Pyramidal Lobe
50% anatomical dissections and more frequently in men than in women.





Breast

- **Week 8** - epidermis down-growth into dermis, modified sweat glands
- **Key Molecular Factors** - *WNT10b*, *Gli3*, *Hh*,
 - epithelia/mesenchyme inductive interaction, mesenchyme forms connective tissue and fat
 - mammary ridges - mammary bud formation, pair of ventral regions axilla to inguinal
 - buds branch to form lactiferous ducts, only main duct formed at birth
 - prior to puberty male and female glands the same



Mouse mammary E14.5 (~Week 9-10)