

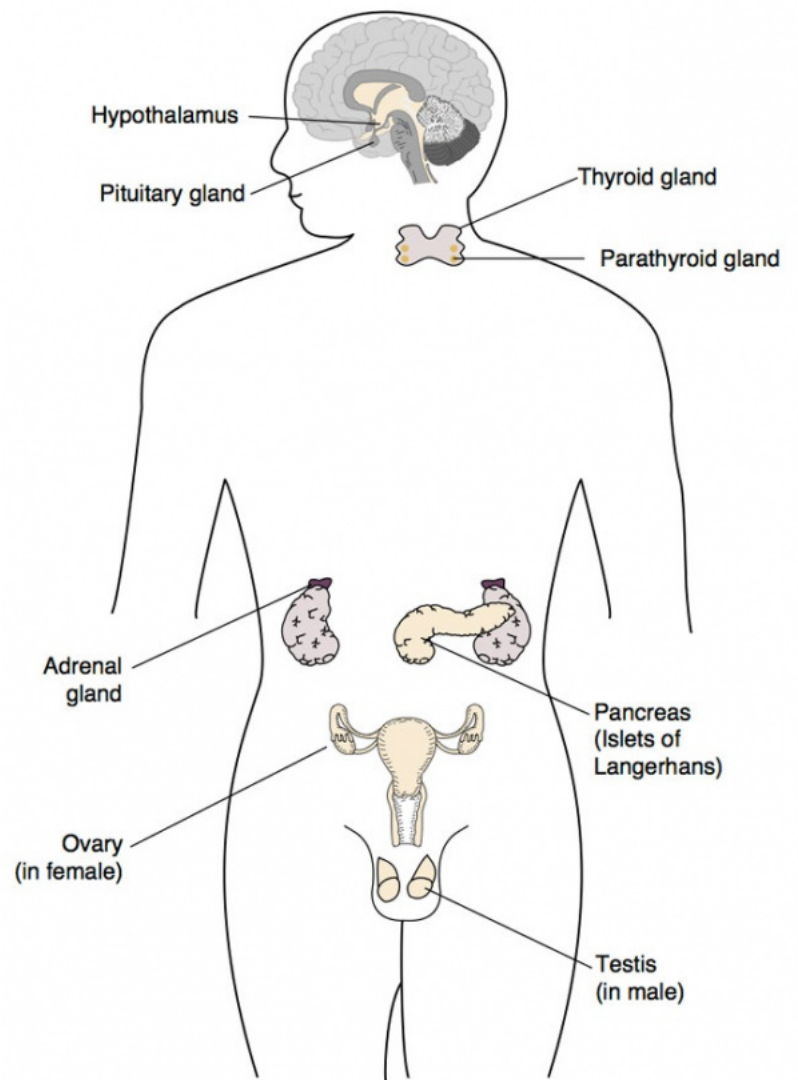
Lecture - Endocrine Development

Introduction

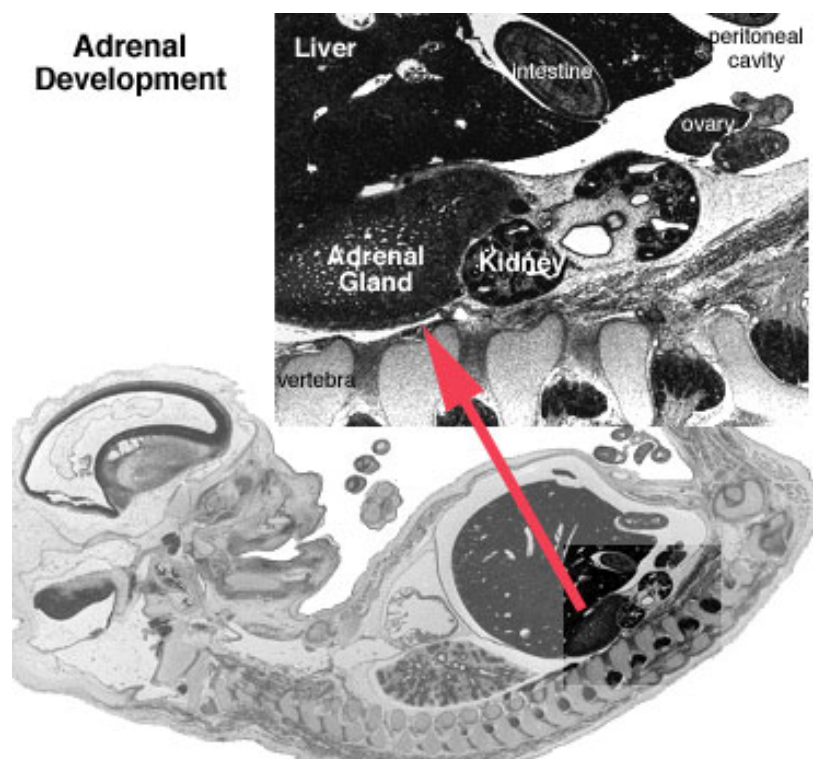
The endocrine system resides within specific endocrine organs and both organs and tissues with other specific functions. Epithelia (ectoderm and endoderm) form the majority of the “ductless” endocrine glands like gastrointestinal and skin associated “ducted” glands.

Differentiation of several also organs involves a epithelial/mesenchyme interaction, seen in repeated in many differentiation of many different tissues. The endocrine glands produce hormones, which are distributed by the vascular system to the many body tissues, subsequently these organs are richly vascularized.

Hormones “orchestrate” responses in other tissues, including other endocrine organs, and these overall effects can be similar or different in different tissues. These signaling pathways are often described as "axes" the two major types are the: **HPA (Hypothalamus-Pituitary-Adrenal)** and **HPG (Hypothalamus-Pituitary-Gonad)**. These hormone effects (like music) can be rapid, slow,



Hypothalamus endocrine system



brief, diurnal, or long-term. Hormone effects can be mimicked, stimulated, and blocked by therapeutic drugs, nutritional and environmental chemicals. Importantly, fetal endocrine development is required for normal fetal growth and differentiation.

2016 Lecture Video Recording [\[Expand\]](#)

Lecture Objectives

- Understanding of hormone types
- Understanding of endocrine gland development
- Understanding of endocrine developmental functions

Endocrine in the News [\[Expand\]](#)

Lecture Resources

Movies [\[Expand\]](#)

References [\[Expand\]](#)

Endocrine Origins

- **Epithelia** - (ectoderm) covering embryo, (endoderm) lining gastrointestinal tract, (mesoderm) lining coelomic cavity
- **Mesenchyme** - (mesoderm) contribution, connective tissue, blood vessels

Hormones

Hormone Types

- **Amino acid derivatives** - noradrenaline (norepinephrine), adrenalin (epinephrine), thyroid hormone
- **Proteins, peptides** - thyroid stimulating hormone, leutenising hormone, follicle stimulating hormone
- **Steroids** - androgens, glucocorticoids, mineralocorticoids

Hormone Actions

- **Autocrine** - acts on self (extracellular fluid)
- **Paracrine** - acts locally (extracellular fluid)
- **Endocrine** - acts by secretion into blood stream (endocrine organs are richly vascularized)

Hormone Receptors

- **Cell surface receptors** - modified amino acids, peptides, proteins
- **Cytoplasmic/Nuclear Receptors** - steroids

Interested in hormone history?

Listen ABC Radio Ockham's

Razor 2005-07-31 6.2 Mb mp3

[Centenary of the word](#)

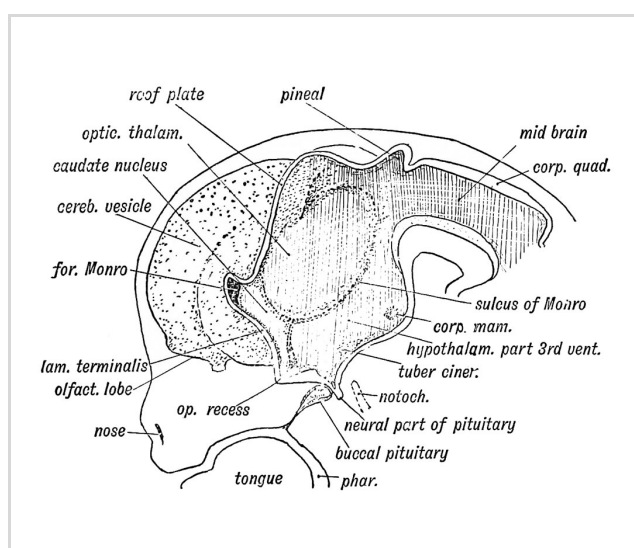
['hormone'](#), Sydney medical

scientist and writer Dr John

Carmody commemorates the

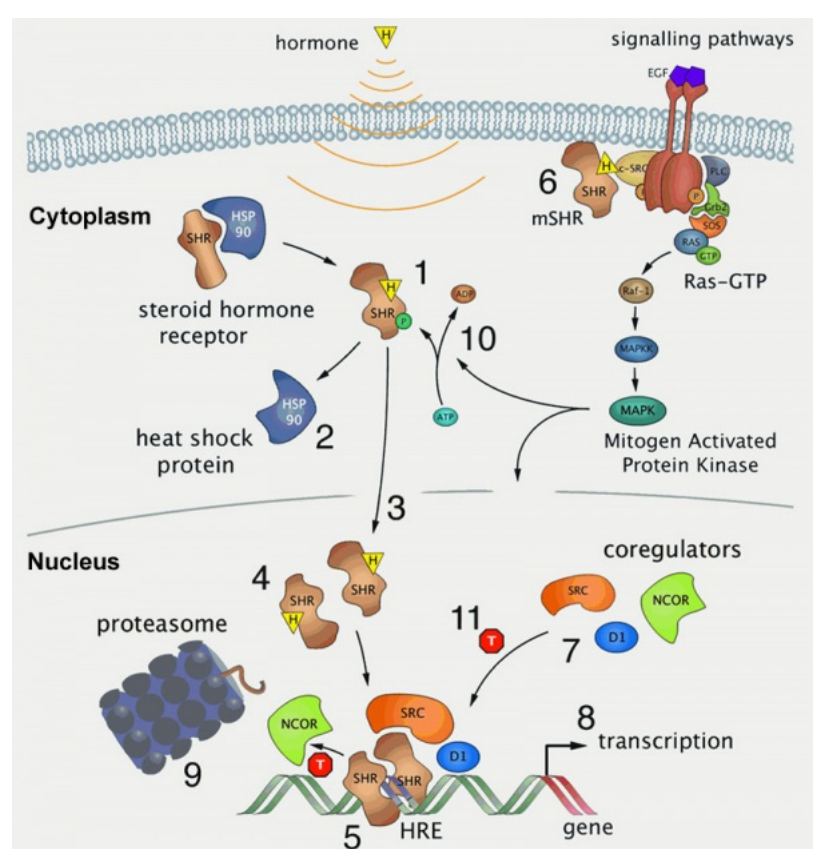
centenary of the entry of the word 'hormone' into the English language.

Pineal Gland

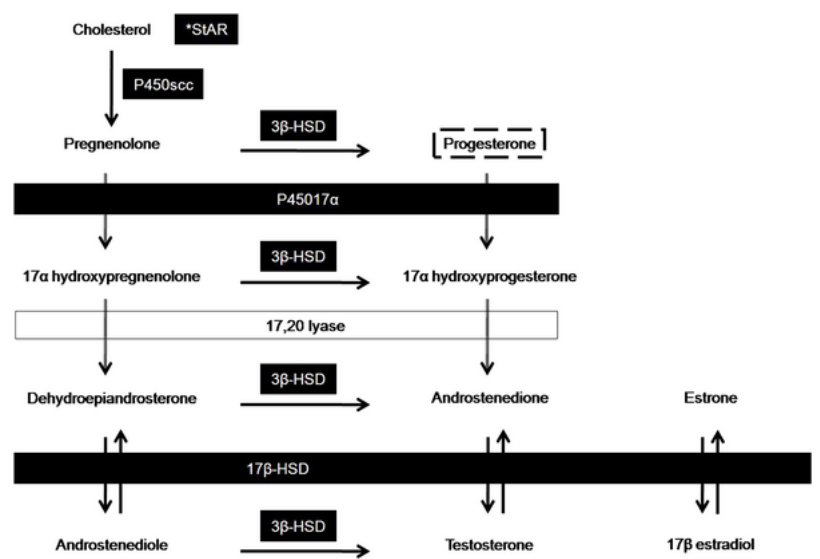


Pineal Development

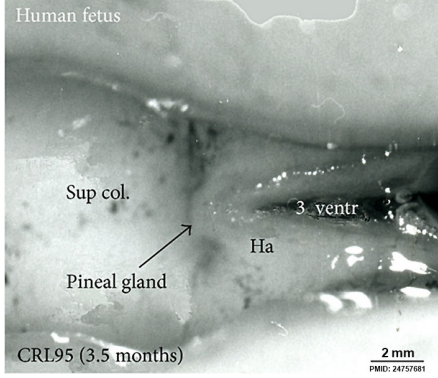
- Neuroectoderm - prosencephalon then diencephalon
- caudal roof, median diverticulum, epiphysis
- Initially a hollow diverticulum, cell proliferation to solid, pinealocytes (neuroglia), cone-shaped gland innervated by epithalamus



Steroid hormone receptor signaling^[1]



Steroid biosynthesis pathway

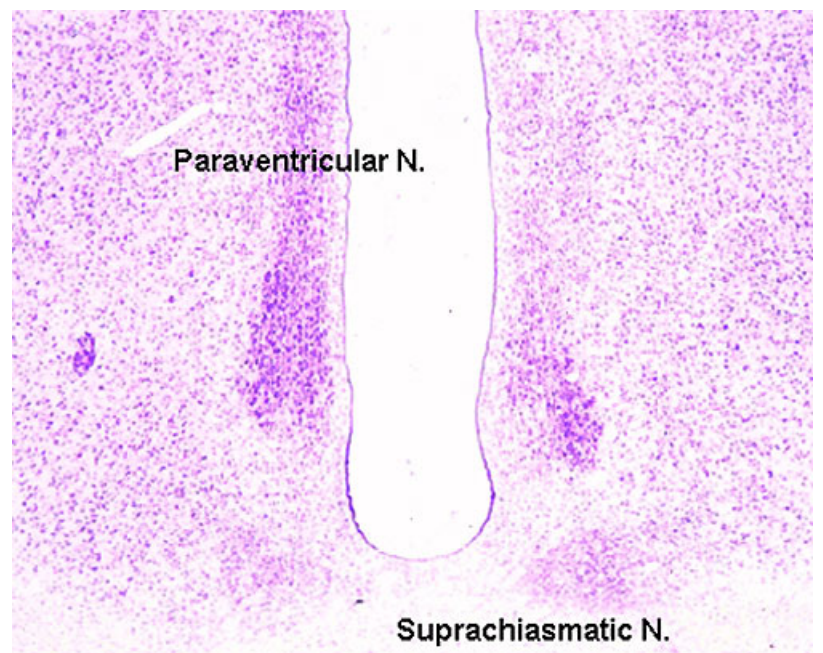


- Human fetus (3.5 month) superior (dorsal) view diencephalic-mesencephalic area.
- Third ventricle (3 ventr) without pial covering is seen to the right.
- Pineal gland is a small protuberance (arrow) and merging via the broad stalk with the habenula (Ha). Superior colliculus (Sup col.)

Links: [Endocrine - Pineal Development](#) | [Endocrinology](#)

Hypothalamus

Hormones - Corticotrophin releasing hormone (CRH), Thyrotrophin releasing hormone (TRH), Arginine vasopressin (AVP), Gonadotrophin releasing hormone (GnRH), Growth hormone releasing hormone (GHRH), Somatostatin, Prolactin relasing factor (PRF), Dopamine



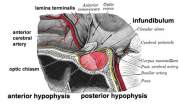

Hypothalamus Development

- Neuroectoderm - prosencephalon then **diencephalon**
- ventro-lateral wall intermediate zone proliferation
- Mamillary bodies - form pea-sized swellings ventral wall of hypothalamus
- Human Embryo Brain (week 4.5 exterior view)
- Human Embryo Brain (week 5 exterior view)
- Human Embryo Brain (week 5 interior view)

- Human Fetal Brain
(3 months)
- Human Fetal Brain
(4 months)

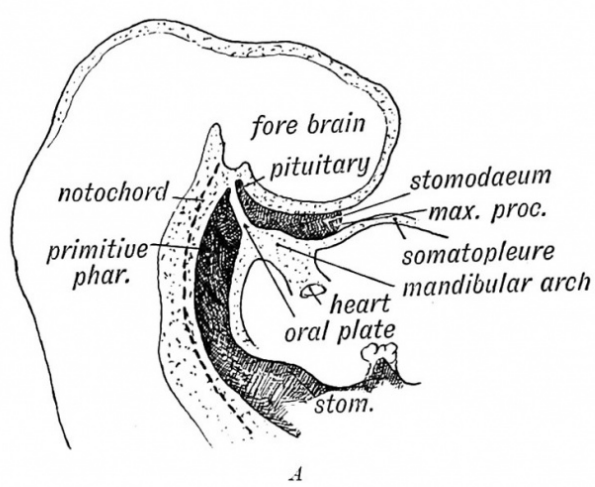
Links: [Endocrine - Hypothalamus Development](#)

Pituitary

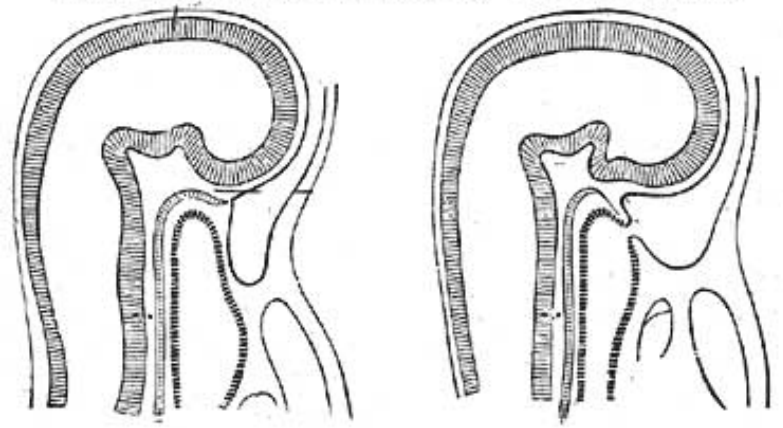
	<p>The pituitary (hypophysis) sits anatomically within the sella turcica, a space within the sphenoid bone.</p> <p>Anterior pituitary hormones - Thyroid-stimulating hormone (TSH), Adrenocorticotrophic hormone (ACTH), Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Somatotrophin/growth hormone (GH), Prolactin (PRL), Melanocyte-stimulating hormone (MSH)</p> <p>Posterior pituitary hormones - Oxytocin, Arginine vasopressin</p>	
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Pituitary Development

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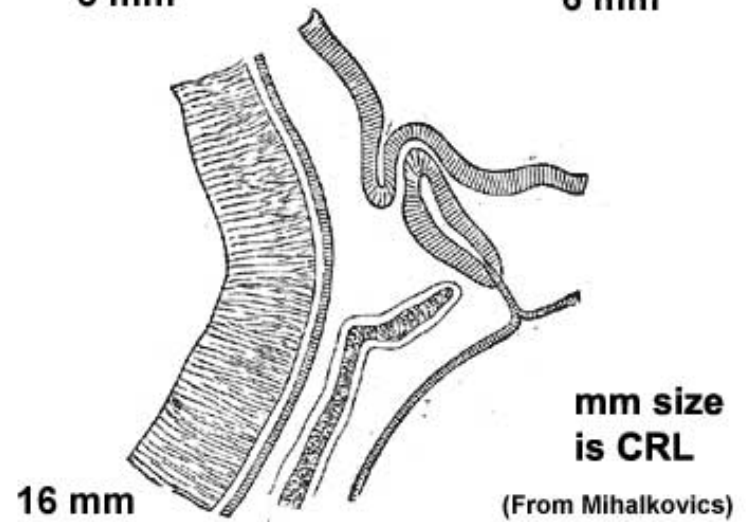


Rabbit Embryo Pituitary Development



5 mm

6 mm



16 mm

mm size
is CRL

(From Mihalkovics)

Development of the Hypophysis



Blue - neural tube ectoderm

Red - surface ectoderm

- Dual ectoderm origins
 - **Ectoderm** - ectoderm roof of stomodeum, Rathke's pouch, adenohypophysis
 - **Neuroectoderm** - prosencephalon then diencephalon, neurohypophysis

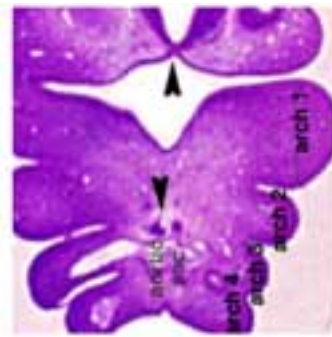
Adenohypophysis

- Anterior wall proliferates - pars distalis
- Posterior wall little growth – pars intermedia

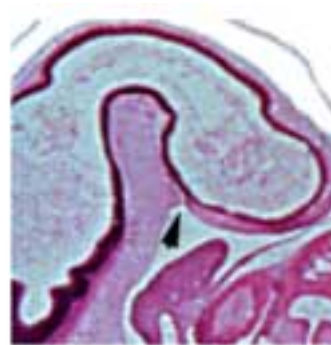
- Rostral growth around infundibular stem – pars tuberalis

Neurohypophysis

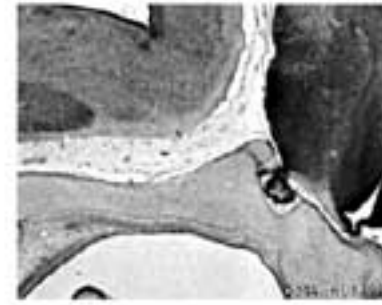
- Infundibulum – median eminence, infundibulum, pars nervosa



Rathke's Pouch
And Thyroid cells



Rathke's Pouch

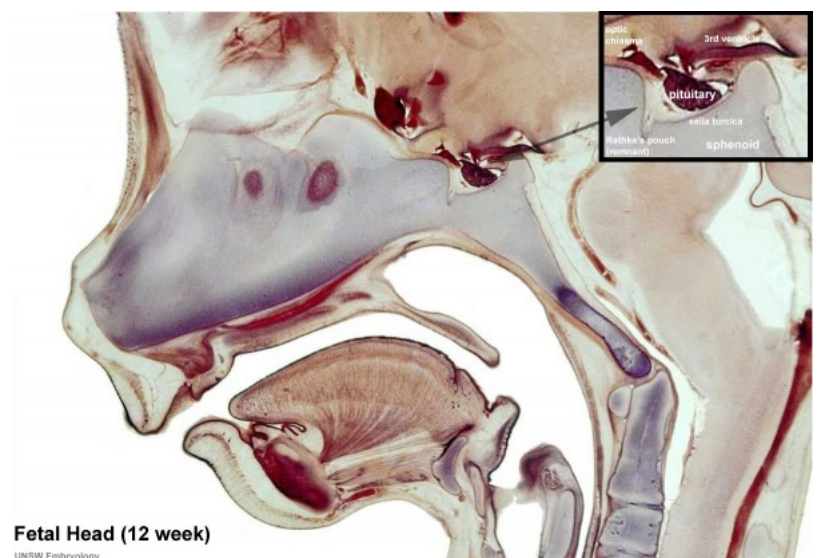


Fetal Pituitary



Pituitary Timeline

- **Week 4** - hypophysial pouch, Rathke's pouch, diverticulum from roof
- **Week 5** - elongation, contacts infundibulum, diverticulum of diencephalon
- **Week 6** - connecting stalk between pouch and oral cavity degenerates
- **Week 8** - basophilic staining cells appear
- **Week 9** - acidophilic staining cells appear



- **Week 10** - growth hormone and ACTH detectable
- **Week 16** - adenohypophysis fully differentiated and TSH increases to peak at 22 weeks
- **Week 20 to 24** - growth hormone levels peak, then decline
- **Birth** - second TSH surge and decreases postnatally

Links: [Endocrine - Pituitary Development](#) | [Embryo Images - Pituitary](#) | [Endocrinology](#)

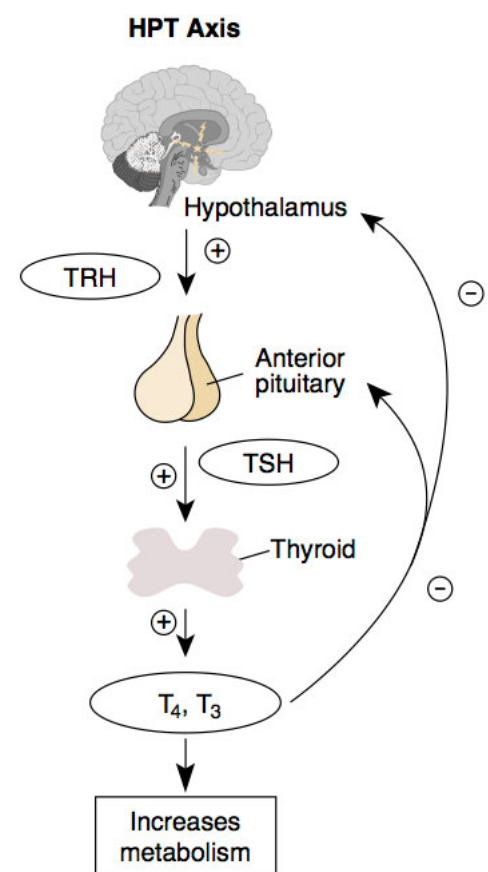
Thyroid

- **Maternal thyroid hormone**
 - required for early stages of brain development
- **Fetal thyroid** - begins function from week 10, (**GA** week 12) required for neural development, stimulates metabolism (protein, carbohydrate, lipid), reduced/absence = cretinism (see abnormalities)

Hormones - TH (amino acid derivatives) Thyroxine (T₄), Triiodothyronine (T₃)

Thyroid Development

- thyroid median endodermal thickening in the floor of pharynx, outpouch – **thyroid diverticulum**.
- tongue grows, cells descend in neck.
- thyroglossal duct - proximal end at the foramen caecum of tongue.
- thyroid diverticulum - hollow then solid, right and left lobes, central isthmus.



Hypothalamus - Pituitary - Thyroid Axis

Thyroid Timeline

- **24 days** - thyroid median endodermal thickening in the floor of pharynx, outpouch – thyroid diverticulum
- **Week 11** - colloid appearance in thyroid follicles, iodine and thyroid hormone (TH) synthesis. Growth factors (insulin-like, epidermal) stimulates follicular growth.
- **Week 16 - 18** - ([GA](#) 18-20 weeks) fully functional

Links: [Box 3.21 Embryology of the thyroid and parathyroid glands](#)

Fetal Thyroid Hormone

- Initial secreted biologically inactivated by modification
 - serum thyroid hormone levels are relatively low and tissue concentration of thyroid hormone is modified by iodothyronine deiodinases
- Iodine deficiency - during this period, leads to neurological defects (cretinism)
- Late fetal secretion - develops brown fat
- Birth - TSH levels increase, thyroxine (T₃) and T₄ levels increase to 24 h, then 5-7 days postnatal decline to normal levels
- Post-natal - TH required for bone development

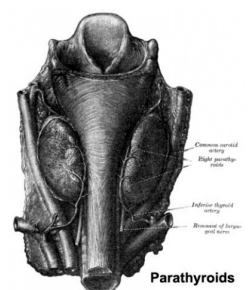
Maternal TH - iodine/thyroid status can affect development.

- recent studies show that both high and low maternal thyroid hormone impact on neural development (PMID 26497402)

Links: [Endocrine - Thyroid Development](#) | [Endocrinology](#) |

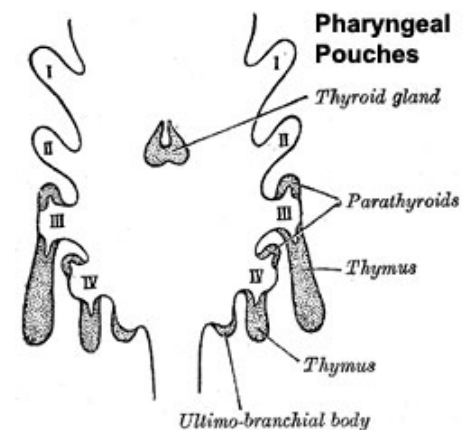
Parathyroid

- Parathyroid Hormone - Increase calcium ions [Ca²⁺], stimulates osteoclasts, increase Ca GIT absorption (opposite effect to calcitonin)
- Adult Calcium and Phosphate - Daily turnover in human with dietary intake of 1000 mg/day
- secreted by chief cells



Parathyroid Development

- Endoderm - third and fourth pharyngeal pouches, could also have ectoderm and neural crest
 - 3rd Pharyngeal Pouch - inferior parathyroid, initially descends with thymus
 - 4th Pharyngeal Pouch - superior parathyroid
- **Week 6** - diverticulum elongate, hollow then solid, dorsal cell proliferation
- Fetal parathyroids - respond to calcium levels, fetal calcium levels higher than maternal
- parathyroid hormone - (PTH, parathormone or parathyrin)



Pharyngeal pouches

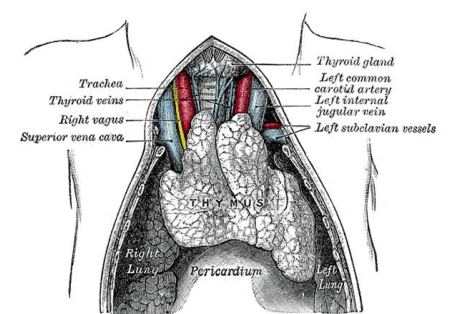
Links: [Endocrine - Parathyroid Development](#) | [Endocrinology](#)

Thymus

- Thymus - bone-marrow lymphocyte precursors become thymocytes, and subsequently mature into T lymphocytes (T cells)
- Thymus hormones - thymosins stimulate the development and differentiation of T lymphocytes

Thymus Development

- Endoderm - third pharyngeal pouch
- **Week 6** - diverticulum elongates, hollow then solid, ventral cell proliferation
- **Thymic primordia** - surrounded by neural crest mesenchyme, epithelia/mesenchyme interaction



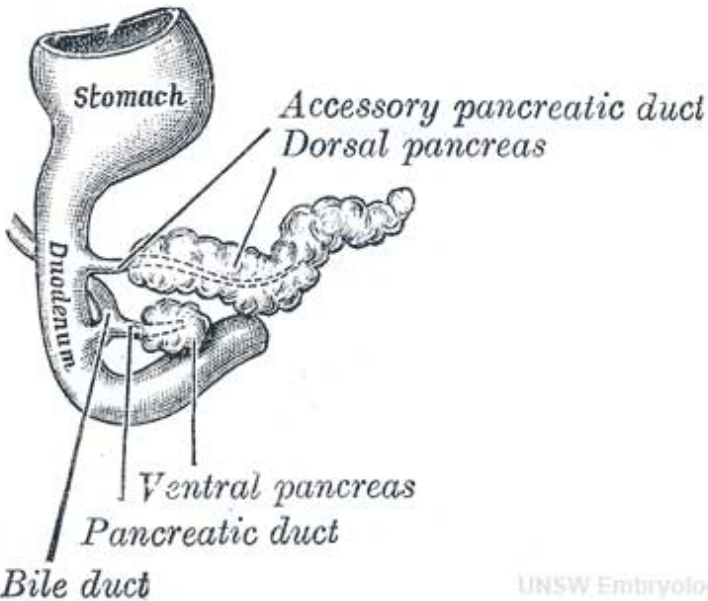
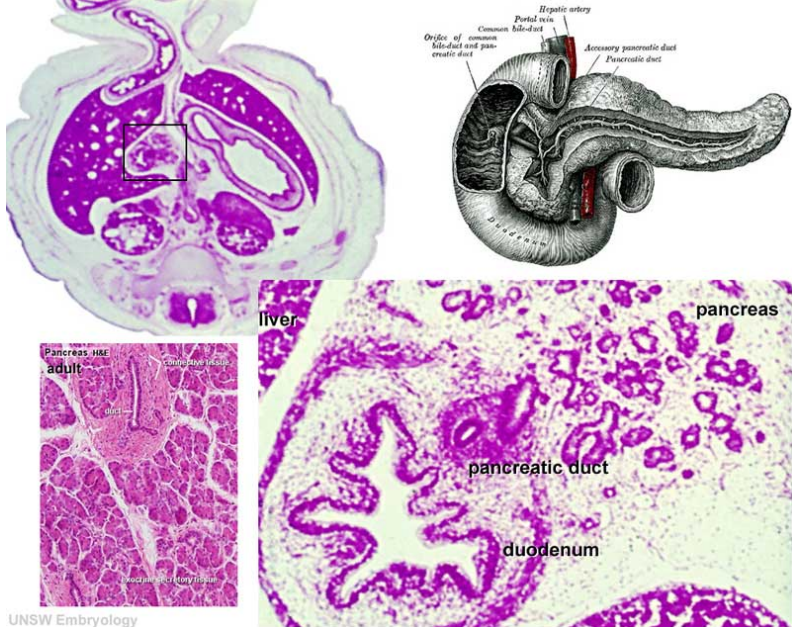
Fetal Thymus

Links: [Endocrine - Thymus Development](#)

Pancreas

Pancreas Development

- Pancreatic buds - duodenal level endoderm, splanchnic mesoderm forms dorsal and ventral mesentery, dorsal bud (larger, first), ventral bud (smaller, later)
- Pancreas Endoderm - pancreas may be opposite of liver
 - Heart cells promote/notochord prevents liver formation
 - Notochord may promote pancreas formation
 - Heart may block pancreas formation

	
<p>Pancreatic buds and duct developing</p>	<p>Pancreas week 8 (Stage 22)</p>

- Duodenum growth/rotation - brings ventral and dorsal buds together, fusion of buds [See Figure 2.32](#)
- Pancreatic duct - ventral bud duct and distal part of dorsal bud, exocrine function
- Islet cells - cords of **endodermal cells** form ducts, from which cells bud off to form islets

Islet [Expand]

Pancreatic Islets

- Islets of Langerhans - 4 endocrine cell types
- **Alpha** - glucagon, mobilizes lipid
- **Beta** - insulin, increase glucose uptake
 - Beta cells, stimulate fetal growth, continue to proliferate to

postnatal, in infancy most abundant

- **Delta** - somatostatin, inhibits glucagon, insulin secretion
- **F-cells** - pancreatic polypeptide

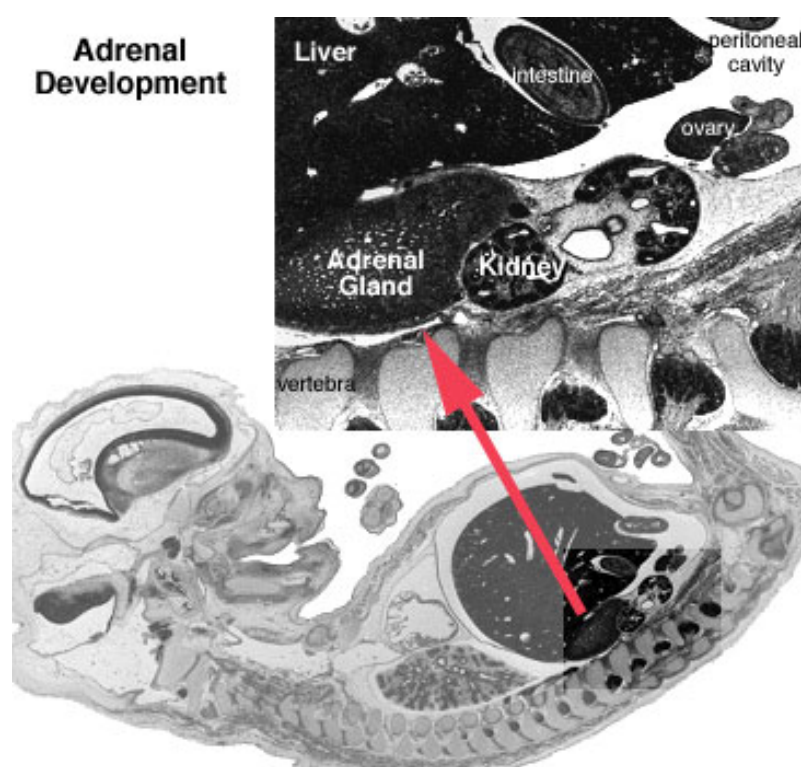
Pancreas Timeline

- **Week 7 to 20** - pancreatic hormones secretion increases, small amount maternal insulin
- **Week 10** - glucagon (alpha) differentiate first, somatostatin (delta), insulin (beta) cells differentiate, insulin secretion begins
- **Week 15** - glucagon detectable in fetal plasma

Links: [Endocrine - Pancreas Development](#) | [Gastrointestinal Tract - Pancreas Development](#) | [Endocrinology](#)

Adrenal

- Richly vascularized - arterioles passing through cortex, capillaries from cortex to medulla, portal-like circulation
- Fetal Cortex - produces a steroid precursor (DEA), converted by placenta into estrogen
- Adult Medulla - produces adrenalin (epinephrine), noradrenaline (norepinephrine)
- Fetal adrenal hormones - influence lung maturation



Fetal adrenal gland (Week 10, [GA](#) week 12)

Adrenal cortical hormones - (steroids) Cortisol, Aldosterone, Dehydroepiandrosterone

- zona glomerulosa - regulated by renin-angiotensin-aldosterone system controlled by the juxtaglomerular apparatus of the kidney.
- zona fasciculata - regulated by hypothalamo-pituitary axis with the

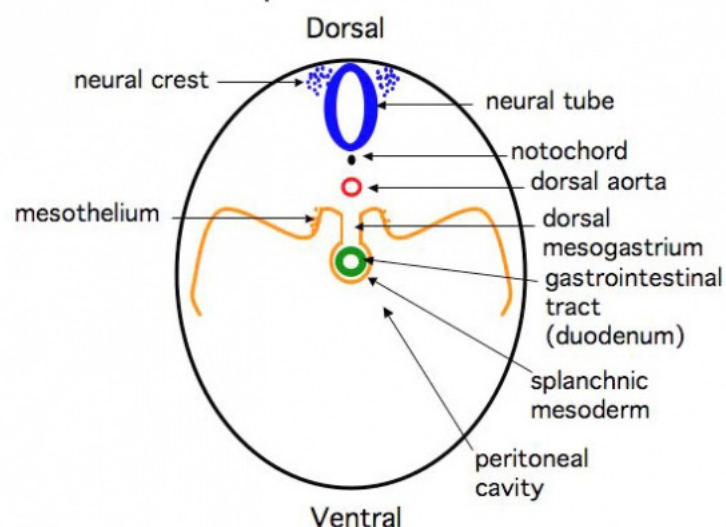
release of CRH and ACTH respectively.

Adrenal medullary hormones - (amino acid derivatives) Epinephrine, Norepinephrine

Adrenal Development

- **Week 6** - fetal cortex, from mesothelium adjacent to dorsal mesentery; Medulla, neural crest cells from adjacent sympathetic ganglia
- Fetal Adrenals - fetal cortex later replaced by adult cortex
- Adult cortex - mesothelium mesenchyme encloses fetal cortex

Adrenal Gland Development



UNSW Embryology
<http://php.med.unsw.edu.au/embryology>

Adrenal Cortex

- Late Fetal Period - differentiates to form cortical zones
- Birth - zona glomerulosa, zona fasciculata present
- Year 3 - zona reticularis present

Adrenal Medulla

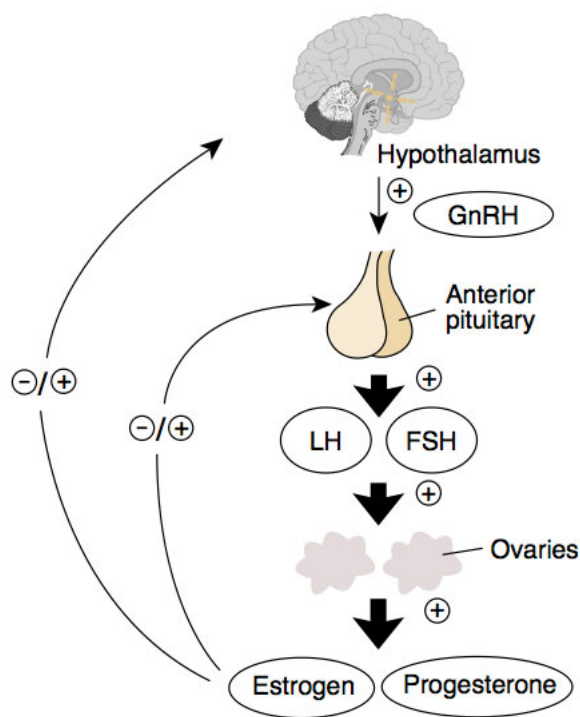
- neural crest origin, migrate adjacent to coelomic cavity, initially uncapsulated and not surrounded by fetal cortex, cells have neuron-like morphology
- 2 cell types - secrete epinephrine (adrenaline) 80%; secrete norepinephrine (noradrenaline* 20%)

Links: [Endocrine - Adrenal Development](#) | [Endocrinology - Adrenal Cortex Development](#) | [Endocrinology](#)

Gonad

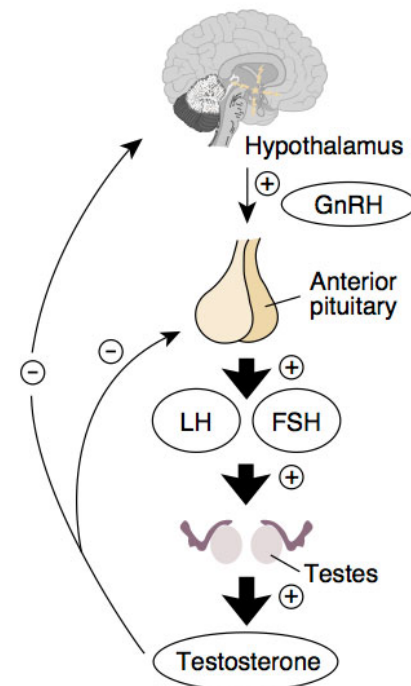
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Female HPG Axis



Adult Hypothalamus - Pituitary - Gonad (female)

Male HPG Axis



Adult Hypothalamus - Pituitary - Gonad (male)

HPG Axis - [Endocrinology - Simplified diagram of the actions of gonadotrophins](#)

Gonad Development

- **mesoderm** - mesothelium and underlying mesenchyme
- **Gonadal ridge** - mesothelium thickening, medial mesonephros
- **Primordial Germ cells** - yolk sac, to mesentery of hindgut, to genital ridge of developing kidney

Differentiation

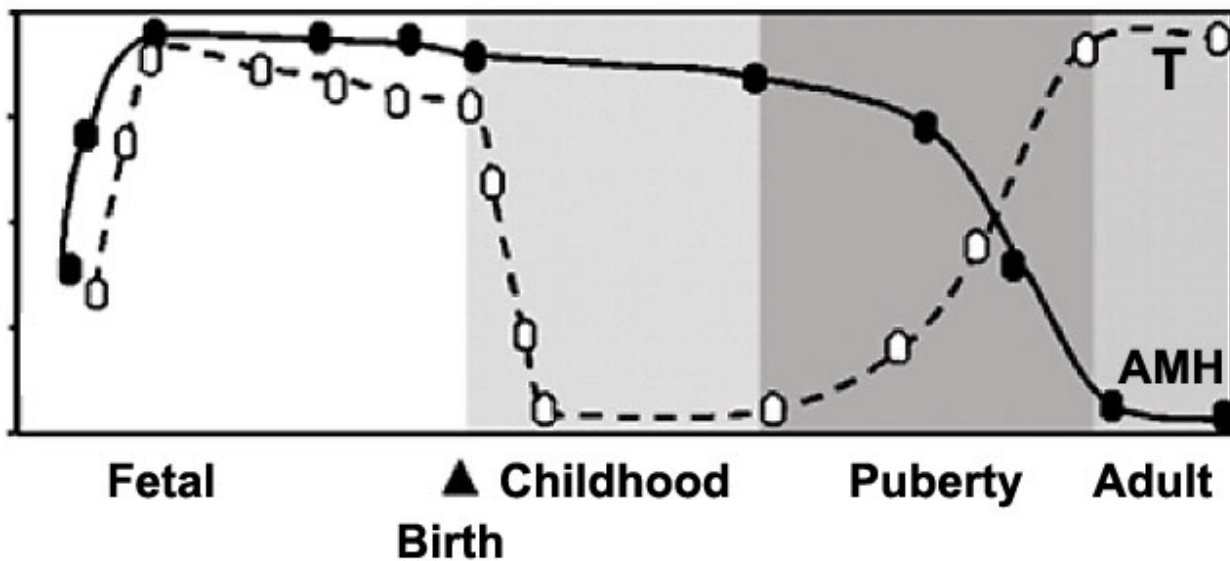
- testis-determining factor (TDF) from Y chromosome: presence (testes), absence (ovaries)

Testis

- **8 Weeks** - mesenchyme, interstitial cells (of Leydig) secrete testosterone, androstenedione.
- **8 to 12 Weeks** - hCG stimulates testosterone production (required for male genital development)

- Sustentacular (Sertoli) cells - produce anti-mullerian hormone (AMH) to puberty.
 - **AMH** - anti-Müllerian hormone (Müllerian inhibiting factor (MIF), Müllerian-inhibiting hormone (MIH), and Müllerian-inhibiting substance (MIS)).

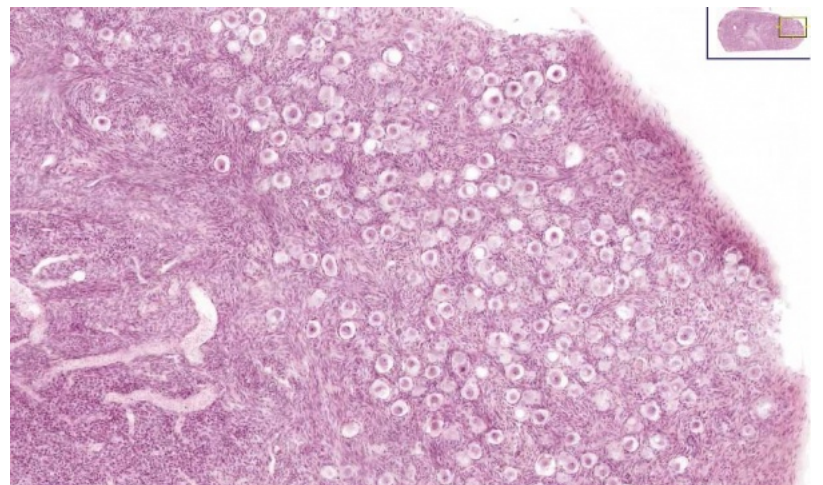
Human Serum Relative Levels



Ovary

- X chromosome genes regulate ovary development
- Hormone levels increase at puberty with follicle development.

I covered this topic in detail in sexual differentiation lecture/practical.

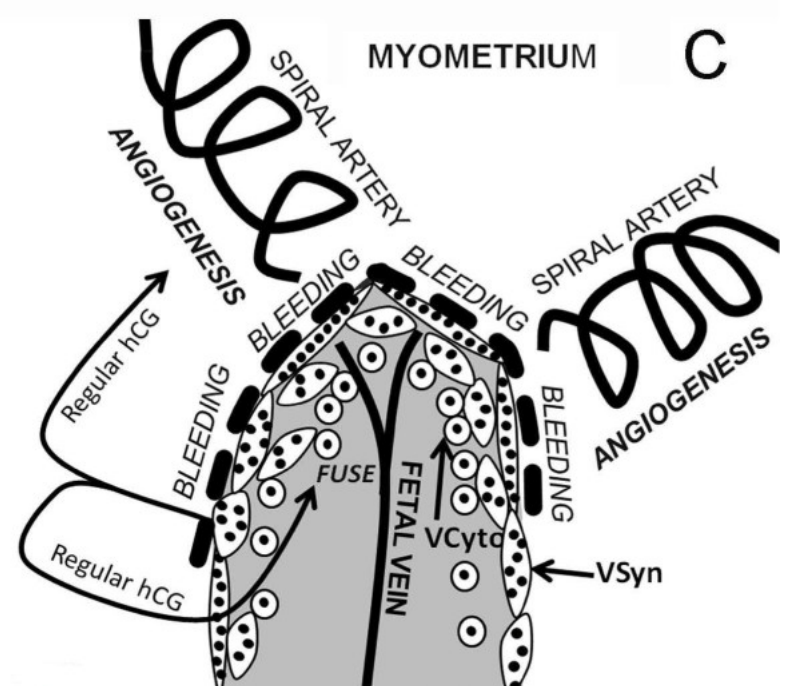
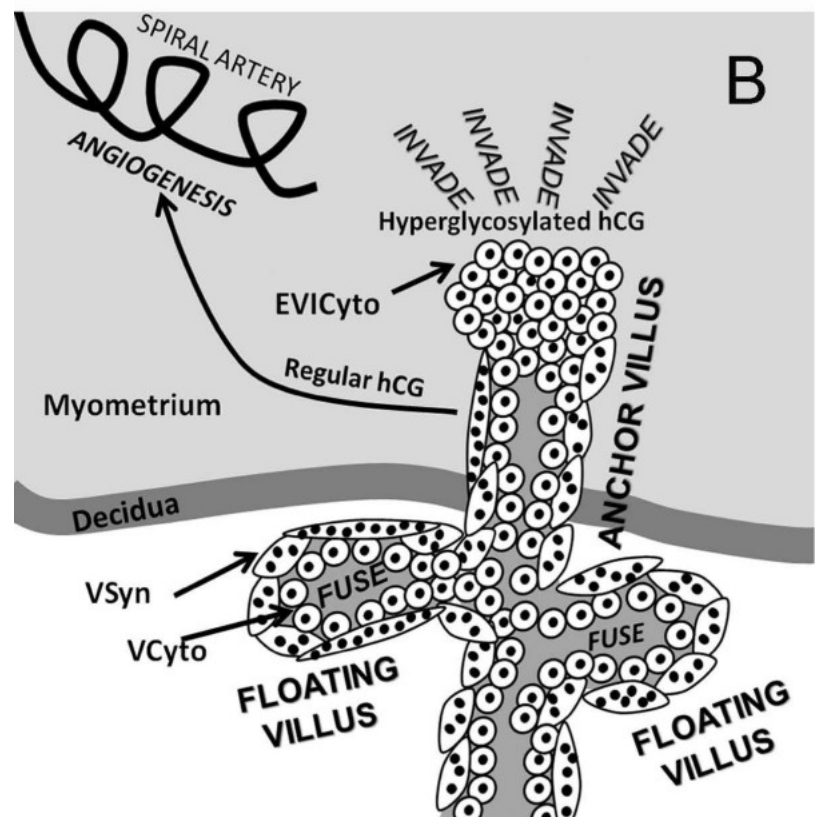
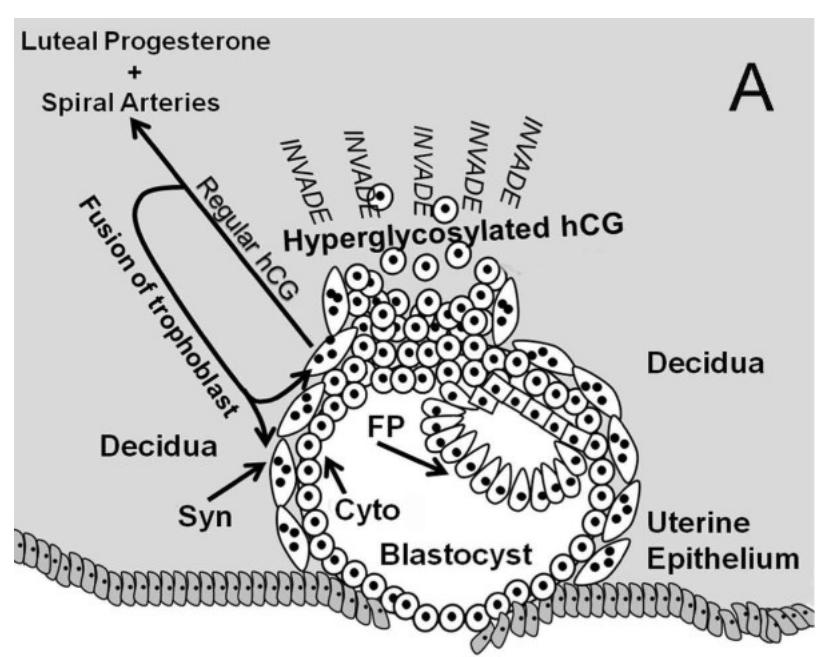


Links: [Endocrine - Gonad Development](#) | [Endocrinology](#)

Placenta

- Human chorionic gonadotrophin (hCG) - like leutenizing hormone, supports corpus luteum in ovary, pregnant state rather than menstrual, maternal urine in some pregnancy testing

- Human chorionic somatomotropin (hCS) - or placental lactogen stimulate (maternal) mammary development
- Human chorionic thyrotropin (hCT)
- Human chorionic corticotropin (hCACTH)
- progesterone and estrogens - support maternal endometrium
- Relaxin
- Placenta - Maternal (decidua) and Fetal (trophoblastic cells, extraembryonic mesoderm) components
- Endocrine function - maternal and fetal precursors, synthesis and secretion
 - Protein Hormones - chorionic gonadotropin (hCG), chorionic somatomammotropin (hCS) or placental lactogen (hPL), chorionic thyrotropin (hCT), chorionic corticotropin (hCACTH)
 - hCG - up to 20 weeks, fetal adrenal cortex growth and maintenance
 - hCS – rise through pregnancy, stimulates maternal metabolic processes, breast growth



- Steroid Hormones - progesterone (maintains pregnancy), estrogens (fetal adrenal/placenta)

Links: [Endocrine - Placenta Development](#)

Other Endocrine

Endocrine Heart

- Atrial natriuretic peptide (ANP) - Increase Filtration rate / decrease Na⁺ reabsorption
- Endothelins - ET-1, ET-2, ET-3, Vasoconstriction / Increase NO
- Nitric oxide (NO) - Vasodilatation

Endocrine Kidney

- Renin - Increase Angiotensin-aldosterone system
- Prostaglandins - decrease Na⁺ reabsorption
- Erythropoietin - Increase Erythrocyte (rbc) production
- 1,25 (OH)₂ vitamin D - calcium homeostasis
- Prekallikreins - Increase Kinin production

GIT Endocrine

Enteric control of digestive function

- Gastrin - Secreted from stomach (G cells), role in control of gastric acid secretion
- Cholecystkinin - small intestine hormone, stimulates secretion of pancreatic enzymes and bile
- Secretin - small intestine hormone (epithelial cells), stimulates secretion of bicarbonate-rich fluids from pancreas and liver

Adipose Tissue

- Leptin - polypeptide hormone produced in adipose and many other tissues with also many different roles
- Adiponectin - regulation of energy homeostasis and glucose and lipid

metabolism, as well as acting as an anti-inflammatory on the cellular vascular wall

- Resistin - (for resistance to insulin, RETN) a 108 amino acid polypeptide and the related resistin-like protein-beta (Resistin-like molecule-beta, RELMbeta) stimulate endogenous glucose production

Links: [Endocrine - Other Tissues](#)

Endocrine Functional Changes

- **Puberty** - Increased activity.
- **Menopause** - Decreased activity.
- **Disease** - (diabetes, thyroid, kidney) suggested trends that genetics, health, nutrition, lifestyle may influence time that these events occur.
- **Pharmaceutical impact** - birth control, steroids, Hormone Replacement Therapy (HRT).

Abnormalities

NIH Genes & Disease [Chapter 41 - Glands and Hormones](#)

Pineal

- hypoplasia - associated with retinal disease.
- tumours - in children are associated with abnormal puberty development.

Pituitary

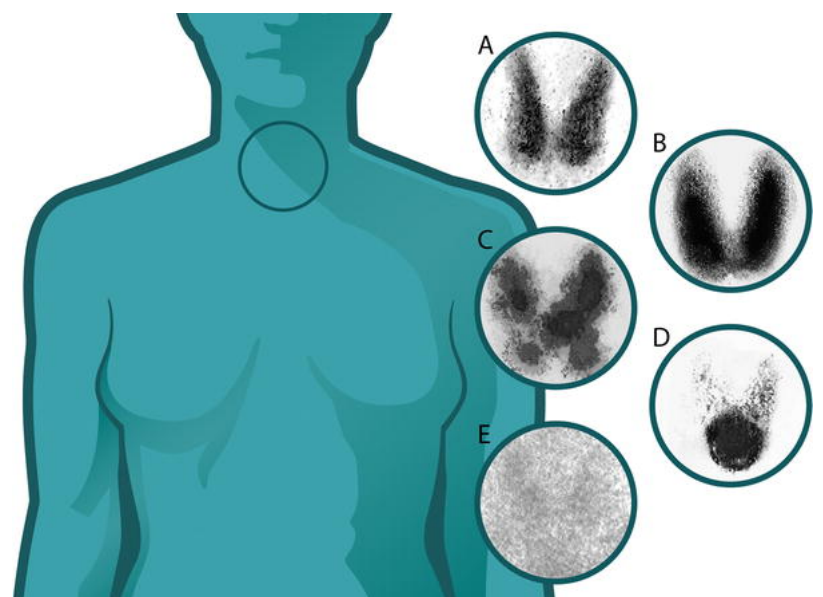
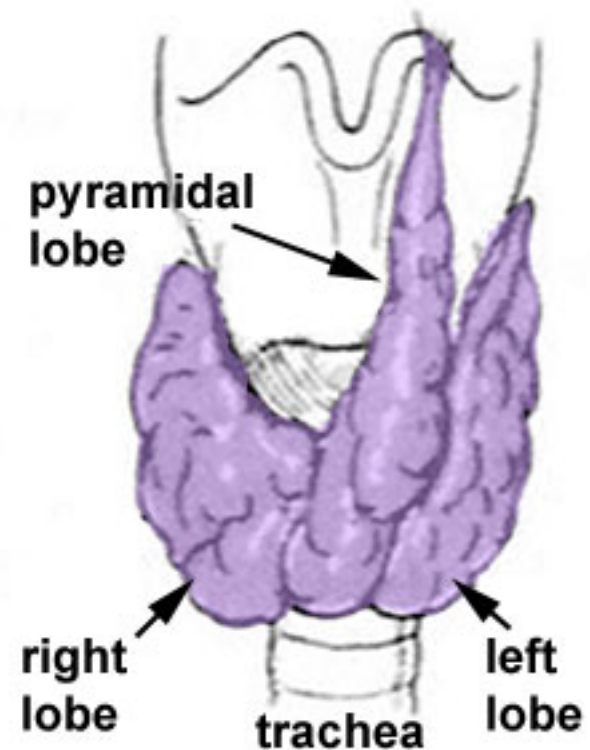
- craniopharyngeal canal - Rathke's pouch abnormality, from the anterior part of the fossa hypophyseos of the sphenoid bone to the under surface of the skull.
- pituitary tumours (adenomas) - several abnormalities associated with abnormal levels of the hormonal output of the pituitary.
 - Growth hormone (GH) adenomas - benign pituitary tumors lead to chronic high GH output levels, that may lead to acromegaly.
- **Cushing's disease** - caused either by a pituitary adenoma produces

excess adrenocorticotrophic hormone (ACTH, corticotropin) or due to ectopic tumors secreting ACTH or corticotropin-releasing hormone (CRH).

Thyroid

- Pyramidal lobe - from isthmus (50% of people) attached to hyoid bone distal end of thyroglossal duct.
- Congenital hypothyroidism - approximately 1 in 3000 births, associated with neurological abnormalities.
- Lingual thyroid gland - failure of thyroid descent.
- Thyroglossal cyst - persistence of thyroglossal duct. [Image - thyroglossal duct](#)
- Thyroglossal fistula - partial degeneration of the thyroglossal duct.
- Abnormal development of the thyroid - incomplete or excessive descent.
- Childhood hypothyroidism delays ossification and bone mineralization.

Thyroid Pyramidal Lobe
(neck ventral view)



Iodine Deficiency

- A teaspoon of iodine, total lifetime requirement, cannot be stored for long periods by our body, tiny amounts are needed regularly
- Areas of endemic iodine deficiency, where soil and therefore crops and grazing animals do not provide sufficient dietary iodine to the populace

- food fortification and supplementation - Iodized salt programs and iodized oil supplements are the most common tools in fight against IDD

Parathyroid

- Usually four glands are present (2 on each side), but three to six glands have been found in human.
- Can have displaced parathyroid development with thymus.
- Lower parathyroid glands arise from the third pharyngeal pouch and descend with the thymus. Variable descent can lead to a range of adult locations, from just beneath the mandible to the anterior mediastinum.

Pancreas

- Type 1 Diabetes - juvenile onset diabetes, more severe form of illness, increases risk of blindness, heart disease, kidney failure, neurological disease, T-lymphocyte-dependent autoimmune disease, infiltration and destruction of the islets of Langerhans, Approx 16 million Americans
- Type 2 Diabetes - loosely defined as "adult onset" diabetes, becoming more common cases of type 2 diabetes seen in younger people
- Risk of developing diabetes - environmental factors (food intake and exercise play an important role, either overweight or obese), Inherited factors (genes involved remain poorly defined)

Adrenal

- Congenital Adrenal Hyperplasia (CAH) - family of inherited disorders of adrenal steroidogenesis enzymes which impairs cortisol production by the adrenal cortex. Androgen excess leads newborn females with external genital ambiguity and postnatal progressive virilization in both sexes.
 - Enzymes most commonly affected: 21-hydroxylase (21-OH), 11beta-hydroxylase, 3beta-hydroxysteroid dehydrogenase.

- Enzymes less commonly affected: 17alpha-hydroxylase/17,20-lyase and cholesterol desmolase.
- Pheochromocytomas (PCC) - Catecholamine-producing (neuro)endocrine tumor located in the adrenal medulla. Similar catecholamine-producing tumors outside the adrenal gland are called paragangliomas (PGL).

Endocrine Disruptors

Exogenous chemicals that interfere with the function of hormones. There are 3 main mechanisms: mimic, block or interfere.

Mimic - effects of natural hormones by binding receptors

- Diethylstilbestrol - (DES or diethylstilbetrol) a drug prescribed to women from 1938-1971 to prevent miscarriage in high-risk pregnancies. Acts as a potent estrogen (mimics natural hormone) and therefore a potential endocrine disruptor. Female fetus, increased risk abnormal reproductive tract and cancer. Male fetus, abnormal genitalia. Banned by USA FDA in 1979 as a teratogen, previously used as livestock growth promoter.

Block - binding of a hormone to receptor or hormone synthesis

- Finasteride - chemical used to prevent male pattern baldness and enlargement of prostate glands. An anti-androgen (blocks synthesis of dihydrotestosterone) and therefore a potential endocrine disruptor, exposed pregnant women can impact on male fetus genital development.
- Vinclozolin - a dicarboximide fungicide, perinatal exposure in rats inhibits morphological sex differentiation. In adult rats, shown to cause gonad tumours (Leydig cell) and atrophy. Chemical has androgen-antagonist (antiandrogenic) activity, metabolites compete with natural androgen

Interfere - with hormone transport or elimination

- Polychlorinated biphenyl pollutants - (PCBs) Rats exposed to PCBs have low levels of thyroid hormone. Compete for binding sites of thyroid hormone transport protein. Without being bound to this protein, thyroid hormones are excreted from the body (McKinney et al. 1985; Morse et al. 1996)

Links:

References

1. ↑ Alexander Griekspoor, Wilbert Zwart, Jacques Neefjes, Rob Michalides **Visualizing the action of steroid hormone receptors in living cells.** Nucl Recept Signal: 2007, 5;e003 [PubMed 17464358](#) | [PMC1853070](#) | [Nucl Recept Signal](#).
 2. ↑ Morten Møller, Pansiri Phansuwan-Pujito, Corin Badiu **Neuropeptide Y in the adult and fetal human pineal gland.** Biomed Res Int: 2014, 2014;868567 [PubMed 24757681](#) | [PMC3976832](#) | [Biomed Res Int](#).
- **Endocrinology: An Integrated Approach** Nussey, S.S. and Whitehead, S.A. London:Taylor & Francis; c2001 [Major hormone types](#)
 - **Genes and Disease**, Bethesda (MD): National Library of Medicine (US), NCBI [Chapter 41 - Glands and Hormones](#)

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Histology

Adult

- Pineal (high power)

- Thyroid (low power)
- Thyroid (high power)
- Parathyroid (low power)
- Parathyroid (high power)
- Pituitary - adenohypophysis
- Pituitary - adenohypophysis
- Pituitary - neurohypophysis
- Adrenal - Cortex and Medulla
- Adrenal - Cortical Zones
- Adrenal - Zona Reticularis and Medulla
-

Embryonic

- Stage 22 - Pancreatic duct
- Stage 22 - Adrenal gland
- Week 10 - Adrenal gland

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