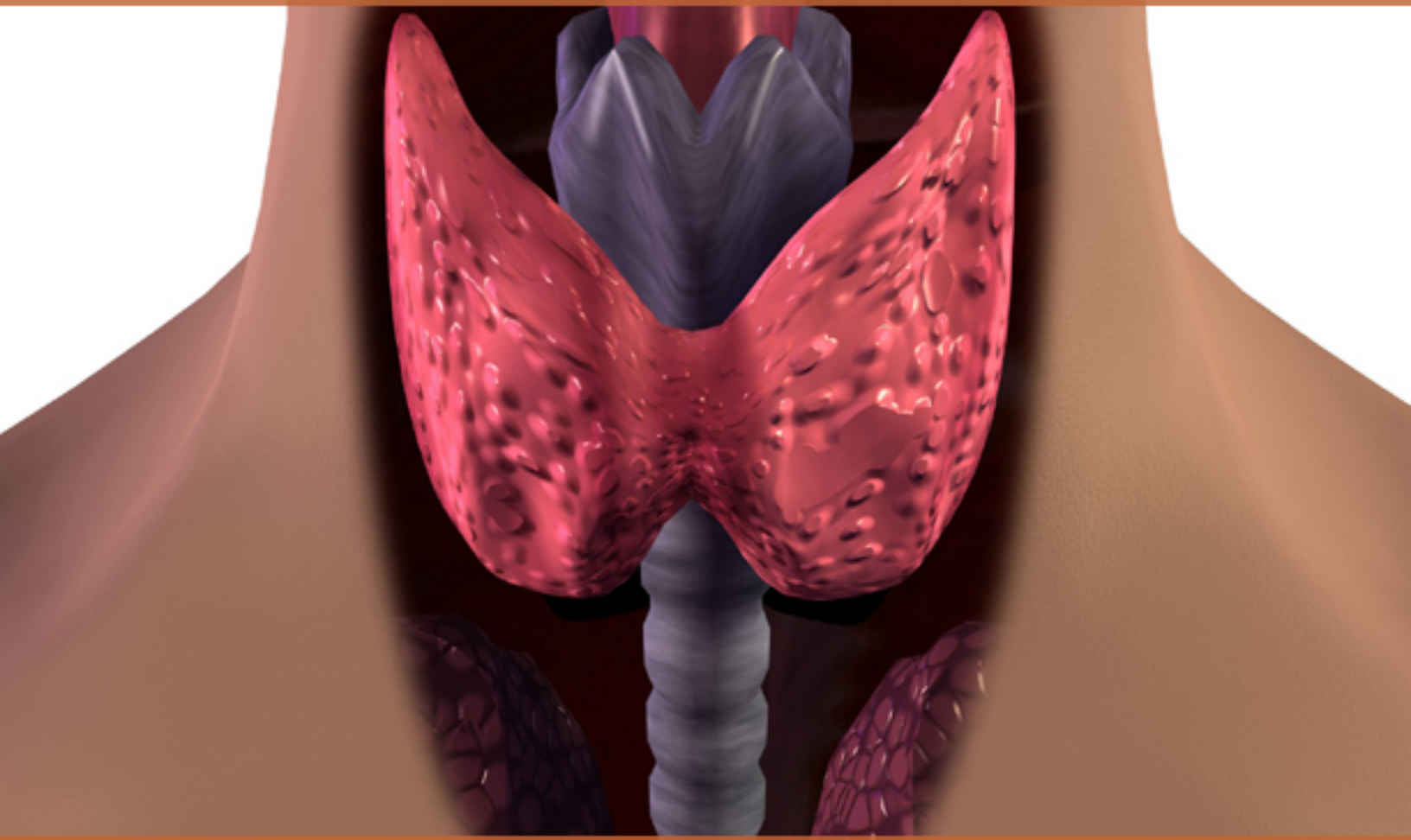
Endocrine System and Diseases



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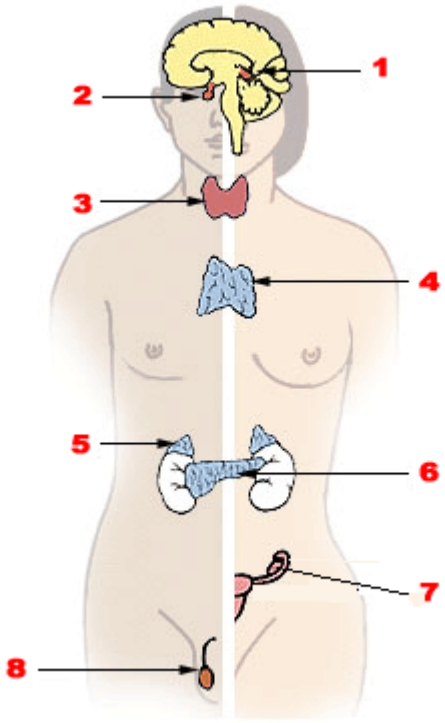
Endocrine System



Major endocrine glands. (Male on the left, female on the right.) ***1.*** *Pineal gland* ***2.*** *Pituitary gland* ***3.*** *Thyroid gland* ***5.*** *Adrenal gland* ***6.*** *Pancreas* ***7.*** *Ovary* ***8.*** *Testis.* [Note: the Thymus (labelled 4.) has endocrine function, though it is not considered to be an endocrine gland.]

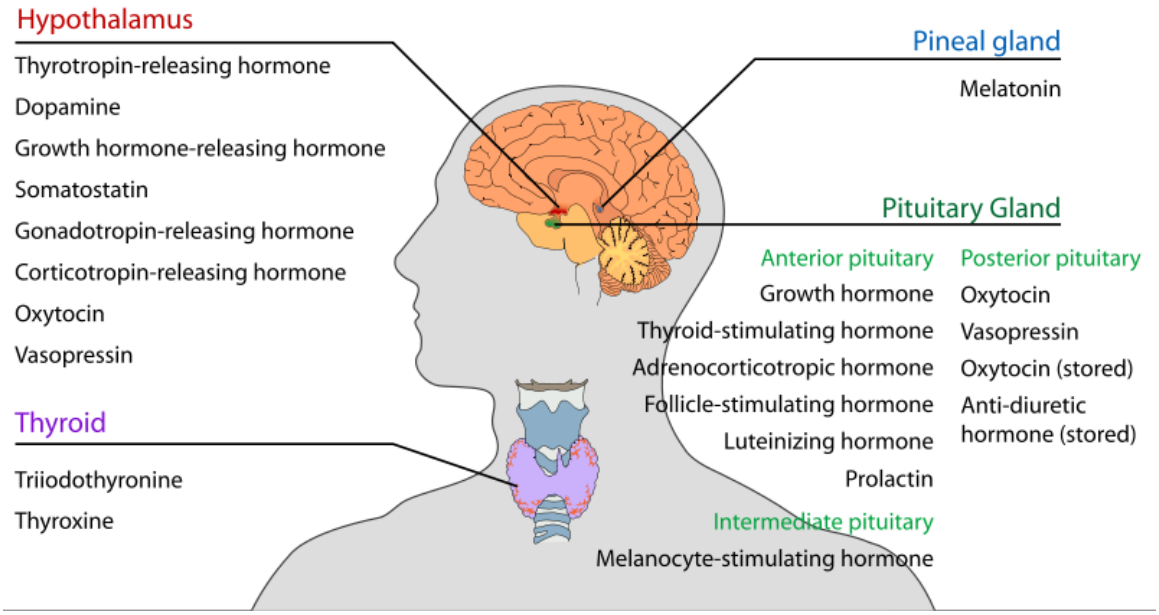
In physiology, the **endocrine system** is a system of glands, each of which secretes a type of hormone into the bloodstream to regulate the body. It derives from the Greek words endo (Greek *ένδο*) meaning inside, within, and crinis (Greek *κρινής*) for secrete. The endocrine system is an information signal system like the nervous system. Hormones are substances (chemical mediators) released from endocrine tissue into the bloodstream that attach to target tissue and allow communication among cells. Hormones regulate many functions of an organism, including mood, growth and development, tissue function, and metabolism. The field of study that deals with disorders of endocrine glands is endocrinology, a branch of internal medicine.

The endocrine system is made up of a series of ductless glands that produce chemicals called hormones. A number of glands that signal each other in sequence is usually referred to as an axis, for example, the hypothalamic-pituitary-adrenal axis. Typical endocrine glands are the pituitary, thyroid, and adrenal glands. Features of endocrine glands are, in general, their ductless nature, their vascularity, and usually the presence of intracellular vacuoles or granules storing their hormones. In contrast, exocrine glands, such as salivary glands, sweat glands, and glands within the gastrointestinal tract, tend to be much less vascular and have ducts or a hollow lumen.

In addition to the specialised endocrine organs mentioned above, many other organs that are part of other body systems, such as the kidney, liver, heart and gonads, have secondary endocrine functions. For example the kidney secretes endocrine hormones such as erythropoietin and renin.

Endocrine organs and secreted hormones

Central nervous system



Endocrine glands in the human head and neck and their hormones

Hypothalamus

Secreted hormone	Abbreviation	Produced by	Effect
Thyrotropin-releasing hormone (Prolactin-releasing hormone)	TRH, TRF, or PRH	Parvocellular neurosecretory neurons	Stimulate thyroid-stimulating hormone (TSH) released from anterior pituitary (primarily) Stimulate prolactin release from anterior pituitary
Dopamine	DA or PIH	Dopamine	Inhibit prolactin released from

(Prolactin-inhibiting hormone)		neurons of the arcuate nucleus	anterior pituitary
Growth hormone-releasing hormone	GHRH	Neuroendocrine neurons of the Arcuate nucleus	Stimulate Growth hormone (GH) release from anterior pituitary
Somatostatin (growth hormone-inhibiting hormone)	SS, GHIH, or SRIF	Neuroendocrine cells of the Periventricular nucleus	Inhibit Growth hormone (GH) release from anterior pituitary Inhibit thyroid-stimulating hormone (TSH) release from anterior pituitary
Gonadotropin-releasing hormone	GnRH or LHRH	Neuroendocrine cells of the Preoptic area	Stimulate follicle-stimulating hormone (FSH) release from anterior pituitary Stimulate luteinizing hormone (LH) release from anterior pituitary
Corticotropin-releasing hormone	CRH or CRF	Parvocellular neurosecretory neurons or the Paraventricular Nucleus	Stimulate adrenocorticotropic hormone (ACTH) release from anterior pituitary
Oxytocin	OT or OXT	Magnocellular neurosecretory neurons of the Supraoptic Nucleus and Paraventricular Nucleus	Uterine contraction Lactation (letdown reflex)
Vasopressin (antidiuretic hormone)	ADH or AVP or VP	Parvocellular neurosecretory neurons, Magnocellular neurosecretory neurons of the Paraventricular Nucleus and Supraoptic Nucleus	Increases water permeability in the distal convoluted tubule and collecting duct of nephrons, thus promoting water reabsorption and increasing blood volume

Pineal body (epiphysis)

Secreted hormone	From cells	Effect
Melatonin	Pinealocytes	Antioxidant Monitors the circadian rhythm including inducement of drowsiness and lowering of the core body temperature

Pituitary Gland (hypophysis)

Anterior pituitary lobe (adenohypophysis)

Secreted hormone	Abbreviation	From cells	Effect
Growth hormone (somatotropin)	GH	Somatotrophs	Stimulates growth and cell reproduction Stimulates Insulin-like growth factor 1 release from liver
Thyroid-stimulating hormone (thyrotropin)	TSH	Thyrotrophs	Stimulates thyroxine (T4) and triiodothyronine (T3) synthesis and release from thyroid gland Stimulates iodine absorption by thyroid gland
Adrenocorticotropic hormone (corticotropin)	ACTH	Corticotrophs	Stimulates corticosteroid (glucocorticoid and mineralcorticoid) and androgen synthesis and release from adrenocortical cells
Beta-endorphin	-	Corticotrophs	Inhibits perception of pain
Follicle-stimulating hormone	FSH	Gonadotrophs	In females: Stimulates maturation of ovarian follicles in ovary In males: Stimulates maturation of seminiferous tubules In males: Stimulates spermatogenesis In males: Stimulates production of androgen-binding protein from Sertoli cells of the testes
Luteinizing hormone	LH	Gonadotrophs	In females: Stimulates ovulation In females: Stimulates formation of corpus luteum In males: Stimulates testosterone synthesis from Leydig cells (interstitial cells)
Prolactin	PRL	Lactotrophs	Stimulates milk synthesis and release from mammary glands

			Mediates sexual gratification

Posterior pituitary lobe (neurohypophysis)

Secreted hormone	Abbreviation	From cells	Effect
Oxytocin		Magnocellular neurosecretory cells	Uterine contraction Lactation (letdown reflex)
Vasopressin (antidiuretic hormone)	ADH or AVP	Parvocellular neurosecretory neurons	Increases water permeability in the distal convoluted tubule and collecting duct of nephrons, thus promoting water reabsorption and increasing blood volume

Oxytocin and anti-diuretic hormone are not secreted in the posterior lobe, merely stored.

Intermediate pituitary lobe (pars intermedia)

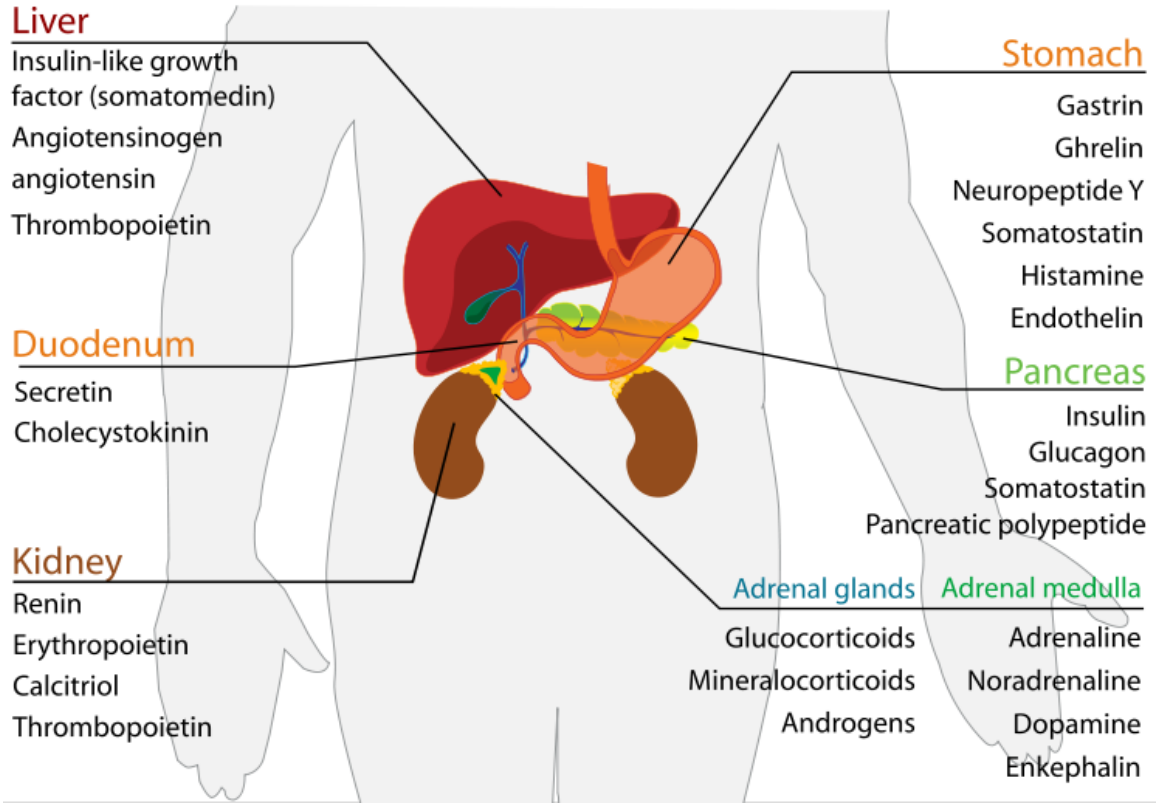
Secreted hormone	Abbreviation	From cells	Effect
Melanocyte-stimulating hormone	MSH	Melanotropes	Stimulates melanin synthesis and release from skin/hair melanocytes

Thyroid

Secreted hormone	Abbreviation	From cells	Effect
Triiodothyronine	T3	Thyroid epithelial cell	(More potent form of thyroid hormone) Stimulates body oxygen and energy consumption, thereby increasing the basal metabolic rate Stimulates RNA polymerase I and II, thereby promoting protein synthesis
Thyroxine (tetraiodothyronine)	T4	Thyroid epithelial cell*s*	(Less active form of thyroid hormone) (Acts as a prohormone to triiodothyronine) Stimulates body oxygen and energy consumption, thereby increasing the basal metabolic rate Stimulates RNA polymerase I and II, thereby promoting protein synthesis
Calcitonin		Parafollicular cell*s*	Stimulates osteoblasts and thus bone construction

Inhibits Ca^{2+} release from bone, thereby reducing blood Ca^{2+}

Alimentary system



Stomach

Secreted hormone	Abbreviation	From cells	Effect
Gastrin (Primarily)		G cells	Secretion of gastric acid by parietal cells
Ghrelin		P/D1 cells	Stimulate appetite, secretion of growth hormone from anterior pituitary gland
Neuropeptide Y	NPY		increased food intake and decreased physical activity
Somatostatin		D cells	Suppress release of gastrin, cholecystokinin (CCK), secretin, motilin, vasoactive intestinal peptide (VIP), gastric inhibitory polypeptide (GIP), enteroglucagon Lowers rate of gastric emptying Reduces smooth muscle contractions and blood

		flow within the intestine.
Histamine	ECL cells	stimulate gastric acid secretion
Endothelin	X cells	Smooth muscle contraction of stomach

Duodenum

Secreted hormone	From cells	Effect
Secretin	S cells	Secretion of bicarbonate from liver, pancreas and duodenal Brunner's glands Enhances effects of cholecystokinin Stops production of gastric juice
Cholecystokinin	I cells	Release of digestive enzymes from pancreas Release of bile from gallbladder hunger suppressant

Liver

Secreted hormone	Abbreviation	From cells	Effect
Insulin-like growth factor (or somatomedin) (Primarily)	IGF	Hepatocytes	insulin-like effects regulate cell growth and development
Angiotensinogen and angiotensin		Hepatocytes	vasoconstriction release of aldosterone from adrenal cortex dipsogen.
Thrombopoietin		Hepatocytes	stimulates megakaryocytes to produce platelets

Pancreas

Secreted hormone	From cells	Effect
Insulin (Primarily)	β Islet cells	Intake of glucose, glycogenesis and glycolysis in liver and muscle from blood intake of lipids and synthesis of triglycerides in adipocytes Other anabolic effects
Glucagon (Also Primarily)	α Islet cells	glycogenolysis and gluconeogenesis in liver increases blood glucose level
Somatostatin	δ Islet cells	Inhibit release of insulin

		Inhibit release of glucagon Suppress the exocrine secretory action of pancreas.
Pancreatic polypeptide	PP cells	Self regulate the pancreas secretion activities and effect the hepatic glycogen levels.

Kidney

Secreted hormone	From cells	Effect
Renin (Primarily)	Juxtaglomerular cells	Activates the renin-angiotensin system by producing angiotensin I of angiotensinogen
Erythropoietin (EPO)	Extraglomerular mesangial cells	Stimulate erythrocyte production
Calcitriol (1,25-dihydroxyvitamin D_3)		Active form of vitamin D_3 Increase absorption of calcium and phosphate from gastrointestinal tract and kidneys inhibit release of PTH
Thrombopoietin		stimulates megakaryocytes to produce platelets

Adrenal glands

Adrenal cortex

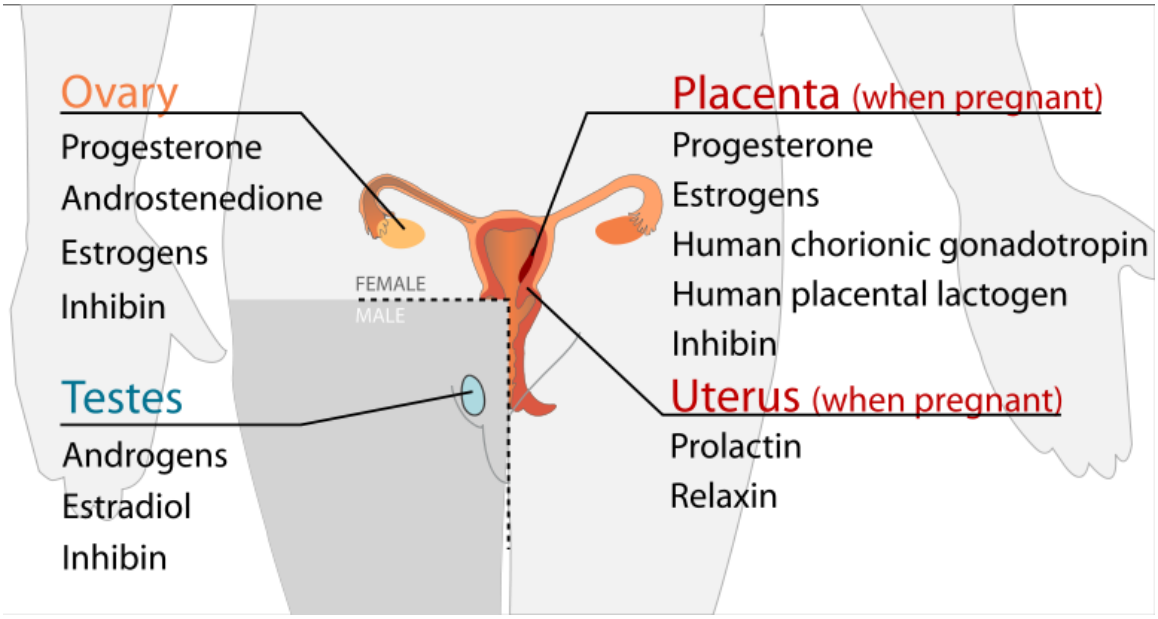
Secreted hormone	From cells	Effect
Glucocorticoids (chiefly cortisol)	zona fasciculata and zona reticularis cells	Stimulates gluconeogenesis Stimulates fat breakdown in adipose tissue Inhibits protein synthesis Inhibits glucose uptake in muscle and adipose tissue Inhibits immunological responses (immunosuppressive) Inhibits inflammatory responses (anti-inflammatory)
Mineralocorticoids (chiefly aldosterone)	Zona glomerulosa cells	Stimulates active sodium reabsorption in kidneys Stimulates passive water reabsorption in kidneys, thus increasing blood volume and blood pressure Stimulates potassium and H^+ secretion into nephron of kidney and subsequent excretion
Androgens (including DHEA	Zona fasciculata and Zona reticularis cells	In males: Relatively small effect compared to androgens from testes

and testosterone)		In females: masculinizing effects (ie. excessive facial hair)

Adrenal medulla

Secreted hormone	From cells	Effect
Adrenaline (epinephrine) (Primarily)	Chromaffin cells	Fight-or-flight response: • Boost the supply of oxygen and glucose to the brain and muscles (by increasing heart rate and stroke volume, vasodilation, increasing catalysis of glycogen in liver, breakdown of lipids in fat cells) • Dilate the pupils • Suppress non-emergency bodily processes (e.g., digestion) • Suppress immune system
Noradrenaline (norepinephrine)	Chromaffin cells	Fight-or-flight response: • Boost the supply of oxygen and glucose to the brain and muscles (by increasing heart rate and stroke volume, vasoconstriction and increased blood pressure, breakdown of lipids in fat cells) • Increase skeletal muscle readiness.
Dopamine	Chromaffin cells	Increase heart rate and blood pressure
Enkephalin	Chromaffin cells	Regulate pain

Reproductive



Testes

Secreted hormone	From cells	Effect
Androgens (chiefly testosterone)	Leydig cells	Anabolic: growth of muscle mass and strength, increased bone density, growth and strength, Virilizing: maturation of sex organs, formation of scrotum, deepening of voice, growth of beard and axillary hair.
Estradiol	Sertoli cells	Prevent apoptosis of germ cells
Inhibin	Sertoli cells	Inhibit production of FSH

Ovarian follicle / Corpus luteum

Secreted hormone	From cells	Effect
Progesterone	Granulosa cells, theca cells	Support pregnancy: • Convert endometrium to secretory stage • Make cervical mucus permeable to sperm. • Inhibit immune response, e.g., towards the human embryo • Decrease uterine smooth muscle contractility • Inhibit lactation

		• Inhibit onset of labor. Other: • Raise epidermal growth factor-1 levels • Increase core temperature during ovulation • Reduce spasm and relax smooth muscle (widen bronchi and regulate mucus) Anti-inflammatory • Reduce gall-bladder activity • Normalize blood clotting and vascular tone, zinc and copper levels, cell oxygen levels, and use of fat stores for energy • Assist in thyroid function and bone growth by osteoblasts • Increase resilience in bone, teeth, gums, joint, tendon, ligament, and skin • Promote healing by regulating collagen • Provide nerve function and healing by regulating myelin • Prevent endometrial cancer by regulating effects of estrogen
Androstenedione	Theca cells	Substrate for estrogen
Estrogens (mainly estradiol)	Granulosa cells	Structural: • Promote formation of female secondary sex characteristics • Accelerate height growth • Accelerate metabolism (burn fat) • Reduce muscle mass • Stimulate endometrial growth • Increase uterine growth • Maintain blood vessels and skin • Reduce bone resorption, increase bone formation

		Protein synthesis: • Increase hepatic production of binding proteins Coagulation: • Increase circulating level of factors 2, 7, 9, 10, antithrombin III, plasminogen • Increase platelet adhesiveness • Increase HDL, triglyceride, height growth • Decrease LDL, fat deposition Fluid balance: • Regulate salt (sodium) and water retention • Increase growth hormone • Increase cortisol, SHBG Gastrointestinal tract: • Reduce bowel motility • Increase cholesterol in bile Melanin: • Increase pheomelanin, reduce eumelanin Cancer: • Support hormone-sensitive breast cancers (Suppression of production in the body of estrogen is a treatment for these cancers.) Lung function: • Promote lung function by supporting alveoli.
Inhibin	Granulosa cells	Inhibit production of FSH from anterior pituitary

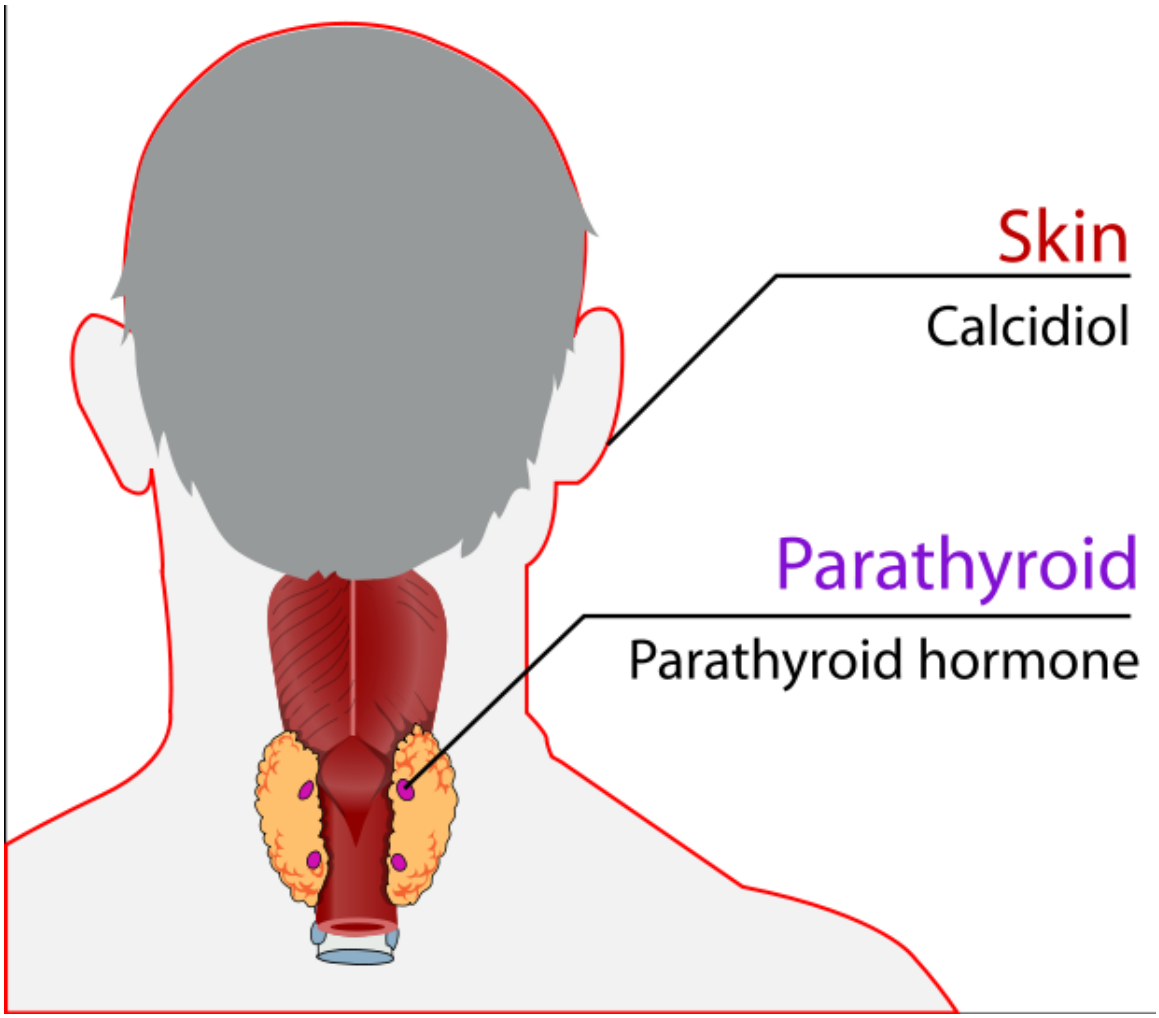
Placenta (when pregnant)

Secreted hormone	Abbreviation	From cells	Effect
Progesterone (Primarily)			Support pregnancy: • Inhibit immune response, towards the fetus. • Decrease uterine smooth muscle contractility • Inhibit lactation • Inhibit onset of labor. • Support fetal production of adrenal mineralo- and glucosteroids.
Estrogens (mainly Estriol) (Also Primarily)			Other effects on mother similar to ovarian follicle-progesterone Effects on mother similar to ovarian follicle estrogen
Human chorionic gonadotropin	HCG	Syncytiotrophoblast	promote maintenance of corpus luteum during beginning of pregnancy Inhibit immune response, towards the human embryo.
Human placental lactogen	HPL	Syncytiotrophoblast	increase production of insulin and IGF-1 increase insulin resistance and carbohydrate intolerance
Inhibin		Fetal Trophoblasts	suppress FSH

Uterus (when pregnant)

Secreted hormone	Abbreviation	From cells	Effect
Prolactin	PRL	Decidual cells	milk production in mammary glands
Relaxin		Decidual cells	Unclear in humans and animals

Calcium regulation



Parathyroid

Secreted hormone	Abbreviation	From cells	Effect
Parathyroid hormone	PTH	Parathyroid chief cell	Calcium: • Stimulates Ca^{2+} release from bone, thereby increasing blood Ca^{2+} • Stimulates osteoclasts, thus breaking down bone • Stimulates Ca^{2+} reabsorption in kidney • Stimulates activated vitamin D production in kidney

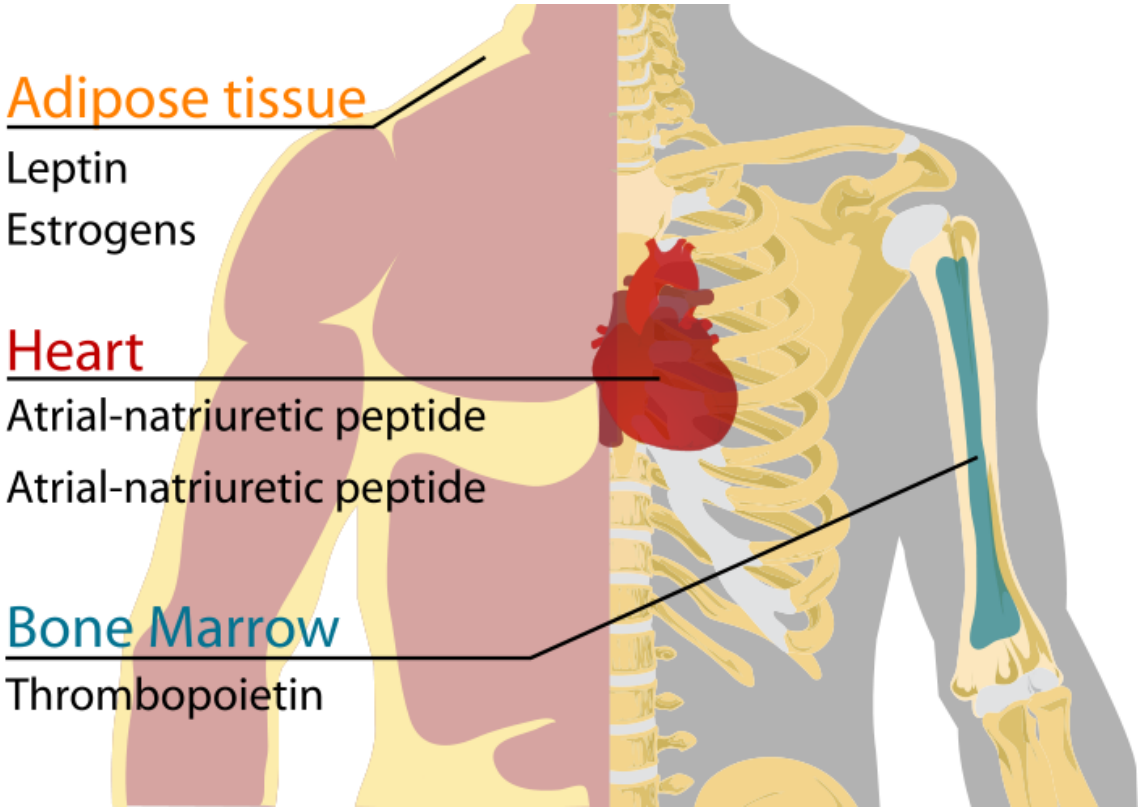
Phosphate:

- Stimulates PO^4 release from bones, thereby increasing blood PO^4.
- Inhibits PO^4 reabsorption in kidney, so more PO^4 = is excreted
- Overall, small net drop in serum PO^4.

Skin

Secreted hormone	From cells	Effect
Calcidiol (25-hydroxyvitamin D_3)		Inactive form of vitamin D_3

Miscellaneous



Heart

Secreted hormone	Abbreviation	From cells	Effect
Atrial-natriuretic peptide	ANP	Cardiac myocytes	Reduce blood pressure by: reducing systemic vascular resistance, reducing blood water, sodium and fats
Brain natriuretic peptide	BNP	Cardiac myocytes	(To a lesser degree than ANP) reduce blood pressure by: reducing systemic vascular resistance, reducing blood water, sodium and fats

Bone Marrow

Secreted hormone	From cells	Effect
Thrombopoietin	liver and kidney cells	stimulates megakaryocytes to produce platelets

Adipose tissue

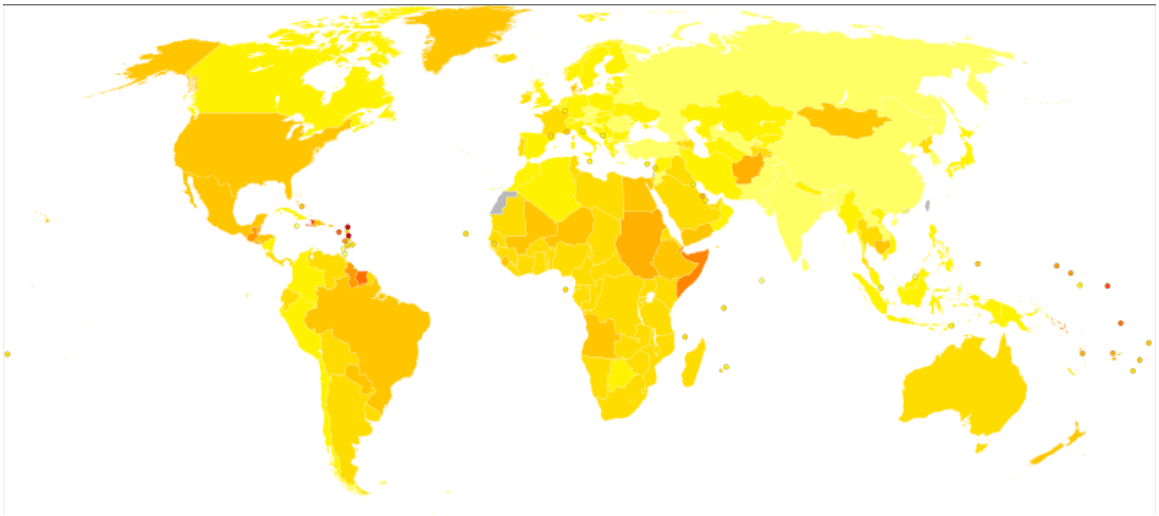
Secreted hormone	From cells	Effect
Leptin (Primarily)	Adipocytes	decrease of appetite and increase of metabolism.
Estrogens (mainly Estrone)	Adipocytes	

Major endocrine systems

The human endocrine system consists of several integrated systems that operate via feedback loops. Several important feedback systems are mediated via the hypothalamus and pituitary.

- TRH - TSH - T3/T4
- GnRH - LH/FSH - sex hormones
- CRH - ACTH - cortisol
- Renin - angiotensin - aldosterone

Diseases



Disability-adjusted life year for endocrine disorders per 100,000 inhabitants in 2002
- no data
- less than 80
- 80-160
- 160-240
- 240-320
- 320-400
- 400-480
- 480-560
- 560-640
- 640-720
- 720-800
- 800-1000
- more than 1000

Diseases of the endocrine system are common, including conditions such as diabetes mellitus, thyroid disease, and obesity. Endocrine disease is characterized by disregulated hormone release (a productive pituitary adenoma), inappropriate response to signaling (hypothyroidism), lack of a gland (diabetes mellitus type 1, diminished erythropoiesis in chronic renal failure), or structural enlargement in a critical site such as the thyroid (toxic multinodular goitre). Hypofunction of endocrine glands can occur as a result of loss of reserve, hyposecretion, agenesis, atrophy, or active destruction. Hyperfunction can occur as a result of hypersecretion, loss of suppression, hyperplastic or neoplastic change, or hyperstimulation.

Endocrinopathies are classified as primary, secondary, or tertiary. Primary endocrine disease inhibits the action of downstream glands. Secondary endocrine disease is indicative of a problem with the pituitary gland. Tertiary endocrine disease is associated with dysfunction of the hypothalamus and its releasing hormones.

As the thyroid, and hormones have been implicated in signaling distant tissues to proliferate, for example, the estrogen receptor has been shown to be involved in certain breast cancers. Endocrine, paracrine, and autocrine signaling have all been implicated in proliferation, one of the required steps of oncogenesis.

Other types of signaling

The typical mode of cell signaling in the endocrine system is endocrine signaling. However, there are also other modes, i.e., paracrine, autocrine, and neuroendocrine signaling. Purely neurocrine signaling between neurons, on the other hand, belongs completely to the nervous system.

Autocrine

Autocrine signaling is a form of signaling in which a cell secretes a hormone or chemical messenger (called the autocrine agent) that binds to autocrine receptors on the same cell, leading to changes in the cells.

Paracrine

Paracrine signaling is a form of cell signaling in which the target cell is near the signal-releasing cell.

Juxtacrine

juxtacrine signaling is a type of intercellular communication that is transmitted via oligosaccharide, lipid, or protein components of a cell membrane, and may affect either the emitting cell or the immediately adjacent cells.

It occurs between adjacent cells that possess broad patches of closely opposed plasma membrane linked by transmembrane channels known as connexons. The gap between the cells can usually be between only 2 and 4 nm.

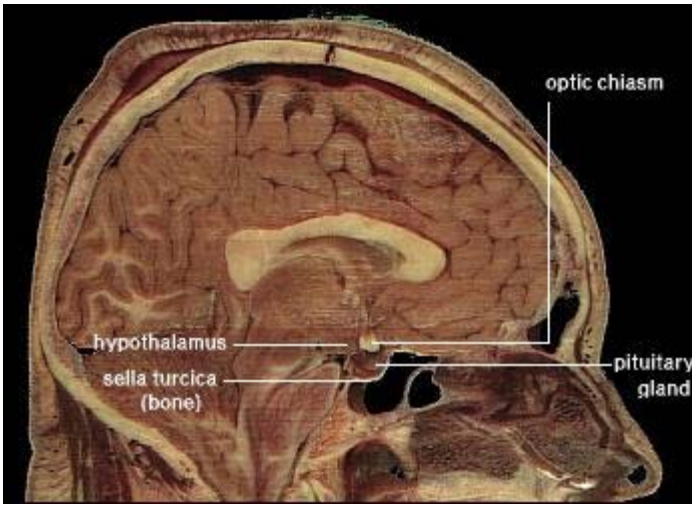
Unlike other types of cell signaling (such as paracrine and endocrine), juxtacrine signaling requires physical contact between the two cells involved.

Juxtacrine signaling has been observed for some growth factors, cytokine and chemokine cellular signals

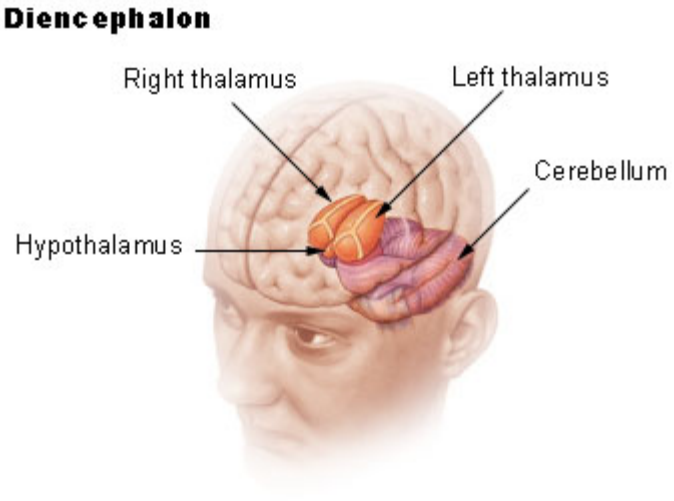
Chapter 2

Hypothalamus

Brain: Hypothalamus



Location of the human hypothalamus



Diencephalon

Latin *hypothalamus*

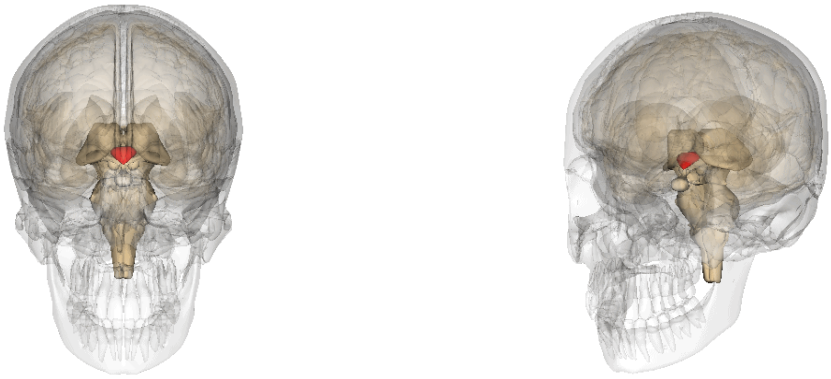
NeuroNames	*hier-358*
MeSH	*Hypothalamus*
NeuroLex ID	*birnlex_734*

The **Hypothalamus** (from Greek *ὑπό = under* and *θάλαμος = room, chamber*) is a portion of the brain that contains a number of small nuclei with a variety of functions. One of the most important functions of the hypothalamus is to link the nervous system to the endocrine system via the pituitary gland (hypophysis).

The hypothalamus is located below the thalamus, just above the brain stem. In the terminology of neuroanatomy, it forms the ventral part of the diencephalon. All vertebrate brains contain a hypothalamus. In humans, it is roughly the size of an almond.

The hypothalamus is responsible for certain metabolic processes and other activities of the autonomic nervous system. It synthesizes and secretes certain neurohormones, often called hypothalamic-releasing hormones, and these in turn stimulate or inhibit the secretion of pituitary hormones. The hypothalamus controls body temperature, hunger, thirst, fatigue, sleep, and circadian cycles.

Inputs



Hypothalamus

The hypothalamus is an extremely complex region in the brain of humans, and even small nuclei within the hypothalamus are involved in many different functions. The paraventricular nucleus and the supraoptic nucleus contain oxytocin and vasopressin (also called antidiuretic hormone) neurons which project to the posterior pituitary, but also contain neurons that regulate ACTH and TSH secretion from the anterior pituitary, as

well as gastric reflexes, maternal behavior, blood pressure, feeding, immune responses, and temperature.

The hypothalamus co-ordinates many hormonal and behavioural circadian rhythms, complex patterns of neuroendocrine outputs, complex homeostatic mechanisms, and many important behaviours.

The hypothalamus must therefore respond to many different signals, some of which are generated externally and some internally. It is thus richly connected with many parts of the central nervous system, including the brainstem reticular formation and autonomic zones, the limbic forebrain (particularly the amygdala, septum, diagonal band of Broca, and the olfactory bulbs, and the cerebral cortex).

The hypothalamus is responsive to:

- Light: daylength and photoperiod for regulating circadian and seasonal rhythms
- Olfactory stimuli, including pheromones
- Steroids, including gonadal steroids and corticosteroids
- Neurally transmitted information arising in particular from the heart, the stomach, and the reproductive tract
- Autonomic inputs
- Blood-borne stimuli, including leptin, ghrelin, angiotensin, insulin, pituitary hormones, cytokines, plasma concentrations of glucose and osmolarity etc.
- Stress
- Invading microorganisms by increasing body temperature, resetting the body's thermostat upward.

Olfactory stimuli

Olfactory stimuli are important for sex and neuroendocrine function in many species. For instance if a pregnant mouse is exposed to the urine of a 'strange' male during a critical period after coitus then the pregnancy fails (the Bruce effect). Thus during coitus, a female mouse forms a precise 'olfactory memory' of her partner which persists for several days. Pheromonal cues aid synchronisation of oestrus in many species; in women, synchronised menstruation may also arise from pheromonal cues, although the role of pheromones in humans is doubted by many.

Blood-borne stimuli

Peptide hormones have important influences upon the hypothalamus, and to do so they must evade the blood-brain barrier. The hypothalamus is bounded in part by specialized brain regions that lack an effective blood-brain barrier; the capillary endothelium at these sites is fenestrated to allow free passage of even large proteins and other molecules. Some of these sites are the sites of neurosecretion - the neurohypophysis and the median eminence. However others are sites at which the brain samples the composition of the blood. Two of these sites, the subfornical organ and the OVLT (organum vasculosum of

the lamina terminalis) are so-called circumventricular organs, where neurons are in intimate contact with both blood and CSF. These structures are densely vascularized, and contain osmoreceptive and sodium-receptive neurons which control drinking, vasopressin release, sodium excretion, and sodium appetite. They also contain neurons with receptors for angiotensin, atrial natriuretic factor, endothelin and relaxin, each of which is important in the regulation of fluid and electrolyte balance. Neurons in the OVLT and SFO project to the supraoptic nucleus and paraventricular nucleus, and also to preoptic hypothalamic areas. The circumventricular organs may also be the site of action of interleukins to elicit both fever and ACTH secretion, via effects on paraventricular neurons.

It is not clear how all peptides that influence hypothalamic activity gain the necessary access. In the case of prolactin and leptin, there is evidence of active uptake at the choroid plexus from blood into CSF. Some pituitary hormones have a negative feedback influence upon hypothalamic secretion; for example, growth hormone feeds back on the hypothalamus, but how it enters the brain is not clear. There is also evidence for central actions of prolactin and TSH.

The hypothalamus functions as a type of thermostat for the body. It sets a desired body temperature, and stimulates either heat production and retention to raise the blood temperature to a higher setting, or sweating and vasodilation to cool the blood to a lower temperature. All fevers result from a raised setting in the hypothalamus; elevated body temperatures due to any other cause are classified as hyperthermia. Rarely, direct damage to the hypothalamus, such as from a stroke, will cause a fever; this is sometimes called a *hypothalamic fever*. However, it is more common for such damage to cause abnormally low body temperatures.

Steroids

The hypothalamus contains neurons that react strongly to steroids and glucocorticoids – (the steroid hormones of the adrenal gland, released in response to ACTH). It also contains specialised glucose-sensitive neurons (in the arcuate nucleus and ventromedial hypothalamus), which are important for appetite. The preoptic area contains thermosensitive neurons; these are important for TRH secretion.

Neural inputs

The hypothalamus receives many inputs from the brainstem; notably from the nucleus of the solitary tract, the locus coeruleus, and the ventrolateral medulla. Oxytocin secretion in response to suckling or vagino-cervical stimulation is mediated by some of these pathways; vasopressin secretion in response to cardiovascular stimuli arising from chemoreceptors in the carotid body and aortic arch, and from low-pressure atrial volume receptors, is mediated by others. In the rat, stimulation of the vagina also causes prolactin secretion, and this results in pseudo-pregnancy following an infertile mating. In the rabbit, coitus elicits reflex ovulation. In the sheep, cervical stimulation in the presence of high levels of estrogen can induce maternal behavior in a virgin ewe. These effects are all

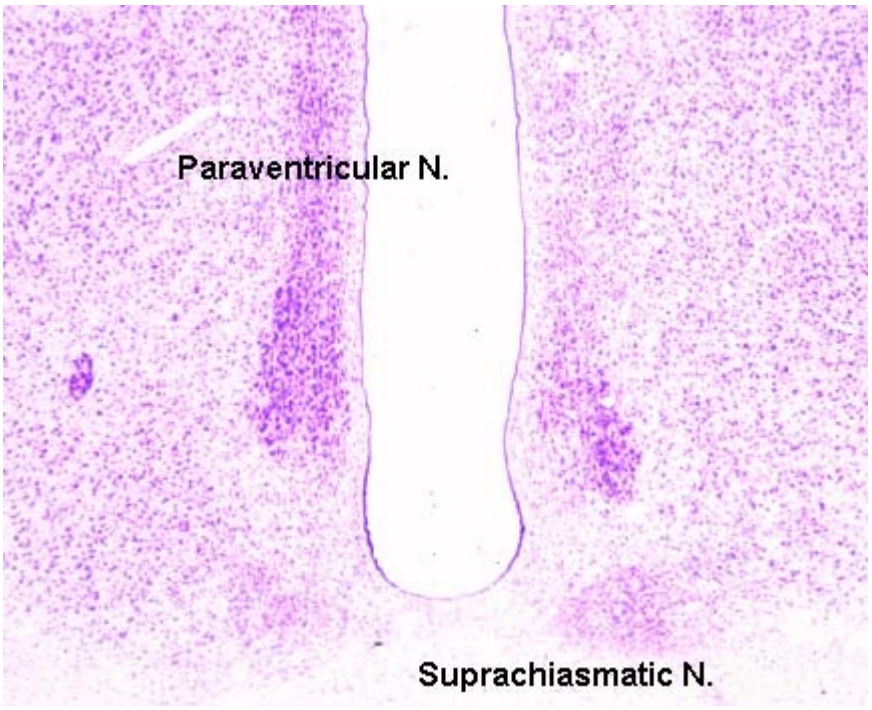
mediated by the hypothalamus, and the information is carried mainly by spinal pathways that relay in the brainstem. Stimulation of the nipples stimulates release of oxytocin and prolactin and suppresses the release of LH and FSH.

Cardiovascular stimuli are carried by the vagus nerve, but the vagus also conveys a variety of visceral information, including for instance signals arising from gastric distension to suppress feeding. Again this information reaches the hypothalamus via relays in the brainstem.

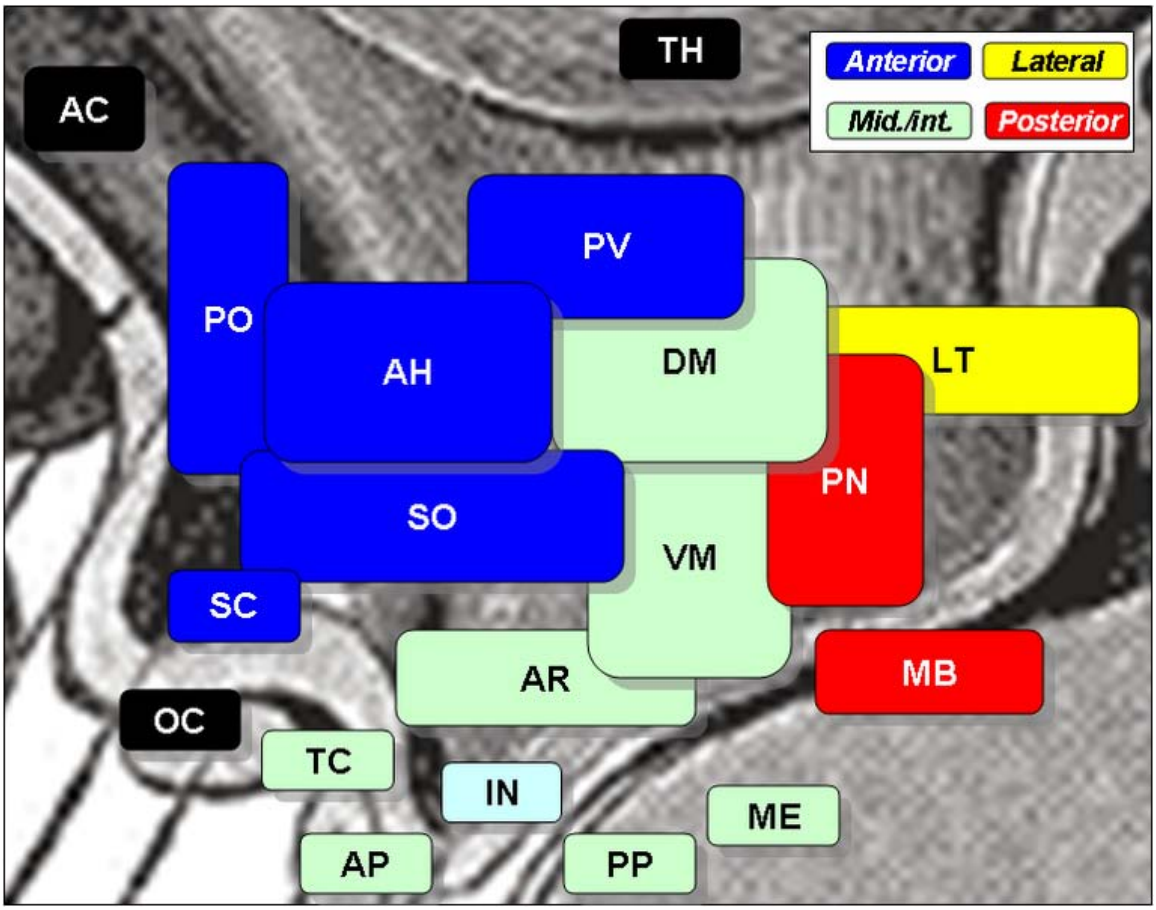
In addition hypothalamic function is responsive to --and regulated by-- levels of all three classical monoamine neurotransmitters, i.e. noradrenaline, dopamine and 5-hydroxytryptamine (serotonin), in those tracts fom which it receives enervation. For example noradrenergic inputs arising from the locus coeruleus have important regulatory effects upon CRH levels.

Nuclei

A cross section of the monkey hypothalamus displays 2 of the major hypothalamic nuclei on either side of the fluid-filled 3rd ventricle



The hypothalamic nuclei include the following:

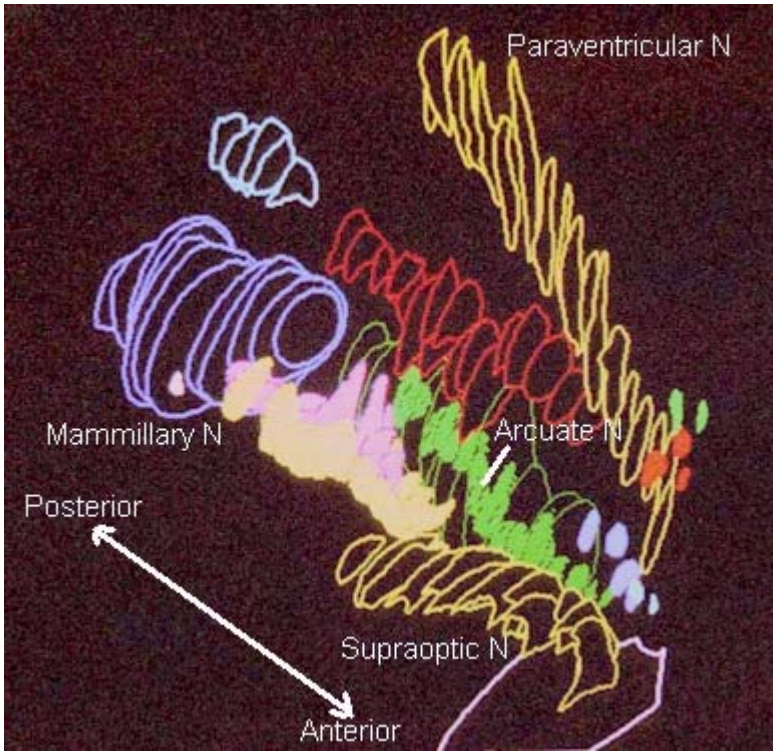


Hypothalamic nuclei

Region	Area	Nucleus	Function
Anterior	Medial	Medial preoptic nucleus	• urinary bladder contraction • Decreased heart rate • Decreased blood pressure
		Supraoptic nucleus (SO)	• oxytocin release • vasopressin release
		Paraventricular nucleus* (PV)	• oxytocin release • vasopressin release
		Anterior hypothalamic nucleus (AH)	• thermoregulation • panting • sweating

			• thyrotropin inhibition
		Suprachiasmatic nucleus (SC)	• vasopressin release • Circadian rhythms
		Lateral preoptic nucleus	
	Lateral	Lateral nucleus (LT)	• thirst and hunger
		Part of supraoptic nucleus (SO)	• vasopressin release
		Dorsomedial hypothalamic nucleus (DM)	• GI stimulation
		Ventromedial nucleus (VM)	• satiety • neuroendocrine control
Tuberal	Medial	Arcuate nucleus (AR)	• Lutenizing Hormone R.H. release • Follicle Stimulating Hormone Releasing Factor • feeding • Dopamine • GHRH
	Lateral	Lateral nucleus (LT)	• thirst and hunger
		Lateral tuberal nuclei	
		Mammillary nuclei (part of mammillary bodies) (MB)	• memory
Posterior	Medial	Posterior nucleus (PN)	• Increase blood pressure • pupillary dilation • shivering
	Lateral	Lateral nucleus (LT)	

- - Note: Paraventricular nucleus is *not* to be confused with periventricular nucleus.



Hypothalamic nuclei on one side of the hypothalamus, shown in a 3-D computer reconstruction

Outputs

The outputs of the hypothalamus can be divided into two categories: neural projections, and endocrine hormones.

Neural projections

Most fiber systems of the hypothalamus run in two ways (bidirectional).

- Projections to areas caudal to the hypothalamus go through the medial forebrain bundle, the mammillotegmental tract and the dorsal longitudinal fasciculus.
- Projections to areas rostral to the hypothalamus are carried by the mammillothalamic tract, the fornix and terminal stria.
- Projections to areas of the sympathetic motor system (lateral horn spinal segments T1-L2/L3 of the) are carried by the hypothalamospinal tract and they activate the sympathetic motor pathway

Endocrine hormones

The hypothalamus affects the endocrine system and governs emotional behavior, such as anger and sexual activity. Most of the hypothalamic hormones generated are distributed

to the pituitary via the hypophyseal portal system. The hypothalamus maintains homeostasis; this includes a regulation of blood pressure, heart rate, and temperature.

Secreted hormone	Abbreviation	Produced by	Effect
Thyrotropin-releasing hormone (Prolactin-releasing hormone)	TRH, TRF, or PRH	Parvocellular neurosecretory neurons	Stimulate thyroid-stimulating hormone (TSH) release from anterior pituitary (primarily) Stimulate prolactin release from anterior pituitary
Dopamine (Prolactin-inhibiting hormone)	DA or PIH	Dopamine neurons of the arcuate nucleus	Inhibit prolactin release from anterior pituitary
Growth hormone-releasing hormone	GHRH	Neuroendocrine neurons of the Arcuate nucleus	Stimulate Growth hormone (GH) release from anterior pituitary
Somatostatin (growth hormone-inhibiting hormone)	SS, GHIH, or SRIF	Neuroendocrine cells of the Periventricular nucleus	Inhibit Growth hormone (GH) release from anterior pituitary Inhibit thyroid-stimulating hormone (TSH) release from anterior pituitary
Gonadotropin-releasing hormone	GnRH or LHRH	Neuroendocrine cells of the Preoptic area	Stimulate follicle-stimulating hormone (FSH) release from anterior pituitary Stimulate luteinizing hormone (LH) release from anterior pituitary
Corticotropin-releasing hormone	CRH or CRF	Parvocellular neurosecretory neurons	Stimulate adrenocorticotropic hormone (ACTH) release from anterior pituitary
Oxytocin		Magnocellular neurosecretory cells	Uterine contraction Lactation (letdown reflex)
Vasopressin (antidiuretic hormone)	ADH or AVP	Magnocellular neurosecretory neurons	Increase in the permeability to water of the cells of distal tubule and collecting duct in the kidney and thus allows water reabsorption and excretion of concentrated urine

Control of food intake

The extreme lateral part of the ventromedial nucleus of the hypothalamus is responsible for the control of food intake. Stimulation of this area causes increased food intake. Bilateral lesion of this area causes complete cessation of food intake. Medial parts of the

nucleus have a controlling effect on the lateral part. Bilateral lesion of the medial part of the ventromedial nucleus causes hyperphagia and obesity of the animal. Further lesion of the lateral part of the ventromedial nucleus in the same animal produces complete cessation of food intake.

There are different hypotheses related to this regulation:

1. Lipostatic hypothesis - this hypothesis holds that adipose tissue produces a humoral signal that is proportionate to the amount of fat and acts on the hypothalamus to decrease food intake and increase energy output. It has been evident that a hormone leptin acts on the hypothalamus to decrease food intake and increase energy output.
2. Gutpeptide hypothesis - gastrointestinal hormones like Grp, glucagons, CCK and others claimed to inhibit food intake. The food entering the gastrointestinal tract triggers the release of these hormones which acts on the brain to produce satiety. The brain contains both CCK-A and CCK-B receptors.
3. Glucostatic hypothesis - the activity of the satiety center in the ventromedial nuclei is probably governed by the glucose utilization in the neurons. It has been postulated that when their glucose utilization is low and consequently when the arteriovenous blood glucose difference across them is low, the activity across the neurons decrease. Under these conditions, the activity of the feeding center is unchecked and the individual feels hungry. Food intake is rapidly increased by intraventricular administration of 2-deoxyglucose therefore decreasing glucose utilization in cells.
4. Thermostatic hypothesis - according to this hypothesis, a decrease in body temperature below a given set point stimulates appetite, while an increase above the set point inhibits appetite.

Sexual dimorphism

Several hypothalamic nuclei are sexually dimorphic, i.e. there are clear differences in both structure and function between males and females.

Some differences are apparent even in gross neuroanatomy: most notable is the sexually dimorphic nucleus within the preoptic area, which is present only in males. However most of the differences are subtle changes in the connectivity and chemical sensitivity of particular sets of neurons.

The importance of these changes can be recognised by functional differences between males and females. For instance, males of most species prefer the odor and appearance of females over males, which is instrumental in stimulating male sexual behavior. If the sexually dimorphic nucleus is lesioned, this preference for females by males diminishes. Also, the pattern of secretion of growth hormone is sexually dimorphic, and this is one reason why in many species, adult males are much larger than females.

Responses to ovarian steroids

Other striking functional dimorphisms are in the behavioral responses to ovarian steroids of the adult. Males and females respond differently to ovarian steroids, partly because the expression of estrogen-sensitive neurons in the hypothalamus is sexually dimorphic, i.e. estrogen receptors are expressed in different sets of neurons.

Estrogen and progesterone can influence gene expression in particular neurons or induce changes in cell membrane potential and kinase activation, leading to diverse non-genomic cellular functions. Estrogen and progesterone bind to their cognate nuclear hormone receptors, which translocate to the cell nucleus and interact with regions of DNA known as hormone response elements (HREs) or get tethered to another transcription factor's binding site. Estrogen receptor (ER) has been shown to transactivate other transcription factors in this manner, despite the absence of an estrogen response element (ERE) in the proximal promoter region of the gene. ERs and progesterone receptors (PRs) are generally gene activators, with increased mRNA and subsequent protein synthesis following hormone exposure.

Male and female brains differ in the distribution of estrogen receptors, and this difference is an irreversible consequence of neonatal steroid exposure. Estrogen receptors (and progesterone receptors) are found mainly in neurons in the anterior and mediobasal hypothalamus, notably:

- the preoptic area (where LHRH neurons are located)
- the periventricular nucleus (where somatostatin neurons are located)
- the ventromedial hypothalamus (which is important for sexual behavior).

Gonadal steroids in neonatal life of rats

In neonatal life, gonadal steroids influence the development of the neuroendocrine hypothalamus. For instance, they determine the ability of females to exhibit a normal reproductive cycle, and of males and females to display appropriate reproductive behaviors in adult life.

- If a *female rat* is injected once with testosterone in the first few days of postnatal life (during the "critical period" of sex-steroid influence), the hypothalamus is irreversibly masculinized; the adult rat will be incapable of generating an LH surge in response to estrogen (a characteristic of females), but will be capable of exhibiting *male* sexual behaviors (mounting a sexually receptive female).
- By contrast, a *male rat* castrated just after birth will be *feminized*, and the adult will show *female* sexual behavior in response to estrogen (sexual receptivity, lordosis behavior).

Androgens in primates

In primates, the developmental influence of androgens is less clear, and the consequences are less understood. Within the brain, testosterone is aromatized to (estradiol), which is the principal active hormone for developmental influences. The human testis secretes high levels of testosterone from about week 8 of fetal life until 5–6 months after birth (a similar perinatal surge in testosterone is observed in many species), a process that appears to underlie the male phenotype. Estrogen from the maternal circulation is relatively ineffective, partly because of the high circulating levels of steroid-binding proteins in pregnancy.

Human sexual orientation and the hypothalamus

According to D.F. Swaab, "Neurobiological research related to sexual orientation in humans is only just gathering momentum, but the evidence already shows that humans have a vast array of brain differences, not only in relation to gender, but also in relation to sexual orientation."

Swaab first reported on the relationship between sexual orientation in males and the hypothalamus's "clock", the suprachiasmatic nucleus (SCN). In 1990, Swaab and Hofman reported that the SCN of heterosexual men was significantly larger than in women, and the SCN of homosexual men was significantly larger than in heterosexual men. Then in 1995, Swaab et al. linked brain development to sexual orientation by treating male rats both pre- and postnatally with ATD, an aromatase blocker in the brain. This produced an enlarged SCN and bisexual behavior in the adult male rats. In 1991, LeVay showed that part of the sexually dimorphic nucleus (SDN), the interstitial nuclei of the anterior hypothalamus (INAH) 3, is twice as large in heterosexual men as homosexual men and heterosexual women, in terms of volume but not number of neurons.

In 2004 and 2006, two studies by Berglund, Lindström, and Savic used Positron Emission Tomography (PET) to observe how the hypothalamus responds to smelling common odors, the scent of testosterone found in male sweat, and the scent of estrogen found in female urine. These studies showed that the hypothalamus of heterosexual men and homosexual women both respond to estrogen. Also, the hypothalamus of homosexual men and heterosexual women both respond to testosterone. The hypothalamus of all four groups did not respond to the common odors, which produced a normal olfactory response in the brain.

Other influences upon hypothalamic development

Sex steroids are not the only important influences upon hypothalamic development; in particular, pre-pubertal stress in early life determines the capacity of the adult hypothalamus to respond to an acute stressor. Unlike gonadal steroid receptors, glucocorticoid receptors are very widespread throughout the brain; in the paraventricular nucleus, they mediate negative feedback control of CRF synthesis and secretion, but elsewhere their role is not well understood.

Chapter 3

Pineal Gland

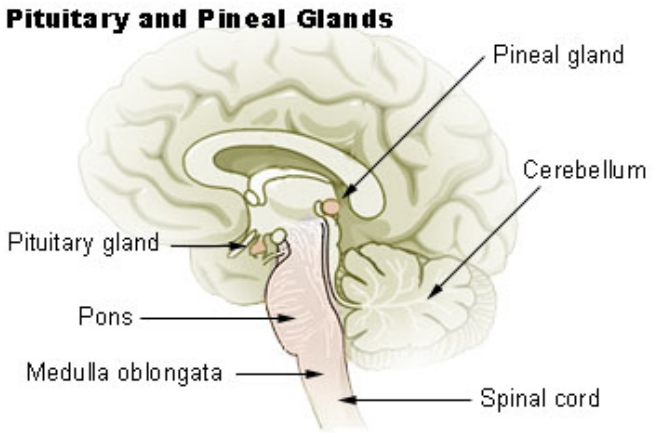
Pineal gland


Diagram of pituitary and pineal glands in the human brain

Latin	*glandula pinealis*
Artery	superior cerebellar artery
Precursor	Neural Ectoderm, Roof of Diencephalon
MeSH	*Pineal+gland*

The **pineal gland** (also called the **pineal body**, **epiphysis cerebri**, **epiphysis** or the "third eye") is a small endocrine gland in the vertebrate brain. It produces the serotonin derivative melatonin, a hormone that affects the modulation of wake/sleep patterns and seasonal functions. Its shape resembles a tiny pine cone (hence its name), and it is located near the center of the brain, between the two hemispheres, tucked in a groove where the two rounded thalamic bodies join.

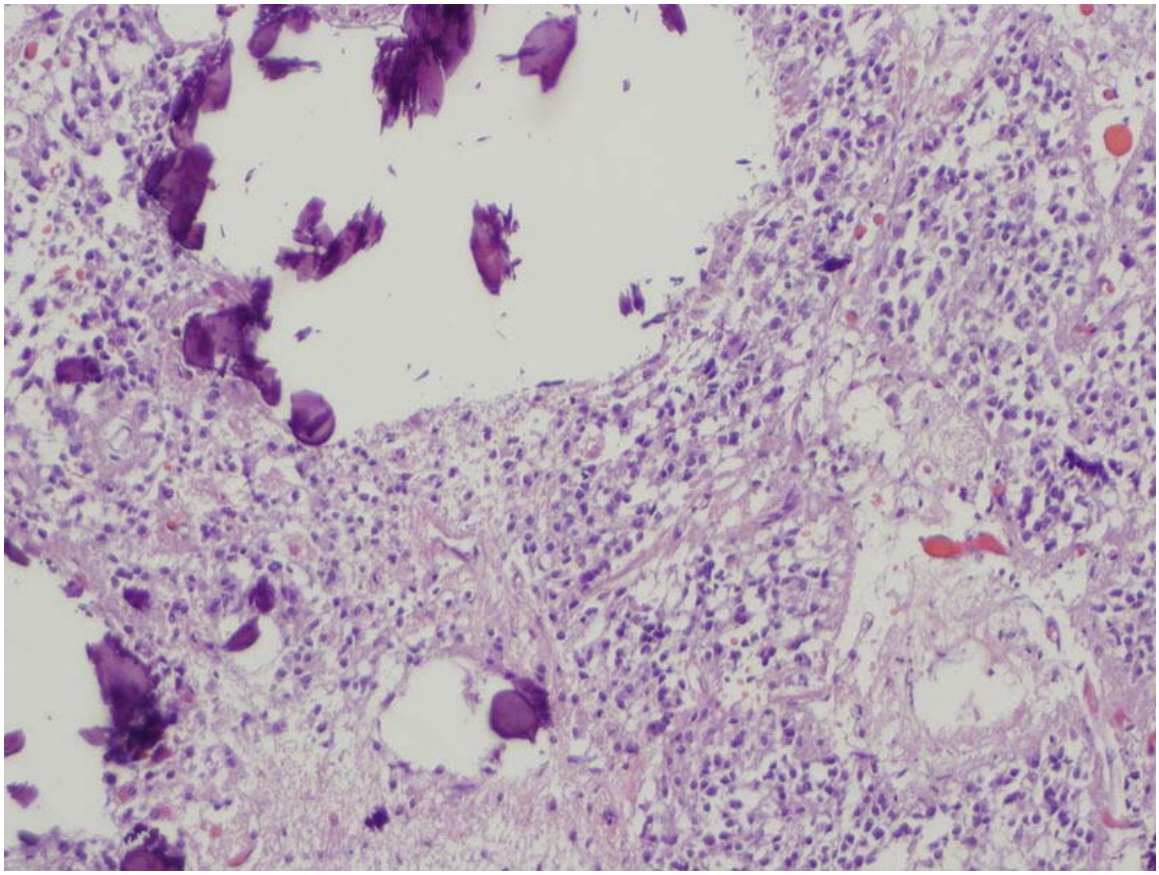
Location

The pineal gland is reddish-gray and about the size of a grain of rice (5–8 mm) in humans, located just rostro-dorsal to the superior colliculus and behind and beneath the

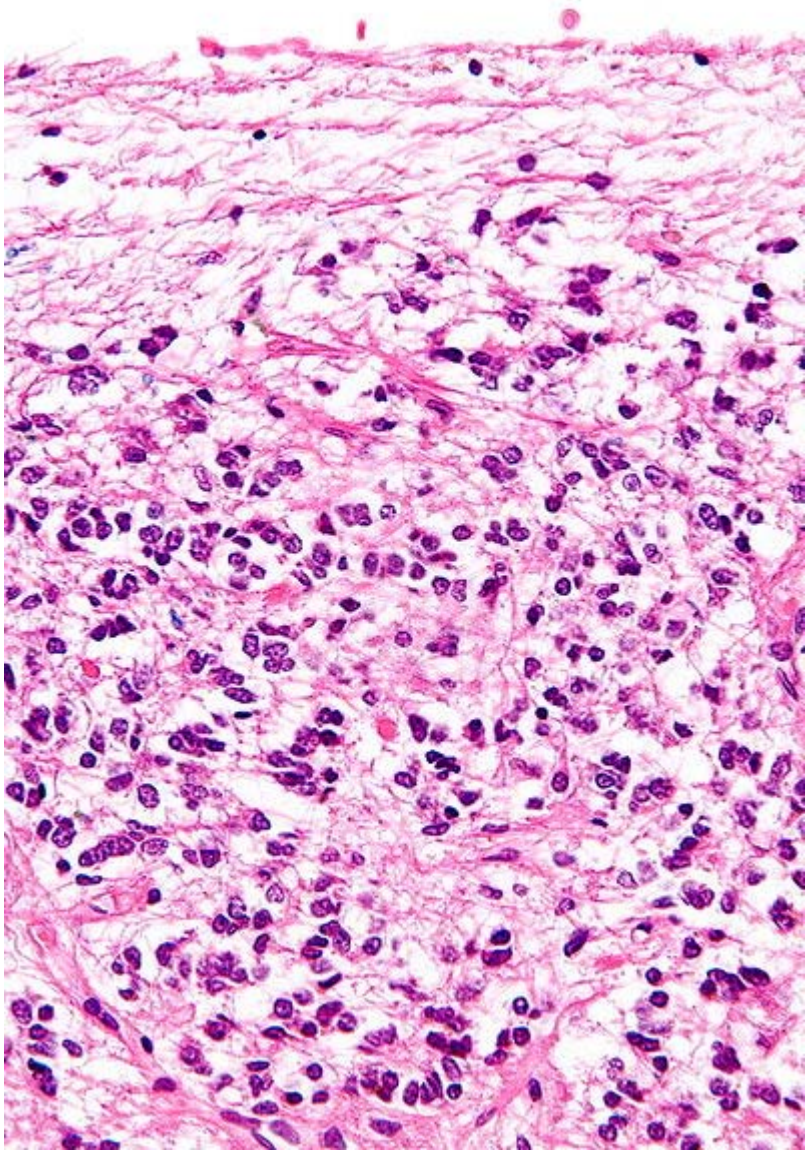
stria medullaris, between the laterally positioned thalamic bodies. It is part of the epithalamus.

The pineal gland is a midline structure, and is often seen in plain skull X-rays, as it is often calcified.

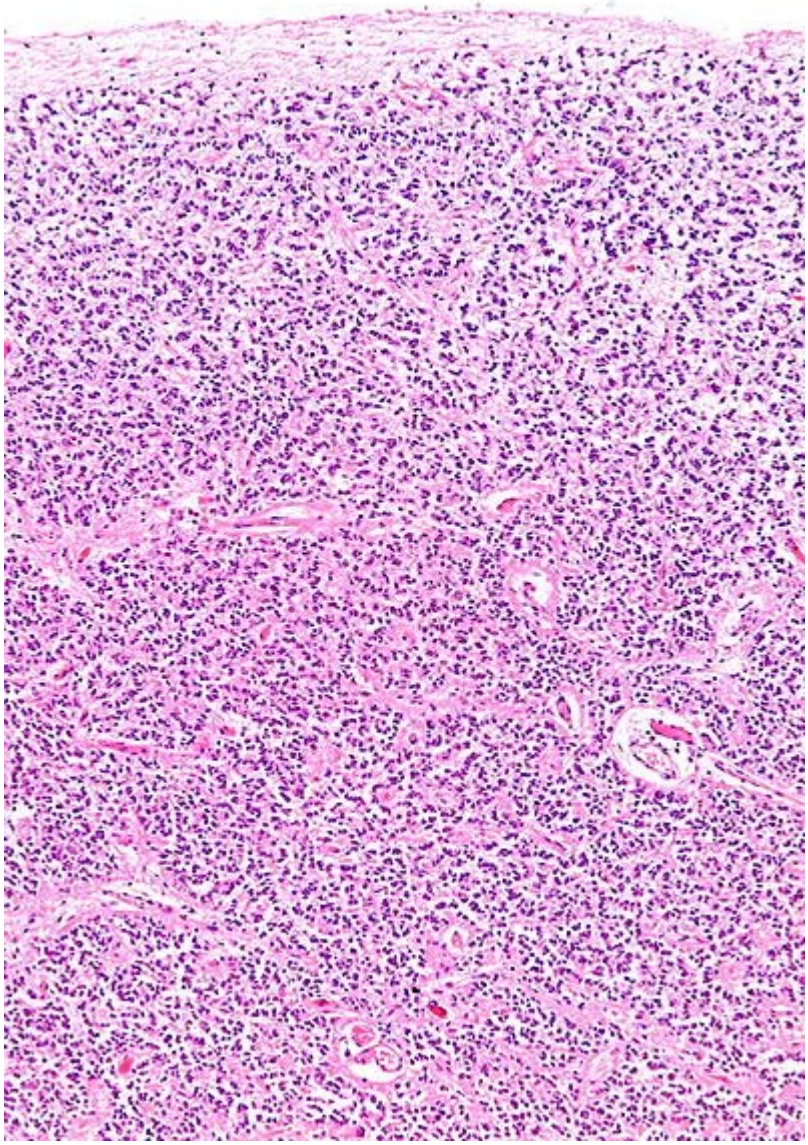
Structure and composition



Pineal gland parenchyma with calcifications



Micrograph of a normal pineal gland – very high magnification



Micrograph of a normal pineal gland – intermediate magnification

The pineal body consists in humans of a lobular parenchyma of pinealocytes surrounded by connective tissue spaces. The gland's surface is covered by a pial capsule.

The pineal gland consists mainly of pinealocytes, but four other cell types have been identified. As it is quite cellular (in relation to the cortex and white matter, it may be mistaken for a neoplasm.

Cell type	Description
Pinealocytes	The pinealocytes consist of a cell body with 4–6 processes emerging. They produce and secrete melatonin. The pinealocytes can be stained by special silver impregnation methods.
Interstitial cells	Interstitial cells are located between the pinealocytes.
Perivascular phagocyte	Many capillaries are present in the gland, and perivascular phagocytes are located close to these blood vessels. The perivascular phagocytes are antigen presenting cells.
pineal neurons	In higher vertebrates neurons are located in the pineal gland. However, these are not present in rodents.
peptidergic neuron-like cells	In some species, neuronal-like peptidergic cells are present. These cells might have a paracrine regulatory function.

The pineal gland receives a sympathetic innervation from the superior cervical ganglion. However, a parasympathetic innervation from the sphenopalatine and otic ganglia is also present. Further, some nerve fibers penetrate into the pineal gland via the pineal stalk (central innervation). Finally, neurons in the trigeminal ganglion innervate the gland with nerve fibers containing the neuropeptide, PACAP. Human follicles contain a variable quantity of gritty material, called corpora arenacea (or "acervuli," or "brain sand"). Chemical analysis shows that they are composed of calcium phosphate, calcium carbonate, magnesium phosphate, and ammonium phosphate. In 2002, deposits of the calcite form of calcium carbonate were described. Calcium, phosphorus and fluoride deposits in the pineal gland have been linked with aging.

Miscellaneous anatomy

Pinealocytes in many non-mammalian vertebrates have a strong resemblance to the photoreceptor cells of the eye. Some evolutionary biologists believe that the vertebrate pineal cells share a common evolutionary ancestor with retinal cells.

In some vertebrates, exposure to light can set off a chain reaction of enzymatic events within the pineal gland that regulate circadian rhythms. Some early vertebrate fossil skulls have a pineal foramen (opening). This correlates with the physiology of the modern "living fossils," the lamprey and the tuatara, and some other vertebrates that have a parietal organ or "third eye," which, in some of them, is photosensitive. The third eye represents evolution's earlier approach to photoreception. The structures of the third eye in the tuatara are homologous to the cornea, lens and retina, though the latter resembles that of an octopus rather than a vertebrate retina. The asymmetrical whole consists of the "eye" to the left and the pineal sac to the right. "In animals that have lost the parietal eye, including mammals, the pineal sac is retained and condensed into the form of the pineal gland."

Unlike much of the rest of the mammalian brain, the pineal gland is not isolated from the body by the blood-brain barrier system; indeed it has profuse blood flow, second only to the kidney.

Fossils seldom preserve soft anatomy. The brain of the Russian *Melovatka* bird, about 90 million years old, is an exception, and it shows a larger-than-expected parietal eye and pineal gland.

In humans and other mammals, the light signals necessary to set circadian rhythms are sent from the eye through the retinohypothalamic system to the suprachiasmatic nuclei (SCN) and the pineal.

Function

The pineal gland was originally believed to be a "vestigial remnant" of a larger organ. In 1917 it was known that extract of cow pineals lightened frog skin. Dermatology professor Aaron B. Lerner and colleagues at Yale University, hoping that a substance from the pineal might be useful in treating skin diseases, isolated and named the hormone melatonin in 1958. The substance did not prove to be helpful as intended, but its discovery helped solve several mysteries such as why removing the rat's pineal accelerated ovary growth, why keeping rats in constant light decreased the weight of their pineals, and why pinealectomy and constant light affect ovary growth to an equal extent; this knowledge gave a boost to the then new field of chronobiology.

Melatonin is N-acetyl-5-methoxy-tryptamine, a derivative of the amino acid tryptophan, which also has other functions in the central nervous system. The production of melatonin by the pineal gland is stimulated by darkness and inhibited by light. Photosensitive cells in the retina detect light and directly signal the SCN, entraining its rhythm to the 24-hour cycle in nature. Fibers project from the SCN to the paraventricular nuclei (PVN), which relay the circadian signals to the spinal cord and out via the sympathetic system to superior cervical ganglia (SCG), and from there into the pineal gland. The function(s) of melatonin in humans is not clear; it is commonly prescribed for the treatment of circadian rhythm sleep disorders.

The compound pinoline is also produced in the pineal gland; it is one of the beta-carbolines.

The human pineal gland grows in size until about 1–2 years of age, remaining stable thereafter, although its weight increases gradually from puberty onwards. The abundant melatonin levels in children are believed to inhibit sexual development, and pineal tumors have been linked with precocious puberty. When puberty arrives, melatonin production is reduced. Calcification of the pineal gland is typical in adults.

In animals, the pineal gland appears to play a major role in sexual development, hibernation, metabolism, and seasonal breeding.

Pineal cytostructure seems to have evolutionary similarities to the retinal cells of chordates. Modern birds and reptiles have been found to express the phototransducing pigment melanopsin in the pineal gland. Avian pineal glands are believed to act like the SCN in mammals.

Studies on rodents suggest that the pineal gland may influence the actions of recreational drugs, such as cocaine, and antidepressants, such as fluoxetine (Prozac), and its hormone melatonin can protect against neurodegeneration.

Metaphysics and philosophy

The secretory activity of the pineal gland is only relatively understood. Historically, its location deep in the brain suggested to philosophers that it possessed particular importance. This combination led to its being a "mystery" gland with myth, superstition and occult theories surrounding its perceived function.

René Descartes, who dedicated much time to the study of the pineal gland, called it the "seat of the soul." He believed that it was the point of connection between the intellect and the body. The relevant quotation as to Descartes' reason for believing this is,

My view is that this gland is the principal seat of the soul, and the place in which all our thoughts are formed. The reason I believe this is that I cannot find any part of the brain, except this, which is not double. Since we see only one thing with two eyes, and hear only one voice with two ears, and in short have never more than one thought at a time, it must necessarily be the case that the impressions which enter by the two eyes or by the two ears, and so on, unite with each other in some part of the body before being considered by the soul. Now it is impossible to find any such place in the whole head except this gland; moreover it is situated in the most suitable possible place for this purpose, in the middle of all the concavities; and it is supported and surrounded by the little branches of the carotid arteries which bring the spirits into the brain. (29 January 1640, AT III:19–20, CSMK 143)

Baruch de Spinoza later refuted:

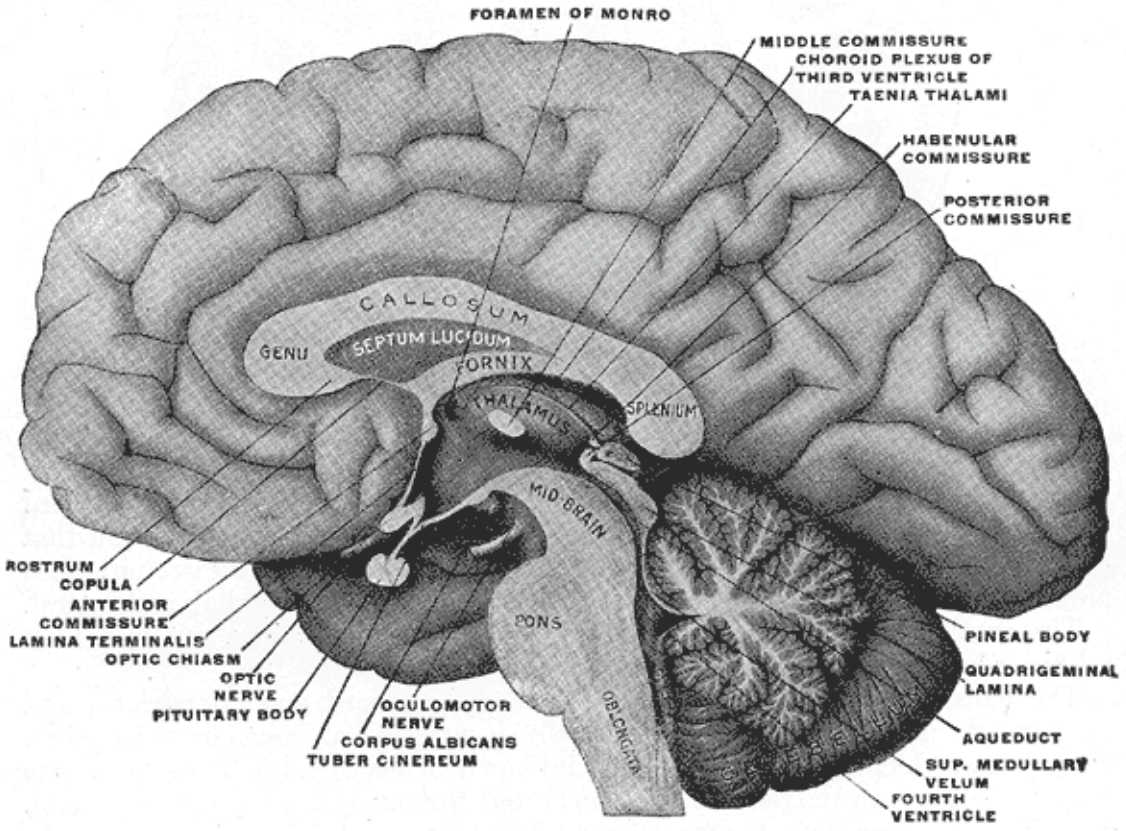
For he [Descartes] maintained, that the soul or mind is specially united to a particular part of the brain, namely, to that part called the pineal gland, by the aid of which the mind is enabled to feel all the movements which are set going in the body, and also external objects, and which the mind by a simple act of volition can put in motion in various ways ... Such is the doctrine of this illustrious philosopher (in so far as I gather it from his own words); it is one which, had it been less ingenious, I could hardly believe to have proceeded from so great a man. Indeed, I am lost in wonder, that a philosopher, who had stoutly asserted, that he would draw no conclusions which do not follow from self-evident premisses, and would affirm nothing which he did not clearly and distinctly perceive, and who had so often taken to task the scholastics for wishing to explain obscurities through occult qualities, could maintain a hypothesis, beside which occult

qualities are commonplace. What does he understand, I ask, by the union of the mind and the body? (Baruch de Spinoza, *Ethics*; part 5)

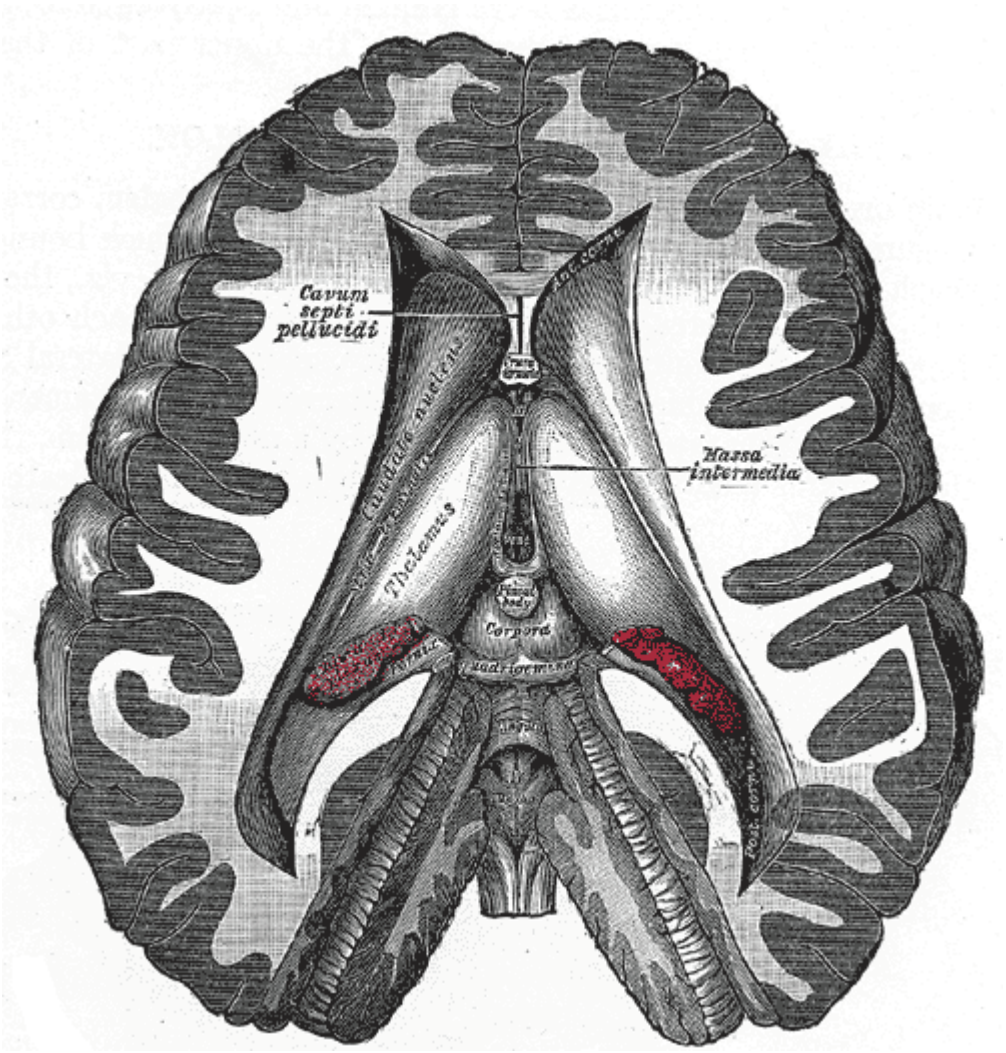
The notion of a "pineal-eye" is central to the philosophy of the French writer Georges Bataille, which is analyzed at length by literary scholar Denis Hollier in his study *Against Architecture*. In this work Hollier discusses how Bataille uses the concept of a "pineal-eye" as a reference to a blind-spot in Western rationality, and an organ of excess and delirium. This conceptual device is explicit in his surrealist texts, *The Jesuve* and *The Pineal Eye*.

Additional images

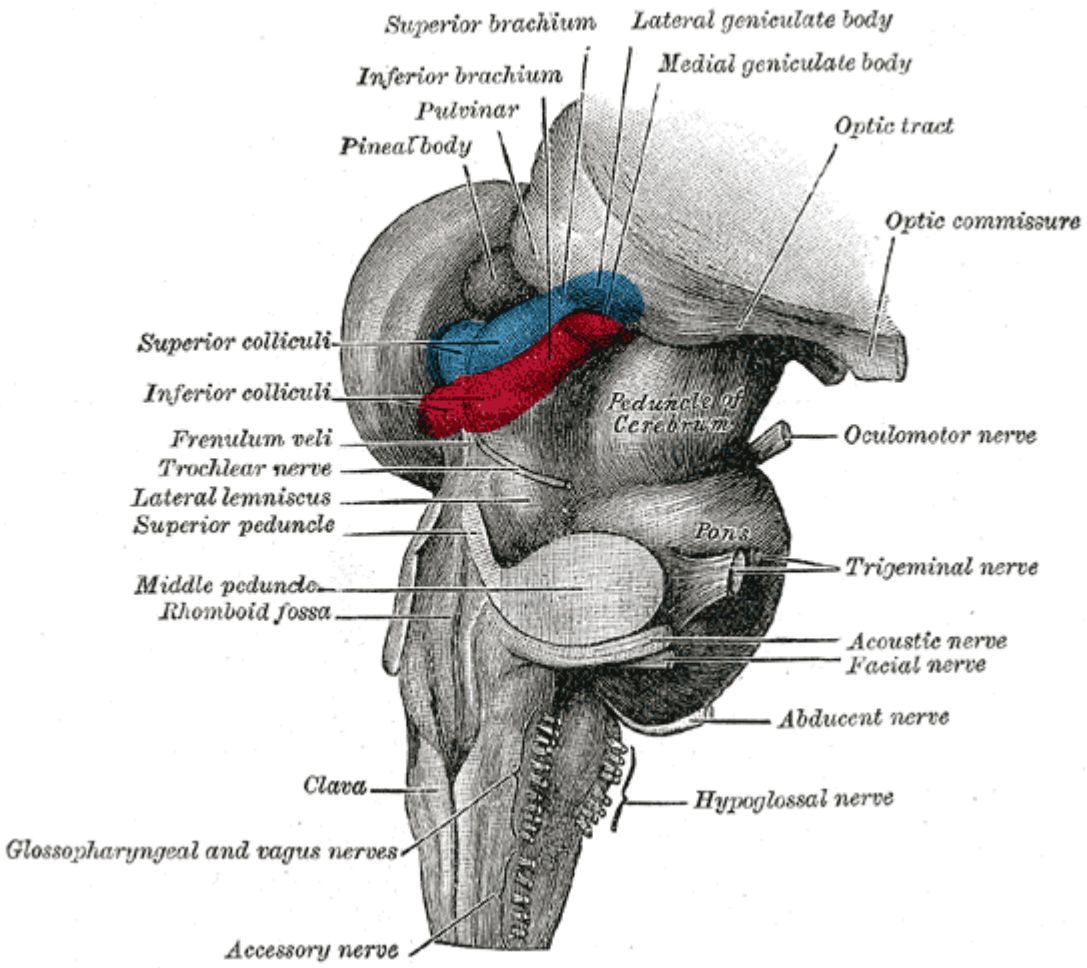
The pineal body is labeled in these images.



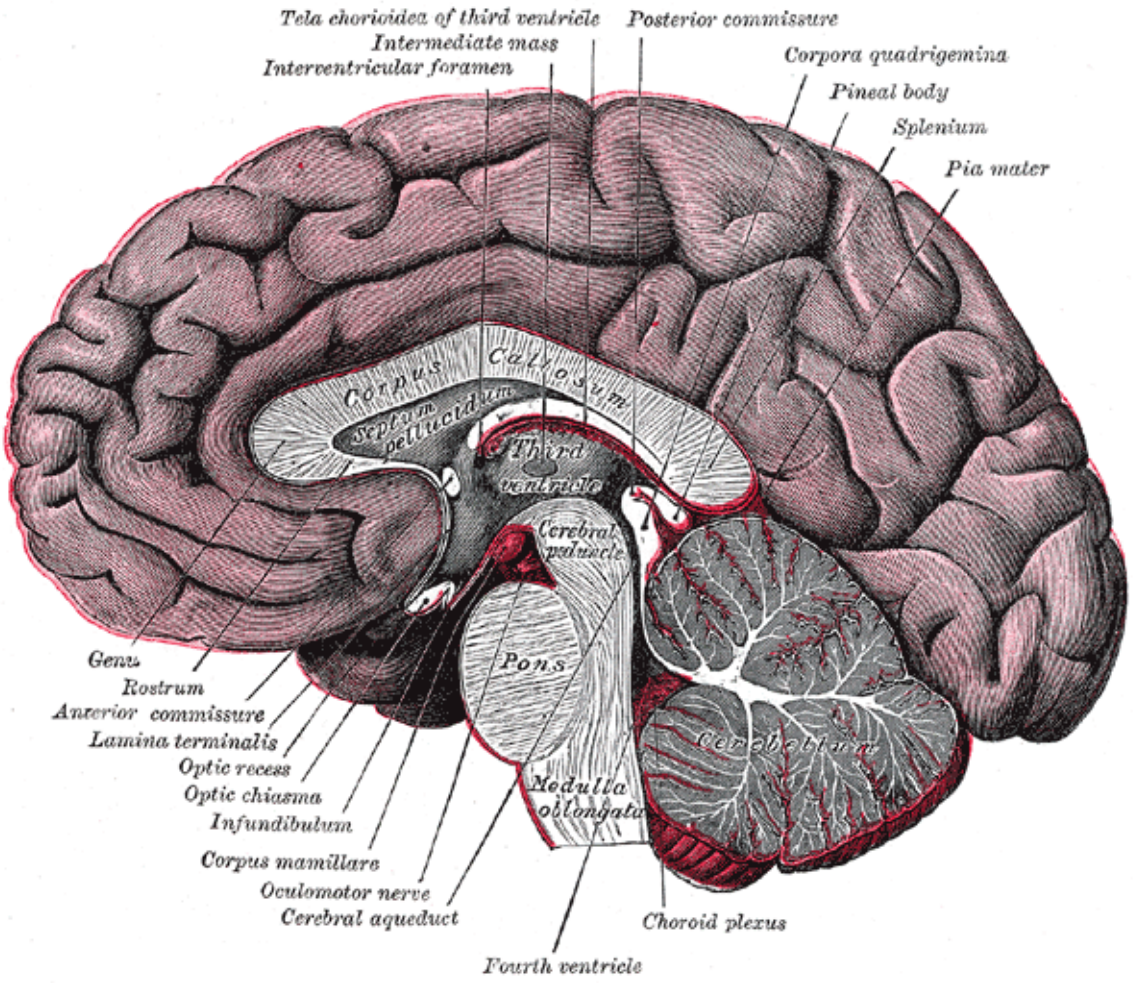
Mesal aspect of a brain sectioned in the median sagittal plane



Dissection showing the ventricles of the brain



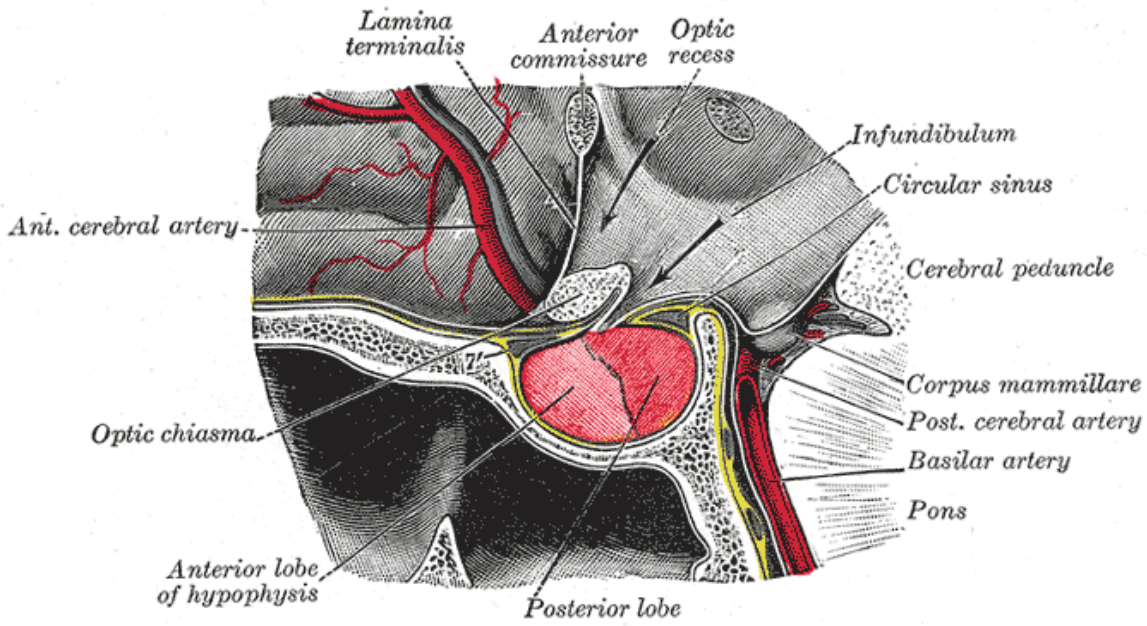
Hind- and mid-brains; postero-lateral view



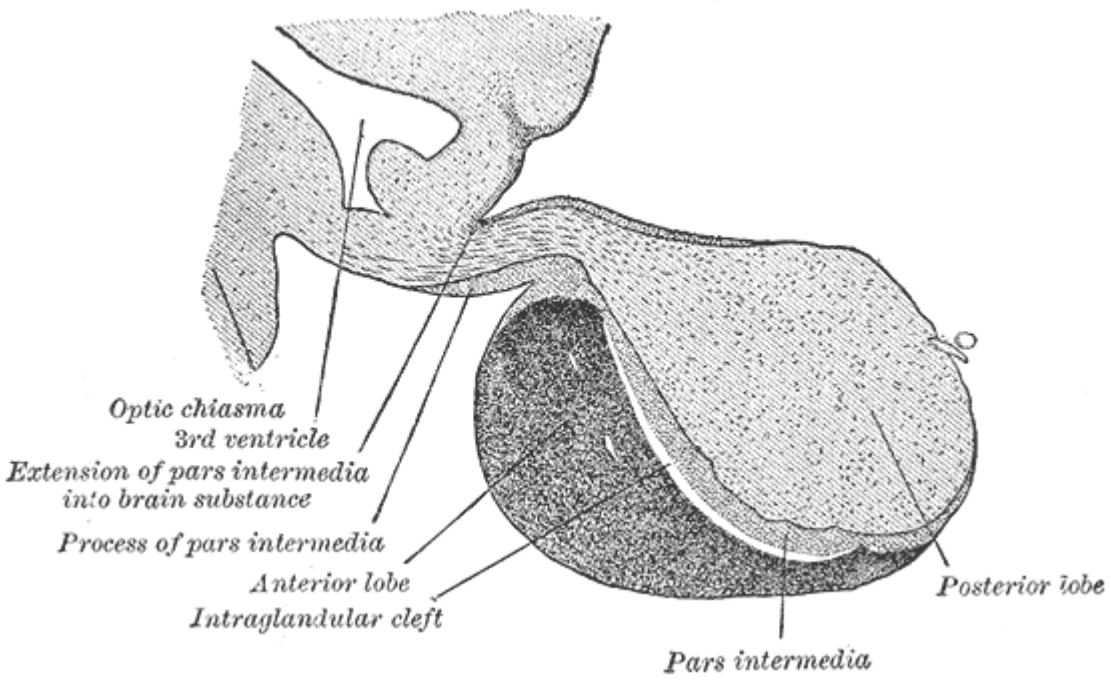
Median sagittal section of brain

Chapter 4

Pituitary Gland



Located at the base of the brain, the pituitary gland is protected by a bony structure called the sella turcica (also known as **turkish saddle**) of the sphenoid bone.



Median sagittal through the hypophysis of an adult monkey. Semidiagrammatic

In vertebrate anatomy the **pituitary gland**, or **hypophysis**, is an endocrine gland about the size of a pea and weighing 0.5 g (0.02 oz.), in humans. It is a protrusion off the bottom of the hypothalamus at the base of the brain, and rests in a small, bony cavity (sella turcica) covered by a dural fold (diaphragma sellae). The pituitary is functionally connected to the hypothalamus by the median eminence via a small tube called the infundibular stem (Pituitary Stalk). The pituitary fossa, in which the pituitary gland sits, is situated in the sphenoid bone in the middle cranial fossa at the base of the brain. The pituitary gland secretes eight hormones that regulate homeostasis.

There is an analogous structure in the octopus brain.

Sections

The pituitary gland consists of two components: the anterior pituitary (or adenohypophysis) and the posterior pituitary (or neurohypophysis), and is functionally linked to the hypothalamus by the pituitary stalk (also named the "infundibular stem", or simply the "infundibulum"). It is from the hypothalamus that hypothalamic tropic factors are released to descend down the pituitary stalk to the pituitary gland where they stimulate the release of pituitary hormones. While the pituitary gland is known as the 'master' endocrine gland, both of the lobes are under the control of the hypothalamus; the anterior pituitary receives its signals from the parvocellular neurons and the posterior pituitary receives its signals from magnocellular neurons

Anterior pituitary (Adenohypophysis)

The anterior pituitary synthesizes and secretes the following important endocrine hormones:

- Adrenocorticotropic hormone (ACTH), release under influence of hypothalamic Corticotropin Releasing Hormone (CRH).
- Thyroid-stimulating hormone (TSH), release under influence of hypothalamic Thyrotropin Releasing Hormone (TRH).
- Growth hormone (also referred to as 'Human Growth Hormone', 'HGH' or 'GH' or somatotropin), release under influence of hypothalamic Growth Hormone Releasing Hormone (GHRH); inhibited by hypothalamic Somatostatin.
- Prolactin (PRL), also known as 'Luteotropic' hormone (LTH), release under influence of multiple hypothalamic Prolactin Releasing Factors (PRH).

The two 'Gonadotropins';

- Luteinizing hormone (also referred to as 'Lutropin' or 'LH', or in males, 'Interstitial Cell Stimulating Hormone' (ICSH)), and
- Follicle stimulating hormone (FSH), both released under influence of Gonadotropin Releasing Hormone (GnRH).

and;

- melanocyte–stimulating hormones (MSH's) or "intermedins" as these are released by the pars intermedia which is "the middle part"; adjacent to the posterior pituitary lobe, pars intermedia is a specific part developed from the anterior pituitary lobe.

These hormones are released from the anterior pituitary under the influence of the hypothalamus. Hypothalamic hormones are secreted to the anterior lobe by way of a special capillary system, called the hypothalamic-hypophysial portal system.

The anterior pituitary is divided into anatomical regions known as the pars tuberalis, pars intermedia, and pars distalis. It develops from a depression in the dorsal wall of the pharynx (stomodial part) known as Rathke's pouch.

Posterior pituitary (Neurohypophysis)

The posterior pituitary stores and releases:

- Oxytocin, most of which is released from the paraventricular nucleus in the hypothalamus

- Antidiuretic hormone (ADH, also known as vasopressin and AVP, arginine vasopressin), the majority of which is released from the supraoptic nucleus in the hypothalamus

Oxytocin is one of the few hormones to create a positive feedback loop. For example, uterine contractions stimulate the release of oxytocin from the posterior pituitary, which, in turn, increases uterine contractions. This positive feedback loop continues throughout labor.

Intermediate lobe

There is also an intermediate lobe in many animals, but is rudimentary in humans. For instance, in fish, it is believed to control physiological color change. In adult humans, it is just a thin layer of cells between the anterior and posterior pituitary. The intermediate lobe produces melanocyte-stimulating hormone (MSH), although this function is often (imprecisely) attributed to the anterior pituitary.

Variations among vertebrates

The pituitary gland is found in all vertebrates, but its structure varies between different groups.

The division of the pituitary described above is typical of mammals, and is also true, to varying degrees, of all tetrapods. However, only in mammals does the posterior pituitary have a compact shape. In lungfishes it is a relatively flat sheet of tissue lying above the anterior pituitary, and in amphibians, reptiles and birds, it becomes increasingly well developed. The intermediate lobe is generally not well developed in tetrapods, and is entirely absent in birds.

Apart from lungfishes, the structure of the pituitary in fish is generally different from that in tetrapods. In general, the intermediate lobe tends to be well developed, and may equal the remainder of the anterior pituitary in size. The posterior lobe typically forms a sheet of tissue at the base of the pituitary stalk, and in most cases sends irregular finger-like projection into the tissue of the anterior pituitary, which lies directly beneath it. The anterior pituitary is typically divided into two regions, a more anterior *rostral* portion and a posterior *proximal* portion, but the boundary between the two is often not clearly marked. In elasmobranchs there is an additional, *ventral lobe* beneath the anterior pituitary proper.

The arrangement in lampreys, which are amongst the most primitive of all fish, may indicate how the pituitary originally evolved in ancestral vertebrates. Here, the posterior pituitary is a simple flat sheet of tissue at the base of the brain, and there is no pituitary stalk. Rathke's pouch remains open to the outside, close to the nasal openings. Closely associated with the pouch are three distinct clusters of glandular tissue, corresponding to the intermediate lobe, and the rostral and proximal portions of the anterior pituitary. These various parts are separated by meningial membranes, suggesting that the pituitary

of other vertebrates may have formed from the fusion of a number of separate, but closely associated, glands.

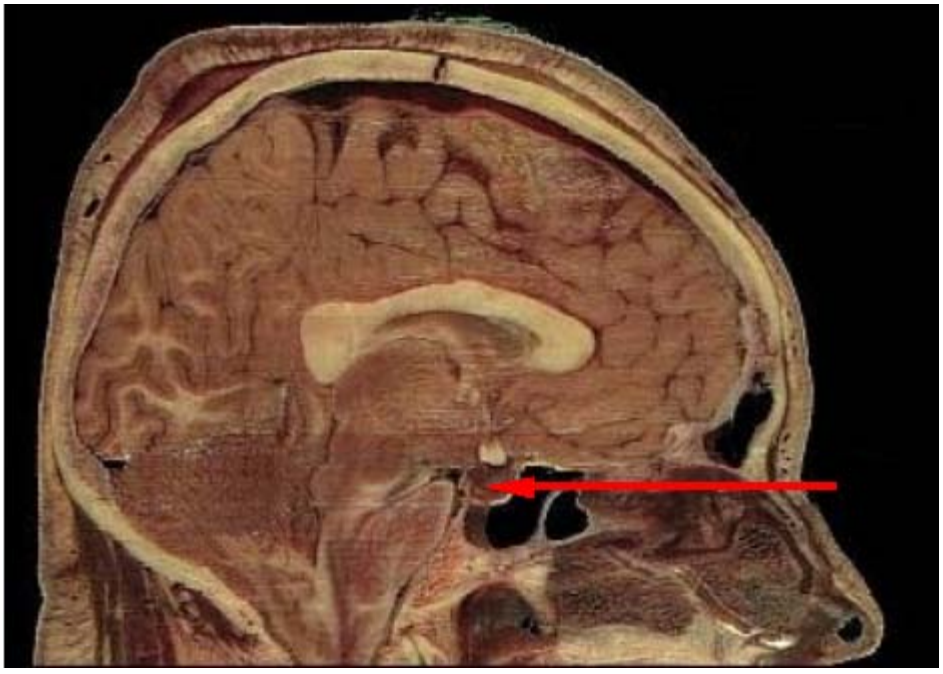
Most fish also possess a urophysis, a neural secretory gland very similar in form to the posterior pituitary, but located in the tail and associated with the spinal cord. This may have a function in osmoregulation.

Functions

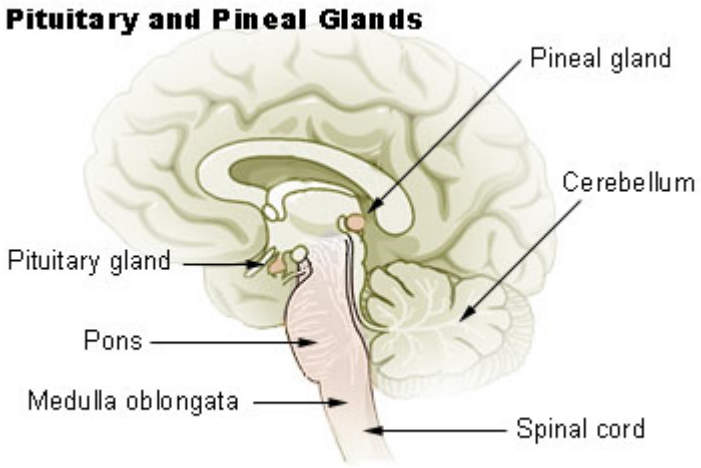
Hormones secreted from the pituitary gland help control the following body processes:

- Growth (Excess of HGH can lead to gigantism and acromegaly.)
- Blood pressure
- Some aspects of pregnancy and childbirth including stimulation of uterine contractions during childbirth
- Breast milk production
- Sex organ functions in both men and women
- Thyroid gland function
- The conversion of food into energy (metabolism)
- Water and osmolarity regulation in the body
- Water balance via the control of reabsorption of water by the kidneys
- Temperature regulation

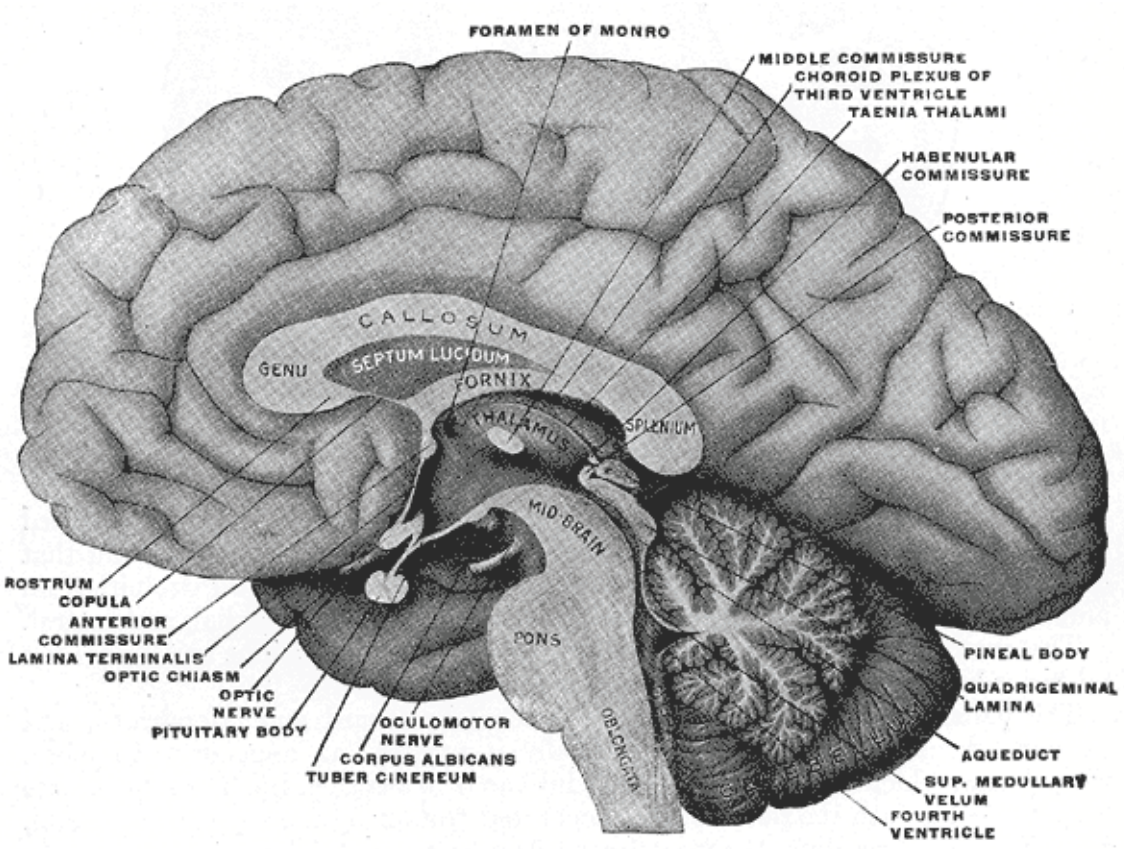
Additional images



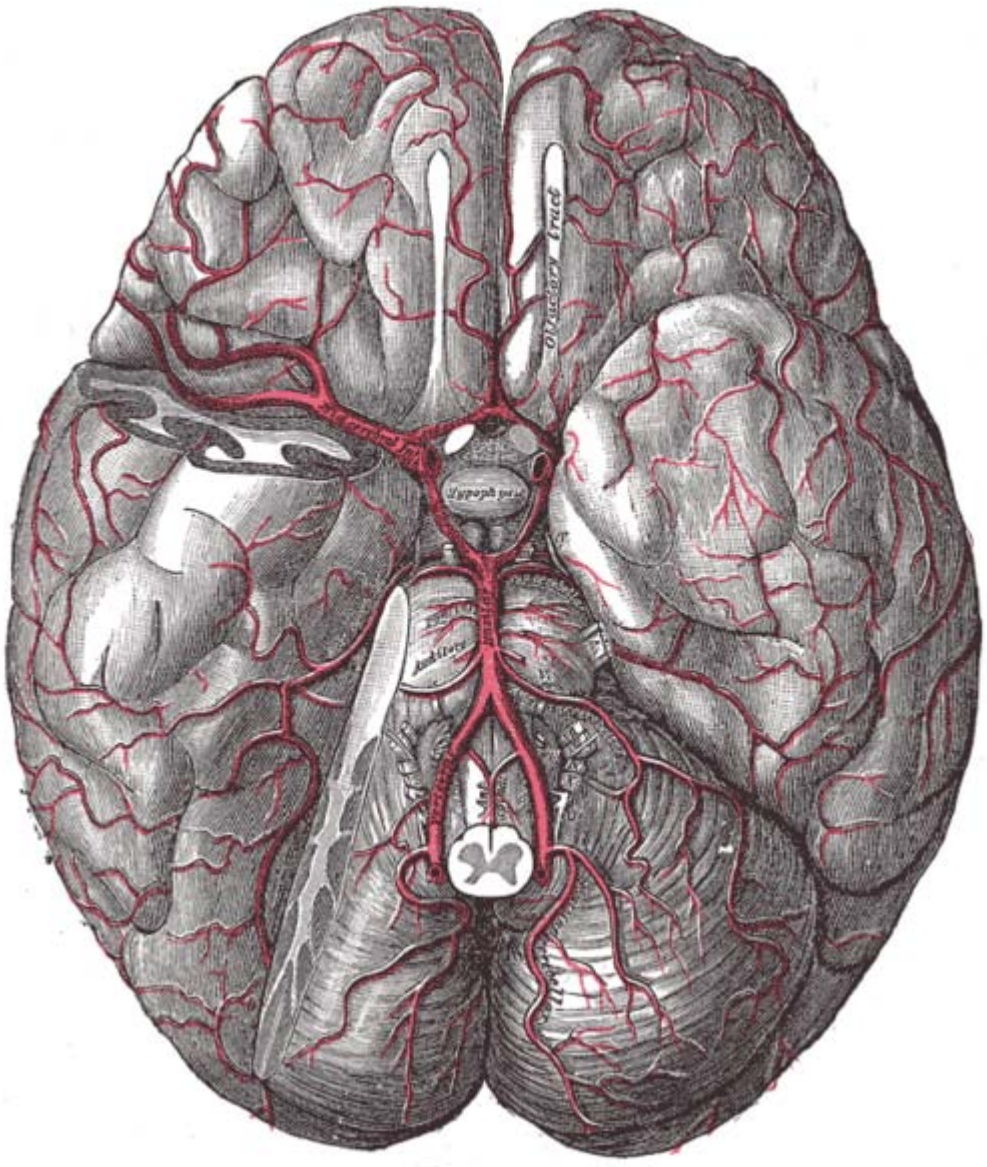
Location of the pituitary gland in the human brain



Pituitary and pineal glands



Mesal aspect of a brain sectioned in the median sagittal plane

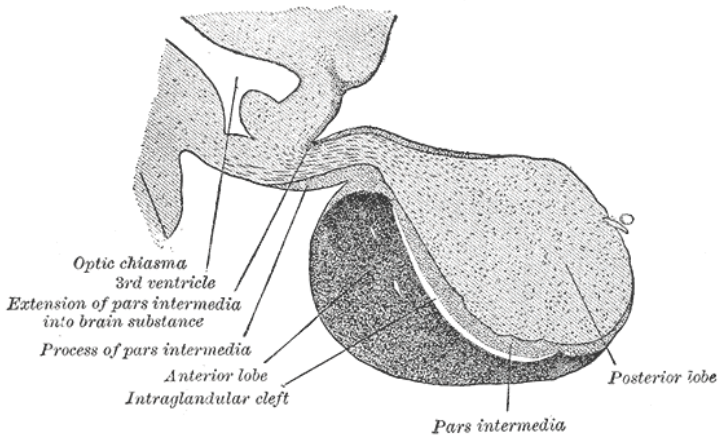


The arteries of the base of the brain

Chapter 5

Anterior Pituitary

Anterior pituitary



Median sagittal through the hypophysis of an adult monkey.

Semidiagrammatic.

Latin	*lobus anterior hypophyseos*
Artery	superior hypophyseal
Vein	hypophyseal
Precursor	oral mucosa (Rathke's pouch)
MeSH	*Anterior+Pituitary+Gland*

A major organ of the endocrine system, the **anterior pituitary**, also called the **adenohypophysis**, is the glandular, anterior lobe of the pituitary gland. The anterior pituitary regulates several physiological processes including stress, growth, and reproduction.

Its regulatory functions are achieved through the secretion of various peptide hormones that act on target organs including the adrenal gland, liver, bone, thyroid gland, and gonads. The anterior pituitary itself is regulated by the hypothalamus and by negative feedback from these target organs.

Disorders of the anterior pituitary are generally classified by the presence of over- or underproduction of pituitary hormones. For example, a prolactinoma is a pituitary adenoma that overproduces prolactin. In Sheehan's syndrome of postpartum hypopituitarism, the anterior pituitary uniformly malfunctions and underproduces all hormones. Proper function of the anterior pituitary and of the organs it regulates can often be ascertained via blood tests that measure hormone levels.

Anatomy

The pituitary gland is a pea-sized gland that sits in a protective bony enclosure called the sella turcica. It is composed of three lobes: anterior, intermediate, and posterior. In many animals, these three lobes are distinct. However, in humans, the intermediate lobe is but a few cell layers thick and indistinct; as a result, it is often considered part of the anterior pituitary. In all animals, the fleshy, glandular anterior pituitary is distinct from the neural composition of the posterior pituitary.

The anterior pituitary is composed of multiple parts:

Pars distalis
The pars distalis, or "distal part", comprises the majority of the anterior pituitary and is where the bulk of pituitary hormone production occurs. Occasionally, "pars distalis" is incorrectly used as a synonym for the anterior pituitary.
Pars tuberalis
The pars tuberalis, or "tubular part", forms a sheath extending up from the pars distalis and wrapping around the pituitary stalk. Its function is poorly understood.
Pars intermedia
The pars intermedia, or "intermediate part", sits between the pars distalis and the posterior pituitary and is often very small in humans.

Hormone secretion

The posterior pituitary as a down growth of the brain, is a neurosecretory organ (Wheater, Burkitt & Daniels, 1987). The secretion of hormones from the posterior pituitary is controlled directly by neurons in the hypothalamus (Marieb, 2004). The connecting stalk between the hypothalamus and the lobes of the pituitary gland, the infundibulum, carries the hormones of the posterior pituitary from nuclei in the hypothalamus. The hypothalmic supraoptic nuclei manufacture anti-diruetic hormone and the hypothalmic paraventricular nuclei manufacture oxytocin. These hormones are then stored in pituitary axons until their release is triggered (Marieb, 2004).

The anterior pituitary is a glandular secretory organ (Wheater, Burkitt & Daniels, 1987). The secretion of hormones from the anterior pituitary is controlled by inhibiting and releasing factors secreted by neurons in the hypothalamus. These inhibiting and releasing factors are release into a primary capillary plexus where they travel, via portal veins, to a secondary capillary plexus where they stimulate the glandular tissue of the anterior pituitary to release its hormones.

Embryology

The anterior pituitary arises from an invagination of the oral ectoderm and forms Rathke's pouch. This contrasts with the posterior pituitary, which originates from neuroectoderm.

Major hormones secreted

Hormone	Other names	Symbol(s)	Structure	Secretory cells	Staining	Target	Effect
Adrenocorticotropic hormone	Corticotropin	ACTH	Polypeptide	Corticotrophs	Basophil	Adrenal gland	Secretion of glucocorticoids
Beta-endorphin			Polypeptide	Corticotrophs	Basophil	Opioid receptor	Inhibit perception of pain
Thyroid-stimulating hormone	Thyrotropin	TSH	Glycoprotein	Thyrotrophs	Basophil	Thyroid gland	Secretion of thyroid hormones
Follicle-stimulating hormone	-	FSH	Glycoprotein	Gonadotrophs	Basophil	Gonads	Growth of reproductive system
Luteinizing hormone	Lutropin	LH, ICSH	Glycoprotein	Gonadotrophs	Basophil	Gonads	Sex hormone production
Growth hormone	Somatotropin	GH, STH	Polypeptide	Somatotrophs	Acidophil	Liver, adipose tissue	Promotes growth; lipid and carbohydrate metabolism
Prolactin	Lactogenic hormone	PRL	Polypeptide	Lactotrophs and Mammotrophs	Acidophil	Ovaries, mammary glands	Secretion of estrogens/progesterone; milk production

The acidophilic cells (GH and PRL) have extensive rough endoplasmic reticulum and produce single chain polypeptides without any glycosylation or phosphorylation. Basophilic staining results from lysosome action modifying the hormones (or prohormones in the case of corticotrophs) by glycosylation.

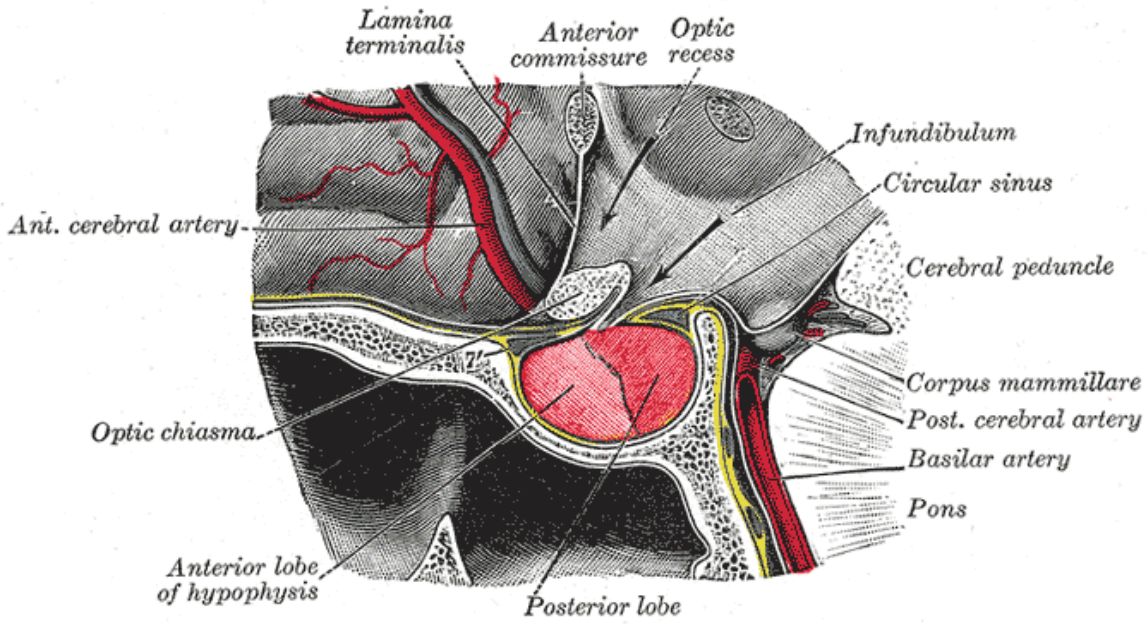
Regulation

Hormone secretion from the anterior pituitary gland is regulated by hormones secreted by the hypothalamus. Neuroendocrine neurons in the hypothalamus project axons to the median eminence, at the base of the brain. At this site, these neurons can release substances into small blood vessels that travel directly to the anterior pituitary gland (the hypothalamo-hypophysial portal vessels).

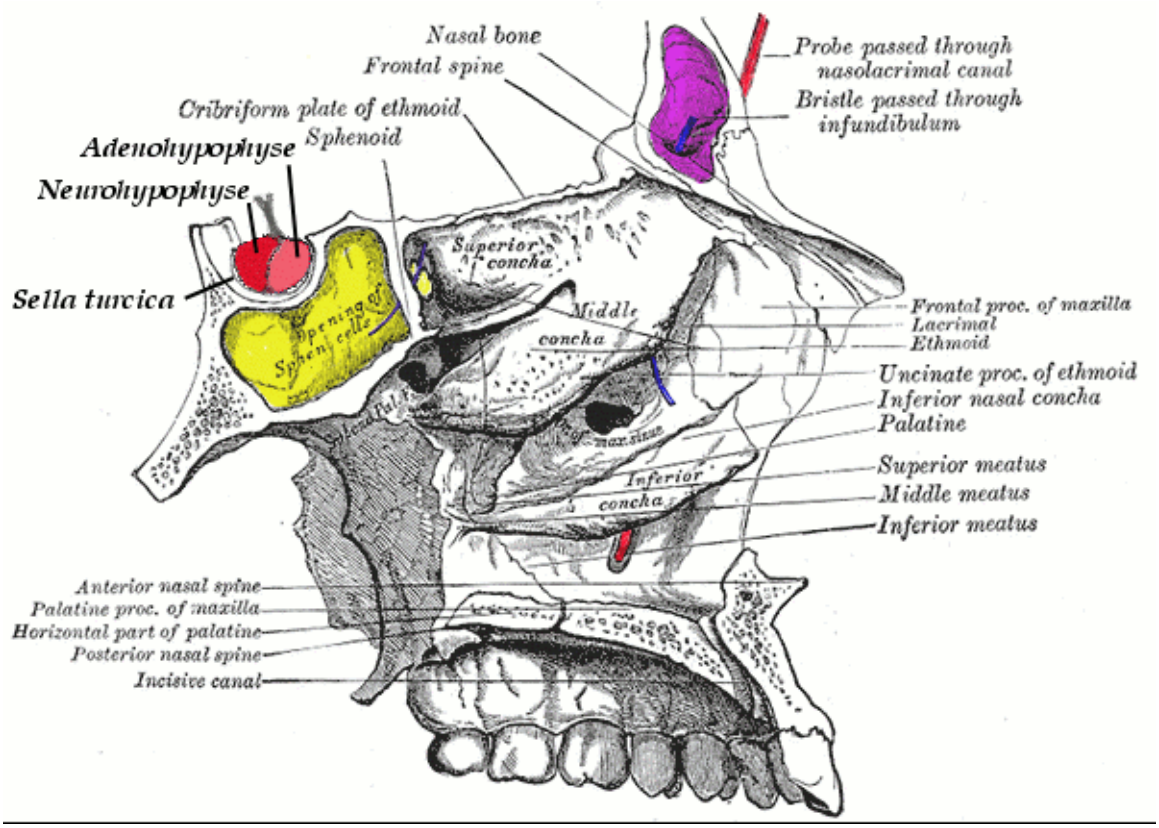
Etymology

The anterior pituitary is also known as the **adenohypophysis**, meaning "glandular undergrowth", from the Greek *adeno* ("gland"), *hypo* ("under"), and *physis* ("growth").

Additional images

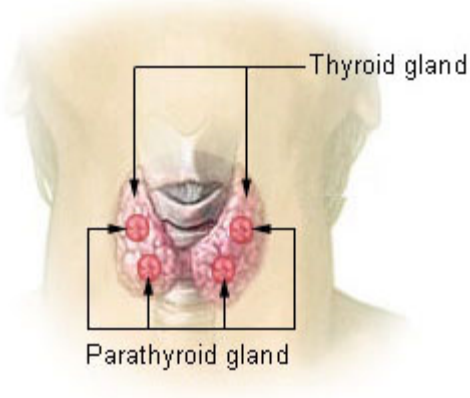


The anterior pituitary is the anterior, glandular lobe of the pituitary gland


Nasal bone
Frontal spine
Cribriform plate of ethmoid
Sphenoid
Adenohypophyse
Neurohypophyse
Sella turcica
Opening of Sphenoidal sinus
Superior concha
Middle concha
Inferior concha
Probe passed through nasolacrimal canal
Bristle passed through infundibulum
Frontal proc. of maxilla
Lacrimal
Ethmoid
Uncinate proc. of ethmoid
Inferior nasal concha
Palatine
Superior meatus
Middle meatus
Inferior meatus
Anterior nasal spine
Palatine proc. of maxilla
Horizontal part of palatine
Posterior nasal spine
Incisive canal

Chapter 6

Thyroid

thyroid	
Thyroid and Parathyroid Glands  Thyroid and parathyroid.	
Latin	*glandula thyroidea*
System	Endocrine system
Precursor	Thyroid diverticulum (an extension of endoderm into 2nd Branchial arch)
MeSH	*Thyroid+Gland*
Dorlands/Elsevier	*Thyroid gland*

In vertebrate anatomy, the **thyroid gland** or simply, the **thyroid**, is one of the largest endocrine glands in the body, and is not to be confused with the parathyroid glands. The thyroid gland is found in the neck, inferior to (below) the thyroid cartilage (also known as the Adam's Apple) and at approximately the same level as the cricoid cartilage. The thyroid controls how quickly the body uses energy, makes proteins, and controls how sensitive the body should be to other hormones.

The thyroid gland participates in these processes by producing thyroid hormones, the principal ones being triiodothyronine (T_3) and thyroxine (T_4). These hormones regulate

the rate of metabolism and affect the growth and rate of function of many other systems in the body. T_3 and T_4 are synthesized utilizing both iodine and tyrosine. The thyroid gland also produces calcitonin, which plays a role in calcium homeostasis.

The thyroid gland is controlled by thyroid-stimulating hormone (TSH) produced by the pituitary (to be specific, the anterior pituitary) and thyrotropin-releasing hormone (TRH) produced by the hypothalamus. The thyroid gland gets its name from the Greek word for "shield", after the shape of the related thyroid cartilage. The most common problems of the thyroid gland consist of an overactive thyroid gland, referred to as hyperthyroidism, and an underactive thyroid gland, referred to as hypothyroidism.

Anatomy

The thyroid gland is a butterfly-shaped organ and is composed of two cone-like lobes or wings, *lobus dexter* (right lobe) and *lobus sinister* (left lobe), connected via the isthmus. The organ is situated on the anterior side of the neck, lying against and around the larynx and trachea, reaching posteriorly the oesophagus and carotid sheath. It starts cranially at the oblique line on the thyroid cartilage (just below the laryngeal prominence, or 'Adam's Apple'), and extends inferiorly to approximately the fifth or sixth tracheal ring. It is difficult to demarcate the gland's upper and lower border with vertebral levels because it moves position in relation to these during swallowing.

The thyroid gland is covered by a fibrous sheath, the *capsula glandulae thyroidea*, composed of an internal and external layer. The external layer is anteriorly continuous with the *lamina pretrachealis fasciae cervicalis* and posteriorolaterally continuous with the carotid sheath. The gland is covered anteriorly with infrahyoid muscles and laterally with the sternocleidomastoid muscle also known as sternomastoid muscle. On the posterior side, the gland is fixed to the cricoid and tracheal cartilage and cricopharyngeus muscle by a thickening of the fascia to form the posterior suspensory ligament of Berry. The thyroid gland's firm attachment to the underlying trachea is the reason behind its movement with swallowing. In variable extent, Lalouette's Pyramid, a pyramidal extension of the thyroid lobe, is present at the most anterior side of the lobe. In this region, the recurrent laryngeal nerve and the inferior thyroid artery pass next to or in the ligament and tubercle.

Between the two layers of the capsule and on the posterior side of the lobes, there are on each side two parathyroid glands.

The thyroid isthmus is variable in presence and size, and can encompass a cranially extending pyramid lobe (*lobus pyramidalis* or *processus pyramidalis*), remnant of the thyroglossal duct. The thyroid is one of the larger endocrine glands, weighing 2-3 grams in neonates and 18-60 grams in adults, and is increased in pregnancy.

The thyroid is supplied with arterial blood from the superior thyroid artery, a branch of the external carotid artery, and the inferior thyroid artery, a branch of the thyrocervical trunk, and sometimes by the thyroid ima artery, branching directly from the

brachiocephalic trunk. The venous blood is drained via superior thyroid veins, draining in the internal jugular vein, and via inferior thyroid veins, draining via the *plexus thyroideus impar* in the left brachiocephalic vein.

Lymphatic drainage passes frequently the lateral deep cervical lymph nodes and the pre- and parathracheal lymph nodes. The gland is supplied by parasympathetic nerve input from the superior laryngeal nerve and the recurrent laryngeal nerve.

Evolution

Thyroid cells phylogenetically derived from primitive iodide-concentrating gastroenteric cells (endostyle) which, during evolution, migrated and specialized in uptake and storage of iodine in follicular cellular structures, also in order to adapt the organisms from iodine-rich sea to iodine-deficient land. Venturi et al.suggested that iodide has an ancestral antioxidant function in all iodide-concentrating cells from primitive algae to more recent vertebrates. In 2008, this ancestral antioxidant action of iodides has been experimentally confirmed by Küpper et al.. Since 700 million years ago thyroxine is present in fibrous exoskeletal scleroproteins of the lowest invertebrates (Porifera and Anthozoa), without showing any hormonal action. When some primitive marine chordates started to emerge from the iodine-rich sea and transferred to iodine-deficient fresh water and finally land, their diet became iodine deficient. Therefore, during progressive slow adaptation to terrestrial life, the primitive vertebrates learned to use the primitive thyroxine in order to transport antioxidant iodide into the cells. Therefore, the remaining triiodothyronine (T_3), the real active hormone, became active in the metamorphosis and thermogenesis for a better adaptation of the organisms to terrestrial environment (fresh water, atmosphere, gravity, temperature and diet). In fact, the U.S. Food and Nutrition Board and Institute of Medicine recommended daily allowance of iodine ranges from 150 micrograms /day for adult humans to 290 micrograms /day for lactating mothers. However, the thyroid gland needs no more than 70 micrograms /day to synthesize the requisite daily amounts of T_4 and T_3. These higher recommended daily allowance levels of iodine seem necessary for optimal function of a number of body systems, including lactating breast, gastric mucosa, salivary glands, oral mucosa, thymus, epidermis, choroid plexus and brain, etc..

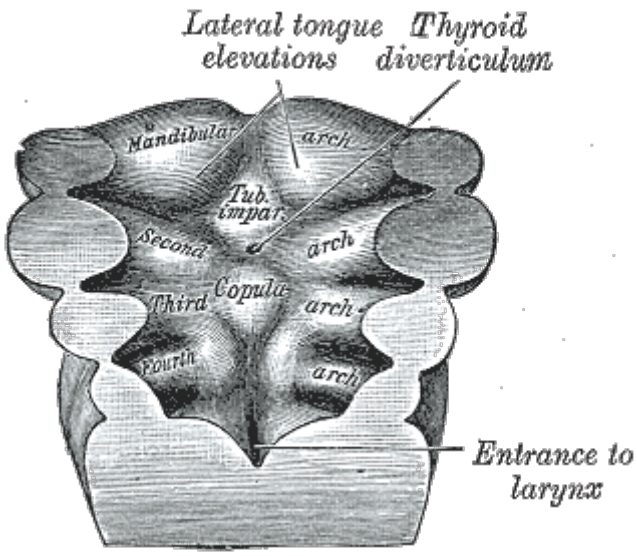
Embryological development

In the fetus, at 3–4 weeks of gestation, the thyroid gland appears as an epithelial proliferation in the floor of the pharynx at the base of the tongue between the tuberculum impar and the copula linguae at a point latter indicated by the foramen cecum. The thyroid then descends in front of the pharyngeal gut as a bilobed diverticulum through the thyroglossal duct. Over the next few weeks, it migrates to the base of the neck. During migration, the thyroid remains connected to the tongue by a narrow canal, the thyroglossal duct.

Thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) start being secreted from the fetal hypothalamus and pituitary at 18-20 weeks of gestation, and fetal production of thyroxine (T_4) reach a clinically significant level at 18–20 weeks.

Fetal triiodothyronine (T_3) remains low (less than 15 ng/dL) until 30 weeks of gestation, and increases to 50 ng/dL at term. Fetal self-sufficiency of thyroid hormones protects the fetus against e.g. brain development abnormalities caused by maternal hypothyroidism. However, preterm births can suffer neurodevelopmental disorders due to lack of maternal thyroid hormones due their own thyroid being insufficiently developed to meet their postnatal needs.

The portion of the thyroid containing the parafollicular C cells, those responsible for the production of calcitonin, are derived from the neural crest. This is first seen as the ultimobranchial body, which joins the primordial thyroid gland during its descent to its final location in the anterior neck.



Histology

At the microscopic level, there are three primary features of the thyroid:

Feature	Description
Follicles	The thyroid is composed of spherical follicles that selectively absorb iodine (as iodide ions, I^-) from the blood for production of thyroid hormones, but also for storage of iodine in thyroglobulin, in fact iodine is necessary for other important iodine-concentrating organs as breast, stomach, salivary glands, thymus etc. Twenty-five percent of all the body's iodide ions are in the thyroid gland. Inside the follicles, colloid serves as a reservoir of materials for thyroid hormone production and, to a lesser extent, acts as a reservoir for the hormones themselves. Colloid is rich in a protein called thyroglobulin.

Thyroid epithelial cells (or "follicular cells")	The follicles are surrounded by a single layer of thyroid epithelial cells, which secrete T_3 and T_4. When the gland is not secreting T_3/T_4 (inactive), the epithelial cells range from low columnar to cuboidal cells. When active, the epithelial cells become tall columnar cells.
Parafollicular cells (or "C cells")	Scattered among follicular cells and in spaces between the spherical follicles are another type of thyroid cell, parafollicular cells, which secrete calcitonin.

Disorders

Disorders of the thyroid gland fall into the following categories:

Hyperthyroidism

Hyperthyroidism, or overactive thyroid, is the overproduction of the thyroid hormones T_3 and T_4, and is most commonly caused by the development of Graves' disease, an autoimmune disease in which antibodies are produced which stimulate the thyroid to secrete excessive quantities of thyroid hormones. The disease can result in the formation of a toxic goiter as a result of thyroid growth in response to a lack of negative feedback mechanisms. It presents with symptoms such as a thyroid goiter, protruding eyes (exopthalmos), palpitations, excess sweating, diarrhea, weight loss, muscle weakness and unusual sensitivity to heat.

Beta blockers are used to decrease symptoms of hyperthyroidism such as increased heart rate, tremors, anxiety and heart palpitations, and anti-thyroid drugs are used to decrease the production of thyroid hormones, in particular, in the case of Graves' disease. These medications take several months to take full effect and have side-effects such as skin rash or a drop in white blood cell count, which decreases the ability of the body to fight off infections. These drugs involve frequent dosing (often one pill every 8 hours) and often require frequent doctor visits and blood tests to monitor the treatment, and may sometimes lose effectiveness over time. Due to the side-effects and inconvenience of such drug regimens, some patients choose to undergo radioactive iodine-131 treatment. Radioactive iodine is administered in order to destroy a proportion of or the entire thyroid gland, since the radioactive iodine is selectively taken up by the gland and gradually destroys the cells of the gland. Alternatively, the gland may be partially or entirely removed surgically, though iodine treatment is usually preferred since the surgery is invasive and carries a risk of damage to the parathyroid glands or the nerves controlling the vocal cords. If the entire thyroid gland is removed, hypothyroidism results.

Hypothyroidism

Hypothyroidism is the underproduction of the thyroid hormones T_3 and T_4. Hypothyroid disorders may occur as a result of congenital thyroid abnormalities, autoimmune disorders such as Hashimoto's thyroiditis, iodine deficiency, especially in poorer countries, or the removal of the thyroid following surgery to treat severe

hyperthyroidism. Typical symptoms are abnormal weight gain, tiredness, baldness, cold intolerance, and bradycardia. Hypothyroidism is treated with hormone replacement therapy, such as levothyroxine, which is typically required for the rest of the patient's life. Thyroid hormone treatment is given under the care of a physician and may take a few weeks to become effective.

Negative feedback mechanisms result in growth of the thyroid gland when thyroid hormones are being produced in sufficiently low quantities as a means of increasing the thyroid output; however, where the hypothyroidism is caused by iodine insufficiency, the thyroid is unable to produce T_3 and T_4 and as a result, the thyroid may continue to grow to form a non-toxic goiter. It is termed non-toxic as it does not produce toxic quantities of thyroid hormones, despite its size.

Initial hyperthyroidism followed by hypothyroidism

This is the overproduction of T_3 and T_4 followed by the underproduction of T_3 and T_4. There are two types: Hashimoto's thyroiditis and postpartum thyroiditis.

Hashimoto's thyroiditis is an autoimmune disorder whereby the body's own immune system reacts with the thyroid tissues. At the beginning, the gland is overactive, and then becomes underactive as the gland is destroyed resulting in too little thyroid hormone production or hypothyroidism. Hashimoto's is most common in middle-age females and tends to run in families. Also more common in individuals with hashimoto's thyroiditis are type 1 diabetes and celiac disease.

Postpartum thyroiditis occurs in some females following delivery. The gland becomes inflamed and the condition initially presents with overactivity of the gland followed by underactivity. In some cases, the gland does recover with time and resume its functions.

Cancers

Cancers do occur in the thyroid gland and are more common in females. In most cases, the thyroid cancer presents as a painless mass in the neck. It is very unusual for the thyroid cancers to present with symptoms, unless it has been neglected. One may be able to feel a hard nodule in the neck. Diagnosis is made using a needle biopsy and various radiological studies.

Non-cancerous nodules

Many individuals may find the presence of small masses (nodules) in the neck. The majority of these thyroid nodules are benign (non cancerous). The presence of a thyroid nodule does not mean that one has thyroid disease. Most thyroid nodules do not cause any symptoms, and most are discovered on an incidental examination. Doctors usually perform a needle aspiration biopsy of the thyroid to determine the status of the nodules. If the nodule is found to be non-cancerous, no other treatment is required. If the nodule is suspicious then surgery is recommended.

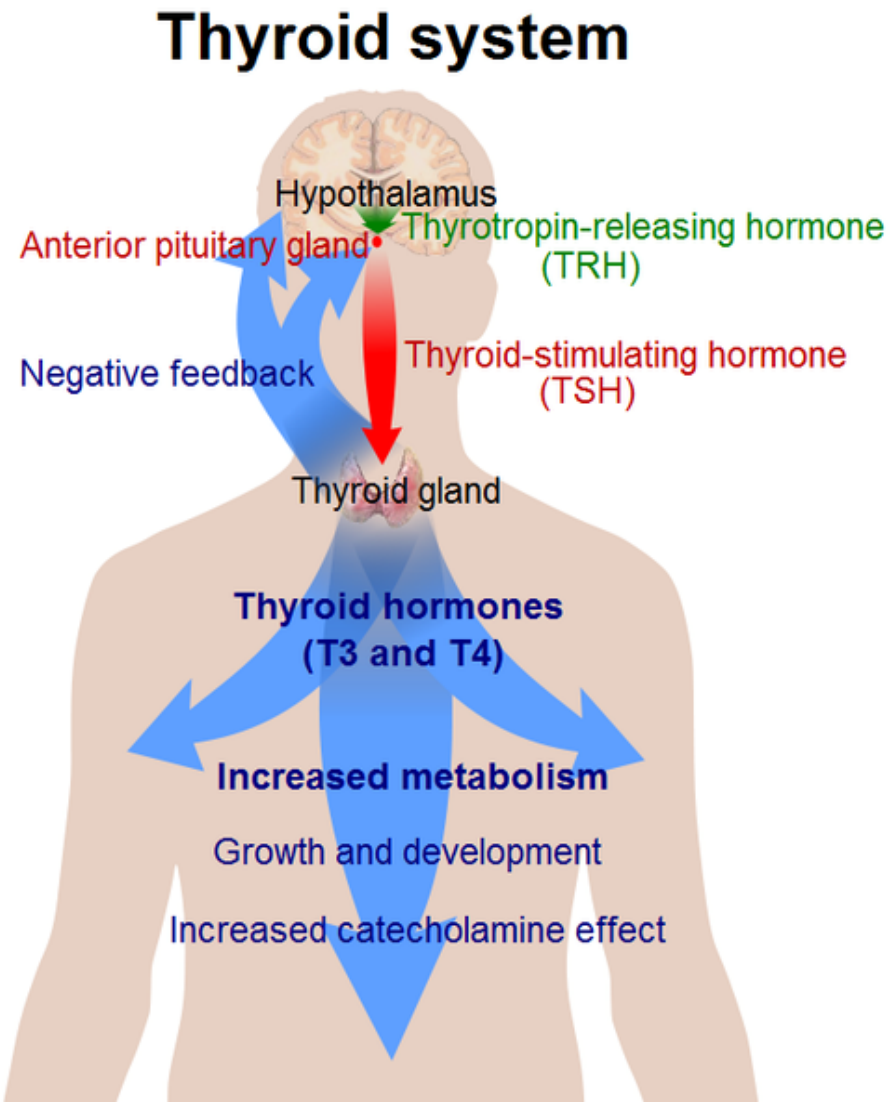
Seasonal Aggravation

Limited research shows that seasonal allergies may trigger episodes of hypo- or hyperthyroidism.

Physiology

The primary function of the thyroid is production of the hormones triiodothyronine (T_3), thyroxine (T_4), and calcitonin. Up to 80% of the T_4 is converted to T_3 by peripheral organs such as the liver, kidney and spleen. T_3 is several times more powerful than T_4, which is largely a prohormone, perhaps four or even ten times more active.

T_3 and T_4 production and action



The system of the thyroid hormones T_3 and T_4

Thyroxine (T_4) is synthesised by the follicular cells from free tyrosine and on the tyrosine residues of the protein called thyroglobulin (Tg). Iodine is captured with the "iodine trap" by the hydrogen peroxide generated by the enzyme thyroid peroxidase (TPO) and linked to the 3' and 5' sites of the benzene ring of the tyrosine residues on Tg, and on free tyrosine. Upon stimulation by the thyroid-stimulating hormone (TSH), the follicular cells reabsorb Tg and cleave the iodinated tyrosines from Tg in lysosomes, forming T_4 and T_3 (in T_3, one iodine atom is absent compared to T_4), and releasing them into the blood. Deiodinase enzymes convert T_4 to T_3. Thyroid hormone secreted from the gland is about 80-90% T_4 and about 10-20% T_3.

Cells of the developing brain are a major target for the thyroid hormones T_3 and T_4. Thyroid hormones play a particularly crucial role in brain maturation during fetal development. A transport protein that seems to be important for T_4 transport across the blood-brain barrier (OATP1C1) has been identified. A second transport protein (MCT8) is important for T_3 transport across brain cell membranes.

Non-genomic actions of T_4 are those that are not initiated by liganding of the hormone to intranuclear thyroid receptor. These may begin at the plasma membrane or within cytoplasm. Plasma membrane-initiated actions begin at a receptor on the integrin alphaV beta3 that activates ERK1/2. This binding culminates in local membrane actions on ion transport systems such as the Na(+)/H(+) exchanger or complex cellular events including cell proliferation. These integrins are concentrated on cells of the vasculature and on some types of tumor cells, which in part explains the proangiogenic effects of iodothyronines and proliferative actions of thyroid hormone on some cancers including gliomas. T_4 also acts on the mitochondrial genome via imported isoforms of nuclear thyroid receptors to affect several mitochondrial transcription factors. Regulation of actin polymerization by T_4 is critical to cell migration in neurons and glial cells and is important to brain development.

T_3 can activate phosphatidylinositol 3-kinase by a mechanism that may be cytoplasmic in origin or may begin at integrin alpha V beta3.

In the blood, T_4 and T_3 are partially bound to thyroxine-binding globulin (TBG), transthyretin, and albumin. Only a very small fraction of the circulating hormone is free (unbound) - T_4 0.03% and T_3 0.3%. Only the free fraction has hormonal activity. As with the steroid hormones and retinoic acid, thyroid hormones cross the cell membrane and bind to intracellular receptors (α_1, α_2, β_1 and β_2), which act alone, in pairs or together with the retinoid X-receptor as transcription factors to modulate DNA transcription.

T_3 and T_4 regulation

The production of thyroxine and triiodothyronine is regulated by thyroid-stimulating hormone (TSH), released by the anterior pituitary. The thyroid and thyrotropes form a negative feedback loop: TSH production is suppressed when the T_4 levels are high. The TSH production itself is modulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus and secreted at an increased rate in situations such as cold

exposure (to stimulate thermogenesis). TSH production is blunted by somatostatin (SRIH), rising levels of glucocorticoids and sex hormones (estrogen and testosterone), and excessively high blood iodide concentration.

An additional hormone produced by the thyroid contributes to the regulation of blood calcium levels. Parafollicular cells produce calcitonin in response to hypercalcemia. Calcitonin stimulates movement of calcium into bone, in opposition to the effects of parathyroid hormone (PTH). However, calcitonin seems far less essential than PTH, as calcium metabolism remains clinically normal after removal of the thyroid (thyroidectomy), but not the parathyroids.

Thyroid function tests

Test	Abbreviation	Normal ranges
Serum thyrotropin/thyroid-stimulating hormone	**TSH**	**0.3–3.0 µU/ml**
Free thyroxine	**FT_4**	**7–18 ng/l = 0.7–1.8 ng/dl**
Serum triiodothyronine	**T_3**	**0.8–1.8 µg/l = 80–180 ng/dl**
Radioactive iodine-123 uptake	**RAIU**	**10–30%**
Radioiodine scan (gamma camera)	N/A	N/A - thyroid contrasted images
Free thyroxine fraction	FT4F	0.03–0.005%
Serum thyroxine	T_4	46–120 µg/l = 4.6–12.0 µg/dl
Thyroid hormone binding ratio	THBR	0.9–1.1
Free thyroxine index	FT4I	4–11
Free triiodothyronine l	FT_3	230–619 pg/d
Free T3 Index	FT3I	80–180
Thyroxine-binding globulin	TBG	12–20 ug/dl T4 +1.8 µg
TRH stimulation test	Peak TSH	9–30 µIU/ml at 20–30 min.
Serum thyroglobulin l	Tg	0-30 ng/m
Thyroid microsomal antibody titer	TMAb	Varies with method
Thyroglobulin antibody titer	TgAb	Varies with method

- µU/ml = mU/l, microunit per milliliter
- ng/dl, nanograms per deciliter
- µg, micrograms
- pg/d, picograms per day
- µIU/ml = mIU/l, micro-international unit per milliliter

Significance of iodine

In areas of the world where iodine is lacking in the diet the thyroid gland can become considerably enlarged, a condition called endemic goiter. Pregnant women on a diet that is severely deficient of iodine can give birth to infants who can present with thyroid hormone deficiency (congenital hypothyroidism), manifesting in problems of physical growth and development as well as brain development (a condition referred to as endemic cretinism). In many developed countries, newborns are routinely tested for congenital hypothyroidism as part of newborn screening. Children with congenital hypothyroidism are treated supplementally with levothyroxine, which facilitates normal growth and development.

Thyroxine is critical to the regulation of metabolism and growth throughout the animal kingdom. Among amphibians, for example, administering a thyroid-blocking agent such as propylthiouracil (PTU) can prevent tadpoles from metamorphosing into frogs; in contrast, administering thyroxine will trigger metamorphosis.

Because the thyroid concentrates this element, it also concentrates various radioactive isotopes of iodine produced by nuclear fission. In the event of large accidental releases of such material into the environment, the uptake of radioactive iodine isotopes by the thyroid can, in theory, be blocked by saturating the uptake mechanism with a large surplus of non-radioactive iodine, taken in the form of potassium iodide tablets. One consequence of the Chernobyl disaster was an increase in thyroid cancers in children in the years following the accident.

The use of iodised salt is an efficient way to add iodine to the diet. It has eliminated endemic cretinism in most developed countries, and some governments have made the iodination of flour, cooking oil, and salt mandatory. Potassium iodide and sodium iodide are typically used forms of supplemental iodine.

As with most substances, either too much or too little can cause problems. Recent studies on some populations are showing that excess iodine intake could cause an inceased prevelence of autoimmune thyroid disease, resulting in permanent hypothyroidism.

History

There are several findings that evidence a great interest for thyroid disorders just in the Medieval Medical School of Salerno (12th century). Rogerius Salernitanus, the Salernitan surgeon and author of "Post mundi fabricam" (around 1180) was considered at that time the surgical text par excellence all over Europe. In the chapter "De bocio" of his magnum opus, he describes several pharmacological and surgical cures, some of which nowadays are reappraised quite scientifically effective.

In modern times, the thyroid was first identified by the anatomist Thomas Wharton (whose name is also eponymised in Wharton's duct of the submandibular gland) in 1656.

Thyroxine was identified only in the 19th century.

In other animals

The thyroid gland is found in all vertebrates. In fish, it is, in general, located below the gills and is not always divided into distinct lobes. However, in some teleosts, patches of thyroid tissue are found elsewhere in the body, associated with the kidneys, spleen, heart, or eyes.

In tetrapods, the thyroid is always found somewhere in the neck region. In most tetrapod species, there are two paired thyroid glands - that is, the right and left lobes are not joined together. However, there is only ever a single thyroid gland in most mammals, and the shape found in humans is common to many other species.

In larval lampreys, the thyroid originates as an exocrine gland, secreting its hormones into the gut, and associated with the larva's filter-feeding apparatus. In the adult lamprey, the gland separates from the gut, and becomes endocrine, but this path of development may reflect the evolutionary origin of the thyroid. For instance, the closest living relatives of vertebrates, the tunicates and *Amphioxus*, have a structure very similar to that of larval lampreys, and this also secretes iodine-containing compounds (albeit not thyroxine).

Additional images

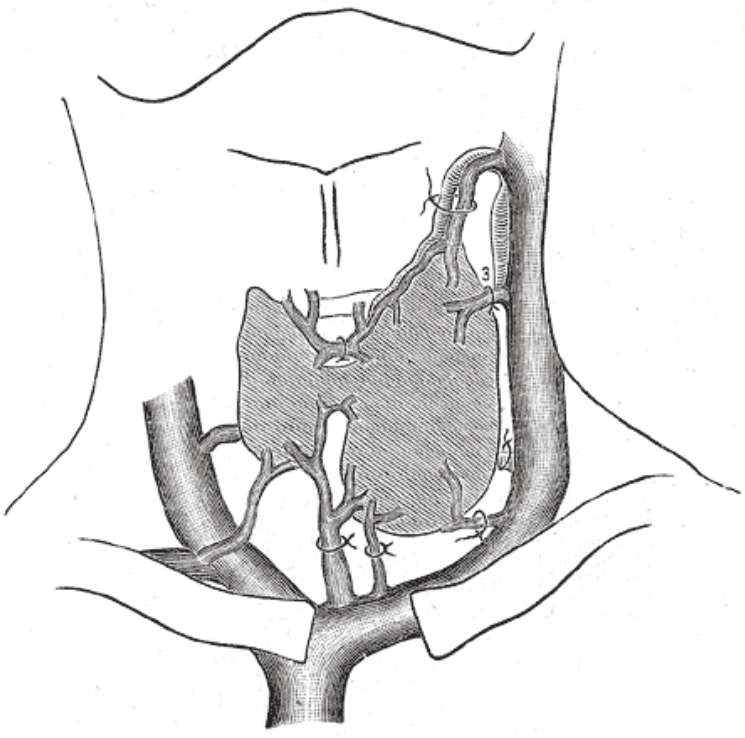
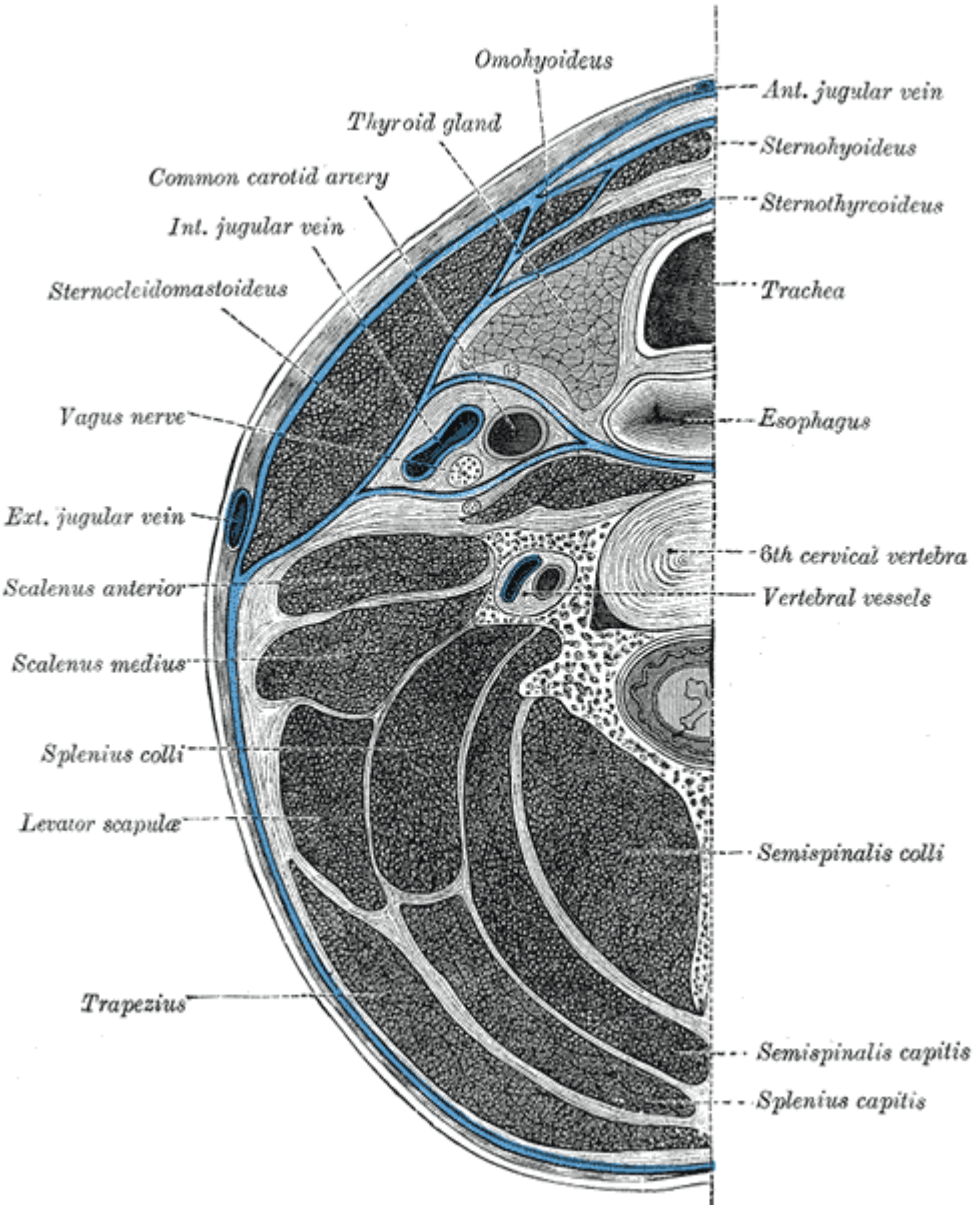
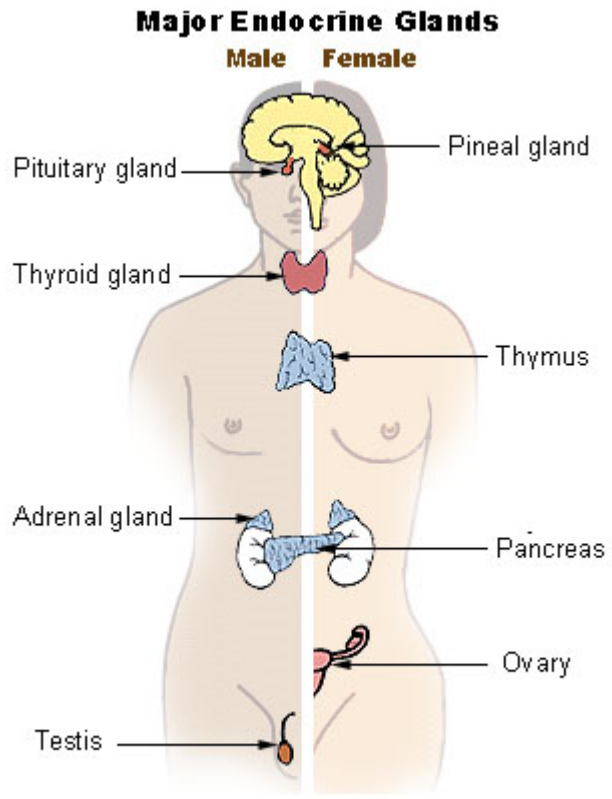


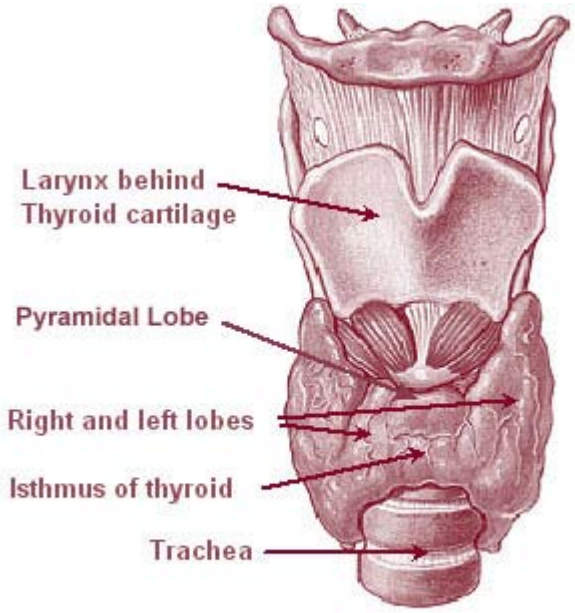
Diagram showing common arrangement of thyroid veins

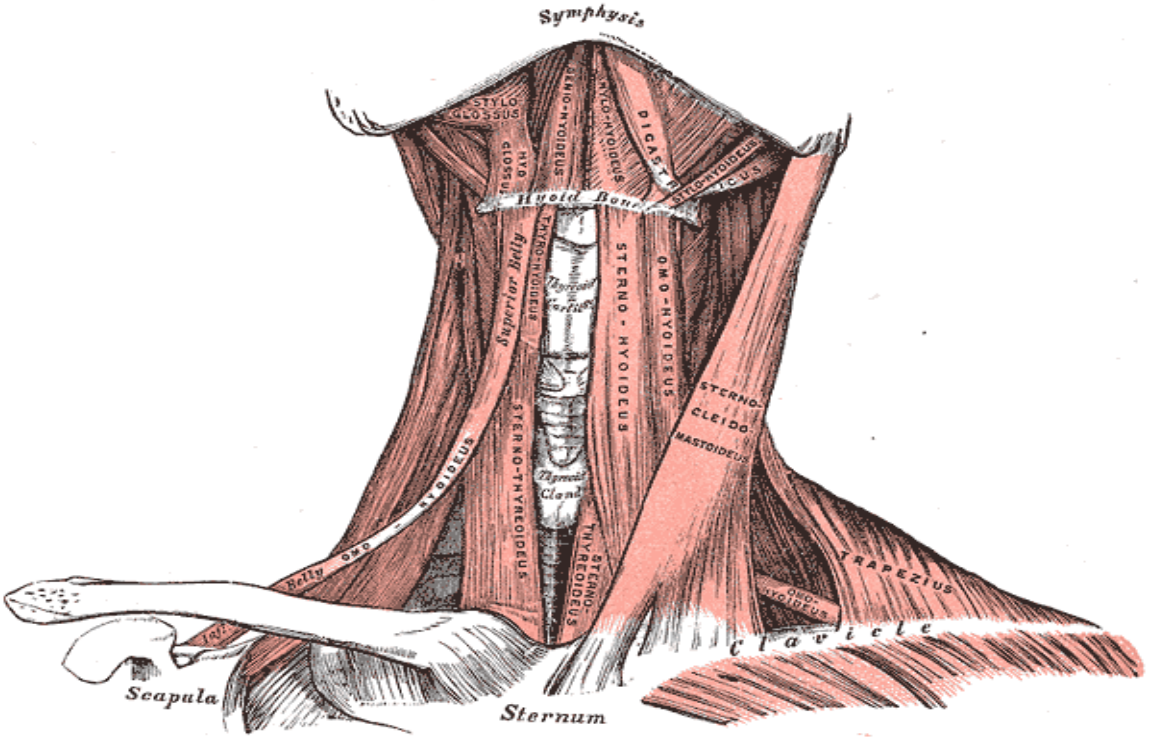


Section of the neck at about the level of the sixth cervical vertebra

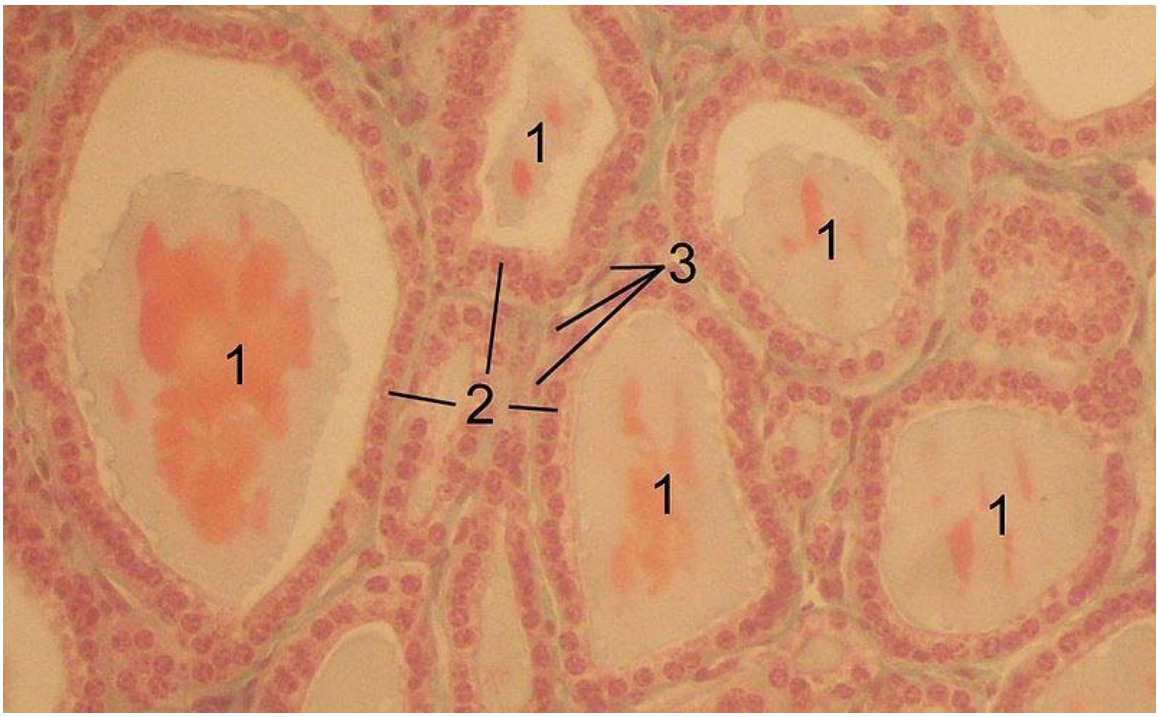


Position of the Thyroid in Males and Females

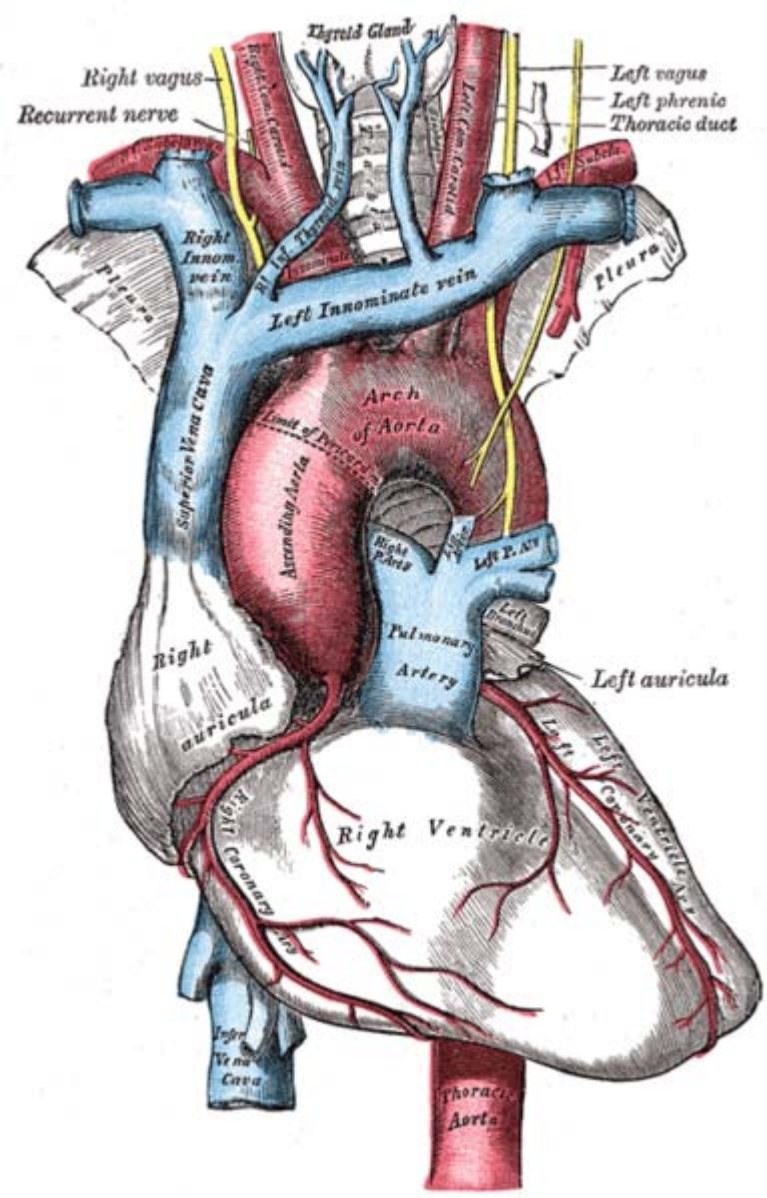




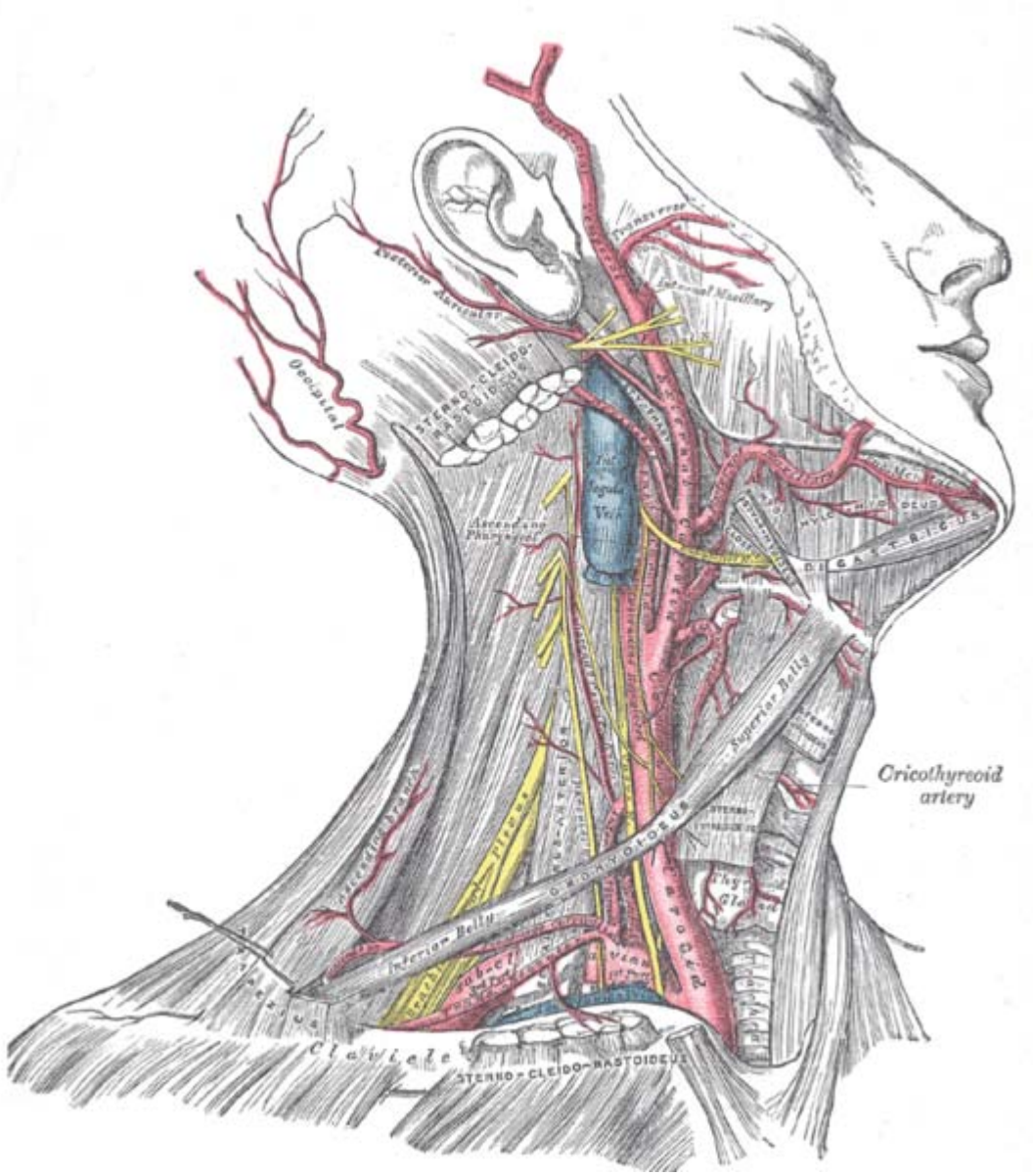
Muscles of the neck. Anterior view



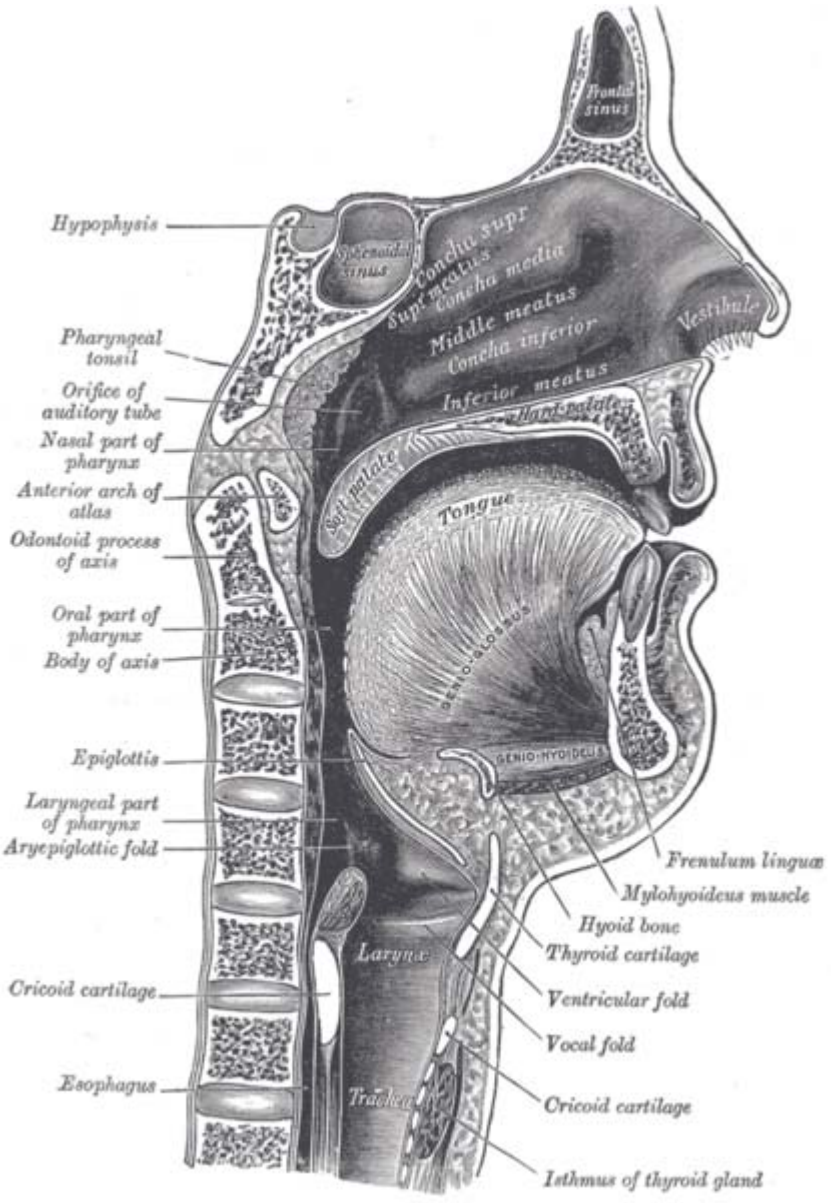
Thyoid histology



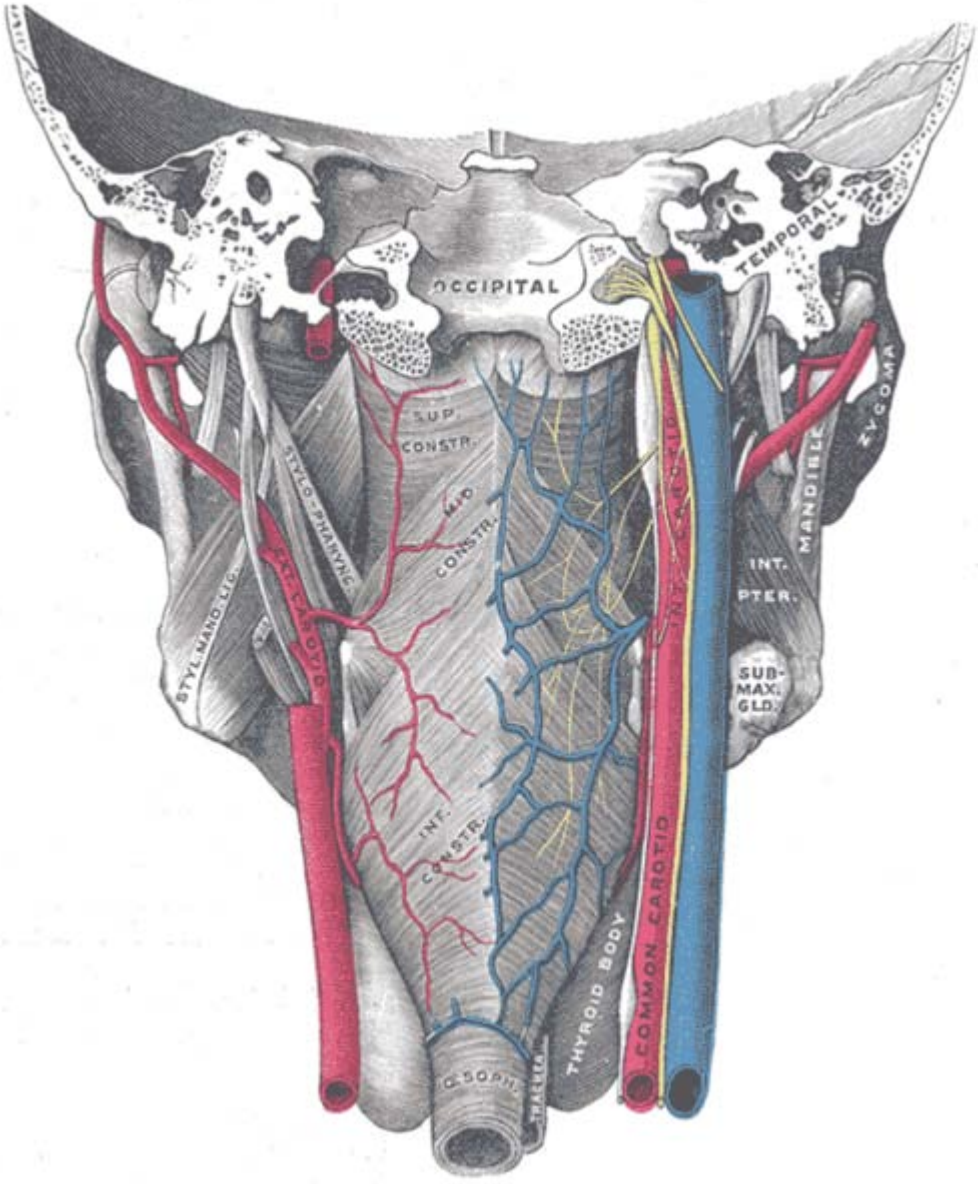
The arch of the aorta, and its branches



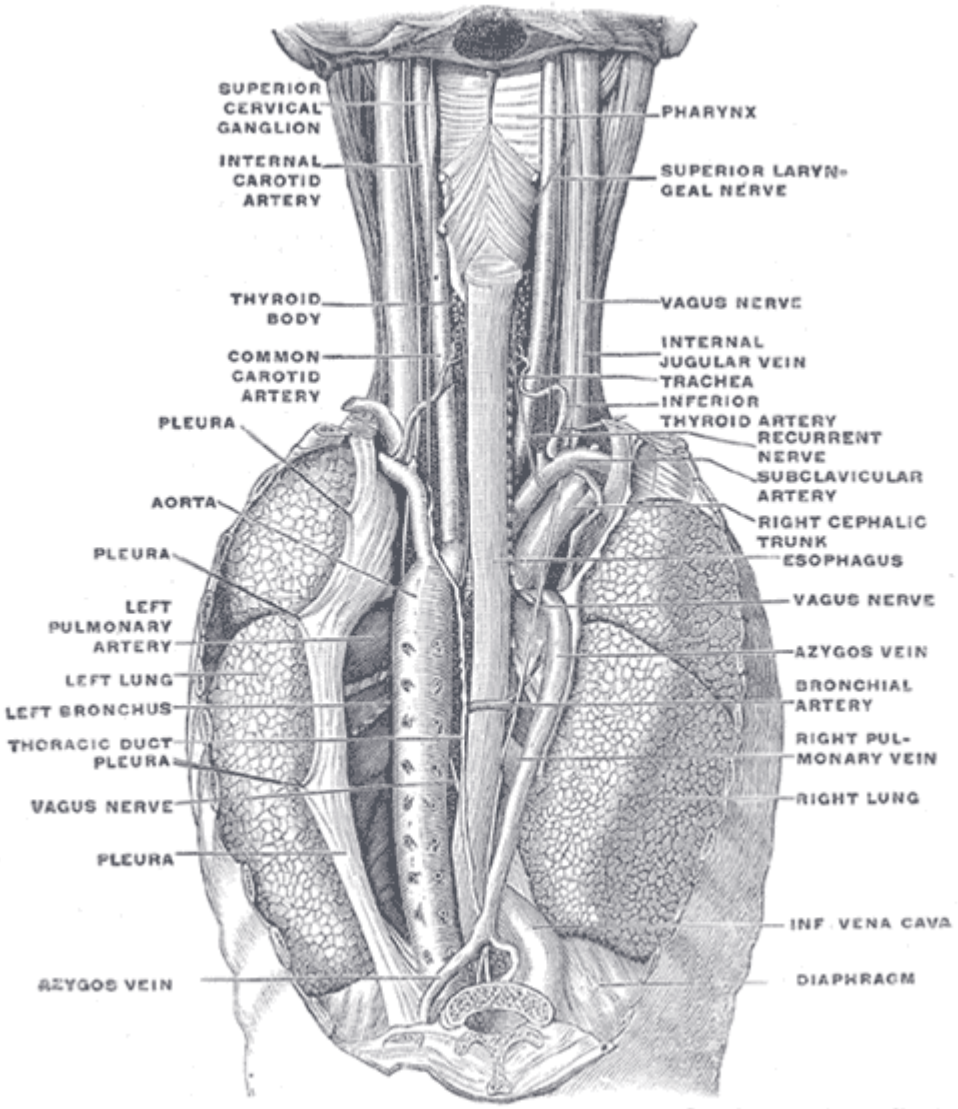
Superficial dissection of the right side of the neck, showing the carotid and subclavian arteries



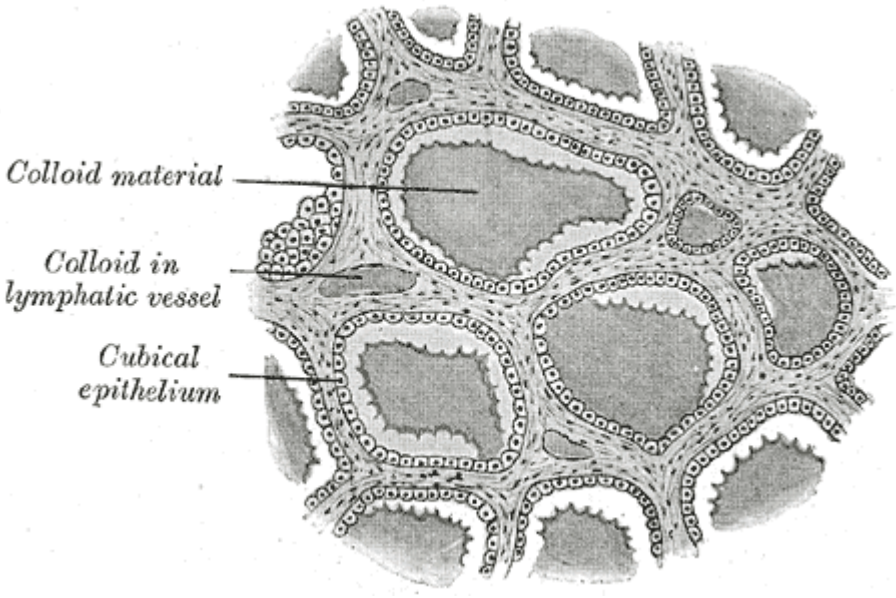
Sagittal section of nose mouth, pharynx, and larynx



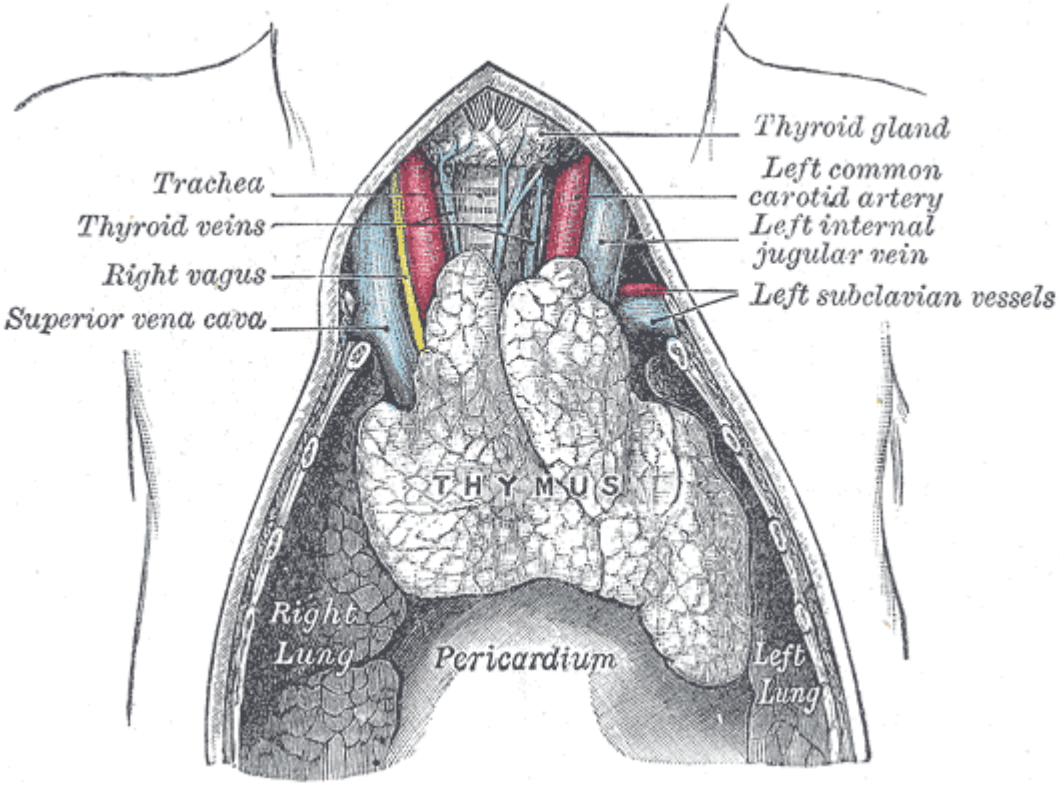
Muscles of the pharynx, viewed from behind, together with the associated vessels and nerves



The position and relation of the esophagus in the cervical region and in the posterior mediastinum. Seen from behind.



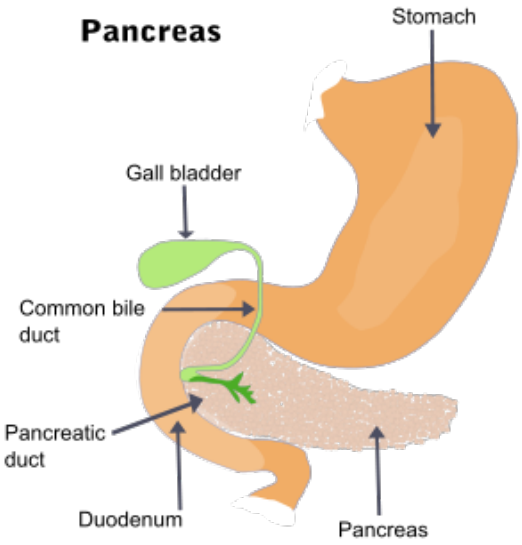
Section of thyroid gland of sheep



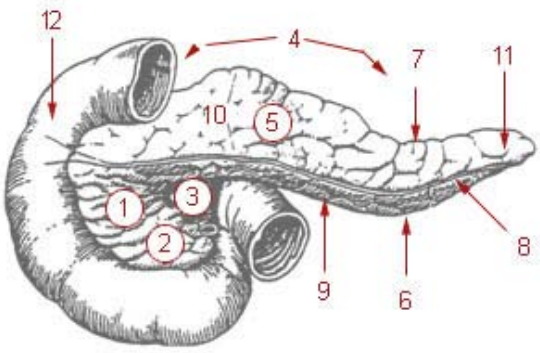
The thymus of a full-term fetus, exposed in situ

Chapter 7

Pancreas



The pancreas



The **pancreas** is a gland organ in the digestive and endocrine system of vertebrates. It is both an endocrine gland producing several important hormones, including insulin, glucagon, and somatostatin, as well as an exocrine gland, secreting pancreatic juice

containing digestive enzymes that pass to the small intestine. These enzymes help to further break down the carbohydrates, proteins, and fats in the chyme.

Histology

Under a microscope, stained sections of the pancreas reveal two different types of parenchymal tissue. Lightly staining clusters of cells are called islets of Langerhans, which produce hormones that underlie the endocrine functions of the pancreas. Darker staining cells form acini connected to ducts. Acinar cells belong to the exocrine pancreas and secrete digestive enzymes into the gut via a system of ducts.

Structure	Appearance	Function
Islets of Langerhans	Lightly staining, large, spherical clusters	Hormone production and secretion (endocrine pancreas)
Pancreatic acini	Darker staining, small, berry-like clusters	Digestive enzyme production and secretion (exocrine pancreas)

Function

The pancreas is a dual-function gland, having features of both endocrine and exocrine glands.

The part of the pancreas with endocrine function is made up of approximately a million cell clusters called islets of Langerhans. Four main cell types exist in the islets. They are relatively difficult to distinguish using standard staining techniques, but they can be classified by their secretion: α cells secrete glucagon (increase glucose in blood), β cells secrete insulin (decrease glucose in blood), δ cells secrete somatostatin (regulates/stops α and β cells), and PP cells secrete pancreatic polypeptide.

The islets are a compact collection of endocrine cells arranged in clusters and cords and are crisscrossed by a dense network of capillaries. The capillaries of the islets are lined by layers of endocrine cells in direct contact with vessels, and most endocrine cells are in direct contact with blood vessels, by either cytoplasmic processes or by direct apposition. According to the volume *The Body,* by Alan E. Nourse, the islets are "busily manufacturing their hormone and generally disregarding the pancreatic cells all around them, as though they were located in some completely different part of the body."

The pancreas as an exocrine gland helps out the digestive system. It secretes pancreatic juice that contains digestive enzymes that pass to the small intestine. These enzymes help to further break down the carbohydrates, proteins, and lipids (fats) in the chyme.

The pancreas receives regulatory innervation via hormones in the blood and through the autonomic nervous system. These two inputs regulate the secretory activity of the pancreas.

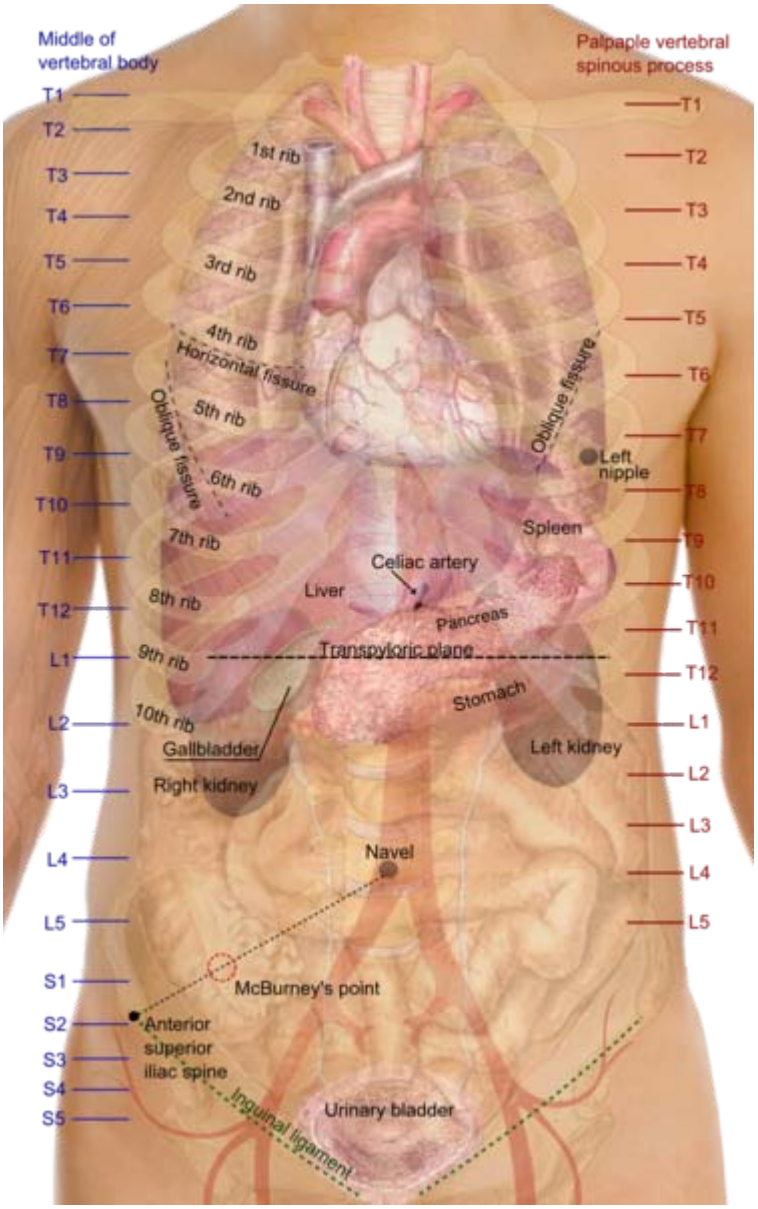
Sympathetic (adrenergic)

α2: decreases secretion from beta cells, increases secretion from alpha cells

Parasympathetic (muscarinic)

M3: increases stimulation of alpha cells and beta cells

Anatomy



Surface projections of the organs of the trunk, showing pancreas at the transpyloric plane

The pancreas lies in the epigastrium and left hypochondrium areas of the abdomen

It is composed of the following parts:

- The *head* lies within the concavity of the duodenum.

- The *uncinate process* emerges from the lower part of head, and lies deep to superior mesenteric vessels.
- The *neck* is the constricted part between the head and the body.
- The *body* lies behind the stomach.
- The *tail* is the left end of the pancreas. It lies in contact with the spleen and runs in the lienorenal ligament.

The superior pancreaticoduodenal artery from gastroduodenal artery and the inferior pancreaticoduodenal artery from superior mesenteric artery run in the groove between the pancreas and duodenum and supply the head of pancreas. The pancreatic branches of splenic artery also supply the neck, body and tail of the pancreas. The largest of those branches is called the arteria pancreatica magna; its occlusion, although rare, is fatal.

The body and neck of the pancreas drain into splenic vein; the head drains into the superior mesenteric and portal veins.

Lymph is drained via the splenic, celiac and superior mesenteric lymph nodes.

Diseases

Because the pancreas is a storage depot for digestive enzymes, injury to the pancreas is potentially very dangerous. A puncture of the pancreas generally requires prompt and experienced medical intervention.

Pancreatic cancers, particularly cancer of the exocrine pancreas, remain one of the most deadly cancers, and the mortality rate is very high.

Diabetes mellitus type 1 is a chronic autoimmune disorder in which the immune system attacks the insulin-secreting cells in the pancreas.

History

The pancreas was first identified for western civilization by Herophilus (335–280 BC), a Greek anatomist and surgeon. Only a few hundred years later, Rufus of Ephesus, another Greek anatomist, gave the pancreas its name. The term "pancreas" is derived from the Greek πᾶν ("all", "whole"), and κρέας ("flesh"). – presumably because of its fleshy consistency.

Embryological development

The pancreas forms from the embryonic foregut and is therefore of endodermal origin. Pancreatic development begins [with] the formation of a ventral and dorsal anlage (or buds). Each structure communicates with the foregut through a duct. The ventral pancreatic bud becomes the head and uncinate process, and comes from the hepatic diverticulum.

Differential rotation and fusion of the ventral and dorsal pancreatic buds results in the formation of the definitive pancreas. As the duodenum rotates to the right, it carries with it the ventral pancreatic bud and common bile duct. Upon reaching its final destination, the ventral pancreatic bud fuses with the much larger dorsal pancreatic bud. At this point of fusion, the main ducts of the ventral and dorsal pancreatic buds fuse, forming the duct of Wirsung, the main pancreatic duct.

Differentiation of cells of the pancreas proceeds through two different pathways, corresponding to the dual endocrine and exocrine functions of the pancreas. In progenitor cells of the exocrine pancreas, important molecules that induce differentiation include follistatin, fibroblast growth factors, and activation of the Notch receptor system. Development of the exocrine acini progresses through three successive stages. These include the predifferentiated, protodifferentiated, and differentiated stages, which correspond to undetectable, low, and high levels of digestive enzyme activity, respectively.

Progenitor cells of the endocrine pancreas arise from cells of the protodifferentiated stage of the exocrine pancreas. Under the influence of neurogenin-3 and Isl-1, but in the absence of notch receptor signaling, these cells differentiate to form two lines of committed endocrine precursor cells. The first line, under the direction of Pax-0, forms α- and γ- cells, which produce glucagon and pancreatic polypeptides, respectively. The second line, influenced by Pax-6, produces β- and δ-cells, which secrete insulin and somatostatin, respectively.

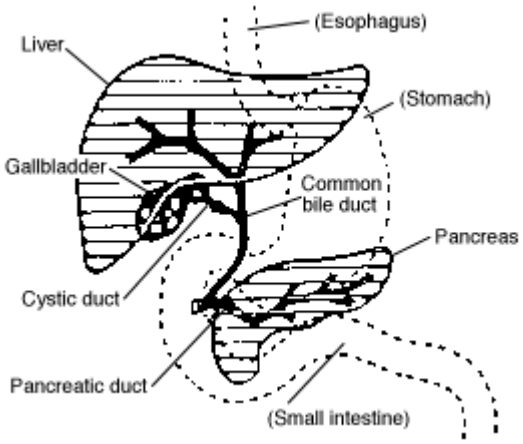
Insulin and glucagon can be detected in the human fetal circulation by the fourth or fifth month of fetal development.

In animals

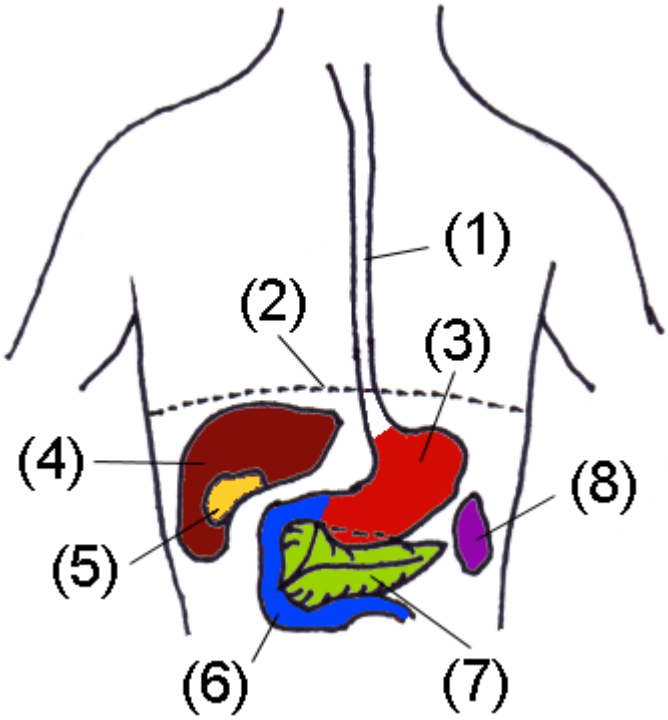
Pancreatic tissue is present in all vertebrate species, but its precise form and arrangement varies widely. There may be up to three separate pancreases, two of which arise from ventral buds, and the other dorsally. In most species (including humans), these fuse in the adult, but there are several exceptions. Even when a single pancreas is present, two or three pancreatic ducts may persist, each draining separately into the duodenum (or equivalent part of the foregut). Birds, for example, typically have three such ducts.

In teleosts, and a few other species (such as rabbits), there is no discrete pancreas at all, with pancreatic tissue being distributed diffusely across the mesentery and even within other nearby organs, such as the liver or spleen. In a few teleost species, the endocrine tissue has fused to form a distinct gland within the abdominal cavity, but otherwise it is distributed amongst the exocrine components. The most primitive arrangement, however, appears to be that of lampreys and lungfish, in which pancreatic tissue is found as a number of discrete nodules within the wall of the gut itself, with the exocrine portions being little different from other glandular structures of the intestine.

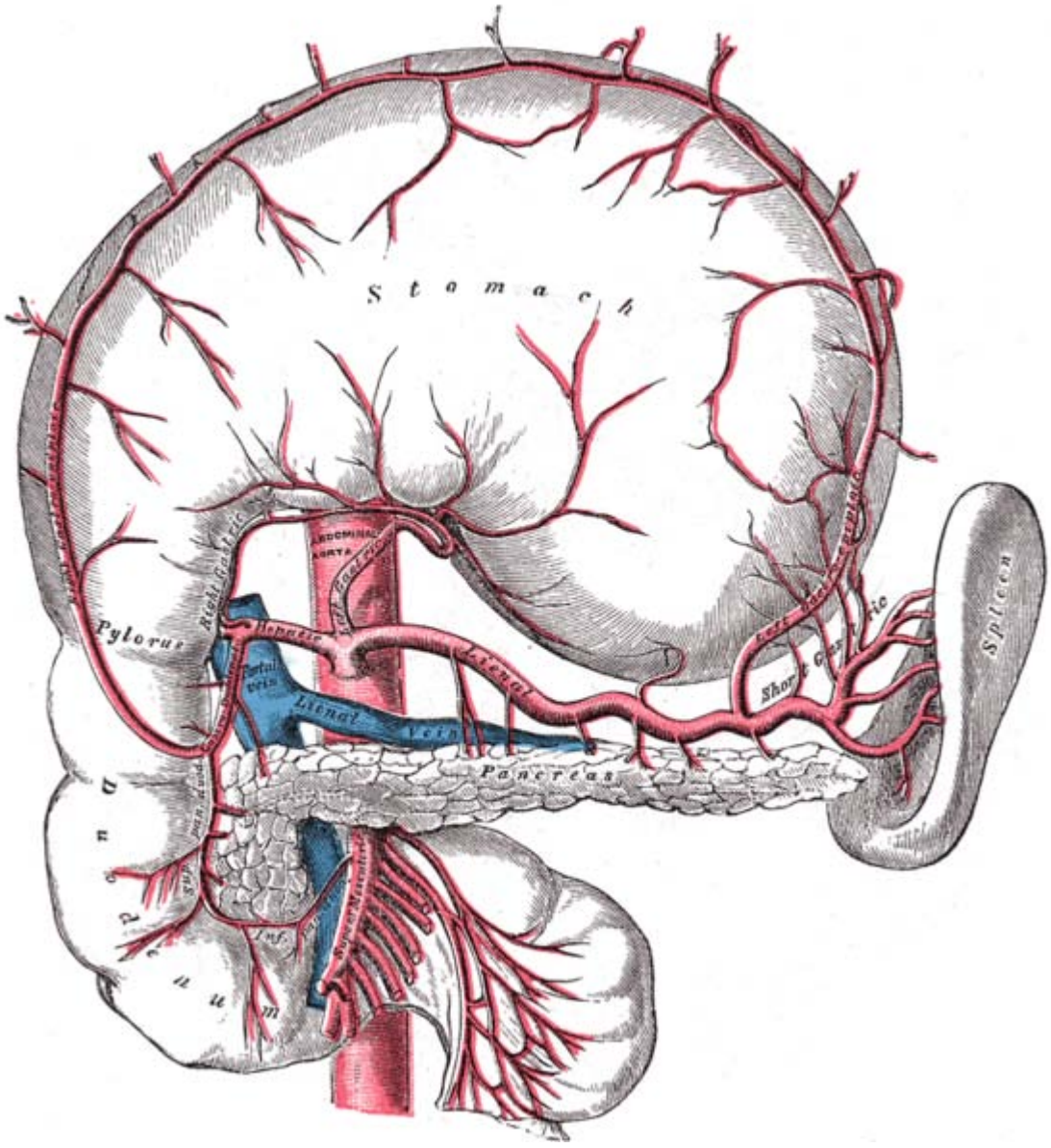
Additional images



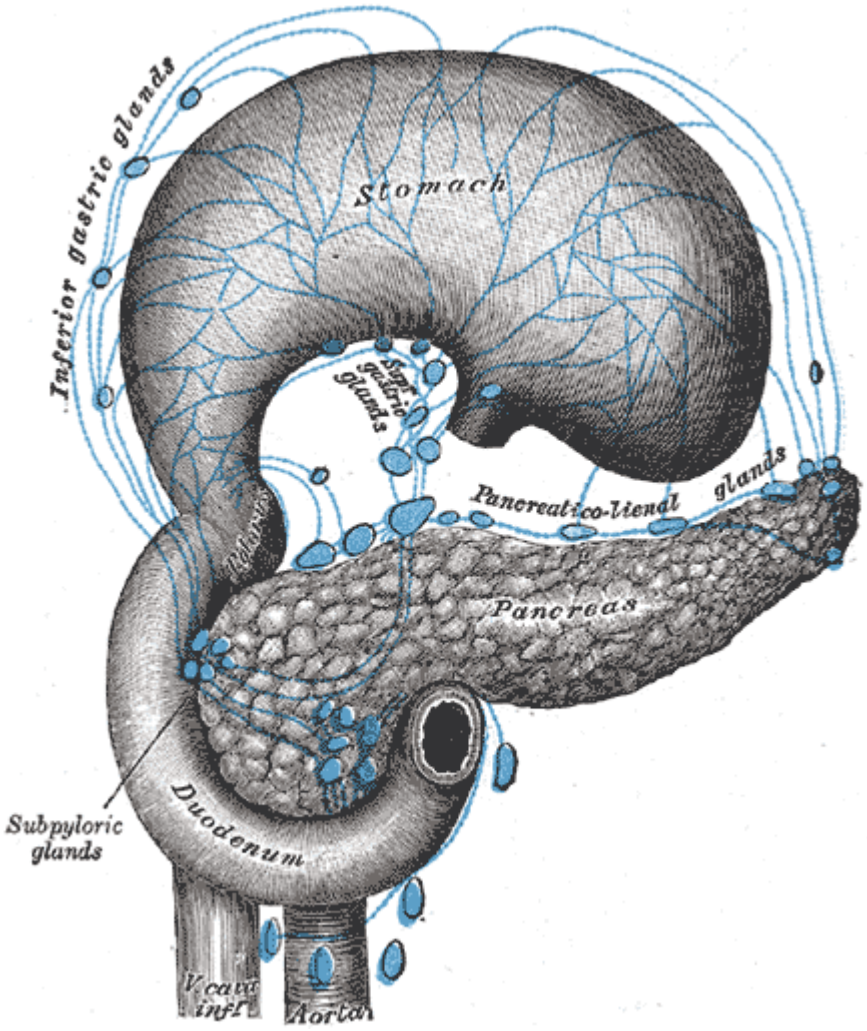
Accessory digestive system



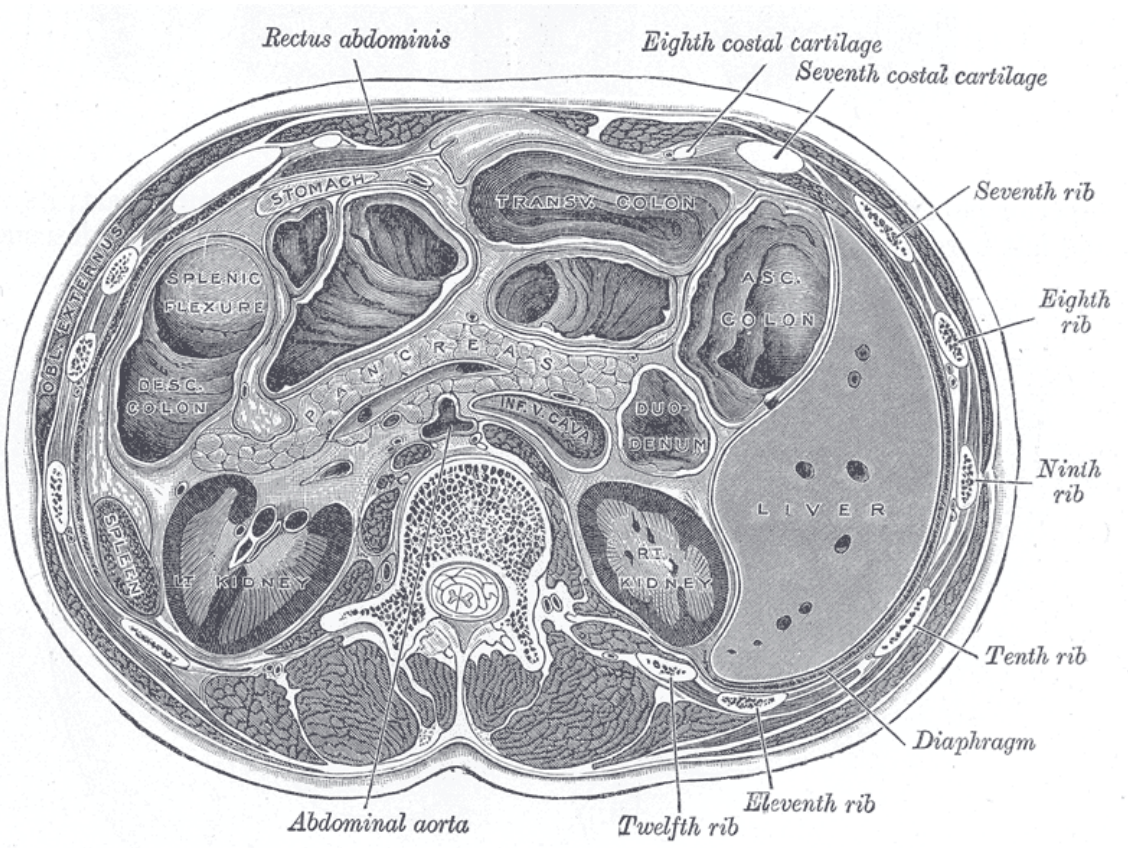
Digestive organs



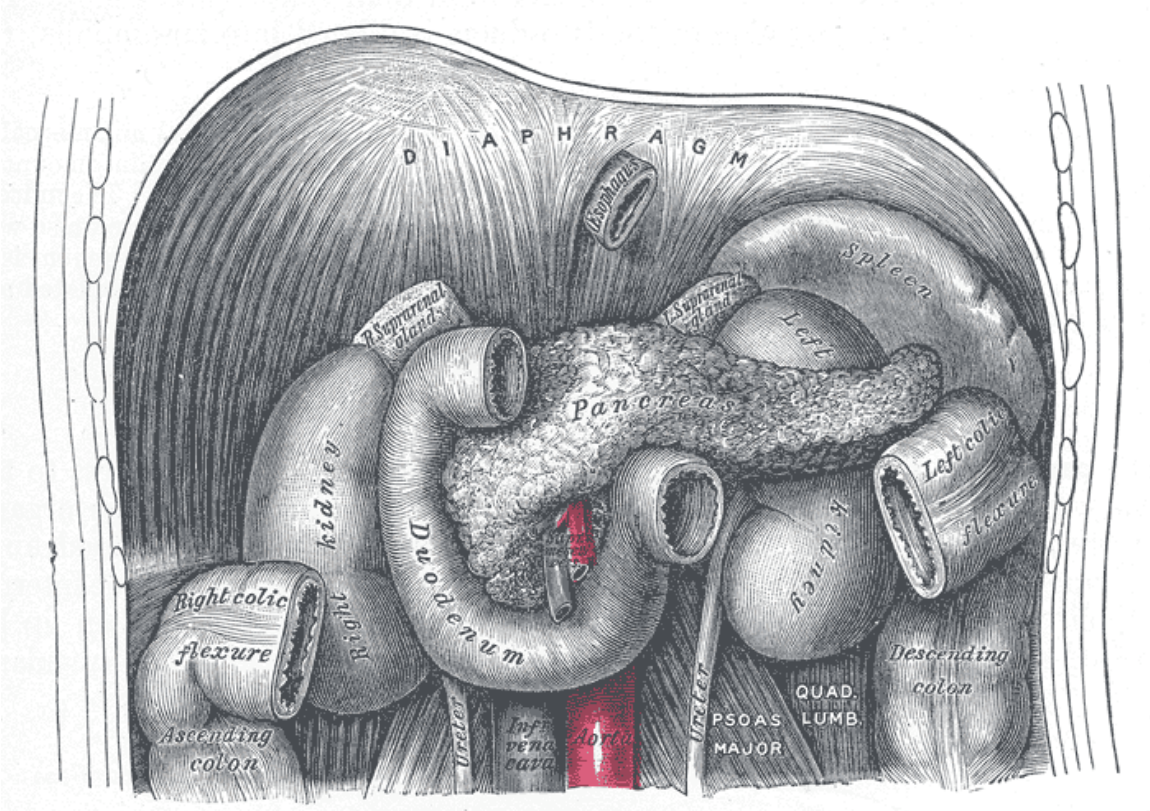
The celiac artery and its branches; the stomach has been raised and the peritoneum removed.



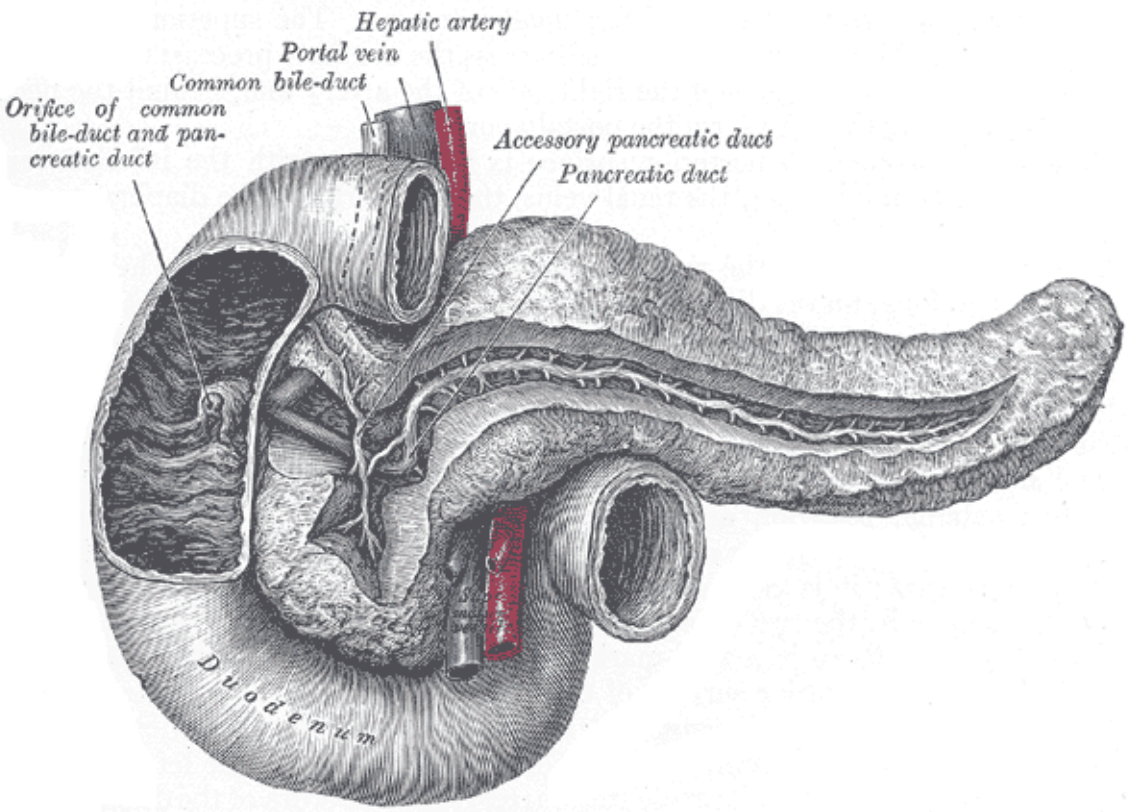
Lymphatics of stomach, etc., the stomach has been turned upward



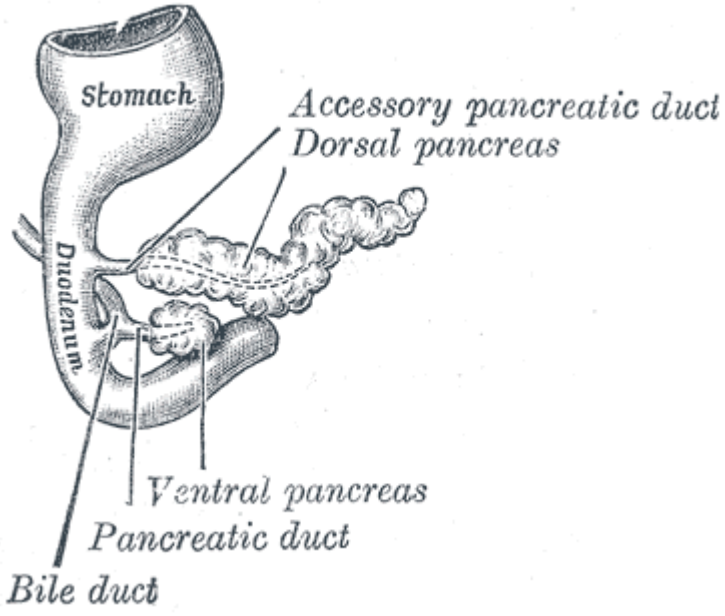
Transverse section through the middle of the first lumbar vertebra, showing the relations of the pancreas



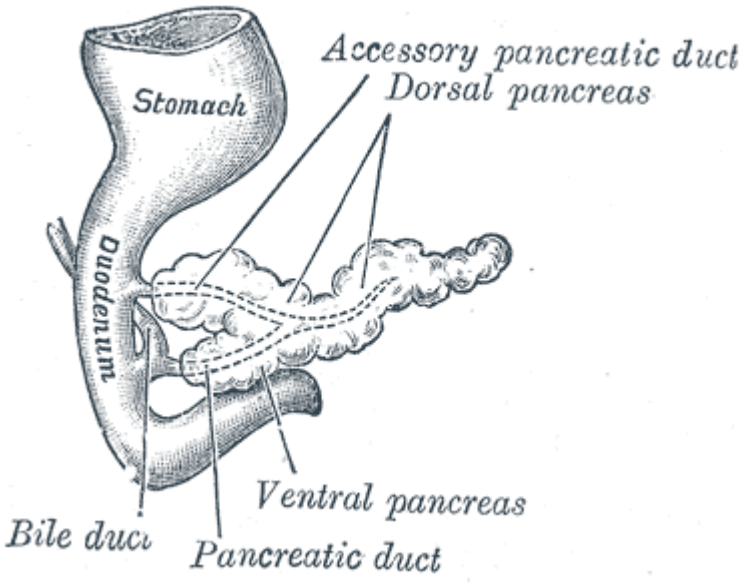
The duodenum and pancreas



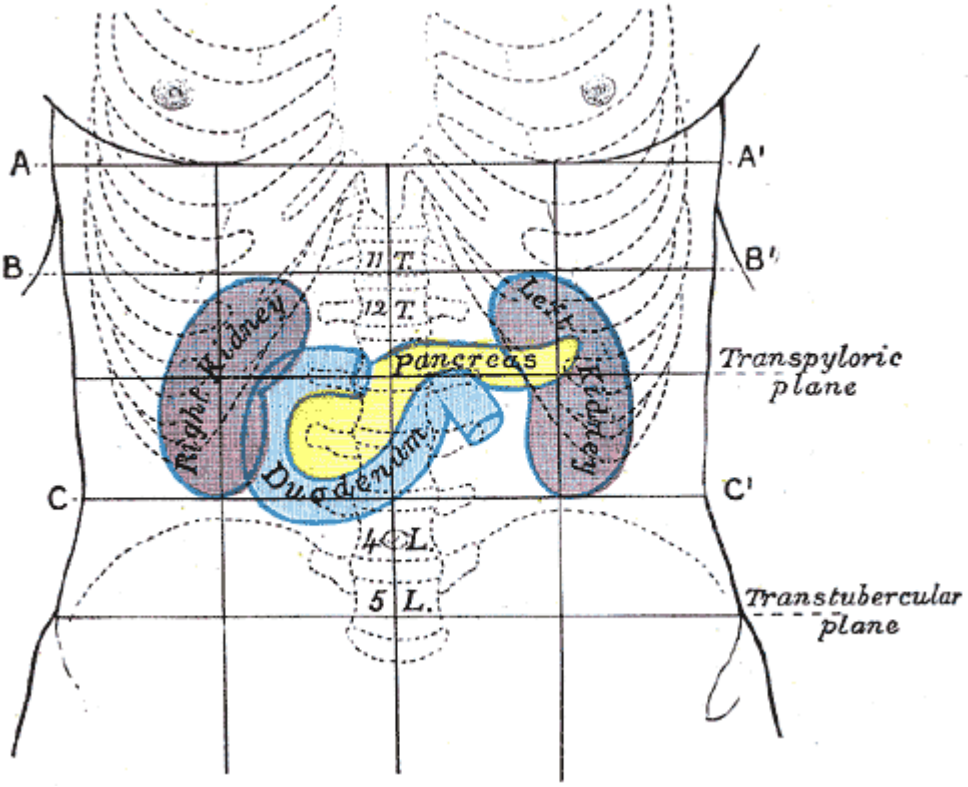
The pancreatic duct



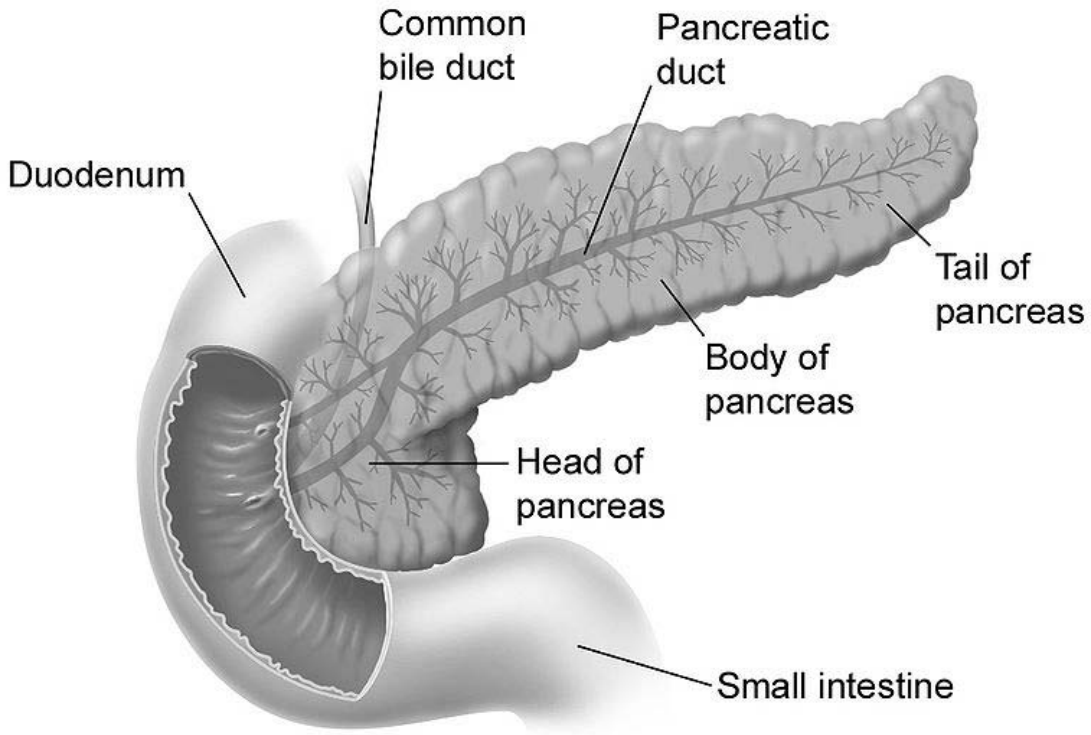
Pancreas of a human embryo of five weeks



Pancreas of a human embryo at end of sixth week



Front of abdomen, showing surface markings for duodenum, pancreas, and kidneys

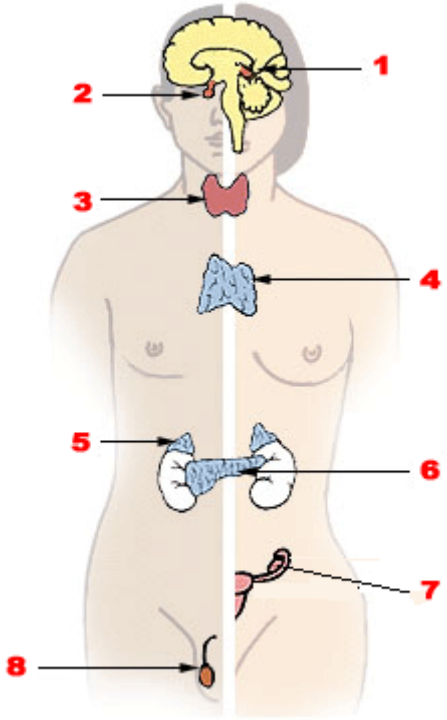


National Cancer Institute

Chapter 8

Endocrine Disease

Endocrine disease



Major endocrine glands. (Male left, female on the right.) **1.** Pineal gland **2.** Pituitary gland **3.** Thyroid gland **4.** Thymus **5.** Adrenal gland **6.** Pancreas **7.** Ovary **8.** Testes

ICD-10	E00-35
ICD-9	240-259
MeSH	D004700

Endocrine diseases are disorders of the endocrine system. The branch of medicine associated with endocrine disorders is known as endocrinology.

Types of endocrine disease

Broadly speaking, endocrine disorders may be subdivided into three groups:

1. Endocrine gland hyposecretion (leading to hormone deficiency)
2. Endocrine gland hypersecretion (leading to hormone excess)
3. Tumours (benign or malignant) of endocrine glands

Endocrine disorders are often quite complex, involving a mixed picture of hyposecretion and hypersecretion because of the feedback mechanisms involved in the endocrine system. For example, most forms of hyperthyroidism are associated with an excess of thyroid hormone and a low level of thyroid stimulating hormone.

Diagnosis of endocrine diseases

Diagnosis of endocrine diseases may be difficult; it is often not possible to directly assay hormone levels in the blood, making indirect measurements necessary. For example, diabetes mellitus is diagnosed via measurements of blood glucose rather than direct assays of plasma insulin; Cushing's syndrome is diagnosed by the dexamethasone suppression test rather than by direct assays of serum.

List of endocrine diseases

Adrenal disorders

- Adrenal insufficiency
  - Addison's disease
  - Mineralocorticoid deficiency
    - Diabetis

- Adrenal hormone excess
  - Conn's syndrome
  - Cushing's syndrome
  - GRA/Glucocorticoid remediable aldosteronism
  - Pheochromocytoma

- Congenital adrenal hyperplasia (adrenogenital syndrome)
- Adrenocortical carcinoma

Glucose homeostasis disorders

- Diabetes mellitus
  - Type 1 Diabetes
  - Type 2 Diabetes
  - Gestational Diabetes
  - Mature Onset Diabetes of the Young

- Hypoglycemia
  - Idiopathic hypoglycemia
  - Insulinoma

- Glucagonoma

Thyroid disorders

- Goitre
- Hyperthyroidism
  - Graves-Basedow disease
  - Toxic multinodular goitre
- Hypothyroidism
- Thyroiditis
  - Hashimoto's thyroiditis

- Thyroid cancer

Calcium homeostasis disorders and Metabolic bone disease

- Parathyroid gland disorders
  - Primary hyperparathyroidism
  - Secondary hyperparathyroidism
  - Tertiary hyperparathyroidism
  - Hypoparathyroidism
    - Pseudohypoparathyroidism

- Osteoporosis
- Osteitis deformans (Paget's disease of bone)
- Rickets and osteomalacia

Pituitary gland disorders

Posterior pituitary

- Diabetes insipidus

Anterior pituitary

- Hypopituitarism (or Panhypopituitarism)

- Pituitary tumors
  - Pituitary adenomas
  - Prolactinoma (or Hyperprolactinemia)
  - Acromegaly, gigantism
  - Cushing's disease

Sex hormone disorders

- Disorders of sex development or intersex disorders
  - Hermaphroditism
  - Gonadal dysgenesis
  - Androgen insensitivity syndromes

- Hypogonadism (Gonadotropin deficiency)
  - Inherited (genetic and chromosomal) disorders
    - Kallmann syndrome
    - Klinefelter syndrome
    - Turner syndrome
  - Acquired disorders
    - Ovarian failure (also known as Premature Menopause)
    - Testicular failure

- Disorders of Gender
  - Gender identity disorder

- Disorders of Puberty
  - Delayed puberty
  - Precocious puberty

- Menstrual function or fertility disorders
  - Amenorrhea
  - Polycystic ovary syndrome

Tumours of the endocrine glands not mentioned elsewhere

- Multiple endocrine neoplasia
  - MEN type 1
  - MEN type 2a
  - MEN type 2b

- Carcinoid syndrome

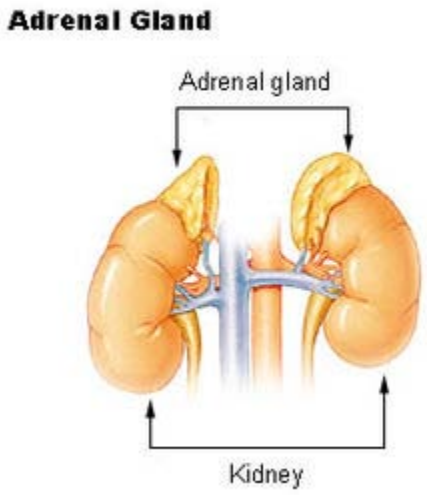
History

Timme's syndrome is a historical term for pluriglandular disease (disease involving a number of endocrine organs) first described in 1919.

Chapter 9

Adrenal Insufficiency

Adrenal insufficiency



Adrenal gland

ICD-10	E27.1-E27.4
ICD-9	255.4
eMedicine	emerg/16
MeSH	D000309

Adrenal insufficiency is a condition in which the adrenal glands, located above the kidneys, do not produce adequate amounts of steroid hormones (chemicals produced by the body that regulate organ function), primarily cortisol, but may also include impaired aldosterone production (a mineralcorticoid) which regulates sodium, potassium and water retention. Craving for salt or salty foods due to the urinary losses of sodium is common.

Addison's disease, congenital adrenal hyperplasia, and Cushing's syndrome can manifest as adrenal insufficiency. If not treated, adrenal insufficiency may result in severe abdominal pains, diarrhea, vomiting, profound muscle weakness and fatigue, depression, extremely low blood pressure (hypotension), weight loss, kidney failure, changes in

mood and personality, and shock (adrenal crisis). An adrenal crisis often occurs if the body is subjected to stress, such as an accident, injury, surgery, or severe infection; death may quickly follow.

Adrenal insufficiency can also occur when the hypothalamus or the pituitary gland, both located at the base of the skull, does not make adequate amounts of the hormones that assist in regulating adrenal function. This is called secondary adrenal insufficiency and is caused by lack of production of ACTH in the pituitary or lack of CRH in the hypothalamus.

Types

There are two major types of adrenal insufficiency.

- *Primary adrenal insufficiency* is due to impairment of the adrenal glands.
    - The most common subtype is called idiopathic or unknown cause of adrenal insufficiency.
    - Some are due to an autoimmune disease called Addison's disease or autoimmune adrenalitis.
    - Other cases are due to congenital adrenal hyperplasia or an adenoma (tumor) of the adrenal gland.

- *Secondary adrenal insufficiency* is caused by impairment of the pituitary gland or hypothalamus. These can be due to a form of cancer: a pituitary microadenoma, or a hypothalamic tumor; Sheehan's syndrome, which is associated with impairment of only the pituitary gland; or a past head injury.

- *Tertiary adrenal insufficiency* is due to hypothalamic disease and decrease in corticotropin releasing factor (CRF).

Causes

Causes of acute adrenal insufficiency are mainly Waterhouse-Friderichsen syndrome, sudden withdrawal of long-term corticosteroid therapy and stress in patients with underlying chronic adrenal insufficiency. The latter is termed critical illness–related corticosteroid insufficiency.

For chronic adrenal insufficiency, the major contributors are autoimmune adrenalitis, tuberculosis, AIDS and metastatic disease. Minor causes of chronic adrenal insufficiency are systemic amyloidosis, fungal infections, hemochromatosis and sarcoidosis.

Autoimmune adrenalitis may be part of Type 2 autoimmune polyglandular syndrome, which can include type 1 diabetes), hyperthyroidism, autoimmune thyroid disease (also known as autoimmune thyroiditis, Hashimoto's thyroiditis and Hashimoto's disease). Hypogonadism and pernicious anemia may also present with this syndrome.

Adrenoleukodystrophy can also cause adrenal insufficiency.

Adrenal Insufficiancy can also be caused is when a patient has a Craniopharyngioma which is a benign tumor that can damage the Pituitary gland causing the Adrenal Glands not to function. This would be an example of Secondary Adrenal Insufficiancy Syndrome.

Symptoms

The person may show symptoms of hypoglycemia, dehydration, weight loss, and disorientation. He or she may experience weakness, tiredness, dizziness, low blood pressure that falls further when standing (orthostatic hypotension), muscle aches, nausea, vomiting, and diarrhea. These problems may develop gradually and insidiously. Addison's can present with tanning of the skin that may be patchy or even all over the body. Characteristic sites of tanning are skin creases (e.g. of the hands) and the inside of the cheek (buccal mucosa). Goitre and vitiligo may also be present.

Diagnosis

If the person is in adrenal crisis, the ACTH stimulation test may be given. If not in crisis, cortisol, ACTH, aldosterone, renin, potassium and sodium are tested from a blood sample before the decision is made if the ACTH stimulation test needs to be performed. X-rays or CT of the adrenals may also be done. The best test for adrenal insufficiency of autoimmune origin, representing more than ninety percent of all cases in a Western population, is measurement of 21-hydroxylase autoantibodies.

Treatment

- Adrenal crisis

- Intravenous fluids
- Intravenous steroid (Solu-Cortef or Solumedrol), later hydrocortisone, prednisone or methylpredisolone tablets
- Rest

- Cortisol deficiency (primary and secondary)

- Adrenal cortical extract (usually in the form of a supplement, non prescription in the United States)
- Hydrocortisone (Cortef) (between 20 and 35 mg)
- Prednisone (Deltasone) (7.5 mg)
- Prednisolone (Delta-Cortef) (7.5 mg)
- Methylprednisolone (Medrol) (6 mg)
- Dexamethasone (Decadron) (0.25 mg, rarely up to 1 mg, but higher doses tend to cause side effects resembling Cushing's disease.)

- Mineralcorticoid deficiency (low aldosterone)
- Fludrocortisone (Florinef) (To balance sodium, potassium and increase water retention)

Simple diagnostic chart

Source of pathology	CRH	**ACTH**	DHEA	**DHEA-S**	cortisol	**aldosterone**	renin	**Na**	K	**Causes**[5]
hypothalamus (tertiary)[1]	low	low	low	low	low[3]	low	low	low	low	tumor of the hypothalamus (adenoma), antibodies, environment (i.e. toxins), head injury
pituitary (secondary)	high[2]	low	low	low	low[3]	low	low	low	low	tumor of the pituitary (adenoma), antibodies, environment, head injury, **surgical removal**[6], Sheehan's syndrome

adrenal glands (primary)[7]	high	high	high	high	low[4]	low	high	low	high	tumor of the adrenal (adenoma), stress, antibodies, environment, Addison's Disease, trauma, surgical removal (resection), miliary tuberculosis of the adrenal

1	Automatically includes diagnosis of secondary (hypopituitarism)
2	Only if CRH production in the hypothalamus is intact
3	Value doubles or more in stimulation
4	Value less than doubles in stimulation
5	Most common, does not include all possible causes
6	Usually because of very large tumor (macroadenoma)
7	Includes Addison's disease

Chapter 10

Addison's Disease

Addison's disease	
ICD-10	E27.1-E27.2
ICD-9	255.4
DiseasesDB	222
MedlinePlus	000378
eMedicine	med/42
MeSH	D000224

Addison's disease (also **chronic adrenal insufficiency**, **hypocortisolism**, and **hypocorticism**) is a rare, chronic endocrine disorder wherein the adrenal glands produce insufficient steroid hormones (glucocorticoids and often mineralocorticoids). Lifelong, continuous treatment with steroid replacement therapy is required, with regular follow-up treatment and monitoring for other health problems.

It is generally diagnosed via blood tests and medical imaging. Treatment involves replacing the absent hormones (oral hydrocortisone and fludrocortisone).

Addison's disease is named after Dr. Thomas Addison, the British physician who first described the condition in *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules* (1849). The adjective "Addisonian" describes features of the condition, and patients suffering Addison's disease. While Addison's six patients in 1855 all had adrenal tuberculosis, the term "Addison's disease" does not imply an underlying disease process.

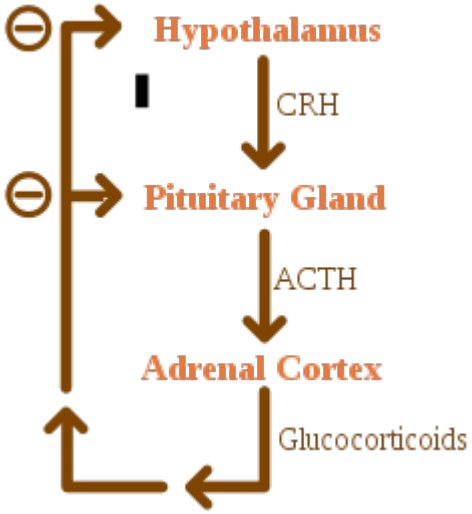
Signs and symptoms

Symptoms

The symptoms of Addison's disease develop insidiously, and it may take some time to be recognized. The most common symptoms are fatigue, lightheadedness upon standing or

while upright, muscle weakness, fever, weight loss, difficulty in standing up, anxiety, nausea, vomiting, diarrhea, headache, sweating, changes in mood and personality, and joint and muscle pains. Some have marked cravings for salt or salty foods due to the urinary losses of sodium. Affected individuals may note increased tanning since adrenal insufficiency is manifested in the skin primarily by hyperpigmentation.

Clinical signs



The negative feedback loop for glucocorticoids. Because primary hypocortisolism is manifested as a deficiency in glucocorticoid release from the adrenal cortex, increased ACTH will be released by the pituitary in order to trigger release of the absent glucocorticoid; it is because of this overstimulation of ACTH that bronzing of the skin occurs. In secondary or tertiary hypocortisolism, there is a deficiency of either CRH or ACTH release by the hypothalamus or pituitary gland, respectively. The former will manifest as no ACTH release while the latter will manifest as physiologic (normal) ACTH release; neither will cause an overproduction of ACTH.

On examination, the following may be noticed:

- Low blood pressure that falls further when standing (orthostatic hypotension)
- In long-standing Addison's Disease, the pinna of the ear may become calcified
- Most people with primary Addison's have darkening (hyperpigmentation) of the skin, including areas not exposed to the sun; characteristic sites are skin creases (e.g. of the hands), nipple, and the inside of the cheek (buccal mucosa), also old scars may darken. This occurs because melanocyte-stimulating hormone (MSH) and adrenocorticotropic hormone (ACTH) share the same precursor molecule, Pro-opiomelanocortin (POMC). After production in anterior pituitary gland, POMC gets cleaved into Gamma-MSH, ACTH and Beta-lipotropin. The subunit ACTH undergoes further cleavage to produce Alpha-MSH, the most important MSH for skin pigmentation. In secondary and tertiary forms of Addison's, skin darkening does not occur.

- Medical conditions such as type I diabetes, autoimmune thyroid disease (Hashimoto's thyroiditis and goiter) and vitiligo often occur together with Addison's (often in the setting of Autoimmune polyendocrine syndrome). Hence, symptoms and signs of any of the former conditions may also be present in the individual with Addison's. The occurrence of Addison's Disease in someone who also has Hashimoto's thyroiditis is called Schmidt syndrome.

Addisonian crisis

An "Addisonian crisis" or "adrenal crisis" is a constellation of symptoms that indicate severe adrenal insufficiency. This may be the result of either previously undiagnosed Addison's disease, a disease process suddenly affecting adrenal function (such as adrenal hemorrhage), or an intercurrent problem (e.g. infection, trauma) in someone known to have Addison's disease. It is a medical emergency and potentially life-threatening situation requiring immediate emergency treatment.

Characteristic symptoms are:

- Sudden penetrating pain in the legs, lower back or abdomen
- Severe vomiting and diarrhea, resulting in dehydration
- Low blood pressure
- Syncope (loss of consciousness and ability to stand)
- Hypoglycemia
- Confusion, psychosis, slurred speech
- Severe lethargy
- Hyperkalemia
- Hypercalcemia
- Convulsions
- Fever

Causes

Causes of adrenal insufficiency can be grouped by the way they cause the adrenals to produce insufficient cortisol. These are *adrenal dysgenesis* (the gland has not formed adequately during development), *impaired steroidogenesis* (the gland is present but is biochemically unable to produce cortisol) or *adrenal destruction* (disease processes leading to the gland being damaged).

Adrenal dysgenesis

All causes in this category are genetic, and generally very rare. These include mutations to the *SF1* transcription factor, congenital adrenal hypoplasia (AHC) due to *DAX-1* gene mutations and mutations to the ACTH receptor gene (or related genes, such as in the Triple A or Allgrove syndrome). *DAX-1* mutations may cluster in a syndrome with glycerol kinase deficiency with a number of other symptoms when *DAX-1* is deleted together with a number of other genes.

Impaired steroidogenesis

To form cortisol, the adrenal gland requires cholesterol, which is then converted biochemically into steroid hormones. Interruptions in the delivery of cholesterol include Smith-Lemli-Opitz syndrome and abetalipoproteinemia.

Of the synthesis problems, congenital adrenal hyperplasia is the most common (in various forms: 21-hydroxylase, 17α-hydroxylase, 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase), lipoid CAH due to deficiency of StAR and mitochondrial DNA mutations. Some medications interfere with steroid synthesis enzymes (e.g. ketoconazole), while others accelerate the normal breakdown of hormones by the liver (e.g. rifampicin, phenytoin).

Adrenal destruction

Autoimmune adrenalitis is the most common cause of Addison's disease in the industrialized world. Autoimmune destruction of the adrenal cortex is cause by an immune reaction against the enzyme 21-hydroxylase (a phenomenon first described in 1992). This may be isolated or in the context of autoimmune polyendocrine syndrome (APS type 1 or 2), in which other hormone-producing organs such as the thyroid and pancreas may also be affected.

Adrenal destruction is also a feature of adrenoleukodystrophy (ALD), and when the adrenal glands are involved in metastasis (seeding of cancer cells from elsewhere in the body, especially lung), hemorrhage (e.g. in Waterhouse-Friderichsen syndrome or antiphospholipid syndrome), particular infections (tuberculosis, histoplasmosis, coccidioidomycosis), deposition of abnormal protein in amyloidosis.

Diagnosis

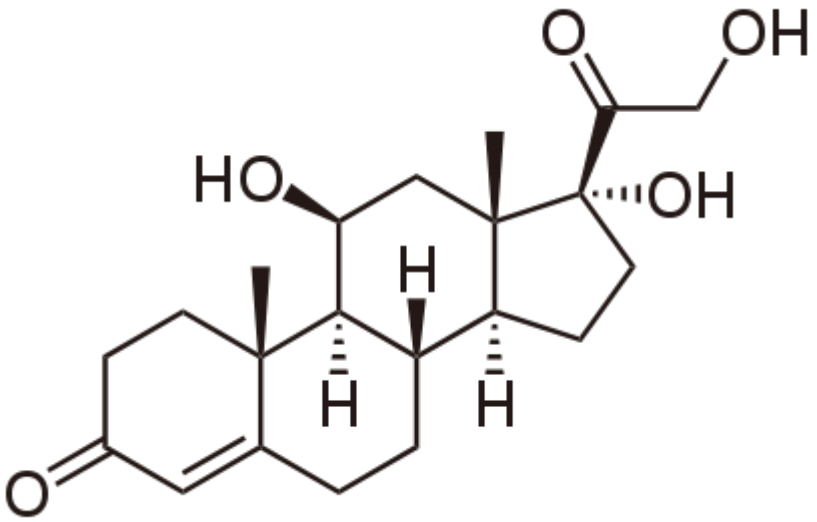
Suggestive features

Routine investigations may show:

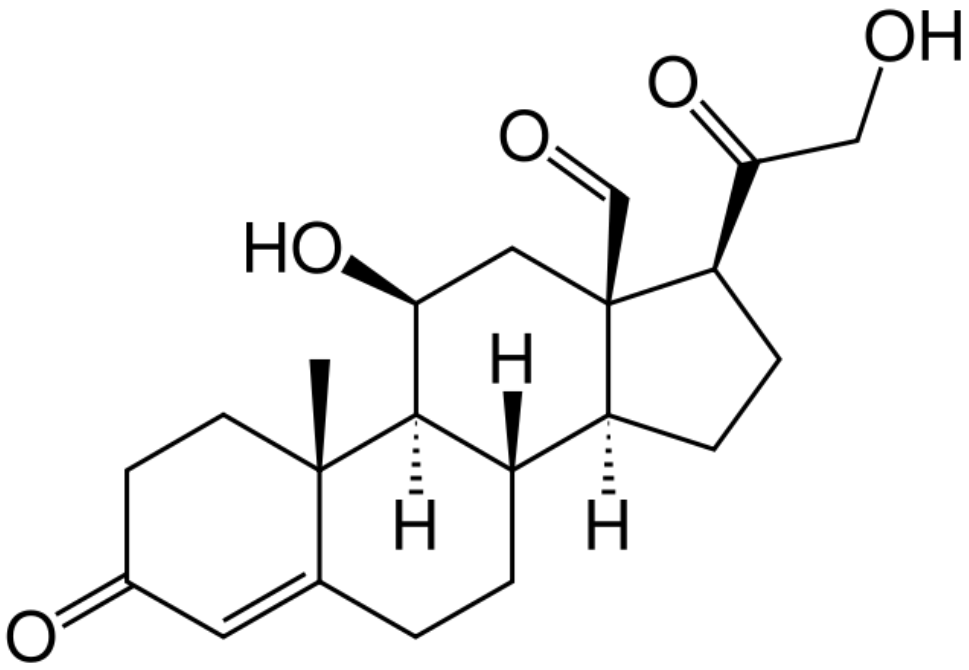
- Hypercalcemia
- Hypoglycemia, low blood sugar (worse in children due to loss of glucocorticoid's glucogenic effects)
- Hyponatraemia (low blood sodium levels), due both to a deficiency in Aldosterone (a mineralocorticoid) dependant Sodium retention and also the effect of Corticotropin-releasing hormone to stimulate secretion of ADH
- Hyperkalemia (raised blood potassium levels), due to loss of production of the hormone aldosterone
- Eosinophilia and lymphocytosis (increased number of eosinophils or lymphocytes, two types of white blood cells)
- Metabolic acidosis (increased blood acidity), also due to loss of the hormone aldosterone because sodium reabsorption in the distal tubule is linked with

acid/hydrogen ion (H+) secretion. Low levels of aldosterone stimulation of the renal distal tubule leads to sodium wasting in the urine and H+ retention in the serum.

Testing



Cortisol



Aldosterone

In suspected cases of Addison's disease, one needs to demonstrate that adrenal hormone levels are low even after appropriate stimulation (called the ACTH stimulation test) with synthetic pituitary ACTH hormone tetracosactide . Two tests are performed, the short and the long test.

The short test compares blood cortisol levels before and after 250 micrograms of tetracosactide (IM/IV) is given. If, one hour later, plasma cortisol exceeds 170 nmol/L and has risen by at least 330 nmol/L to at least 690 nmol/L, adrenal failure is excluded. If the short test is abnormal, the long test is used to differentiate between primary adrenal failure and secondary adrenocortical failure.

The long test uses 1 mg tetracosactide (IM). Blood is taken 1, 4, 8, and 24 hours later. Normal plasma cortisol level should reach 1000 nmol/L by 4 hours. In primary Addison's disease, the cortisol level is reduced at all stages whereas in secondary corticoadrenal insufficiency, a delayed but normal response is seen.

Other tests that may be performed to distinguish between various causes of hypoadrenalism are renin and adrenocorticotropic hormone levels, as well as medical imaging - usually in the form of ultrasound, computed tomography or magnetic resonance imaging (MRI).

Adrenoleukodystrophy, and the milder form, adrenomyeloneuropathy, cause adrenal insufficiency combined with neurological symptoms. These diseases are estimated to be the cause of adrenal insufficiency in approximately 35% of male patients with idiopathic Addison’s disease and should be considered in the differential diagnosis of any male with adrenal insufficiency. Diagnosis is made by a blood test to detect very long chain fatty acids (VLCFA).

Treatment

Maintenance

Treatment for Addison's disease involves replacing the missing cortisol, sometimes in the form of hydrocortisone tablets, or prednisone tablets in a dosing regimen that mimics the physiological concentrations of cortisol. Alternatively one quarter as much prednisolone may be used for equal glucocorticoid effect as hydrocortisone. Treatment must usually be continued for life. In addition, many patients require fludrocortisone as replacement for the missing aldosterone. Caution must be exercised when the person with Addison's disease becomes unwell with infection, has surgery or other trauma, or becomes pregnant. In such instances, their replacement glucocorticoids, whether in the form of hydrocortisone, prednisone, prednisolone, or other equivalent, often need to be increased. Inability to take oral medication may prompt hospital attendance to receive steroids intravenously. People with Addison's are often advised to carry information on them (e.g. in the form of a MedicAlert bracelet) for the attention of emergency medical services personnel who might need to attend to their needs.

Crisis

Standard therapy involves intravenous injections of glucocorticoids and large volumes of intravenous saline solution with dextrose, a type of sugar. This treatment usually brings rapid improvement. When the patient can take fluids and medications by mouth, the amount of glucocorticoids is decreased until a maintenance dose is reached. If aldosterone is deficient, maintenance therapy also includes oral doses of fludrocortisone acetate.

Epidemiology

The frequency rate of Addison's disease in the human population is sometimes estimated at roughly 1 in 100,000. Some research and information sites put the number closer to 40-60 cases per 1 million population. (1/25,000-1/16,600) (Determining accurate numbers for Addison's is problematic at best and some incidence figures are thought to be underestimates.) Addison's can afflict persons of any age, gender, or ethnicity, but it typically presents in adults between 30 and 50 years of age. Research has shown no significant predispositions based on ethnicity.

Prognosis

With proper medication, patients can expect to live a healthy and normal life.

A person with adrenal insufficiency should always carry identification stating their condition in case of an emergency. The card should alert emergency personnel about the need to inject 100 mg of cortisol if its bearer is found severely injured or unable to answer questions. The card should also include the doctor's name and telephone number and the name and telephone number of the nearest relative to be notified. When traveling, a needle, syringe, and an injectable form of cortisol should be carried for emergencies. A person with Addison's disease also should know how to increase medication during periods of stress or mild upper respiratory infections. Immediate medical attention is needed when severe infections, vomiting, or diarrhea occur, as these conditions can precipitate an Addisonian crisis. A patient who is vomiting may require injections of hydrocortisone, since oral hydrocortisone supplements cannot be adequately metabolised.

Famous Addisonians

United States president John F. Kennedy (1961-63), probably the single most famous case of Addison's Disease

- United States President John F. Kennedy was one of the best-known Addison's disease sufferers. He was possibly one of the first Addisonians to survive major surgery. There was substantial secrecy surrounding his health during his years as president, and the 25th amendment to the U.S. constitution was introduced at least in part as a result of this secrecy.
- Eunice Kennedy Shriver, one of John F. Kennedy's sisters, was believed to have Addison's disease as well.
- Popular singer Helen Reddy.
- Scientist Eugene Merle Shoemaker, co-discoverer of the Comet Shoemaker-Levy 9.
- French Carmelite nun and religious writer Blessed Elizabeth of the Trinity
- American artist Ferdinand Louis Schlemmer died from Addison's disease.
- Some have suggested that Jane Austen was an *avant la lettre* case, but others have disputed this.
- According to Dr. Carl Abbott, a Canadian medical researcher, Charles Dickens may also have been affected.

- Osama bin Laden may be an Addisonian. Lawrence Wright noted that bin Laden manifests all the key symptoms, such as "low blood pressure, weight loss, muscle fatigue, stomach irritability, sharp back pains, dehydration, and an abnormal craving for salt". Bin Laden is known to have consumed large amounts of the drug Sulbutiamine to treat his symptoms.

In other animals

The condition has been diagnosed in all breeds of dogs. In general, it is underdiagnosed, and one must clinically suspect it as an underlying disorder for many presenting complaints. Females are overrepresented, and the disease often appears in middle age (4–7 years), although any age or gender may be affected. Genetic continuity between dogs and humans helps to explain the occurrence of Addison's disease in both species.

Hypoadrenocorticism is treated with fludrocortisone or a monthly injection called Percorten V (desoxycorticosterone pivlate (DOCP)) and prednisone. Routine blood work is necessary in the initial stages until a maintenance dose is established.

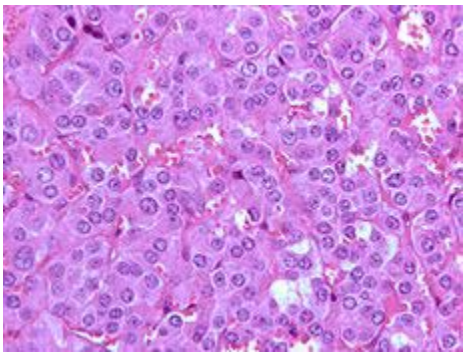
Most of the medications used in the therapy of hypoadrenocorticism cause excessive thirst and urination, making it important to provide enough drinking water.

If the owner knows about an upcoming stressful situation (shows, traveling etc.), patients generally need an increased dose of prednisone to help deal with the added stress. Avoidance of stress is important for dogs with hypoadrenocorticism.

Chapter 11

Pheochromocytoma

Pheochromocytoma



High magnification micrograph of a **pheochromocytoma** showing the nested arrangement of cells (Zellballen) and stippled chromatin. H&E stain.

ICD-10	C74.1
ICD-9	255.6
ICD-O:	M8700/0
OMIM	171300
DiseasesDB	9912
MedlinePlus	000340
eMedicine	med/1816 radio/552 ped/1788
MeSH	D010673

A **pheochromocytoma** or **phaeochromocytoma** (**PCC**) is a neuroendocrine tumor of the medulla of the adrenal glands (originating in the chromaffin cells), or extra-adrenal chromaffin tissue that failed to involute after birth and secretes excessive amounts of catecholamines, usually adrenaline (epinephrine) if in the adrenal gland and not extra-adrenal, and noradrenaline (norepinephrine). Extra-adrenal paragangliomas (often

described as extra-adrenal pheochromocytomas) are closely related, though less common, tumors that originate in the ganglia of the sympathetic nervous system and are named based upon the primary anatomical site of origin.

Signs and symptoms

The signs and symptoms of a pheochromocytoma are those of sympathetic nervous system hyperactivity, including:

- Skin sensations
- Flank pain
- Elevated heart rate
- Elevated blood pressure, including paroxysmal (sporadic, episodic) high blood pressure, which sometimes can be more difficult to detect; another clue to the presence of pheochromocytoma is orthostatic hypotension (a fall in systolic blood pressure greater than 20 mmHg or a fall in diastolic blood pressure greater than 10 mmHg on making the patient stand)
- Palpitations
- Anxiety often resembling that of a panic attack
- Diaphoresis (excessive sweating)
- Headaches
- Pallor
- Weight loss
- Localized amyloid deposits found microscopically
- Elevated blood glucose level (due primarily to catecholamine stimulation of lipolysis (breakdown of stored fat) leading to high levels of free fatty acids and the subsequent inhibition of glucose uptake by muscle cells. Further, stimulation of beta-adrenergic receptors leads to glycogenolysis and gluconeogenesis and thus elevation of blood glucose levels).

A pheochromocytoma can also cause resistant arterial hypertension. A pheochromocytoma can be fatal if it causes malignant hypertension, or severely high blood pressure. This hypertension is not well controlled with standard blood pressure medications.

Not all patients experience all of the signs and symptoms listed. The most common presentation is headache, excessive sweating, and increased heart rate, with the attack subsiding in less than one hour.

Tumors may grow very large, but most are smaller than 10 cm.

Statistics

- About 10% of adrenal cases are bilateral (suggesting hereditary disease)
- About 10% of adrenal cases occur in children (also suggesting hereditary disease)

- About 15% are extra-adrenal (located in any orthosympathetic tissue): of these 9% are in the abdomen and 1% are located elsewhere. Some extra-adrenal pheochromocytomas are probably actually paragangliomas, but the distinction is only possible after surgical resection.
- About 11.1% of adrenal cases are malignant, but this rises to 30% for extra-adrenal cases
- About 26% are hereditary (earlier opinion had 10%)
- About 3% recur after being resected
- About 14% of affected individuals do not have arterial hypertension (Campbell's Urology)

Cause

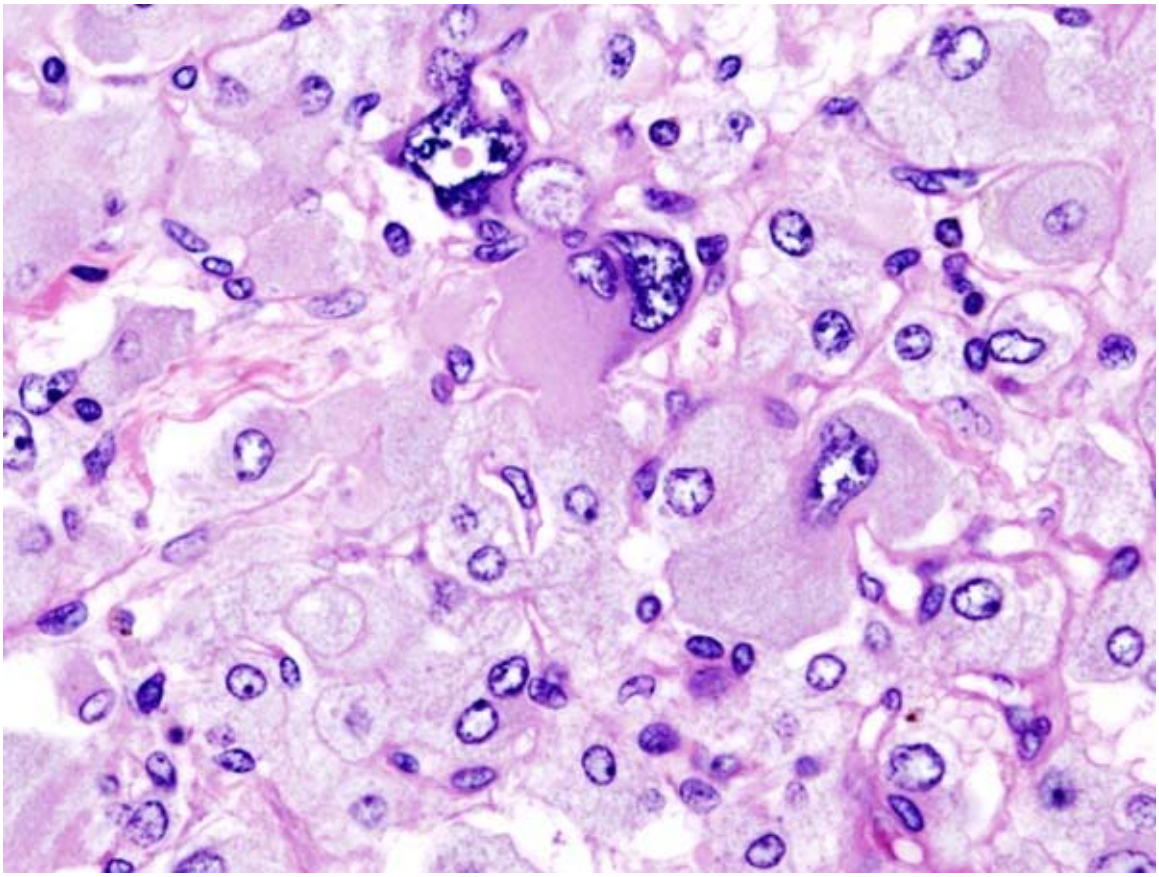
Up to 25% of pheochromocytomas may be familial. Mutations of the genes *VHL*, *RET*, *NF1*, *SDHB* and *SDHD* are all known to cause familial pheochromocytoma/extra-adrenal paraganglioma.

Pheochromocytoma is a tumor of the multiple endocrine neoplasia syndrome, type IIA and type IIB (also known as MEN IIA and MEN IIB, respectively). The other component neoplasms of that syndrome include parathyroid adenomas, and medullary thyroid cancer. Mutations in the autosomal RET proto-oncogene drives these malignancies . Common mutations in the RET oncogene may also account for medullary sponge kidney as well.

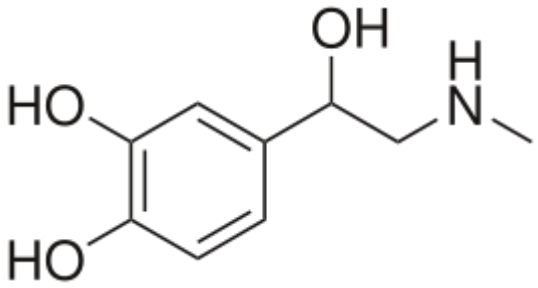
Pheochromocytoma linked to MEN II can be caused by RET oncogene mutations. Both syndromes are characterized by pheochromocytoma as well as thyroid cancer (thyroid medullary carcinoma). MEN IIA also presents with hyperparathyroidism, while MEN IIB also presents with mucosal neuroma. It is now postulated that Lincoln suffered from MEN IIB, rather than Marfan's syndrome as previously thought, though this is uncertain.

Pheochromocytoma is also associated with neurofibromatosis.

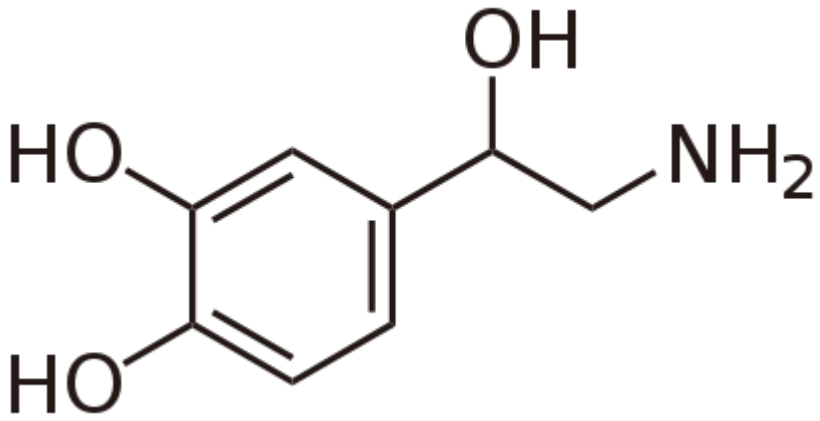
Diagnosis



Histopathology of adrenal pheochromocytoma. Adrenectomy specimen.



Epinephrin



Norepinephrine

The diagnosis can be established by measuring catecholamines and metanephrines in plasma (blood) or through a 24-hour urine collection. Care should be taken to rule out other causes of adrenergic (adrenalin-like) excess like hypoglycemia, stress, exercise, and drugs affecting the catecholamines like stimulants, methyldopa, dopamine agonists, or ganglion blocking antihypertensives. Various foodstuffs (e.g. vanilla ice cream) can also affect the levels of urinary metanephrine and VMA (vanillylmandelic acid). Imaging by computed tomography or a T2 weighted MRI of the head, neck, and chest, and abdomen can help localize the tumor. Tumors can also be located using Iodine-123 meta-iodobenzylguanidine (I123 MIBG) imaging.

Pheochromocytomas occur most often during young-adult to mid-adult life.

These tumors can form a pattern with other endocrine gland cancers which is labeled multiple endocrine neoplasia (MEN). Pheochromocytoma may occur in patients with MEN 2 and MEN 3 (MEN 2B). Von Hippel Lindau patients may also develop these tumors.

Patients experiencing symptoms associated with pheochromocytoma should be aware that it is rare. However, it often goes undiagnosed until autopsy; therefore patients might wisely choose to take steps to provide a physician with important clues, such as recording whether blood pressure changes significantly during episodes of apparent anxiety.

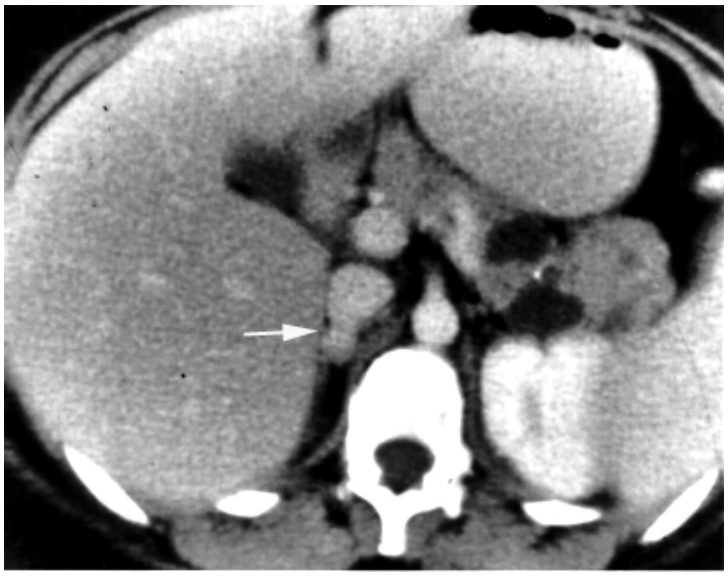
Testing

- **Blood Tests**: analysis of free metanephrine in blood plasma. High levels are indicative of pheochromocytoma

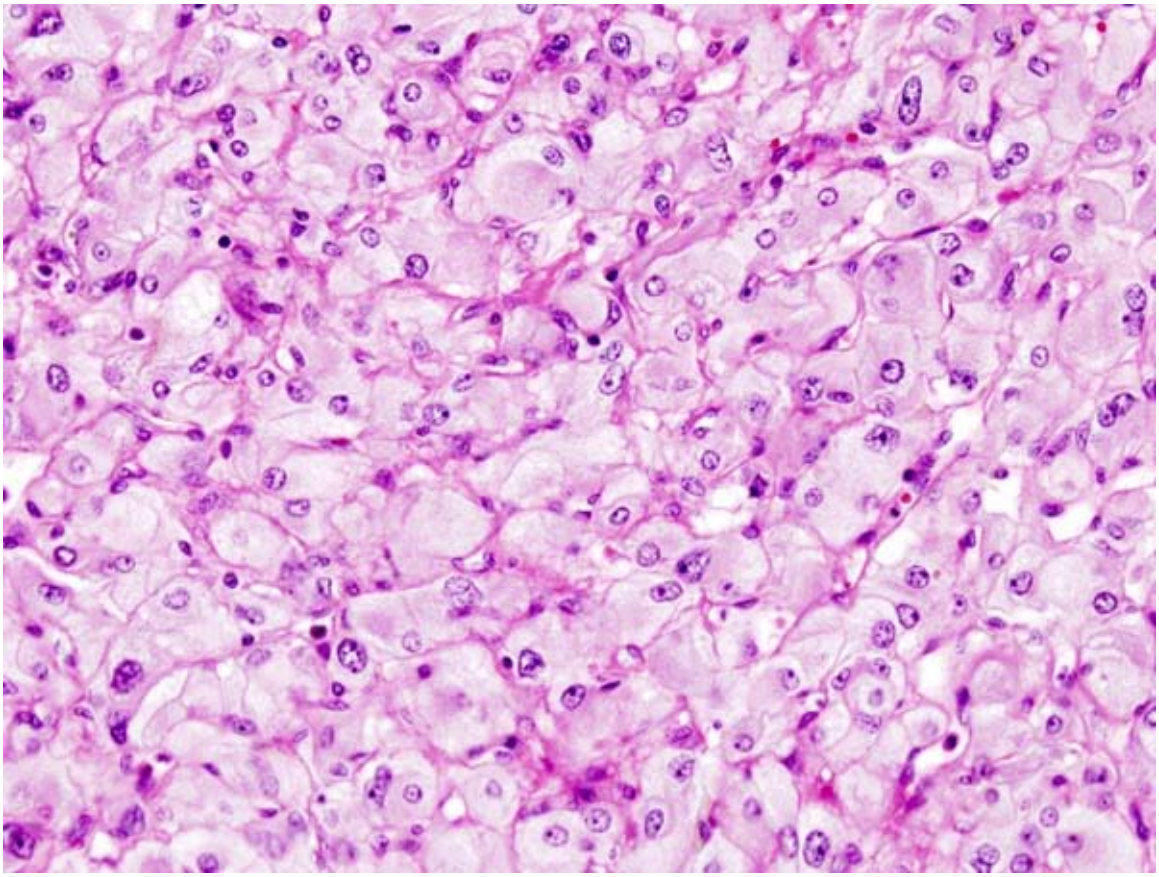
- **Urine Tests**: Although this test is slightly less effective than plasma testing it is still considered highly effective in diagnosis. Usually the metabolites of norepinephrine and epinephrine, vanillylmandelic acid (VMA) and homovanillic

acid (HVA) are found in relatively small amounts in normal humans. The increased intermittent excretion of these metabolites is indicative of the disease, but does not completely rule out other diseases which may cause the same excretion values.

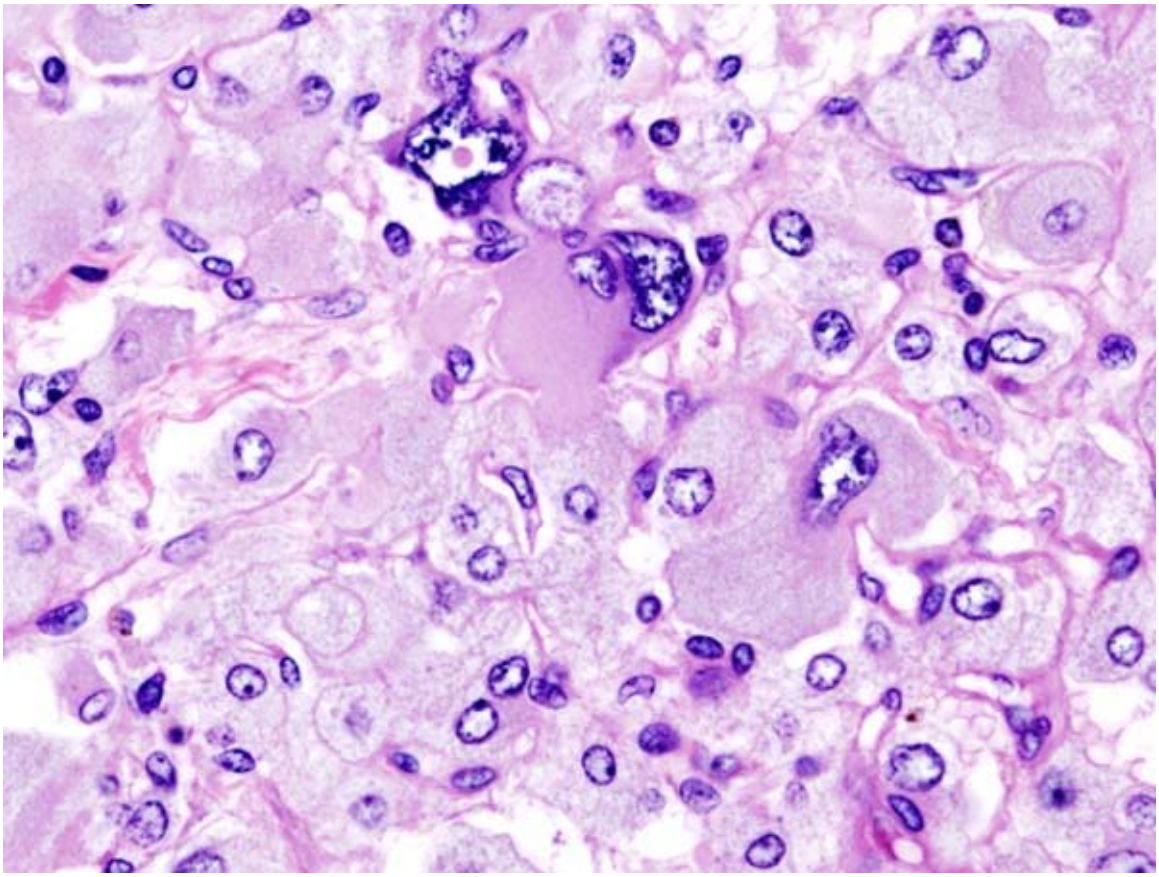
- **Other Tests**:
    - One diagnostic test used in the past for a pheochromocytoma is to administer clonidine, a centrally-acting alpha-2 agonist used to treat high blood pressure. Clonidine mimics catecholamines in the brain, causing it to reduce the activity of the sympathetic nerves controlling the adrenal medulla. A healthy adrenal medulla will respond to the clonidine suppression test by reducing catecholamine production; the lack of a response is evidence of pheochromocytoma.
    - Another test is for the clinician to press gently on the adrenal gland. A pheochromocytoma will often release a burst of catecholamines, with the associated signs and symptoms quickly following. This method is NOT recommended because of possible complications arising from a potentially massive release of catecholamines.
    - **Warning**: Testing via histamine and tyramine is dangerous and should not be used.



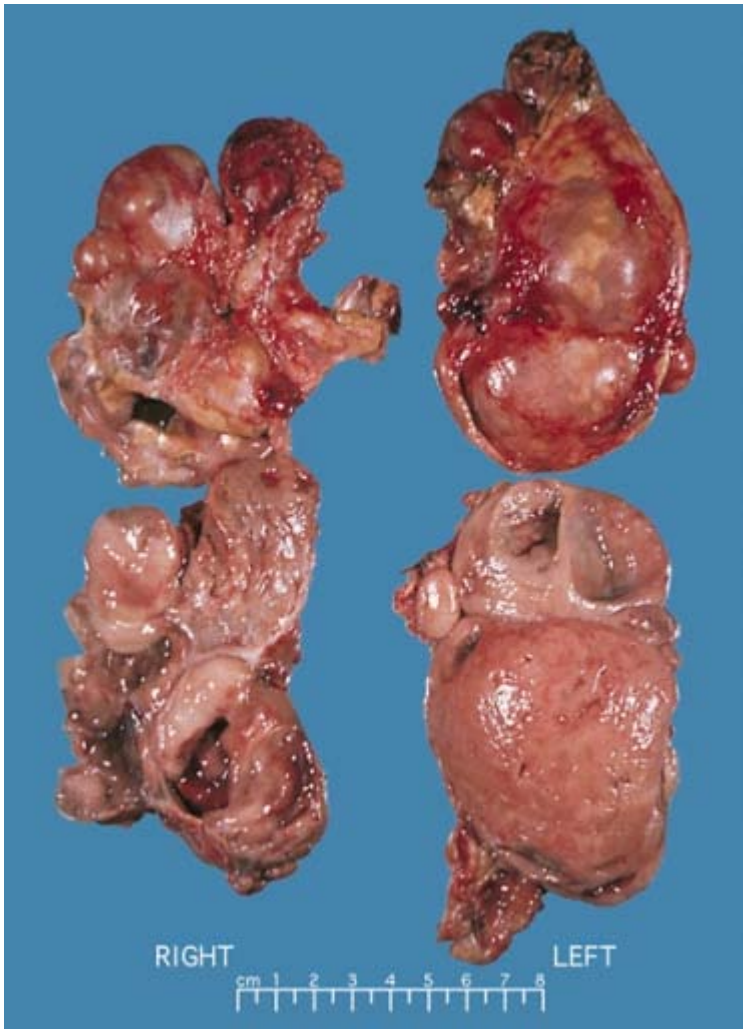
Pheochromocytoma. CT abdomen.



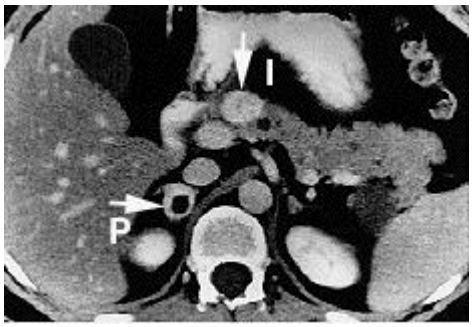
Micrograph of pheochromocytoma



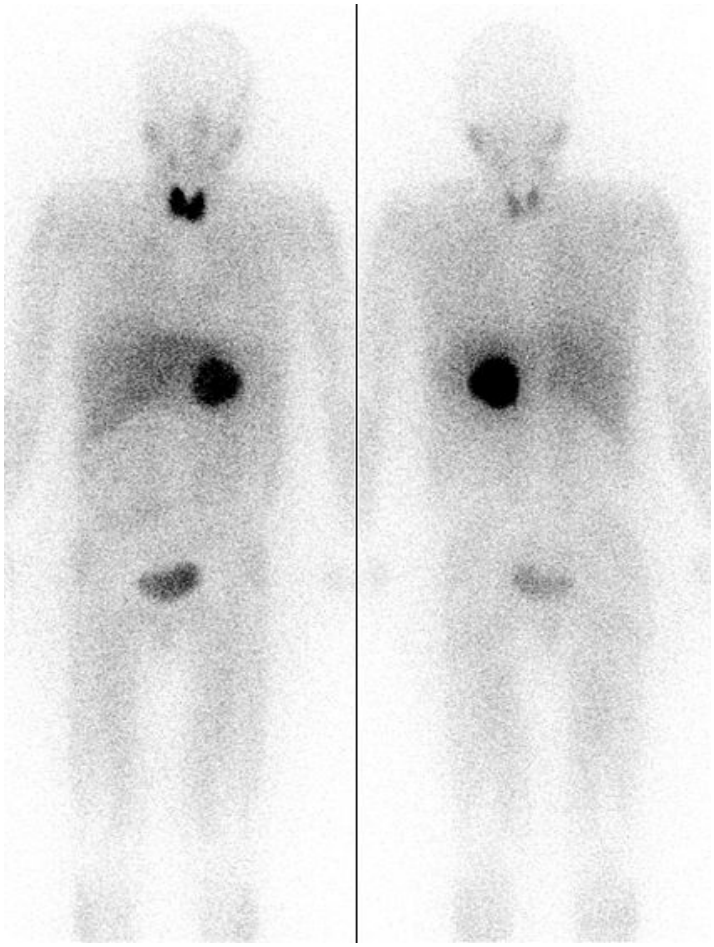
Micrograph of pheochromocytoma



Bilateral pheochromocytoma in MEN2



Pheochromocytoma. CT abdomen.



Pheochromocytoma. MIBG scintigraphy.

Tumor location

In adults, approximately 80% of pheochromocytomas are unilateral and solitary, 10% are bilateral, and 10% are extra-adrenal. In children, a fourth of tumors are bilateral, and an additional fourth are extra-adrenal. Solitary lesions inexplicably favor the right side. Although pheochromocytomas may grow to large size (>3 kg), most weigh <100 g and are <10 cm in diameter. Pheochromocytomas are highly vascular.

The tumors are made up of large, polyhedral, pleomorphic chromaffin cells. Fewer than 10% of these are malignant. As with several other endocrine tumors, malignancy cannot be determined from the histologic appearance; tumors that contain large number of aneuploid or tetraploid cells, as determined by flow cytometry, are more likely to recur. Local invasion of surrounding tissues or distant metastases indicate malignancy.

Extra-adrenal Pheochromocytomas: Extra-adrenal pheochromocytomas usually weigh 20 to 40 g and are <5 cm in diameter. Most are located within the abdomen in association with the celiac, superior mesenteric, inferior mesenteric ganglia and Organ of Zuckerkandl. Approximately 10% are in the thorax, 1% are within the urinary bladder,

and less than 3% are in the neck, usually in association with the sympathetic ganglia or the extracranial branches of the ninth cranial nerves.

Differential diagnosis

The differential diagnoses of pheochromocytoma include:

- Anxiety disorders
- Paragangliomas
- Essential hypertension
- Hyperthyroidism
- Insulinoma
- Mercury poisoning
- Paroxysmal supraventricular tachycardia
- Renovascular hypertension
- Carcinoid

Treatment

Surgical resection of the tumor is the treatment of first choice, either by open laparotomy or else laparoscopy. Given the complexity of perioperative management, and the potential for catastrophic intra and postoperative complications, such surgery should be performed only at centers experienced in the management of this disorder. In addition to the surgical expertise that such centers can provide, they will also have the necessary endocrine and anesthesia resources. It may also be necessary to carry out adrenalectomy, a complete surgical removal of the affected adrenal gland(s).

Either surgical option requires prior treatment with the non-specific and irreversible alpha adrenoceptor blocker Phenoxybenzamine (Irreversible blockade is important because a massive release of catecholamines from the tumor may overcome a reversible blockade). Doing so permits the surgery to proceed while minimizing the likelihood of severe intraoperative hypertension (as might occur when the tumor is manipulated). Some authorities would recommend that a combined alpha/beta blocker such as labetalol also be given in order to slow the heart rate. Regardless, a "pure" beta blocker such as atenolol must never be used in the presence of a pheochromocytoma due to the risk of such treatment leading to unopposed alpha agonism and, thus, severe and potentially refractory hypertension.

The patient with pheochromocytoma is invariably volume depleted. In other words, the chronically elevated adrenergic state characteristic of an untreated pheochromocytoma leads to near-total inhibition of renin-angiotensin activity, resulting in excessive fluid loss in the urine and thus reduced blood volume. Hence, once the pheochromocytoma has been resected, thereby removing the major source of circulating catecholamines, a situation arises where there is both very low sympathetic activity and volume depletion. This can result in profound hypotension. Therefore, it is usually advised to "salt load" pheochromocytoma patients before their surgery. This may consist of simple

interventions such as consumption of high salt food pre-operatively, direct salt replacement or through the administration of intravenous saline solution.

Epidemiology

Pheochromocytoma is seen in between 2–8 in 1,000,000, with approximately 1000 cases diagnosed in United States yearly. It mostly occurs in young or middle age adults, though presents earlier in hereditary cases.

History

In 1886, Fränkel made the first description of a patient with pheochromocytoma, however the term was first coined by Ludwig Pick, a pathologist, in 1912. In 1926, Roux (in Switzerland) and Mayo (in U.S.A.) were the first surgeons to remove pheochromocytomas.

Chapter 12

Diabetes Mellitus

Diabetes mellitus

Universal blue circle symbol for diabetes.

ICD-10	E10.–E14.
ICD-9	250
MedlinePlus	001214
eMedicine	med/546 emerg/134
MeSH	*C18.452.394.750*

Diabetes mellitus, often simply referred to as **diabetes**—is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger).

There are three main types of diabetes:

- Type 1 diabetes: results from the body's failure to produce insulin, and presently requires the person to inject insulin. (Also referred to as *insulin-dependent* diabetes mellitus, *IDDM* for short, and *juvenile* diabetes.)
- Type 2 diabetes: results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. (Formerly referred to as *non-insulin-dependent* diabetes mellitus, *NIDDM* for short, and *adult-onset* diabetes.)
- Gestational diabetes: is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of type 2 DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

All forms of diabetes have been treatable since insulin became available in 1921, and type 2 diabetes may be controlled with medications. Both type 1 and 2 are chronic conditions that usually cannot be cured. Pancreas transplants have been tried with limited success in type 1 DM; gastric bypass surgery has been successful in many with morbid obesity and type 2 DM. Gestational diabetes usually resolves after delivery. Diabetes without proper treatments can cause many complications. Acute complications include hypoglycemia, diabetic ketoacidosis, or nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, chronic renal failure, retinal damage. Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as smoking cessation and maintaining a healthy body weight.

As of 2000 at least 171 million people worldwide suffer from diabetes, or 2.8% of the population. Type 2 diabetes is by far the most common, affecting 90 to 95% of the U.S. diabetes population.

Definition

The word diabetes is from the Greek *diabanein* which means to pass through, in reference to the excessive urine produced as a symptom of these diseases. The term *diabetes*, without qualification, usually refers to diabetes mellitus, which roughly translates to excessive sweet urine (known as "glycosuria"). Several rare conditions are also named diabetes. The most common of these is diabetes insipidus in which large amounts of urine are produced (polyuria), which is not sweet (insipidus meaning "without taste" in Latin).

The term "type 1 diabetes" has replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and non-insulin-dependent diabetes mellitus (NIDDM).

Beyond these two types, there is no agreed-upon standard nomenclature. Various sources have defined "type 3 diabetes" as: gestational diabetes, insulin-resistant type 1 diabetes (or "double diabetes"), type 2 diabetes which has progressed to require injected insulin, and latent autoimmune diabetes of adults (or LADA or "type 1.5" diabetes)

Classification

Most cases of diabetes mellitus fall into three broad categories: type 1, type 2, and gestational diabetes. A few other types are described.

Type 1 diabetes

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency. This type of diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack. There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children.

Type 2 diabetes

Type 2 diabetes mellitus is characterized by insulin resistance which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus due to a known defect are classified separately. Type 2 diabetes is the most common type.

In the early stage of type 2 diabetes, the predominant abnormality is reduced insulin sensitivity. At this stage hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver.

Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%–5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%–50% of affected women develop type 2 diabetes later in life.

Even though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system anomalies, and skeletal muscle malformations.

Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A cesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

A 2008 study completed in the U.S. found that the number of American women entering pregnancy with preexisting diabetes is increasing. In fact the rate of diabetes in expectant mothers has more than doubled in the past 6 years. This is particularly problematic as diabetes raises the risk of complications during pregnancy, as well as increasing the potential that the children of diabetic mothers will also become diabetic in the future.

Other types

Pre-diabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 diabetes. Many people destined to develop type 2 diabetes spend many years in a state of pre-diabetes which has been termed "America's largest healthcare epidemic."

Latent autoimmune diabetes of adults is a condition in which Type 1 diabetes develops in adults. Adults with LADA are frequently initially misdiagnosed as having Type 2 diabetes, based on age rather than etiology.

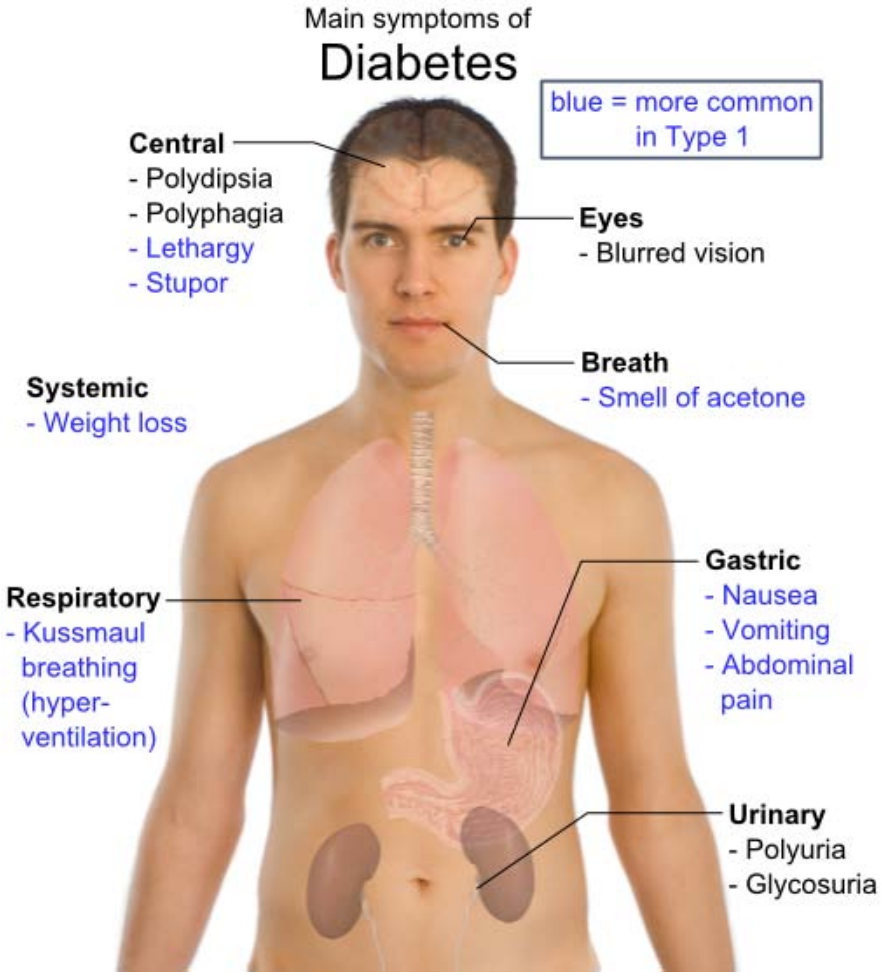
Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, *malnutrition-related diabetes mellitus* (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization when the current taxonomy was introduced in 1999.

Following is a comprehensive list of other causes of diabetes:

- Genetic defects of β-cell Function
  - Maturity onset diabetes of the young (MODY)
  - Mitochondrial DNA mutations
- Genetic defects in insulin processing or insulin action
- Endocrinopathies
  - Growth hormone excess (acromegaly)
  - Cushing syndrome
  - Hyperthyroidism
  - Pheochromocytoma
  - Glucagonoma

    - Defects in proinsulin conversion
    - Insulin gene mutations
    - Insulin receptor mutations
- Exocrine Pancreatic Defects
    - Chronic pancreatitis
    - Pancreatectomy
    - Pancreatic neoplasia
    - Cystic fibrosis
    - Hemochromatosis
    - Fibrocalculous pancreatopathy
- Infections
    - Cytomegalovirus infection
    - Coxsackievirus B
- Drugs
    - Glucocorticoids
    - Thyroid hormone
    - β-adrenergic agonists

Signs and symptoms



Overview of the most significant symptoms of diabetes

The classical symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). Symptoms may develop rapidly

(weeks or months) in type 1 diabetes while in type 2 diabetes they usually develop much more slowly and may be subtle or absent.

Prolonged high blood glucose causes glucose absorption, which leads to changes in the shape of the lenses of the eyes, resulting in vision changes; sustained sensible glucose control usually returns the lens to its original shape. Blurred vision is a common complaint leading to a diabetes diagnosis; type 1 should always be suspected in cases of rapid vision change, whereas with type 2 change is generally more gradual, but should still be suspected.

People (usually with type 1 diabetes) may also present with diabetic ketoacidosis, a state of metabolic dysregulation characterized by the smell of acetone; a rapid, deep breathing known as Kussmaul breathing; nausea; vomiting and abdominal pain; and an altered states of consciousness.

A rarer but equally severe possibility is hyperosmolar nonketotic state, which is more common in type 2 diabetes and is mainly the result of dehydration. Often, the patient has been drinking extreme amounts of sugar-containing drinks, leading to a vicious circle in regard to the water loss.

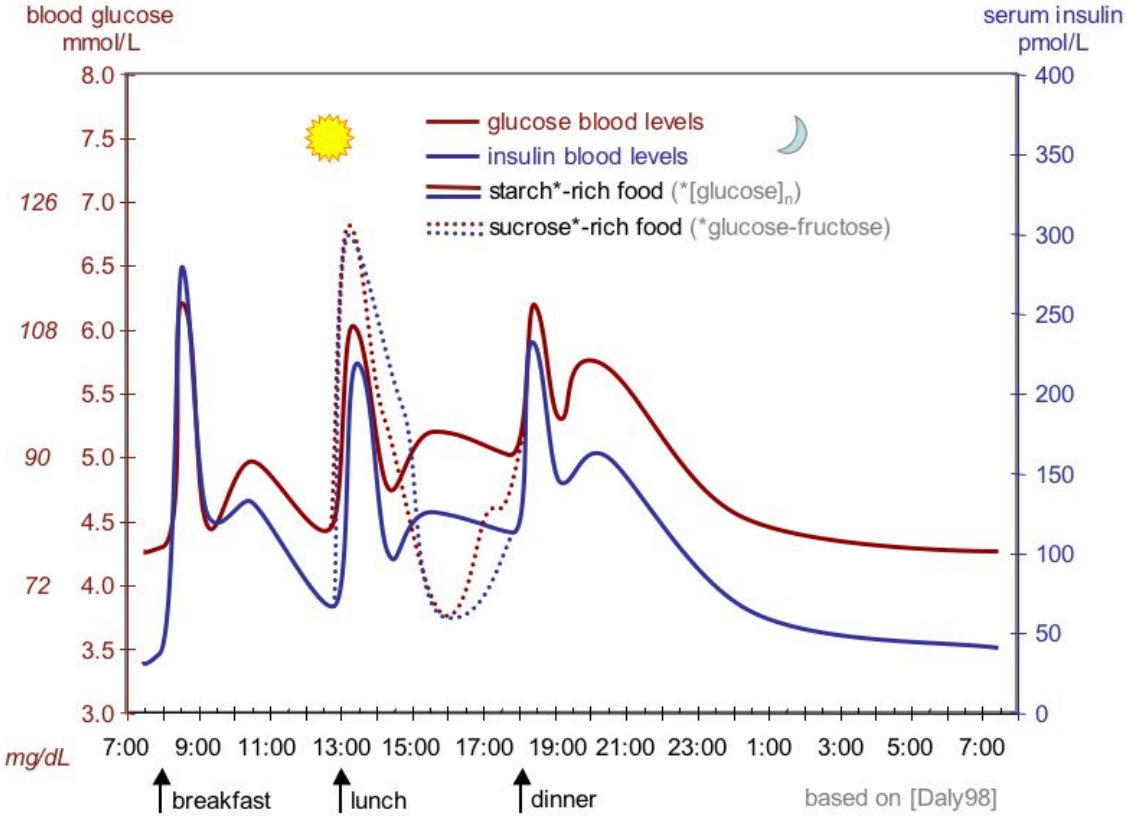
A number of skin rashes can occur in diabetes that are collectively known as diabetic dermadromes.

Causes

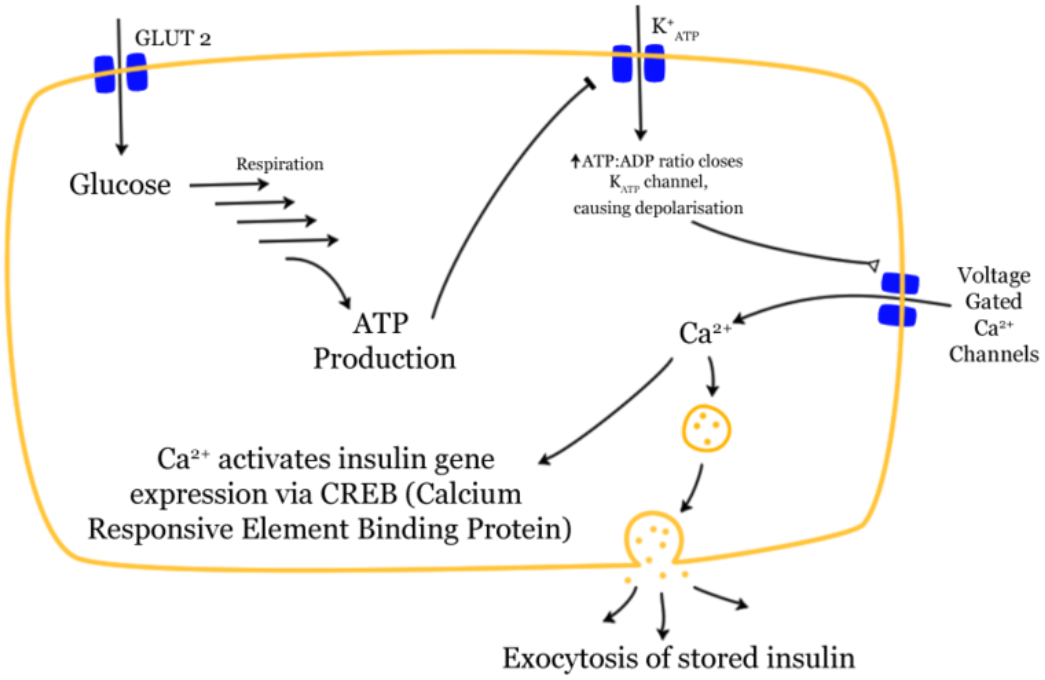
The cause of diabetes depends on the type. Type 2 diabetes is due primarily to lifestyle factors and genetics.

Type 1 diabetes is also partly inherited and then triggered by certain infections, with some evidence pointing at Coxsackie B4 virus. There is a genetic element in individual susceptibility to some of these triggers which has been traced to particular HLA genotypes (i.e., the genetic "self" identifiers relied upon by the immune system). However, even in those who have inherited the susceptibility, type 1 diabetes mellitus seems to require an environmental trigger.

Pathophysiology



The fluctuation of blood sugar (red) and the sugar-lowering hormone insulin (blue) in humans during the course of a day with three meals. One of the effects of a sugar-rich vs a starch-rich meal is highlighted.



Mechanism of insulin release in normal pancreatic beta cells. Insulin production is more or less constant within the beta cells, irrespective of blood glucose levels. It is stored within vacuoles pending release, via exocytosis, which is primarily triggered by food, chiefly food containing absorbable glucose. The chief trigger is a rise in blood glucose levels after eating

Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells (primarily muscle and fat cells, but not central nervous system cells). Therefore deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus.

Humans are capable of digesting some carbohydrates, in particular those most common in food; starch, and some disaccharides such as sucrose, are converted within a few hours to simpler forms most notably the monosaccharide glucose, the principal carbohydrate energy source used by the body. The rest are passed on for processing by gut flora largely in the colon. Insulin is released into the blood by beta cells (β-cells), found in the Islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage.

Insulin is also the principal control signal for conversion of glucose to glycogen for internal storage in liver and muscle cells. Lowered glucose levels result both in the reduced release of insulin from the beta cells and in the reverse conversion of glycogen to glucose when glucose levels fall. This is mainly controlled by the hormone glucagon which acts in the opposite manner to insulin. Glucose thus forcibly produced from internal liver cell stores (as glycogen) re-enters the bloodstream; muscle cells lack the

necessary export mechanism. Normally liver cells do this when the level of insulin is low (which normally correlates with low levels of blood glucose).

Higher insulin levels increase some anabolic ("building up") processes such as cell growth and duplication, protein synthesis, and fat storage. Insulin (or its lack) is the principal signal in converting many of the bidirectional processes of metabolism from a catabolic to an anabolic direction, and vice versa. In particular, a low insulin level is the trigger for entering or leaving ketosis (the fat burning metabolic phase).

If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or resistance), or if the insulin itself is defective, then glucose will not have its usual effect so that glucose will not be absorbed properly by those body cells that require it nor will it be stored appropriately in the liver and muscles. The net effect is persistent high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis.

When the glucose concentration in the blood is raised beyond its renal threshold (about 10 mmol/L, although this may be altered in certain conditions, such as pregnancy), reabsorption of glucose in the proximal renal tubuli is incomplete, and part of the glucose remains in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst.

Diagnosis

2006 WHO Diabetes criteria edit

Condition	**2 hour glucose** mmol/l(mg/dl)	**Fasting glucose** mmol/l(mg/dl)
Normal	<7.8 (<140)	<6.1 (<110)
Impaired fasting glycaemia	<7.8 (<140)	≥ 6.1(≥110) & <7.0(<126)
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL).
- Plasma glucose ≥ 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test.
- Symptoms of hyperglycemia and casual plasma glucose ≥ 11.1 mmol/L (200 mg/dL).

- Glycated hemoglobin (Hb A1C) ≥ 6.5%.

A positive result, in the absence of unequivocal hyperglycemia, should be confirmed by a repeat of any of the above-listed methods on a different day. It is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test. According to the current definition, two fasting glucose measurements above 126 mg/dL (7.0 mmol/L) is considered diagnostic for diabetes mellitus.

People with fasting glucose levels from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) are considered to have impaired fasting glucose. Patients with plasma glucose at or above 140 mg/dL (7.8 mmol/L), but not over 200 mg/dL (11.1 mmol/L), two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these two pre-diabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus as well as cardiovascular disease.

Management

Diabetes mellitus is a chronic disease which is difficult to cure. Management concentrates on keeping blood sugar levels as close to normal ("euglycemia") as possible without presenting undue patient danger. This can usually be with close dietary management, exercise, and use of appropriate medications (insulin only in the case of type 1 diabetes mellitus. Oral medications may be used in the case of type 2 diabetes, as well as insulin).

Patient education, understanding, and participation is vital since the complications of diabetes are far less common and less severe in people who have well-managed blood sugar levels. Wider health problems may accelerate the deleterious effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise.

Lifestyle modifications

There are roles for patient education, dietetic support, sensible exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure.

Medications

Oral medications

Routine use of aspirin has not been found to improve outcomes in uncomplicated diabetes.

Insulin

Type 1 treatments usually include combinations of regular or NPH insulin, and/or synthetic insulin analogs.

Support

In countries using a general practitioner system, such as the United Kingdom, care may take place mainly outside hospitals, with hospital-based specialist care used only in case of complications, difficult blood sugar control, or research projects. In other circumstances, general practitioners and specialists share care of a patient in a team approach. Optometrists, podiatrists/chiropodists, dietitians, physiotherapists, nursing specialists (e.g., DSNs (Diabetic Specialist Nurse)), nurse practitioners, or Certified Diabetes Educators, may jointly provide multidisciplinary expertise. In countries where patients must provide for their own health care (e.g. in the US, and in much of the undeveloped world).

Peer support links people living with diabetes. Within peer support, people with a common illness share knowledge and experience that others, including many health workers, do not have. Peer support is frequent, ongoing, accessible and flexible and can take many forms—phone calls, text messaging, group meetings, home visits, and even grocery shopping. It complements and enhances other health care services by creating the emotional, social and practical assistance necessary for managing disease and staying healthy.

Prognosis

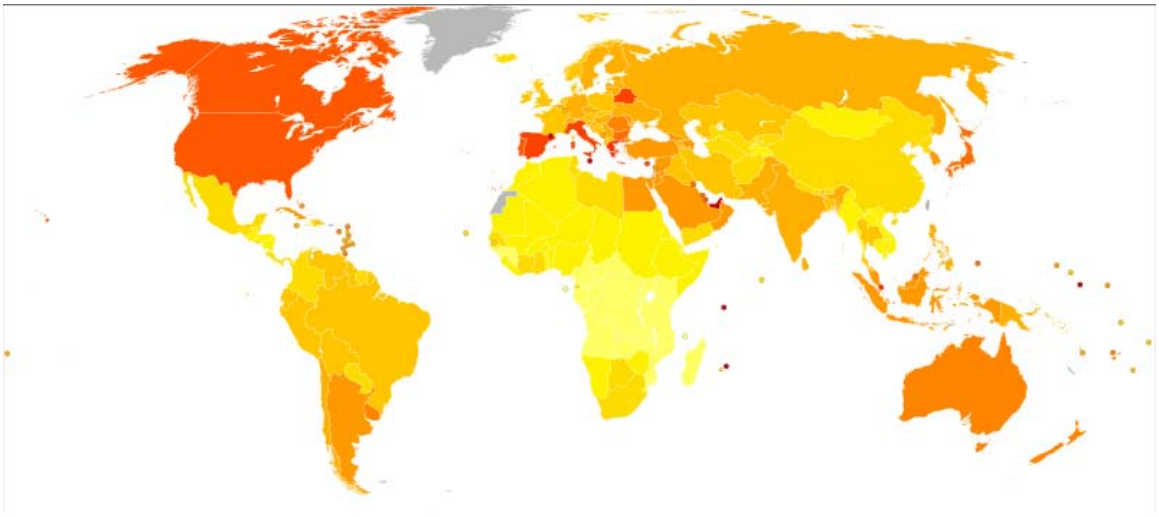
Diabetes doubles the risk of vascular problems, including cardiovascular disease.

According to one study, women with high blood pressure (hypertension) were three times more likely to develop type 2 diabetes as compared with women with optimal BP after adjusting for various factors such as age, ethnicity, smoking, alcohol intake, body mass index (BMI), exercise, family history of diabetes, etc. The study was conducted by researchers from the Brigham and Women's Hospital, Harvard Medical School and the Harvard School of Public Health, USA, who followed over 38,000 female health professionals for ten years.

Except in the case of type 1 diabetes, which always requires insulin replacement, the way type 2 diabetes is managed may change with age. Insulin production decreases because of age-related impairment of pancreatic beta cells. Additionally, insulin resistance increases because of the loss of lean tissue and the accumulation of fat, particularly intra-abdominal fat, and the decreased tissue sensitivity to insulin. Glucose tolerance progressively declines with age, leading to a high prevalence of type 2 diabetes and postchallenge hyperglycemia in the older population. Age-related glucose intolerance in humans is often accompanied by insulin resistance, but circulating insulin levels are similar to those of younger people. Treatment goals for older patients with diabetes vary with the

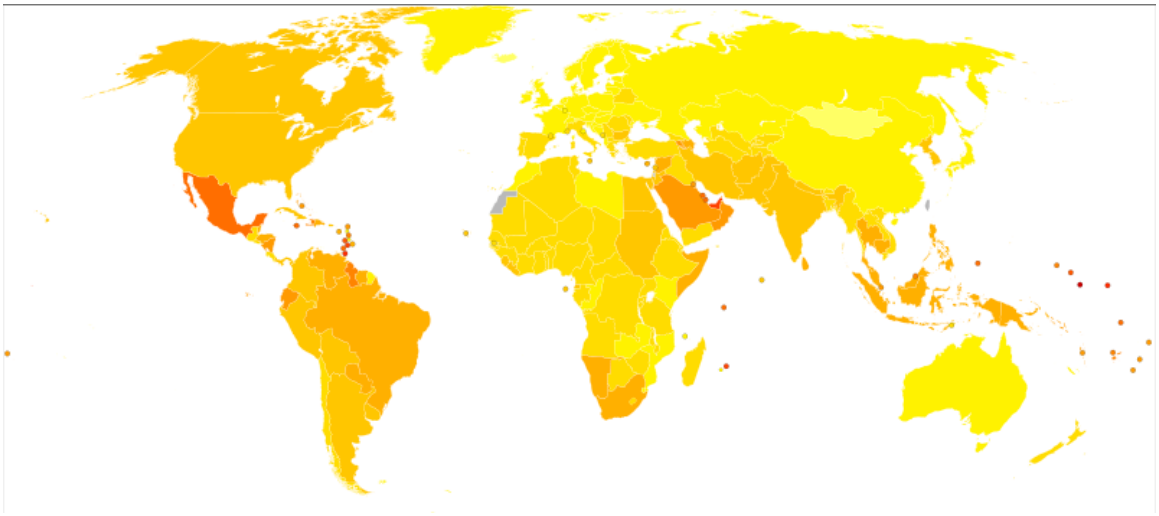
individual, and take into account health status, as well as life expectancy, level of dependence, and willingness to adhere to a treatment regimen. Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause.

Epidemiology



Prevalence of diabetes worldwide in 2000 (per 1000 inhabitants). World average was 2.8%.

- no data
- ≤ 7.5
- 7.5–15
- 15–22.5
- 22.5–30
- 30–37.5
- 37.5–45
- 45–52.5
- 52.5–60
- 60–67.5
- 67.5–75
- 75–82.5
- ≥ 82.5



Disability-adjusted life year for diabetes mellitus per 100,000 inhabitants in 2002.
no data
≤ 100
100-200
200-300
300-400
400-500
500-600
600-700
700-800
800-900
900-1000
1000-1500
≥ 1500

In 2000, according to the World Health Organization, at least 171 million people worldwide suffer from diabetes, or 2.8% of the population. Its incidence is increasing rapidly, and it is estimated that by 2030, this number will almost double. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries. The greatest increase in prevalence is, however, expected to occur in Asia and Africa, where most patients will probably be found by 2030. The increase in incidence of diabetes in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism(s) at present, though there is much speculation, some of it most compellingly presented.

For at least 20 years, diabetes rates in North America have been increasing substantially. In 2010 nearly 26 million people have diabetes in the United States alone, from those 7 million people remain undiagnosed. Other 57 million people are estimated to have pre-diabetes.

The Centers for Disease Control has termed the change an epidemic. The National Diabetes Information Clearinghouse estimates that diabetes costs $132 billion in the United States alone every year. About 5%–10% of diabetes cases in North America are type 1, with the rest being type 2. The fraction of type 1 in other parts of the world differs. Most of this difference is not currently understood. The American Diabetes Association cite the 2003 assessment of the National Center for Chronic Disease Prevention and Health Promotion (Centers for Disease Control and Prevention) that 1 in 3 Americans born after 2000 will develop diabetes in their lifetime.

According to the American Diabetes Association, approximately 18.3% (8.6 million) of Americans age 60 and older have diabetes. Diabetes mellitus prevalence increases with age, and the numbers of older persons with diabetes are expected to grow as the elderly population increases in number. The National Health and Nutrition Examination Survey (NHANES III) demonstrated that, in the population over 65 years old, 18% to 20% have diabetes, with 40% having either diabetes or its precursor form of impaired glucose tolerance.

Indigenous populations in first world countries have a higher prevalence and increasing incidence of diabetes than their corresponding non-indigenous populations. In Australia the age-standardised prevalence of self-reported diabetes in Indigenous Australians is almost 4 times that of non-indigenous Australians. Preventative community health programs such as Sugar Man (diabetes education) are showing some success in tackling this problem.

History

The term *diabetes* (Greek: διαβήτης, *diabētēs*) was coined by Aretaeus of Cappadocia. It was derived from the Greek verb διαβαίνειν, *diabaínein*, itself formed from the prefix *dia*-, "across, apart," and the verb *bainein*, "to walk, stand." The verb *diabeinein* meant "to stride, walk, or stand with legs asunder"; hence, its derivative *diabētēs* meant "one that straddles," or specifically "a compass, siphon." The sense "siphon" gave rise to the use of *diabētēs* as the name for a disease involving the discharge of excessive amounts of urine. Diabetes is first recorded in English, in the form diabete, in a medical text written around 1425. In 1675, Thomas Willis added the word *mellitus*, from the Latin meaning "honey", a reference to the sweet taste of the urine. This sweet taste had been noticed in urine by the ancient Greeks, Chinese, Egyptians, Indians, and Persians. In 1776, Matthew Dobson confirmed that the sweet taste was because of an excess of a kind of sugar in the urine and blood of people with diabetes.

Diabetes mellitus appears to have been a death sentence in the ancient era. Hippocrates makes no mention of it, which may indicate that he felt the disease was incurable. Aretaeus did attempt to treat it but could not give a good prognosis; he commented that "life (with diabetes) is short, disgusting and painful."

Sushruta (6th century BCE) identified diabetes and classified it as *Medhumeha*. He further identified it with obesity and sedentary lifestyle, advising exercises to help "cure"

it. The ancient Indians tested for diabetes by observing whether ants were attracted to a person's urine, and called the ailment "sweet urine disease" (Madhumeha). The Chinese, Japanese and Korean words for diabetes are based on the same ideographs (糖尿病) which mean "sugar urine disease".

In medieval Persia, Avicenna (980–1037) provided a detailed account on diabetes mellitus in *The Canon of Medicine*, "describing the abnormal appetite and the collapse of sexual functions," and he documented the sweet taste of diabetic urine. Like Aretaeus before him, Avicenna recognized a primary and secondary diabetes. He also described diabetic gangrene, and treated diabetes using a mixture of lupine, trigonella (fenugreek), and zedoary seed, which produces a considerable reduction in the excretion of sugar, a treatment which is still prescribed in modern times. Avicenna also "described diabetes insipidus very precisely for the first time", though it was later Johann Peter Frank (1745–1821) who first differentiated between diabetes mellitus and diabetes insipidus.

Although diabetes has been recognized since antiquity, and treatments of various efficacy have been known in various regions since the Middle Ages, and in legend for much longer, pathogenesis of diabetes has only been understood experimentally since about 1900. The discovery of a role for the pancreas in diabetes is generally ascribed to Joseph von Mering and Oskar Minkowski, who in 1889 found that dogs whose pancreas was removed developed all the signs and symptoms of diabetes and died shortly afterwards. In 1910, Sir Edward Albert Sharpey-Schafer suggested that people with diabetes were deficient in a single chemical that was normally produced by the pancreas—he proposed calling this substance *insulin*, from the Latin *insula*, meaning island, in reference to the insulin-producing islets of Langerhans in the pancreas.

The endocrine role of the pancreas in metabolism, and indeed the existence of insulin, was not further clarified until 1921, when Sir Frederick Grant Banting and Charles Herbert Best repeated the work of Von Mering and Minkowski, and went further to demonstrate they could reverse induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs. Banting, Best, and colleagues (especially the chemist Collip) went on to purify the hormone insulin from bovine pancreases at the University of Toronto. This led to the availability of an effective treatment—insulin injections—and the first patient was treated in 1922. For this, Banting and laboratory director MacLeod received the Nobel Prize in Physiology or Medicine in 1923; both shared their Prize money with others in the team who were not recognized, in particular Best and Collip. Banting and Best made the patent available without charge and did not attempt to control commercial production. Insulin production and therapy rapidly spread around the world, largely as a result of this decision. Banting is honored by World Diabetes Day which is held on his birthday, November 14.

The distinction between what is now known as type 1 diabetes and type 2 diabetes was first clearly made by Sir Harold Percival (Harry) Himsworth, and published in January 1936.

Despite the availability of treatment, diabetes has remained a major cause of death. For instance, statistics reveal that the cause-specific mortality rate during 1927 amounted to about 47.7 per 100,000 population in Malta.

Other landmark discoveries include:

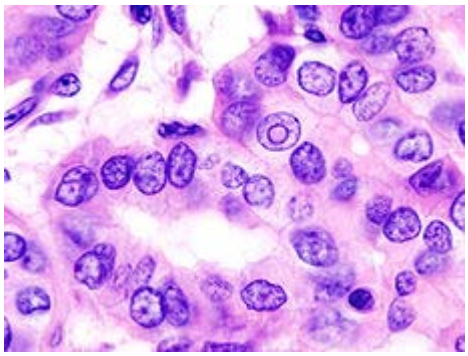
- Identification of the first of the sulfonylureas in 1942
- Reintroduction of the use of biguanides for Type 2 diabetes in the late 1950s. The initial phenformin was withdrawn worldwide (in the U.S. in 1977) due to its potential for sometimes fatal lactic acidosis and metformin was first marketed in France in 1979, but not until 1994 in the US.
- The determination of the amino acid sequence of insulin (by Sir Frederick Sanger, for which he received a Nobel Prize)
- The radioimmunoassay for insulin, as discovered by Rosalyn Yalow and Solomon Berson (gaining Yalow the 1977 Nobel Prize in Physiology or Medicine)
- The three-dimensional structure of insulin (PDB 2INS)
- Dr Gerald Reaven's identification of the constellation of symptoms now called metabolic syndrome in 1988
- Demonstration that intensive glycemic control in type 1 diabetes reduces chronic side effects more as glucose levels approach 'normal' in a large longitudinal study, and also in type 2 diabetics in other large studies
- Identification of the first thiazolidinedione as an effective insulin sensitizer during the 1990s

In 1980, U.S. biotech company Genentech developed human insulin. The insulin is isolated from genetically altered bacteria (the bacteria contain the human gene for synthesizing human insulin), which produce large quantities of insulin. The purified insulin is distributed to pharmacies for use by diabetes patients.

Chapter 13

Thyroid Cancer

Thyroid cancer

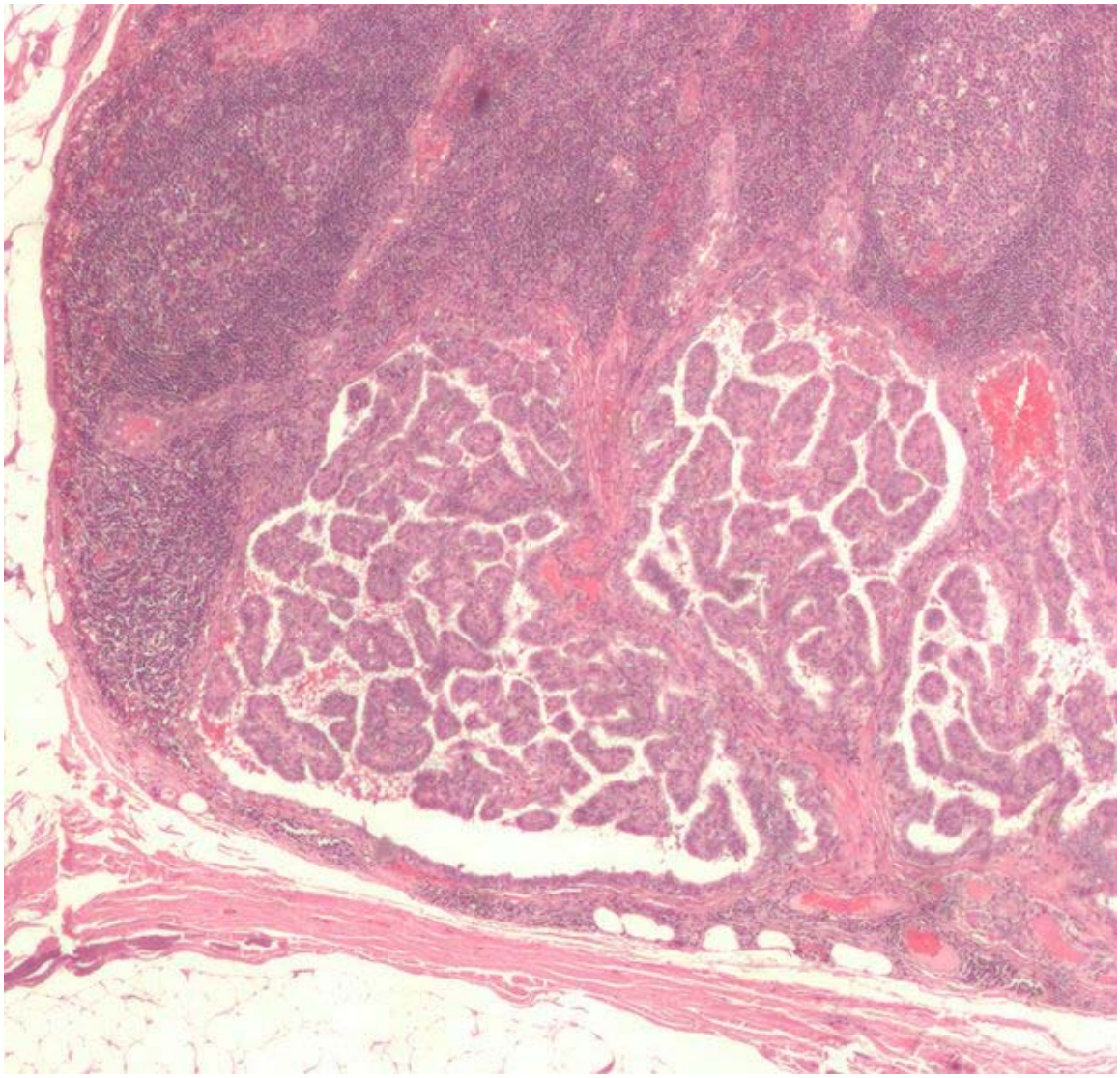


Micrograph (high power view) of papillary thyroid carcinoma demonstrating diagnostic features (nuclear clearing and overlapping nuclei). H&E stain.

ICD-10	C73.
ICD-9	193
eMedicine	ent/646
MeSH	D013964

Thyroid cancer is a thyroid neoplasm that is malignant. It can be treated with radioactive iodine or surgical resection of the thyroid gland. Chemotherapy or radiotherapy may also be used.

Symptoms



Micrograph of a lymph node with papillary thyroid carcinoma

Most often the first symptom of thyroid cancer is a nodule in the thyroid region of the neck. However, many adults have small nodules in their thyroids, but typically under 5% of these nodules are found to be malignant. Sometimes the first sign is an enlarged lymph node. Later symptoms that can be present are pain in the anterior region of the neck and changes in voice.

Thyroid cancer is usually found in a euthyroid patient, but symptoms of hyperthyroidism or hypothyroidism may be associated with a large or metastatic well-differentiated tumor.

Thyroid nodules are of particular concern when they are found in those under the age of 20. The presentation of benign nodules at this age is less likely, and thus the potential for malignancy is far greater.

Diagnosis

After a thyroid nodule is found during a physical examination, a referral to an endocrinologist, a thyroidologist or otolaryngologist may occur. Most commonly an ultrasound is performed to confirm the presence of a nodule, and assess the status of the whole gland. Measurement of thyroid stimulating hormone and anti-thyroid antibodies will help decide if there is a functional thyroid disease such as Hashimoto's thyroiditis present, a known cause of a benign nodular goiter.

Classification

Thyroid cancers can be classified according to their histopathological characteristics. The following variants can be distinguished (distribution over various subtypes may show regional variation):

- Papillary thyroid cancer (75% to 85% of cases) - often in young females - excellent prognosis
- Follicular thyroid cancer (10% to 20% of cases)
- Medullary thyroid cancer (5% to 8% of cases)- cancer of the parafollicular cells, part of MEN-2.
- Anaplastic thyroid cancer (Less than 5%). It is not responsive to treatment and can cause pressure symptoms.
- Others
    - Lymphoma
    - Squamous cell carcinoma, sarcoma

The follicular and papillary types together can be classified as "differentiated thyroid cancer". These types have a more favorable prognosis than the medullary and undifferentiated types.

- Papillary microcarcinoma is a subset of papillary thyroid cancer defined as measuring less than or equal to 1 cm. The highest incidence of papillary thyroid microcarcinoma in autopsy series was reported by Harach et al. in 1985, who found 36 of 101 consecutive autopsies were found to have an incidental microcarcinoma. Michael Pakdaman et al. report the highest incidence in a retrospective surgical series at 49.9% of 860 cases. Management strategies for incidental papillary microcarcinoma on ultrasound (and confirmed on FNAB) range from total thyroidectomy with radioactive iodine ablation to observation alone. Harach et al. suggest using the term "occult papillary tumor" to avoid giving patients distress over having cancer.It was Woolner et al. who first arbitrarily coined the term "occult papillary carcinoma" in 1960, to describe papillary carcinomas ≤ 1.5 cm in diameter.

Etiology

From the 1940s to 1960s, external, low-dose radiation to the head and neck during infancy and childhood was used to treat many benign diseases. This type of therapy has been shown to predispose persons to thyroid cancer. The younger the patient was at time of exposure, the higher the risk of developing cancer.

Another cause may be due to high-dose irradiation to the head and neck. Patients with Hodgkin lymphoma treated with mantlefield irradiation have an increased risk of developing thyroid cancer, although hypothyroidism is more likely.

Treatment

Thyroid cancer may require surgery. Common surgeries include thyroidectomy, lobectomy, and tracheostomy.

Radioactive Iodine-131 is used in patients with papillary or follicular thyroid cancer for ablation of residual thyroid tissue after surgery and for the treatment of thyroid cancer. Patients with medullary, anaplastic, and most Hurthle cell cancers do not benefit from this therapy.

External irradiation may be used when the cancer is unresectable, when it recurs after resection, or to relieve pain from bone metastasis.

Sorafenib and sunitinib, approved for other indications show promise for thyroid cancer and are being used for some patients who do not qualify for clinical trials. Numerous agents are in phase II clinical trials and XL184 has started a phase III trial.

Prognosis

The prognosis of thyroid cancer is among the best of all cancers.

By European statistics, the overall relative 5-year survival rate for thyroid cancer is 85% for females and 74% for males.

Prognosis is better in younger people than older ones.

Prognosis depends mainly on the type of cancer and cancer stage.

Thyroid cancer type	5-year survival					10-year survival
	Stage I	Stage II	Stage III	Stage IV	Overall	Overall
Papillary	100%	100%	93%	51%	96% or 97%	93%
Follicular	100%	100%	71%	50%	91%	85%
Medullary	100%	98%	81%	28%	80%, 83% or 86%	75%
Anaplastic	(always stage IV)			7%	7% or 14%	(no data)

Charitable foundation

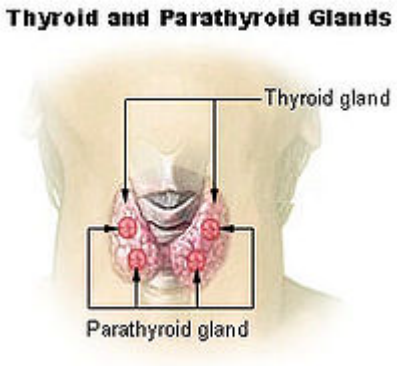
Major league baseball player Craig Breslow in 2008 started the Strike 3 Foundation, after having witnessed his sister Lesley's battle with pediatric thyroid cancer. It is a non-profit charity that raises awareness, support, and funding for pediatric cancer research, and which has teamed up with CureSearch, which unites the National Childhood Cancer Foundation and the Children's Oncology Group, the world's largest childhood cancer research organization. "Something as traumatic as that has a lasting impact," Breslow said. His sister in 2008 was a 15-year cancer survivor, and expecting her first child.

Breslow hopes to hold annual events in New Haven and Minnesota, as well as in Florida during spring training. His first benefit raised $100,000 and his second benefit more than $85,000.

Chapter 14

Primary Hyperparathyroidism

Primary hyperparathyroidism



Thyroid and parathyroid.

ICD-10	E21.0
ICD-9	252.01
DiseasesDB	6283
eMedicine	radio/355
MeSH	D049950

Primary hyperparathyroidism causes hypercalcemia (elevated blood calcium levels) through the excessive secretion of parathyroid hormone (PTH), usually by an adenoma (benign tumors) of the parathyroid glands. Its incidence is approximately 42 per 100,000 people. It is almost exactly three times as common in women as men.

Signs and Symptoms

The signs and symptoms of primary hyperparathyroidism are those of hypercalcemia. They are classically summarized by the mnemonic "stones, bones, abdominal groans and psychiatric moans".

- "Stones" refers to kidney stones, nephrocalcinosis, and diabetes insipidus (polyuria and polydipsia). These can ultimately lead to renal failure.
- "Bones" refers to bone-related complications. The classic bone disease in hyperparathyroidism is osteitis fibrosa cystica, which results in pain and sometimes pathological fractures. Other bone diseases associated with hyperparathyroidism are osteoporosis, osteomalacia, and arthritis.
- "Abdominal groans" refers to gastrointestinal symptoms of constipation, indigestion, nausea and vomiting. Hypercalcemia can lead to peptic ulcers and acute pancreatitis.
- "Psychiatric moans" refers to effects on the central nervous system. Symptoms include lethargy, fatigue, depression, memory loss, psychosis, ataxia, delirium, and coma.
- Left ventricular hypertrophy.
- Increased all cause mortality

The German description of the same symptoms is "Stein-, Bein- und Magenpein", literally "stone, leg, and stomach-pain".

Other signs include proximal muscle weakness, itching, and band keratopathy of the eyes.

Diagnosis

The diagnosis of primary hyperparathyroidism is made by blood tests. Serum calcium levels are elevated.

The serum chloride phosphate ratio is 33 or more in most patients with primary hyperparathyroidism. However, thiazide medications have been reported to causes ratios above 33.

Urinary cAMP is occasionally measured; this is generally elevated..

Parathyroid hormone activity

Intact PTH levels are also elevated.

Causes

The most common cause of primary hyperparathyroidism is a sporadic, single parathyroid adenoma resulting from a clonal mutation (~97%). Less common are parathyroid hyperplasia (~2.5%), parathyroid carcinoma (malignant tumor), and adenomas in more than one gland (together ~0.5%).

Primary hyperparathyroidism is also a feature of several familial endocrine disorders: Multiple endocrine neoplasia type 1 and type 2A (MEN type 1 and MEN type 2A), and familial hyperparathyroidism.

Genetic associations include:

OMIM	Name	Gene
145000	HRPT1	MEN1, HRPT2
145001	HRPT2	HRPT2
610071	HRPT3	unknown at 2p13.3-14

In all cases, the disease is idiopathic, but is thought to involve inactivation of tumor suppressor genes (Menin gene in MEN1), or involve gain of function mutations (RET proto-oncogene MEN 2a).

Complications

The classic bone disease in hyperparathyroidism is osteitis fibrosa cystica, which results in pain and sometimes pathological fractures. Other bone diseases associated with hyperparathyroidism are osteoporosis, osteomalacia, and arthritis.

Treatment

Treatment is usually surgical removal of the gland(s) containing adenomas.

Medications

Medications include estrogen replacement therapy in postmenopausal women and bisphosphonates. Bisphosphonates may improve bone turnover. Newer medications termed "calcimimetics" used in secondary hyperparathyroidism are now being used in Primary hyperparathyroidism. Calcimimetics reduce the amount of parathyroid hormone released by the parathyroid glands. They are recommended in patients in whom surgery is inappropriate.

Surgery

The symptoms of the disease, listed above, are indications for surgery. Surgery reduces all cause mortality as well as resolving symptoms. However, cardiovascular mortality is not significantly reduced

A consensus statement in 2002 recommended the following indications for surgery in asymptomatic hyperparathyroidism:

- Serum calcium (above upper limit of normal): 1.0 mg/dl
- 24-h urinary calcium >400 mg
- Creatinine clearance reduced by 30% compared with age-matched subjects.
- Bone mineral density t-score <−2.5 at any site
- Age <50

More recently, three randomized controlled trials have studied the role of surgery in patients with asymptomatic hyperparathyroidism. The largest study reported that surgery showed increase in bone mass, but no improvement in quality of life after one to two years among patients with:

- Untreated, asymptomatic primary hyperparathyroidism
- Serum calcium between 2.60–2.85 mmol/liter (10.4–11.4 mg/dl)
- Age between 50 and 80 yr
- No medications interfering with Ca metabolism
- No hyperparathyroid bone disease
- No previous operation in the neck
- Creatinine level < 130 μmol/liter (<1.47 mg/dl)

Two other trials reported improvements in bone density and some improvement in quality of life with surgery.

Non-invasive tratment

The French company Theraclion developed a new device named **"TH-One"** for the non-invasive treatment (no scars) of fine endocrine targets such as thyroid nodules and parathyroids. TH-One uses High Intensity Focused Ultrasound (HIFU), which is a process that allows the delivery of a large amount of acoustic energy to a confined space resulting in localized tissue necrosis.

The **TH-One** enables to treat primary hyperparathyroidism by ablating the adenoma. It also allows to lower in a control manner the PTH level for secondary hyperparathyroidism patients. It is scar-less, totally non invasive.

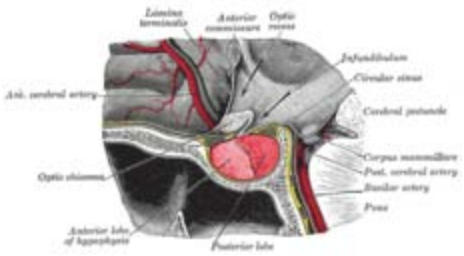
Future therapies

Future developments such as calcimemetic agents (e.g. cinacalcet) which activate the parathyroid calcium-sensing receptor may offer a good alternative to surgery.

Chapter 15

Hypopituitarism

Hypopituitarism



The pituitary gland on a plate from Gray's Anatomy (1918). The anterior lobe is on the left, and the posterior lobe on the right, both in red.

ICD-10	E23.0, E89.3
ICD-9	253.7
DiseasesDB	6522
MedlinePlus	000343
eMedicine	emerg/277 med/1137 ped/1130

Hypopituitarism is the decreased (*hypo*) secretion of one or more of the eight hormones normally produced by the pituitary gland at the base of the brain. If there is decreased secretion of most pituitary hormones, the term **panhypopituitarism** (*pan* meaning "all") is used.

The signs and symptoms of hypopituitarism vary, depending on which hormones are undersecreted and on the underlying cause of the abnormality. The diagnosis of hypopituitarism is made by blood tests, but often specific scans and other investigations are needed to find the underlying cause, such as tumors of the pituitary, and the ideal treatment. Most hormones controlled by the secretions of the pituitary can be replaced by tablets or injections. Hypopituitarism is a rare disease, but may be significantly

underdiagnosed in people with previous traumatic brain injury. The first description of the condition was made in 1914 by the German physician Dr Morris Simmonds.

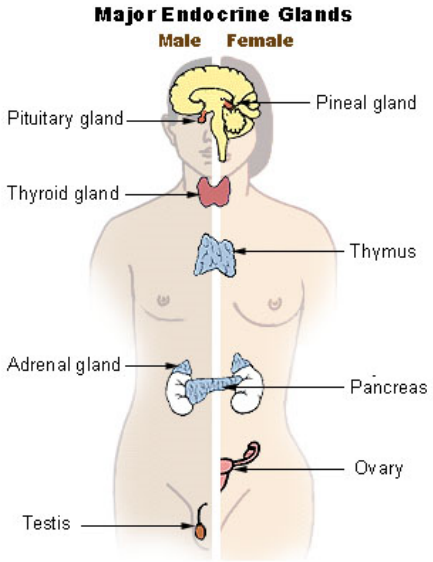
Signs and symptoms

The hormones of the pituitary have different actions in the body, and the symptoms of hypopituitarism therefore depend on which hormone is deficient. The symptoms may be subtle and are often initially attributed to other causes. In most of the cases, three or more hormones are deficient. The most common problem is insufficiency of follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH) leading to sex hormone abnormalities. Growth hormone deficiency is more common in people with an underlying tumor than those with other causes.

Sometimes, there are additional symptoms that arise from the underlying cause; for instance, if the hypopituitarism is due to a growth hormone-producing tumor, there may be symptoms of acromegaly (enlargement of the hands and feet, coarse facial features), and if the tumor extends to the optic nerve or optic chiasm, there may be visual field defects. Headaches may also accompany pituitary tumors, as well as pituitary apoplexy (stroke of the pituitary gland) and lymphocytic hypophysitis (autoimmune inflammation of the pituitary).

Pituitary failure results in many changes in the skin, hair and nails as a result of the absence of pituitary hormone action on these sites.

Anterior pituitary



The major endocrine glands of the body. Pituitary hormones control the function of the adrenal gland, thyroid gland and the gonads (testes and ovaries).

Deficiency of all anterior pituitary hormones is more common than individual hormone deficiency.

Deficiency of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), together referred to as the gonadotropins, leads to different symptoms in men and women. Women experience oligo- or amenorrhea (infrequent/light or absent menstrual periods respectively) and infertility. Men lose facial, scrotal and trunk hair, as well as suffering decreased muscle mass and anemia. Both sexes may experience a decrease in libido and loss of sexual function, and have an increased risk of osteoporosis (bone fragility). Lack of LH/FSH in children is associated with delayed puberty.

Growth hormone (GH) deficiency leads to a decrease in muscle mass, central obesity (increase in body fat around the waist) and impaired attention and memory. Children experience growth retardation and short stature.

Adrenocorticotropic hormone (ACTH) deficiency leads to adrenal insufficiency, a lack of production of glucocorticoids such as cortisol by the adrenal gland. If the problem is chronic, symptoms consist of fatigue, weight loss, failure to thrive (in children), delayed puberty (in adolescents), hypoglycemia (low blood sugar levels), anemia and hyponatremia (low sodium levels). If the onset is abrupt, collapse, shock and vomiting may occur. ACTH deficiency is highly similar to Addison's disease, which is cortisol deficiency as the result of direct damage to the adrenal glands; the latter form, however, often leads to hyperpigmentation of the skin, which does not occur in ACTH deficiency.

Thyroid-stimulating hormone (TSH) deficiency leads to hypothyroidism (lack of production of thyroxine (T4) and triiodothyronine (T3) in the thyroid). Typical symptoms are tiredness, intolerance to cold, constipation, weight gain, hair loss and slowed thinking, as well as a slowed heart rate and low blood pressure. In children, hypothyroidism leads to delayed growth and in extreme inborn forms to a syndrome called *cretinism*.

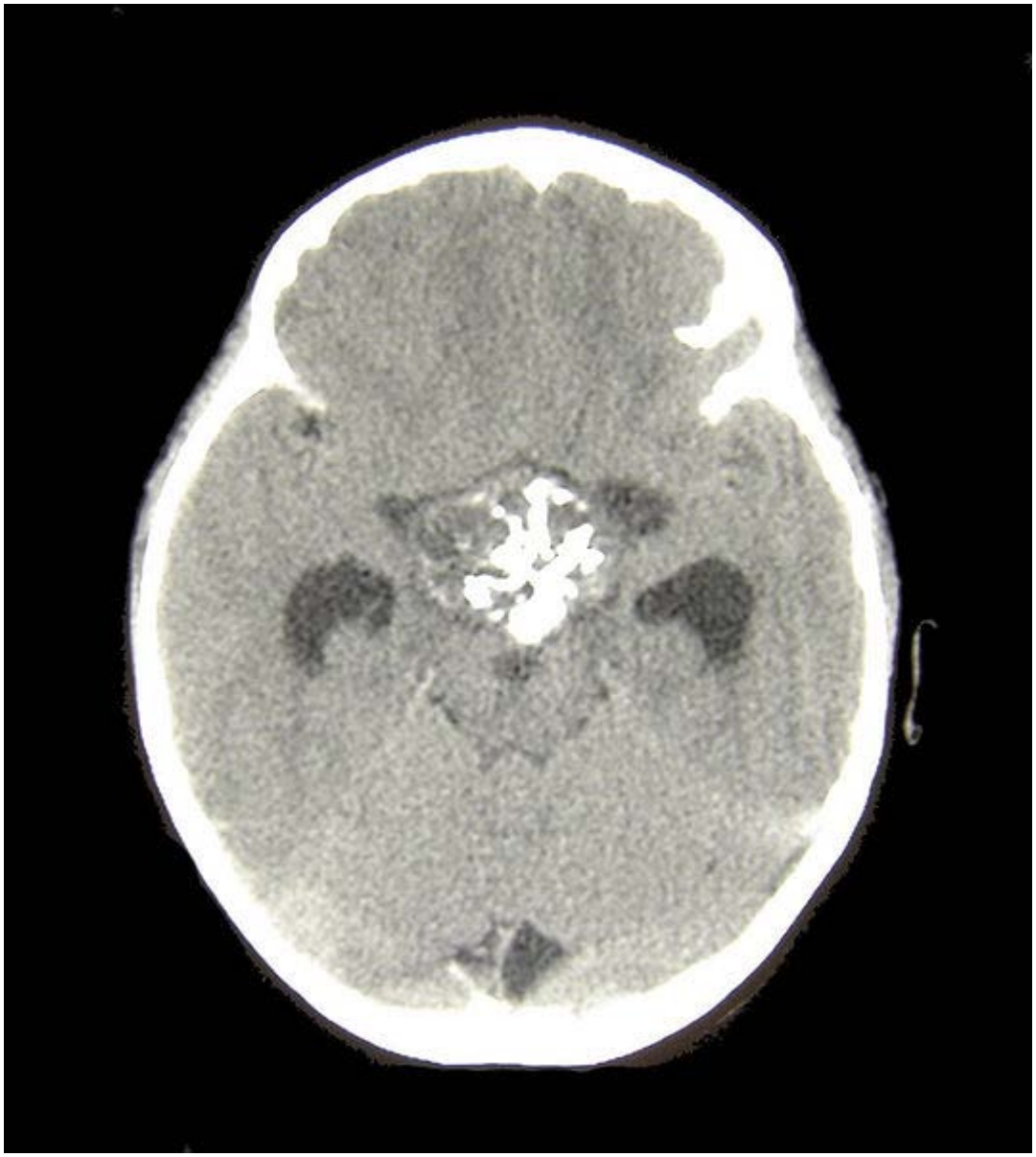
Prolactin plays a role in breastfeeding, and inability to breastfeed may point at abnormally low prolactin levels.

Posterior pituitary

Antidiuretic hormone (ADH) deficiency leads to the syndrome of *diabetes insipidus* (unrelated to diabetes mellitus): inability to concentrate the urine, leading to polyuria (production of large amounts of clear urine) that is low in solutes, dehydration and—in compensation—extreme thirst and constant need to drink (polydipsia), as well as hypernatremia (high sodium levels in the blood). ADH deficiency may be masked if there is ACTH deficiency, with symptoms only appearing when cortisol has been replaced.

Oxytocin deficiency generally causes few symptoms, as it is only required at the time of childbirth and breastfeeding.

Diagnosis



CT scan of the brain showing a craniopharyngioma (white structure in the center of the image). This tumor may cause hypopituitarism and requires surgical removal.

The diagnosis of hypopituitarism is made on blood tests. Two types of blood tests are used to confirm the presence of a hormone deficiency: basal levels, where blood samples are taken–usually in the morning–without any form of stimulation, and dynamic tests, where blood tests are taken after the injection of a stimulating substance. Measurement of ACTH and growth hormone usually requires dynamic testing, whereas the other hormones (LH/FSH, prolactin, TSH) can typically be tested with basal levels. There is no adequate direct test for ADH levels, but ADH deficiency can be confirmed indirectly; oxytocin levels are not routinely measured.

Generally, the finding of a combination of a low pituitary hormone together with a low hormone from the effector gland is indicative of hypopituitarism. Occasionally, the pituitary hormone may be normal but the effector gland hormone decreased; in this case, the pituitary is not responding appropriately, and the combination of findings is still suggestive of hypopituitarism.

Basal tests

Levels of LH/FSH may be suppressed by a raised prolactin level, and are therefore not interpretable unless prolactin is low or normal. In men, the combination of low LH and FSH in combination with a low testosterone confirms LH/FSH deficiency; a high testosterone would indicate a source elsewhere in the body (such as a testosterone-secreting tumor). In women, the diagnosis of LH/FSH deficiency depends on whether the woman has been through the menopause. Before the menopause, abnormal menstrual periods together with low estradiol and LH/FSH levels confirm a pituitary problem; after the menopause (when LH/FSH levels are normally elevated and the ovaries produce less estradiol), inappropriately low LH/FSH alone is sufficient. Stimulation tests with GnRH are possible, but their use is not encouraged.

For TSH, basal measurements are usually sufficient, as well as measurements of thyroxine to ensure that the pituitary is not simply suppressing TSH production in response to hyperthyroidism (an overactive thyroid gland). A stimulation test with thyrotropin-releasing hormone (TRH) is not regarded as useful. Prolactin can be measured by basal level, and is required for the interpretation of LH and FSH results in addition to the confirmation of hypopituitarism or diagnosis of a prolactin-secreting tumor.

Stimulation tests

Growth hormone deficiency is almost certain if all other pituitary tests are also abnormal, and insulin-like growth factor 1 (IGF-1) levels are decreased. If this is not the case, IGF-1 levels are poorly predictive of the presence of GH deficiency; stimulation testing with the insulin tolerance test is then required. This is performed by administering insulin to lower the blood sugar to a level below 2.2 mmol/l. Once this occurs, growth hormone levels are measured. If they are low despite the stimulatory effect of the low blood sugars, growth hormone deficiency is confirmed. The test is not without risks, especially in those prone to seizures or are known to have heart disease, and causes the unpleasant symptoms of hypoglycemia. Alternative tests (such as the growth hormone releasing hormone stimulation test) are less useful, although a stimulation test with arginine may be used for diagnosis, especially in situations where an insulin tolerance test is thought to be too dangerous. If GH deficiency is suspected, and all other pituitary hormones are normal, two different stimulation tests are needed for confirmation.

If morning cortisol levels are over 500 nmol/l, ACTH deficiency is unlikely, whereas a level less than 100 is indicative. Levels between 100-500 require a stimulation test. This, too, is done with the insulin tolerance test. A cortisol level above 500 after achieving a

low blood sugar rules out ACTH deficiency, while lower levels confirm the diagnosis. A similar stimulation test using corticotropin-releasing hormone (CRH) is not sensitive enough for the purposes of the investigation. If the insulin tolerance test yields an abnormal result, a further test measuring the response of the adrenal glands to synthetic ACTH (the ACTH stimulation test) can be performed to confirm the diagnosis. Stimulation testing with metyrapone is an alternative. Some suggest that an ACTH stimulation test is sufficient as first-line investigation, and that an insulin torlerance test is only needed if the ACTH test is equivocal. The insulin tolerance test is discouraged in children. None of the tests for ACTH deficiency are perfect, and further tests after a period of time may be needed if initial results are not conclusive.

Symptoms of diabetes insipidus should prompt a formal fluid deprivation test to assess the body's response to dehydration, which normally causes concentration of the urine and increasing osmolarity of the blood. If these parameters are unchanged, desmopressin (an ADH analogue) is administered. If the urine then becomes concentrated and the blood osmolarity falls, there is a lack of ADH due to lack of pituitary function ("cranial diabetes insipidus"). In contrast, there is no change if the kidneys are unresponsive to ADH due to a different problem ("nephrogenic diabetes insipidus").

Further investigations

If one of these tests shows a deficiency of hormones produced by the pituitary, magnetic resonance imaging (MRI) scan of the pituitary is the first step in identifying an underlying cause. MRI may show various tumors and may assist in delineating other causes. Tumors smaller than 1 cm are referred to as *microadenomas*, and larger lesions are called *macroadenomas*. Computed tomography with radiocontrast may be used if MRI is not available. Formal visual field testing by perimetry is recommended, as this would show evidence of optic nerve compression by a tumor.

Other tests that may assist in the diagnosis of hypopituitarism, especially if no tumor is found on the MRI scan, are ferritin (elevated in hemochromatosis), angiotensin converting enzyme (ACE) levels (often elevated in sarcoidosis), and human chorionic gonadotropin (often elevated in tumor of germ cell origin). If a genetic cause is suspected, genetic testing may be performed.

Causes

Type	Causes
Tumors	Most cases of hypopituitarism are due to pituitary adenomas compressing the normal tissue in the gland, and rarely other brain tumors outside the gland—craniopharyngioma, meningioma, chordoma, ependymoma, glioma or metastasis from cancer elsewhere in the body.
Infection, inflammation	The pituitary may also be affected by infections of the brain (brain abscess, meningitis, encephalitis) or

and infiltration	of the gland itself, or it may be infiltrated by abnormal cells (neurosarcoidosis, histiocytosis) or excessive iron (hemochromatosis). Empty sella syndrome is unexplained disappearance of pituitary tissue, probably due to outside pressure. Autoimmune or lymphocytic hypophysitis occurs when the immune system directly attacks the pituitary.
Vascular	As a pregnancy comes to term, a pregnant woman's pituitary gland is vulnerable to low blood pressure, such as may result form hemorrhage; pituitary damage due to bleeding after childbirth is called Sheehan's syndrome. Pituitary apoplexy is hemorrhage or infarction (loss of blood supply) of the pituitary. Other forms of stroke are increasingly recognized as a cause for hypopituitarism.
Physical	External physical causes for hypopituitarism include traumatic brain injury, subarachnoid hemorrhage, neurosurgery and ionizing radiation (e.g. radiation therapy for a previous brain tumor).
Congenital	Congenital hypopituitarism (present at birth) may be the result of complications around delivery, or may be the result of insufficient development (hypoplasia) of the gland, sometimes in the context of specific genetic abnormalities. Mutations of *HESX1* (linked to septo-optic dysplasia), *LHX1*, *PROP1* and *POU1F1*, as well as several others, may cause either insufficient development of the gland or decreased function. Kallmann syndrome causes deficiency of the gonadotropins only. Bardet-Biedl syndrome and Prader-Willi syndrome have been associated with pituitary hormone deficiencies.

Pathophysiology

The pituitary gland is located at the base of the brain, and intimately connected with the hypothalamus. It consists of two lobes: the posterior pituitary, which consists of nervous tissue branching out of the hypothalamus, and the anterior pituitary, which consists of hormone-producing epithelium. The posterior pituitary secretes antidiuretic hormone, which regulates osmolarity of the blood, and oxytocin, which causes contractions of the uterus in childbirth and participates in breastfeeding.

The pituitary develops in the third week of embryogenesis from interactions between the diencephalon part of the brain and the nasal cavity. The brain cells secrete FGF-8, Wnt5a

and BMP-4, and the nasal cavity BMP-2. Together, these cellular signals stimulate a group of cells from the nasal cavity to form Rathke's pouch, which becomes independent of the nasal cavity and develops into the anterior pituitary; this process includes the suppression of production of a protein called Sonic hedgehog by the cells of Rathke's pouch. The cells then differentiate further into the various hormone-producing cells of the pituitary. This requires particular transcription factors that induce the expression of particular genes. Some of these transcription factors have been found to be deficient in some forms of rare combined pituitary hormone deficiencies (CPHD) in childhood. These are *HESX1*, *PROP1*, *POU1F1*, *LHX3*, *LHX4*, *TBX19*, *SOX2* and *SOX3*. Each transcription factor acts in particular groups of cells. Therefore, various genetic mutations are associated with specific hormone deficiencies. For instance, *POU1F1* (also known as Pit-1) mutations cause specific deficiencies in growth hormone, prolactin and TSH. In addition to the pituitary, some of the transcription factors are also required for the development of other organs; some of these mutations are therefore also associated with specific birth defects.

Hypothalamic-pituitary-end organ axis

	Thyroid	**Adrenal**	**Gonads**	**Growth**	**Breast**
Releasing hormone	TRH	CRH	GnRH	GHRH	Dopamine (inhibitor)
Pituitary cells	Thyrotrope	Corticotrope	Gonadotrope	Somatotrope	Lactotrope
Pituitary hormone	TSH	ACTH	LH/FSH	GH	Prolactin
End organ	Thyroid	Adrenal	Testes or ovaries	Liver	Breast gland
Product	Thyroxine	Cortisol	Testosterone or estradiol	IGF-1	Milk (no feedback)

Most of the hormones in the anterior pituitary are each part of an *axis* that is regulated by the hypothalamus. The hypothalamus secretes a number of releasing hormones, often according to a circadian rhythm, into blood vessels that supply the anterior pituitary; most of these are stimulatory (thyrotropin-releasing hormone, corticotropin-releasing hormone, gonadotropin-releasing hormone and growth hormone-releasing hormone), apart from dopamine, which suppresses prolactin production. In response to the releasing hormone rate, the anterior pituitary produces its hormones (TSH, ACTH, LH, FSH, GH) that stimulate effector hormone glands in the body, although prolactin acts directly on the breast gland. Once the effector glands produce sufficient hormones (thyroxine, cortisol, estradiol or testosterone and IGF-1), both the hypothalamus and the pituitary cells sense their abundance and reduce their secretion of stimulating hormones. The hormones of the posterior pituitary are produced in the hypothalamus and are carried by nerve endings to

the posterior lobe; their feedback system is therefore located in the hypothalamus, but damage to the nerve endings would still lead to a deficiency in hormone release.

Unless the pituitary damage is being caused by a tumor that overproduces a particular hormone, it is the lack of pituitary hormones that leads to the symptoms described above, and an excess of a particular hormone would indicate the presence of a tumor. The exception to this rule is prolactin: if a tumor compresses the pituitary stalk, a decreased blood supply means that the lactotrope cells, which produce prolactin, are not receiving dopamine and therefore produce excess prolactin. Hence, mild elevations in prolactin are attributed to stalk compression. Very high prolactin levels, though, point more strongly towards a prolactinoma (prolactin-secreting tumor).

Treatment

Treatment of hypopituitarism is threefold: removing the underlying cause, treating the hormone deficiencies, and addressing any other repercussions that arise from the hormone deficiencies.

Underlying cause

Pituitary tumors require treatment when they are causing specific symptoms, such as headaches, visual field defects or excessive hormone secretion. Transsphenoidal surgery (removal of the tumor by an operation through the nose and the sphenoidal sinuses) may, apart from addressing symptoms related to the tumor, also improve pituitary function, although the gland is sometimes damaged further as a result of the surgery. When the tumor is removed by craniotomy (opening the skull), recovery is less likely–but sometimes this is the only suitable way to approach the tumor. After surgery, it may take some time for hormone levels to change significantly. Retesting the pituitary hormone levels is therefore performed 2 to 3 months later.

Prolactinomas may respond to dopamine agonist treatment–medication that mimics the action of dopamine on the lactrotrope cells, usually bromocriptine or cabergoline. This approach may improve pituitary hormone secretion in more than half the cases, and obviate the need for supplementary treatment.

Other specific underlying causes are treated as normally. For example, hemochromatosis is treated by venesection, the regular removal of a fixed amount of blood. Eventually, this decreases the iron levels in the body and improves the function of the organs in which iron has accumulated.

Hormone replacement

Most pituitary hormones can be replaced indirectly by administering the products of the effector glands: hydrocortisone (cortisol) for adrenal insufficiency, levothyroxine for hypothyroidism, testosterone for male hypogonadism, and estradiol for female hypogonadism (usually with a progestagen to inhibit unwanted effects on the uterus).

Growth hormone is available in synthetic form, but needs to be administered parenterally (by injection). Antidiuretic hormone can be replaced by desmopressin (DDAVP) tablets or nose spray. Generally, the lowest dose of the replacement medication is used to restore wellbeing and correct the deranged results, as excessive doses would cause side-effects or complications. Those requiring hydrocortisone are usually instructed to increase their dose in physically stressful events such as injury, hospitalization and dental work as these are times when the normal supplementary dose may be inadequate, putting the patient at risk of adrenal crisis.

Long-term follow up by specialists in endocrinology is generally needed for people with known hypopituitarism. Apart from ensuring the right treatment is being used and at the right doses, this also provides an opportunity to deal with new symptoms and to address complications of treatment.

Difficult situations arise in deficiencies of the hypothalamus-pituitary-gonadal axis in people (both men and women) who experience infertility; infertility in hypopituitarism may be treated with subcutaneous infusions of FSH, human chorionic gonadotropin–which mimics the action of LH–and occasionally GnRH.

Complications

Several hormone deficiencies associated with hypopituitarism may lead to secondary diseases. For instance, growth hormone deficiency is associated with obesity, raised cholesterol and the metabolic syndrome, and estradiol deficiency may lead to osteoporosis. While effective treatment of the underlying hormone deficiencies may improve these risks, it is often necessary to treat them directly.

Prognosis

Several studies have shown that hypopituitarism is associated with an increased risk of cardiovascular disease and some also an increased risk of death of about 50% to 150% the normal population. It has been difficult to establish which hormone deficiency is responsible for this risk, as almost all patients studied had growth hormone deficiency. The studies also do not answer the question as to whether the hypopituitarism itself causes the increased mortality, or whether some of the risk is to be attributed to the treatments, some of which (such as sex hormone supplementation) have a recognized adverse effect on cardiovascular risk.

The largest study to date followed over a thousand people for eight years; it showed an 87% increased risk of death compared to the normal population. Predictors of higher risk were: female sex, absence of treatment for sex hormone deficiency, younger age at the time of diagnosis, and a diagnosis of craniopharyngioma. Apart from cardiovascular disease, this study also showed an increased risk of death from lung disease.

Quality of life may be significantly reduced, even in those people on optimum medical therapy. Many report both physical and psychological problems. It is likely that the

commonly used replacement therapies still do not completely mimic the natural hormone levels in the body. Health costs remain about double those of the normal population.

Epidemiology

There is only one study that has measured the prevalence (total number of cases in a population) and incidence (annual number of new cases) of hypopituitarism. This study was conducted in Northern Spain and used hospital records in a well-defined population. The study showed that 45.5 people out of 100,000 had been diagnosed with hypopituitarism, with 4.2 new cases per year. 61% were due to tumors of the pituitary gland, 9% due to other types of lesions, and 19% due to other causes; in 11% no cause could be identified.

Recent studies have shown that people with a previous traumatic brain injury, spontaneous subarachnoid hemorrhage (a type of stroke) or radiation therapy involving the head have a higher risk of hypopituitarism. After traumatic brain injury, as much as a quarter have persistent pituitary hormone deficiencies. Many of these people may have subtle or non-specific symptoms that are not linked to pituitary problems but attributed to their previous condition. It is therefore possible that many cases of hypopituitarism remain undiagnosed, and that the annual incidence would rise to 31 per 100,000 annually if people from these risk groups were to be tested.

History

The pituitary was known to the ancients, such as Galen, and various theories were proposed about its role in the body, but major clues as to the actual function of the gland were not advanced until the late 19th century, when acromegaly due to pituitary tumors was described. The first known report of hypopituitarism was made by the German physician and pathologist Dr Morris Simmonds. He described the condition on autopsy in a 46-year old woman who had suffered severe puerperal fever eleven years earlier, and subsequently suffered amenorrhea, weakness, signs of rapid aging and anemia. The pituitary gland was very small and there were few remnants of both the anterior and the posterior pituitary. The eponym *Simmonds' syndrome* is used infrequently for acquired hypopituitarism, especially when cachexia (general ill health and malnutrition) predominates. Most of the classic causes of hypopituitarism were described in the 20th century; the early 21st century saw the recognition of how common hypopituitarism could be in previous head injury victims.

Until the 1950s, the diagnosis of pituitary disease remained based on clinical features and visual field examination, sometimes aided by pneumoencephalography and X-ray tomography. Nevertheless, the field of pituitary surgery developed during this time. The major breakthrough in diagnosis came with the discovery of the radioimmunoassay by Rosalyn Yalow and Solomon Berson in the late 1950s. This allowed the direct measurement of the hormones of the pituitary, which as a result of their low concentrations in blood had previously been hard to measure. Stimulation tests were developed in the 1960s, and in 1973 the triple bolus test was introduced, a test that

combined stimulation testing with insulin, GnRH and TRH. Imaging of the pituitary, and therefore identification of tumors and other structural causes, improved radically with the introduction of computed tomography in the late 1970s and magnetic resonance imaging in the 1980s.