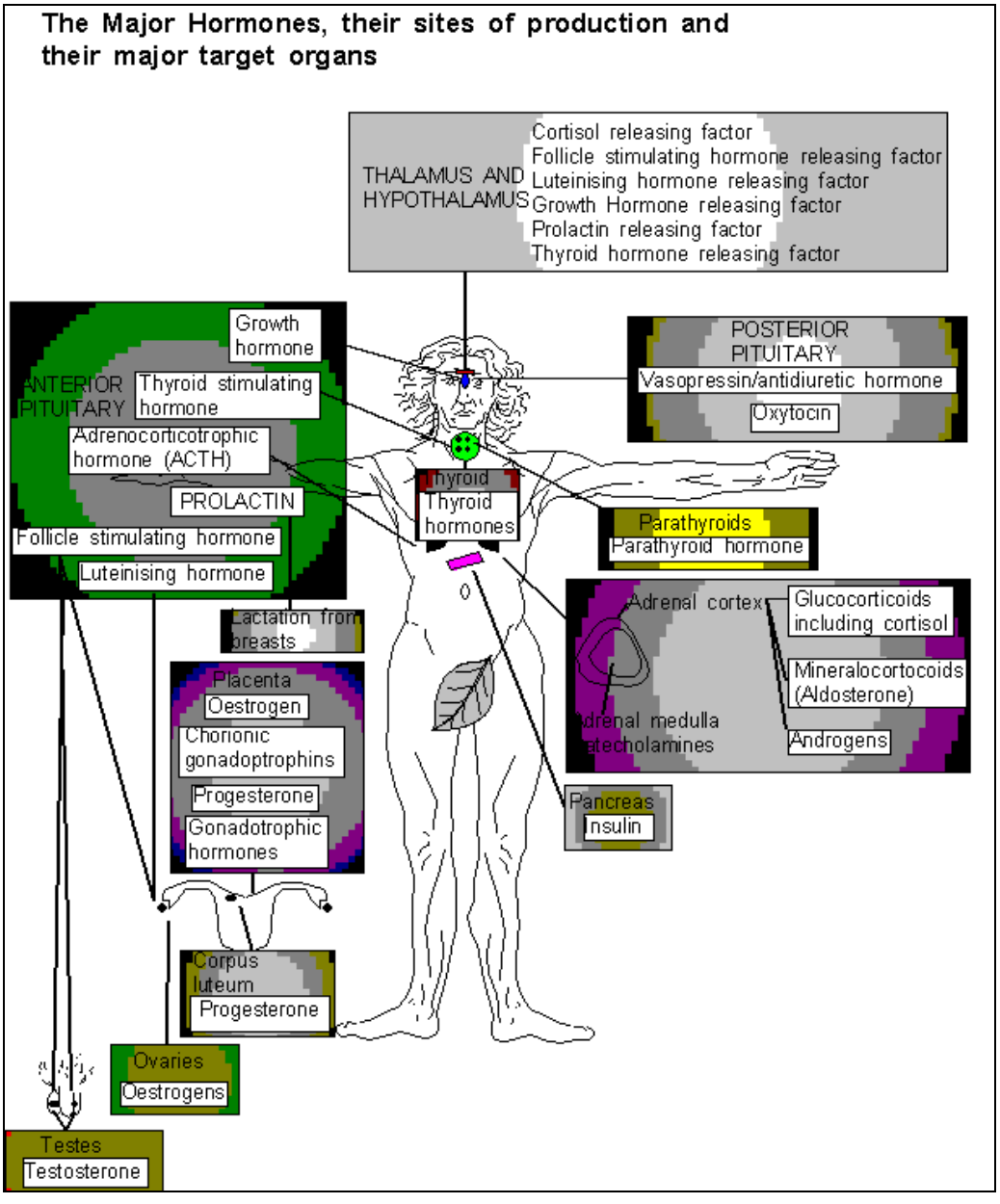
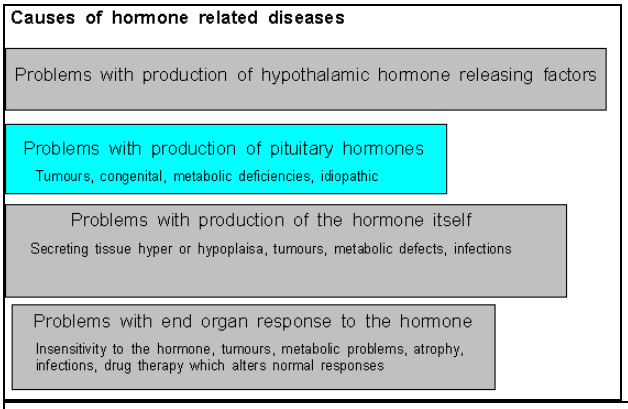
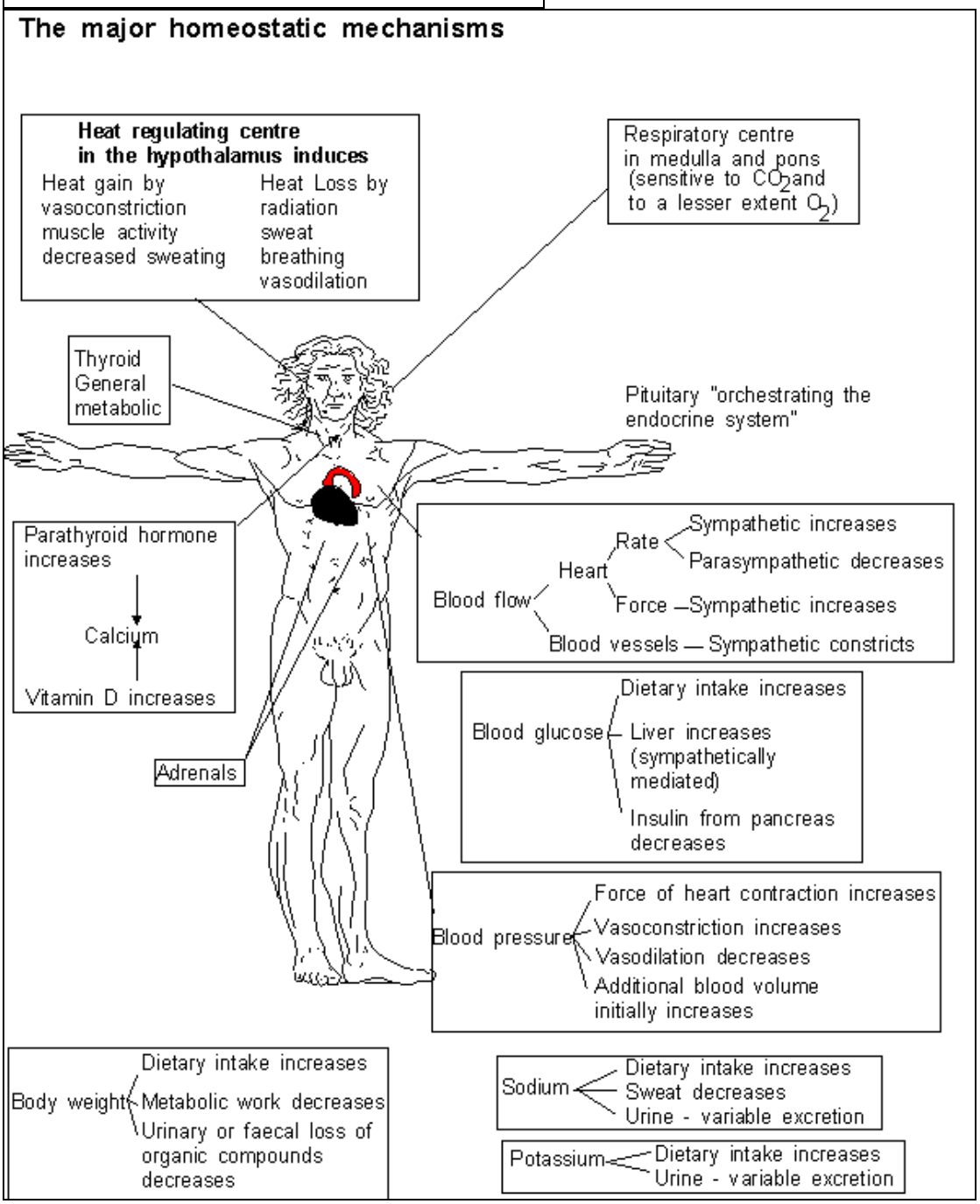
HORMONES AND THEIR ACTIONS

The body has two message bearing systems, the electric rapidly reacting nervous system and a slower chemical system using the hormones. The nervous system and the endocrine system interface at the pituitary or at the adrenal medulla.

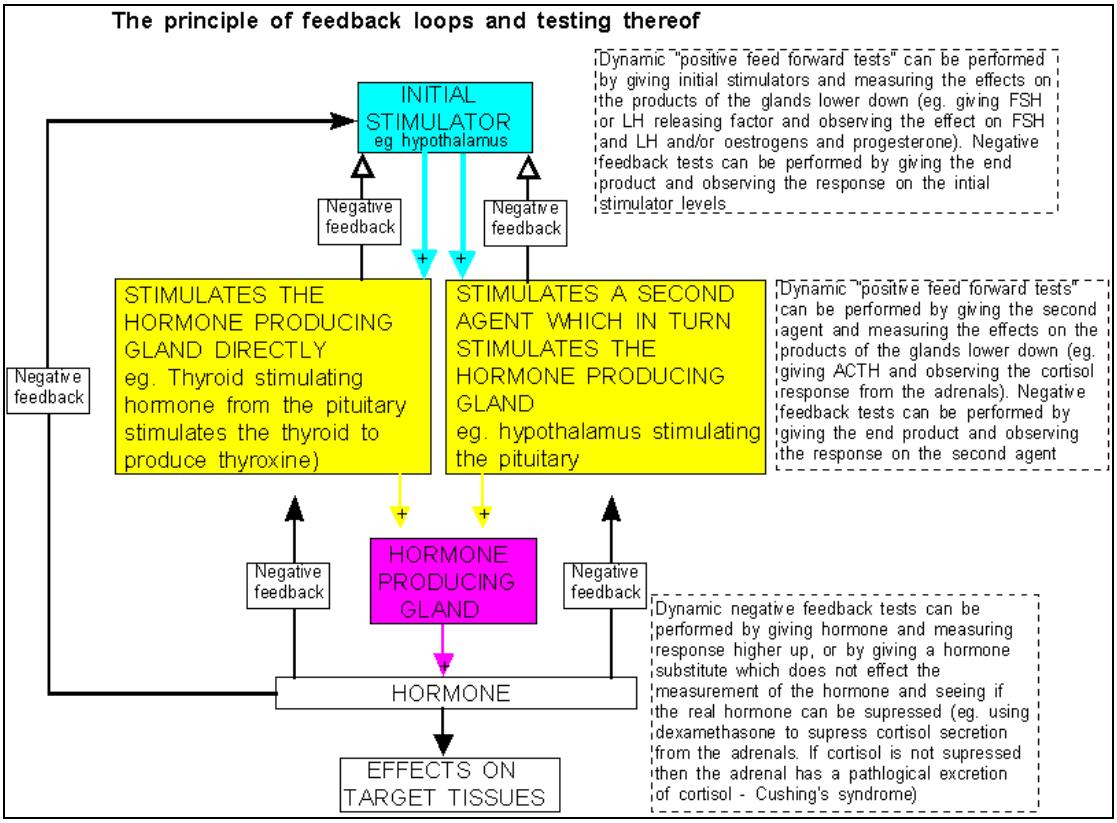
A hormone is a chemical messenger substance which when carried to a target tissue, influences its functional activity. The hormonal (endocrine) ductless glands secrete internally, usually into the blood (*eccrine* glands such as sweat and mammary glands secrete externally, usually via ducts). Some glands have both endocrine and eccrine functions. The pancreas for example secretes enzymes into the gut and insulin and glucagon into the blood. Hormones are usually targeted towards specific cells or tissues of the body (thyroid hormones and adrenaline which may affect many systems are exceptions).



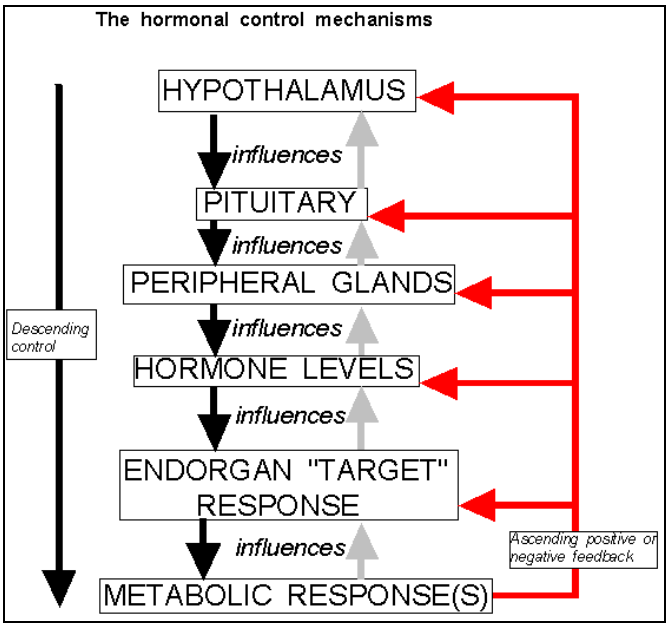




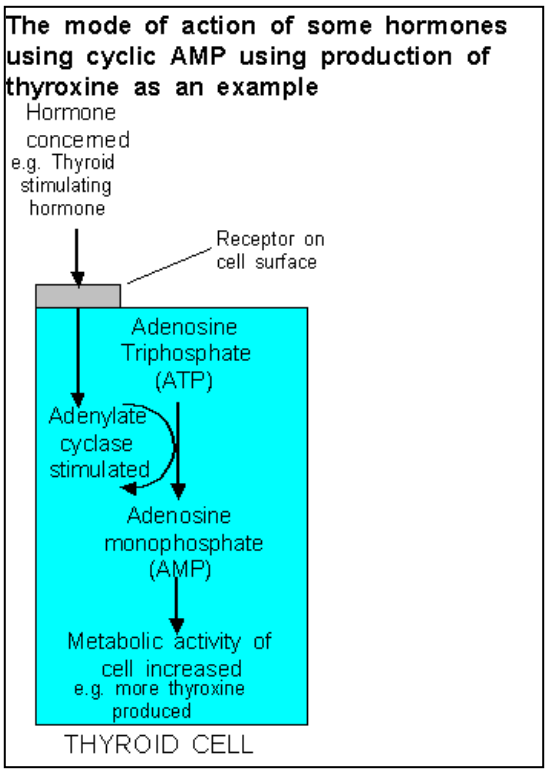
The metabolically active part of a hormone may participate in feedback loops.



It is the free “unbound” part of a hormone which usually activates target cells via binding sites “receptors” on target cell surfaces.



One of the best understood intracellular targets for hormonal action is an enzyme, adenylate cyclase, whose catalyst action can either be stimulated or inhibited by the appropriate hormone to vary the intracellular levels of cyclic AMP which is “the second messenger,” which can then modify (usually increasing) some of the general or specific actions of the cell involved.



Using this and other mechanisms thyroid stimulating hormone increases the production of thyroid hormone, adrenocorticotrophic hormone stimulates part of the adrenal cortex to produce cortisol, and follicle stimulating hormone stimulates the female ovarian follicles. Adrenaline however affects several target cells, stimulating the actions of adenylate cyclase in some sites but inhibiting it in others by binding onto different receptor sites - alpha sites (to stimulate smooth muscle to contract) or beta sites (to stimulate smooth muscle contraction and to increase the rate and force of heart muscle contraction).

Some hormones are metabolised within minutes, and thus have a short half-life, but others have intrinsically longer half-lives. Some hormones are partially protected from breakdown by the liver and/or excretion by the kidneys by binding to proteins (corticosteroid binding globulin and sex-hormone binding globulin for example).

Obviously diagnosis of hormone dysfunction initially depends upon clinical suspicion and for many hormone disorders a blood specimen taken at an appropriate time may be highly suggestive, but levels of certain hormone levels may vary through the course of a day (corticosteroids) or menstrual cycle (oestrogens). Often dynamic tests (giving stimulating or inhibiting stimuli) are used, particularly if feedback mechanisms involving the hypothalamus, pituitary and peripheral organs are involved.

Hormones produced by tissues derived from embryonic ectoderm or endoderm (including the pituitary, parathyroids and pancreas) are proteins, peptides, or amino acids and cannot be given by mouth as they would be digested. Hormones secreted from mesodermally derived tissues (gonads, adrenal cortex and placenta) are steroids and can usually be given by mouth.

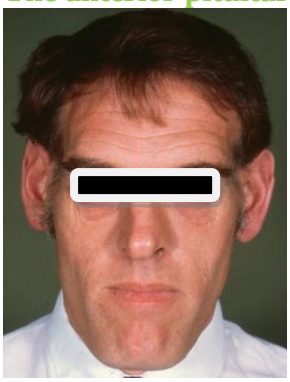
The Pituitary

A simplified account of the sites of production of the major hormones from the hypothalamus, pituitary, peripheral glands and their actions on peripheral tissues is shown below. Hormone-related diseases may be caused by several mechanisms.

There are many more hormones, some of which will be mentioned under their relevant chapters. About 50 percent of pituitary tumours may secrete trophic (=stimulating) hormones which then cause abnormal function of their target organs. Additionally, both secretory and non-secretory pituitary tumours hormones, may present with:

- Signs from pressure on the optic nerves (classically a bitemporal hemianopia
- Pituitary hypofunction caused by compression
- Headache

The anterior pituitary



Underproduction of growth hormone by the anterior pituitary during childhood leads to retarded growth and dwarfism, whereas overproduction *in childhood* leads to giantism with overgrowth of the long bones of the limbs. Overproduction of growth hormone in adults leads to overgrowth of the bones of the hands, feet, and head to produce acromegaly.

Prolactin

Prolactin stimulates milk secretion and reduces ovarian secretion of oestrogens or testicular secretion of testosterone. It can block luteinising hormone effects to produce hypogonadism. In females hyperprolacinaemia usually presents with amenorrhoea and in males with lack of libido.

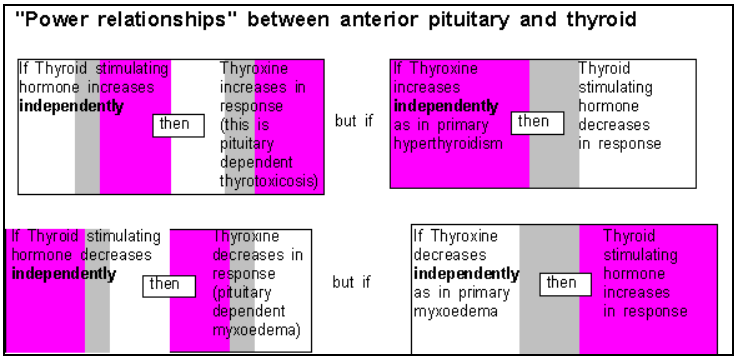
The posterior pituitary

The posterior pituitary is derived from Rathke's pouch, originally an outpouching of the fish mouth which presumably responded to changes in water, and indeed the human posterior pituitary retaines water balance as one of its functions by production of antidiuretic hormone (vasopressin). Antidiuretic hormone causes the distal convoluted kidney tubules and collecting ducts to retain water (link). Failure of antidiuretic hormone production (or insensitivity of the kidneys to it) causes diabetes insipidus with production of large volumes of dilute urine. Oxytocin, the other hormone produced by the posterior pituitary, has an important role in the physiology of childbirth and in the let-down reflex of lactation.

PERIPHERAL GLAND DYSFUNCTION

Thyroid

Iodine is taken up by the thyroid (= shield shaped) gland and is eventually processed along with tyrosine (an amino acid) to produce thyroxine and triiodothronine which are general metabolic stimulants. Thyroid stimulating hormone is produced by the anterior pituitary and is the main stimulator of this process. Both thyroxine and triiodothyronine are bound to proteins in the blood but it is the unbound (free) levels that are physiologically important. Thyroxine is converted to the more active triiodothyronine in peripheral tissues. In areas where iodine deficiency is common enlarged thyroid (a goitre) may result.



Causes of thyroid disease

Immune mechanisms produce hypothyroidism by initiating thyroid overactivity leading to "burnout", or by producing thyroid inflammation. In Grave's disease circulating antibodies to thyroid stimulating hormone receptors present on thyroid cells stimulate the receptors to cause diffuse thyroid enlargement (a goitre) and thyroid overactivity

Inborn metabolic errors

Nutritional defects (especially involving iodine)

Developmental defects

Benign tumours

Focal thyroid diseases, including cysts and tumours, may produce focal enlargement of the thyroid whereas generalised disease may cause generalised thyroid enlargement

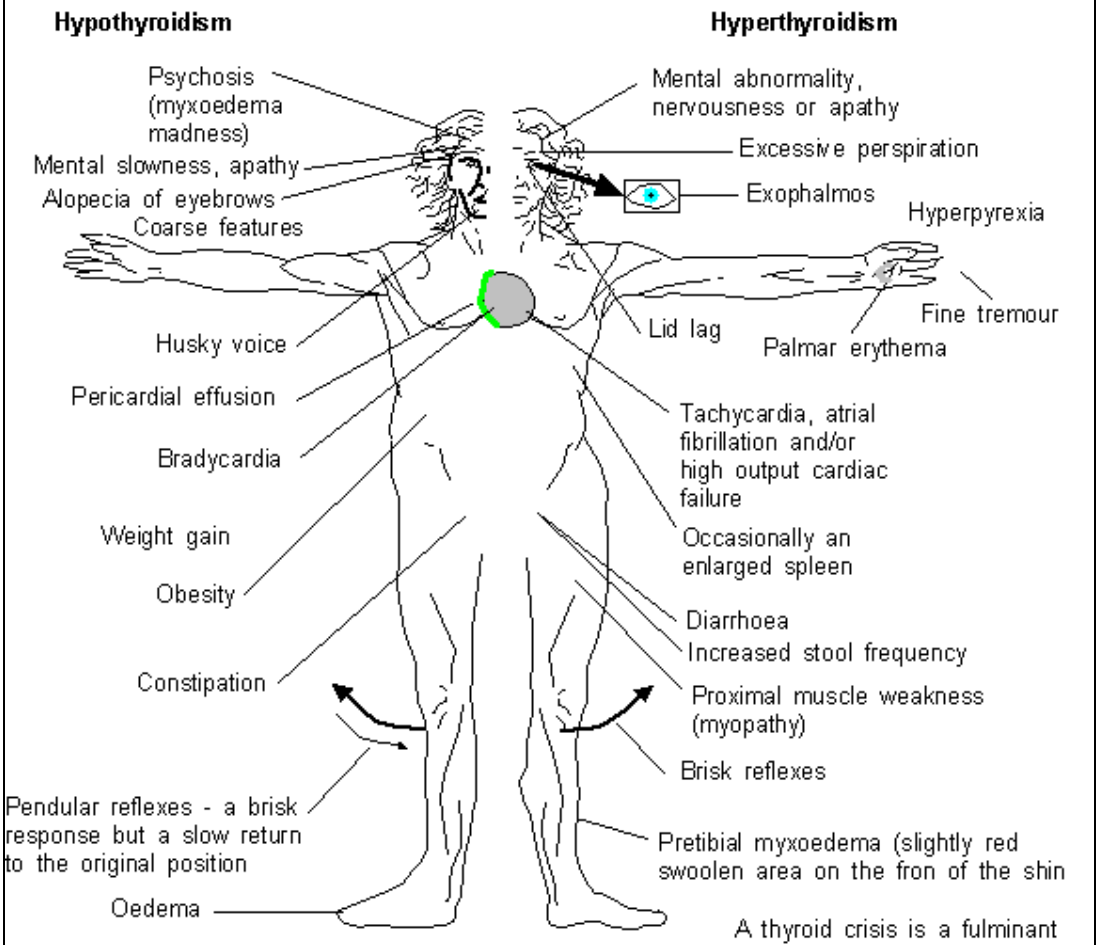
Maliganant tumours

Previous treatment (including surgery)

Immune mediated processes

Drug treatments

The possible symptoms and signs of hyper and hypo thyroidism

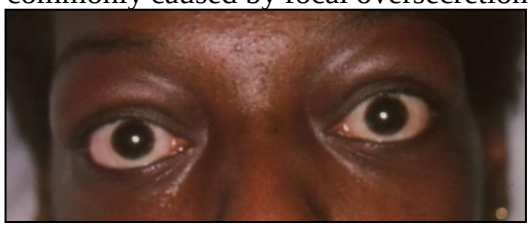


Hyper or hypo thyroidism
Generalised weakness
Enlarged thyroid
Vitiligo
Heart failure

A thyroid crisis is a fulminant exacerbation of all thyrotoxic symptoms and signs, usually with fever and gross tachycardia

Hyperthyroidism

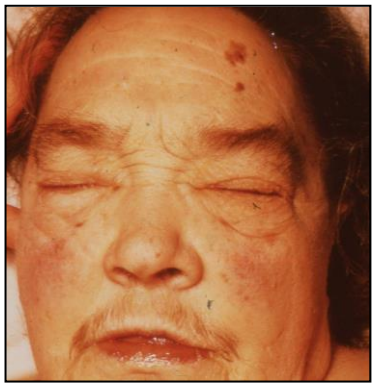
Hyperthyroidism results when the thyroid produces excessive thyroxine and triiodothyronine. If the hyperthyroidism is caused by primary thyroid hyperactivity the thyroxine and triiodotyronine levels are increased which supresses thyroid stimulating hormone. In contrast if the hyperactivity is secondary to pituitary overproduction, which is rare, the thyroid stimulating hormone level will be raised. Hyperthyroidism is usually caused by immune mediated mechanisms and less commonly caused by focal oversecretion by thyroid nodules (toxic adenomas).



Hyperthyroidism caused by diffuse thyroid overactivity (Grave's disease) may be associated with protrusion of one or both eyes (exophthalmos).

Retraction of the upper eyelid, and delay in descent of the upper eyelid as the eye is rotated downwards – lidlag – mayoccur in all types of hyperthyroidism.

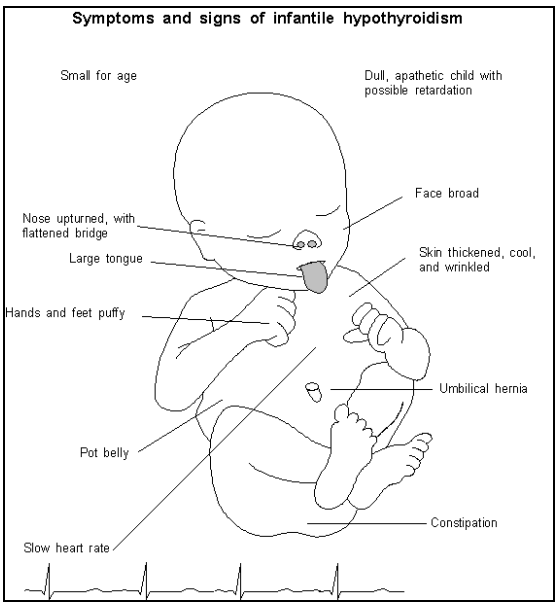
Treatment of hyperthyroidism is with anti-thyroid drugs, radioactive iodine or surgery. Beta-blocking drugs (link) are useful for initial treatment as they block the "pseudo-adrenergic" overdrive caused by high levels of thyroid hormones.



Hyperthyrodism

In primary hypothyroidism the thyroxine and triiodothyronine levels are low. The thyroid stimulating hormone levels are high as the pituitary tries drive the failing thyroid harder. Indeed a raised thyroid stimulating hormone may be the first indication of impending hypothyroidism.

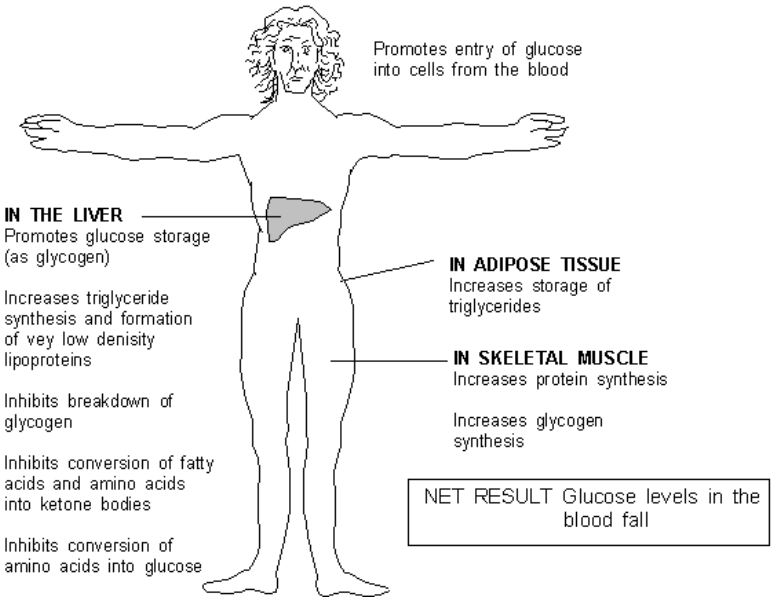
Hypothyroidism may be present at, or develop shortly after, birth and cause cretinism.



The endocrine pancreas

The pancreas increases peripheral tissue utilisation of glucose. Too little insulin, or too great a demand for insulin leads to diabetes mellitus with a high plasma glucose which functions as an osmotic diuretic to produce dehydration and coma. Glucagon, which causes glucose release from glycogen, is also produced by the pancreas.

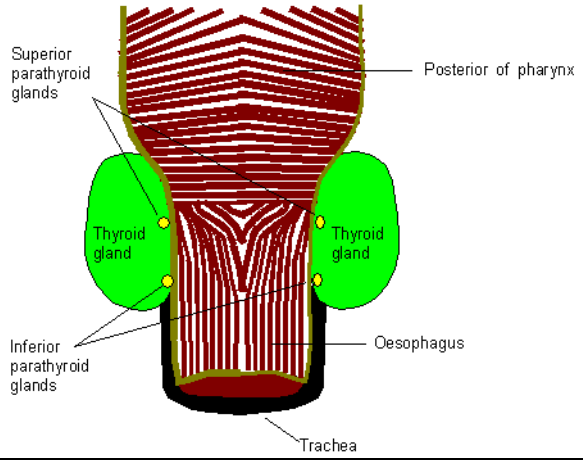
The major actions of insulin



Parathyroids

The parathyroid glands (view from behind the pharynx)

There are usually four parathyroid glands, which usually lie between the posterior thyroid and its capsule



Parathormone and vitamin D affect calcium and phosphorus levels. If free ionised calcium falls or phosphate increases the parathyroids excrete extra parathormone which tries to restore the free ionised calcium to normal by:

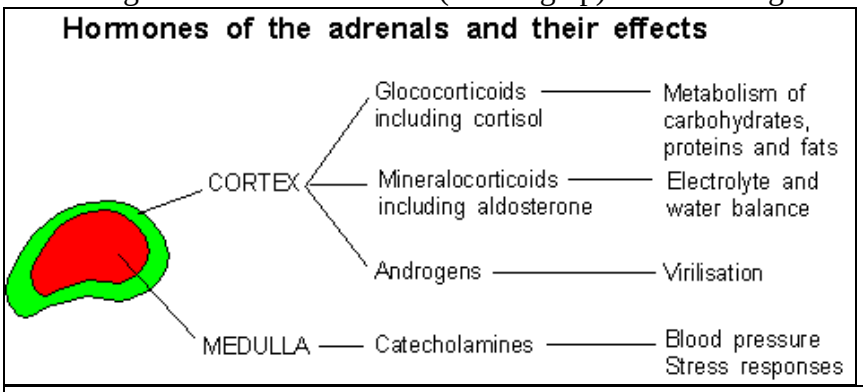
- Stimulating release of calcium from bone
- Increasing the loss of phosphate in the urine and increasing calcium reabsorption by the kidney
- Favouring of active forms of Vitamin D that promote gastrointestinal absorption of calcium

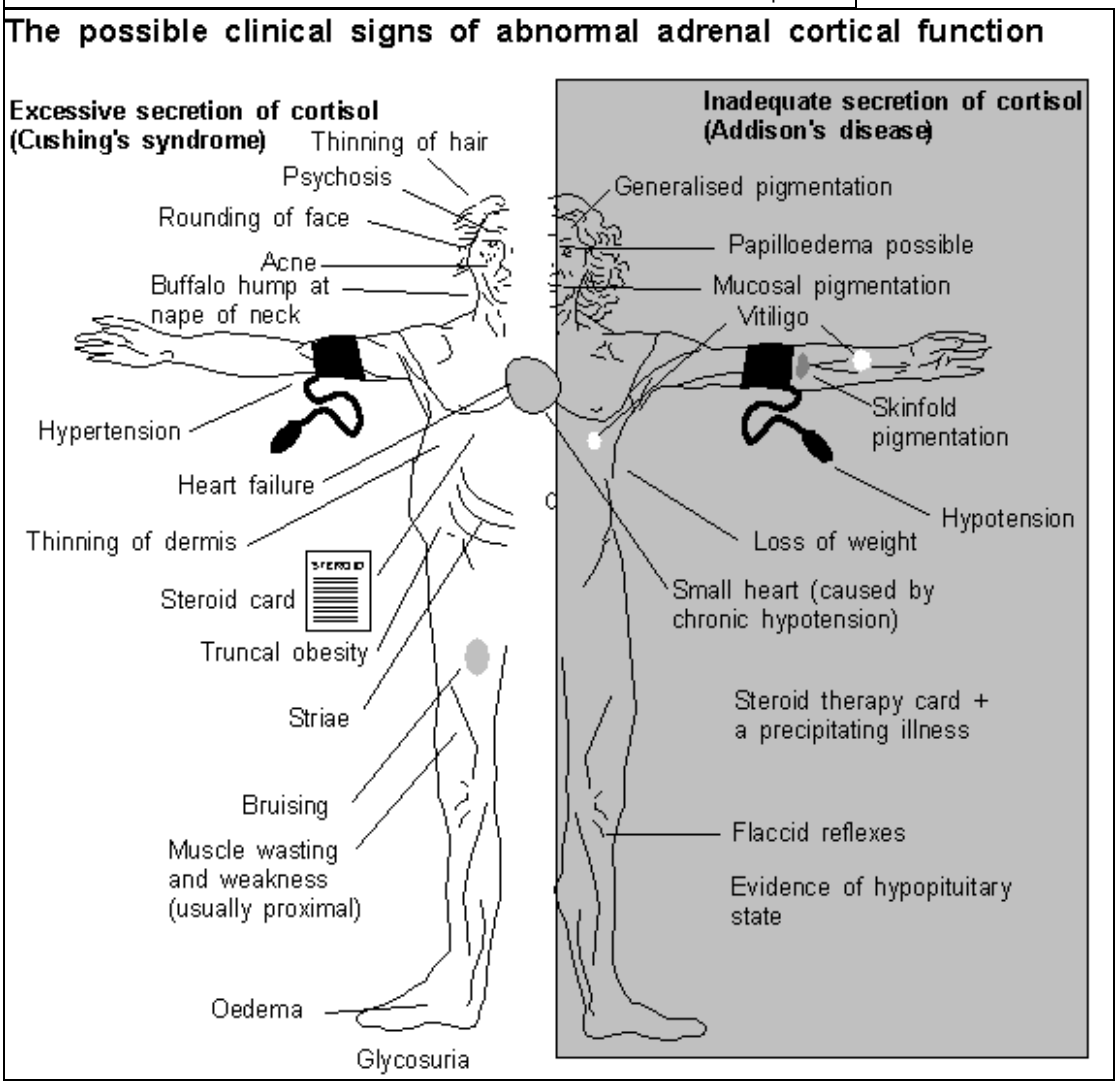
THE ADRENALS

Adrenal cortex

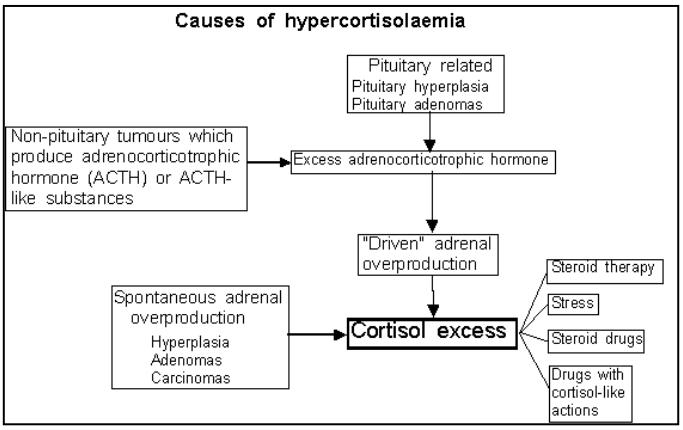
The adrenal cortex secretes three main classes of hormones:

- Glucocorticoids (including cortisol) which affect carbohydrate, protein and fat metabolism
- Mineralocorticoids (including aldosterone) which affect electrolyte and water regulation
- Androgens which are anabolic (building up) and virilising in action





Adrenal cortical hyperfunction

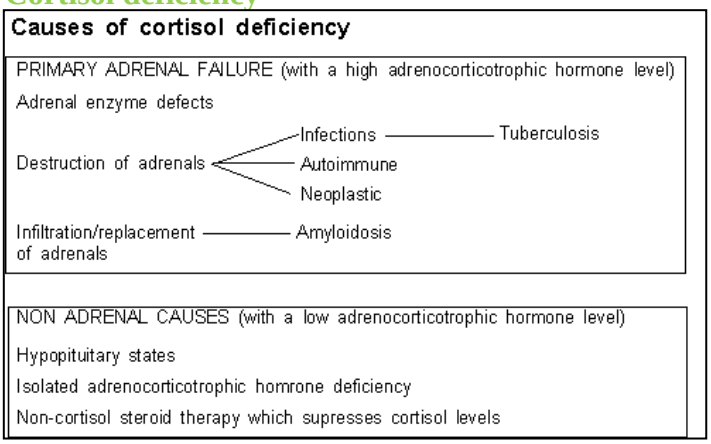


Adrenal cortical hyperfunction may be caused by adrenal cortical overdevelopment (hyperplasia), benign glandular tumours (adenomas), or adenocarcinomas. Cushing's syndrome is caused by overproduction of cortisol by the adrenal cortex, either primary or secondary to pituitary overproduction of adrenocorticotrophic hormone. The causes of hypercortisolaemia are shown above.

Treatment can be with surgery or radiotherapy or with drugs which block adrenal production of cortisol.

Aldosterone overproduction causes excessive sodium retention and excessive potassium excretion by the distal convoluted tublules of the kidney. Renin concentrations in primary hyperaldosteronism are low and aldosterone/renin levels are high. Reduced pefusion of the kidneys with overproduction of renin induces extra secretion of aldosterone - secondary hyperaldosteronism. Excessive production of androgens causes virilism.

Cortisol deficiency



The principle features of cortisol deficiency are sodium depletion, water depletion, a high serum potassium, and a raised urea (caused by dehydration). With severe deficiencies there is a fast heart rate, a low blood pressure and dehydration possibly leading to hypovolaemic shock.

If hypocortisolaemia is caused by adrenal cortex failure (Addison's disease) rather than by pituitary failure there may be increased pigmentation of pressure points, skin creases, and lining of the cheeks. This is caused by increased adrenocorticotrophic hormone production by the pituitary (as it attempts to drive the failing adrenal cortex) and adrenocortocotrophic hormone co-stimulates the production of melanocyte –

stimulation hormone, the pigment producing cells of the skin) to produce a brownish discolouration. These effects do not occur if the cause is primary pituitary failure.

If a low cortisol is caused by pituitary failure (with lack of adrenocorticotrophic hormone) the signs are usually less dramatic - mostly because the continued production of aldosterone (link) by the adrenal cortex continues.

The adrenal medulla (medulla = pith)
The adrenal medulla is innervated by the sympathetic nervous system and produces several catecholamines, notably adrenaline (epinephrine) and nonadrenaline. Catecholamines are responsible for "adrenergic" responses to physical and mental stress and produce a fast heart rate, nervousness, and mobilisation of energy.

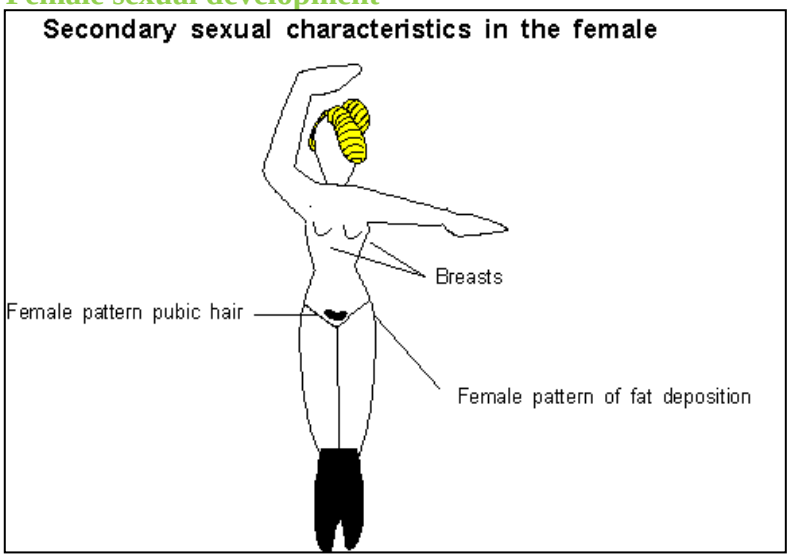
SEX HORMONES

Male sexual development

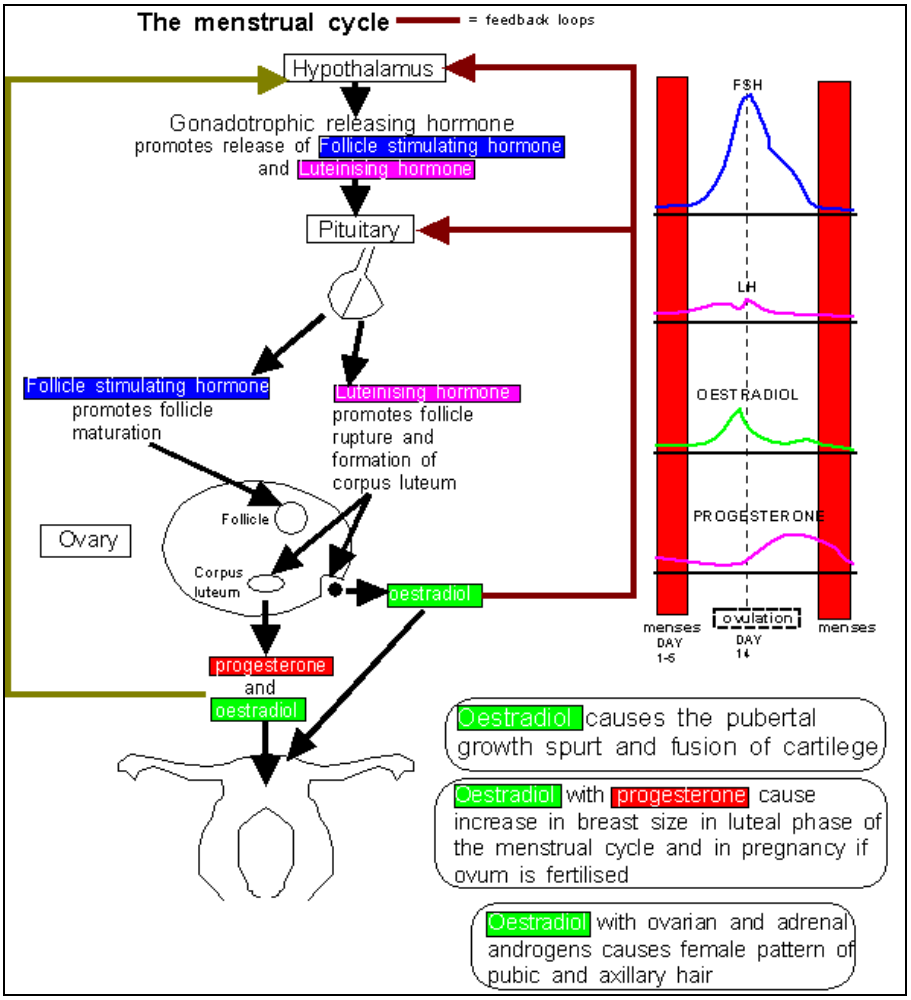
Functional testes are necessary for male pattern growth, sexual differentiation and function, penile growth, secondary sexual characteristics and behaviour. The secondary male characteristics are mediated by testosterone (or dihydrotestosterone). Interestingly males and females use the same hormones, almost certainly because maleness only emerges when a an X chromosome is replaced by a Y chromosome. In the male the production of follicle stimulating hormone and luteinising hormone are constant whereas production in the female is cyclical.

After puberty in the male (usually between 10-15 years) the testes produce androgens (testosterone and dihydrotestosterone) in response to pituitary-derived luteininsing hormone. Spermatozoa are produced in response to the combination of follicle stimulating hormone and testosterone. The androgens (=male makers) along with growth hormone cause the pubertal growth spurt. The sex hormone binding globulins decrease at puberty which releases more free hormones.

Female sexual development



At puberty, which usually occurs two years earlier in the female, follicle stimulating hormone causes maturation of ovarian follicles (follicle = small sac or gland) and luteinising hormone causes ovarian follicles to rupture and the corpus luteum (the mass formed in the uterine wall after the follicle has discharged the ovum) to develop. The various feedback systems and actions of these hormones in relationship to the menstrual cycle are shown below.



Following menstruation, follicle stimulating hormone rises, follicle development is thereby stimulated, with follicles secreting oestrogen. One follicle becomes predominant, matures and secretes oestradiol that suppresses competing follicles, and inhibits the pituitary from secreting further follicle stimulating hormone. Just before menstruation the oestradiol levels fall and luteinising hormone increases which induces the ripe follicle to ovulate – "burst"- and the remaining tissue to form the Corpus luteum which secretes progesterone and oestradiol to maintain a receptive endometrium in case fertilization and implantation occur. In the absence of fertilization the Corpus luteum withers, progesterone levels fall, and the inner surface layers of the endometrium are shed (menstruation)

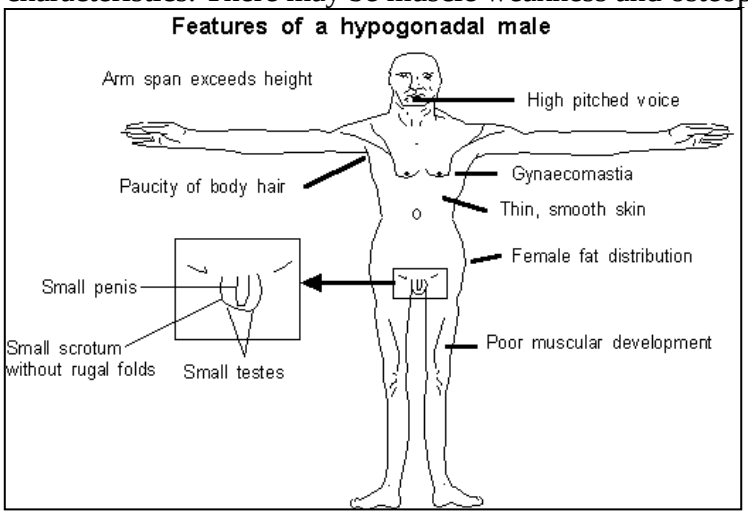
If fertilization occurs, the fertilized ovum penetrates the uterine inner wall (endometrium) and it and the placenta secrete chorionic gonadotrophins (oestrogens, progesterone, and gonadotrophic hormones) that constitute the ovum's version of luteinising hormone. These stop the Corpus luteum degenerating and thus the early pregnancy in maintained. Progesterone also stimulates the oestrogen-primed breast in the luteal phase and prepares the breast for lactation. Prolactin has a more important role later on in pregnancy and in the post-partum state.

Hypogonadism

There are several syndromes that are associated with hypogonadism. Rather that present the numerous syndromes the following is a brief review of the principle mechanisms and manifestations.

Male hypogonadism

Male hypogonadism results from inadequate testosterone production from the testes, pituitary dysfunction or hypothalamic dysfunction. Male hyopogonadism, particularly if occurring before puberty, may result in subnormal height, lack of bodily hair, an unbroken voice, small testes, poor muscle development, and a small penis and scrotum. Bone epiphyses may fail to fuse and a final adult height may be greater than normal. In post-pubertal males, hypogonadism is usually of slow onset with decreased libido and, when severe, less need to shave and regression of secondary sexual characteristics. There may be muscle weakness and osteoporosis.



In postpubertal males hypogonadism is usually of slow onset with decreased libido and, when severe, less need to shave and regression of secondary sexual characteristics.

Female hypogonadism

If there is primary ovarian hypofunction the pituitary-derived follicle stimulating hormone and/or the luteinising hormone are often raised in an attempt to stimulate the failing ovaries. If the ovarian dysfunction is secondary to other causes (such as weight loss in anorexia nervosa) the follicle stimulating hormone and luteinising hormone are low with low oestradiol and progesterone levels leading to absence of periods (amenorrhoea).

During the normal cessation of menstruation, the menopause, oestradiol levels become low and follicle stimulating hormone levels rise - as if to stimulate the failing ovaries. The lack of oestrogen is associated with vaginal dryness, infertility, amenorrhoea, lack of libido, breast atrophy and bone loss (the traditional hot flushes are caused by sympathetic nervous system activation).

Problems of sexual differentiation

What follows is an unashamedly simple summary of a complex subject. In the male abnormalities of normal sexual differentiation may be caused by hypothalamic and/or pituitary hypofunction with low follicle stimulating and luteinising hormones levels. In contrast testicular causes of male hypogonadism may be associated with high follicle stimulating and/or luteinisng hormones which are “trying to drive the failing

testes." Enlargement of the breasts in the male is usually produced by absolute or relative excess of oestrogens or oestrogen-like drugs.

In genetic males a testicular feminisation syndrome results if there is end-organ unresponsiveness to testosterone. Those affected cannot develop the normal male genitalia. This syndrome usually presents with failure to menstruate in a genetically male patient of superficially female appearance who has sparse pubic hair, normal external female genitalia, but with a "blind pouch" vagina, and who lacks a uterus or ovaries. Undeveloped testes may be palpated in the groin

In genetic females abnormalities of sexual differentiation may be caused *in utero* by excess androgens, usually initiated by deficient cortisol production by the adrenals. The high adrenocorticotrophic hormone cannot produce cortisol from the foetal adrenals but, as a side effect, they do produce excessive androgens. Female babies thus have virilized genitalia (the genitalia of affected male babies are usually normal). Both males and females babies may present with signs of acute cortisol deficiency.

In adult females virilisation may be caused by adrenal or ovarian adenomas or adenocarcinomas. Hirsutism is a male pattern of bodily (particularly pubic) hair which may be caused by adrenal or ovarian androgen overproduction but frequently is of no significance unless there is also virilisation with frontal balding, enlargement of the clitoris or deepening of the voice.

There are numerous other tissues which secrete hormones including the pineal (which secretes melatonin which is responsible for light-adapted body systems), the thymus, the atria of the heart, the stomach, the small intestine, and areas adjacent to the kidney glomerulus (which produce renin).