

Hormones are **in red.**

Organized by Organ/Location

Hypothalamus

**Thyrotropin-releasing hormone (TRH)**

TRH is a tripeptide (GluHisPro).

When it reaches the anterior lobe of the pituitary it stimulates the release there of  
thyroid-stimulating hormone (TSH)  
prolactin (PRL)

**Gonadotropin-releasing hormone (GnRH)**

GnRH is a peptide of 10 amino acids.

Primary Effects

FSH and LH Up

Secondary Effects

estrogen and progesterone Up (in females)

testosterone Up (in males)

GnRH Clinical

A hyosecretion of GnRH may result from  
intense physical training  
anorexia nervosa

Synthetic agonists of GnRH are used to treat  
inherited or acquired deficiencies of GnRH secretion.  
prostate cancer. In this case, high levels of the GnRH agonist reduces the  
number of GnRH receptors in the pituitary, which  
reduces its secretion of FSH and LH, which  
reduces the secretion of testosterone, which  
reduces the stimulation of the cells of the prostate.

**Growth-hormone releasing hormone (GHRH)**

GHRH is a mixture of two peptides, one containing 40 amino acids, the other 44.

As its name indicates, GHRH stimulates cells in the anterior lobe of the pituitary to secrete  
growth hormone (GH).

**Corticotropin-releasing hormone (CRH)**

CRH is a peptide of 41 amino acids.

As its name indicates, its acts on cells in the anterior lobe of the pituitary to release  
adrenocorticotrophic hormone (ACTH)

CRH is also synthesized by the placenta and seems to determine the duration of pregnancy.  
It may also play a role in keeping the T cells of the mother from mounting an immune attack  
against the fetus.

**Somatostatin**

Somatostatin is a mixture of two peptides, one of 14 amino acids, the other of 28.

Somatostatin acts on the anterior lobe of the pituitary to

inhibit the release of growth hormone (GH)

inhibit the release of thyroid-stimulating hormone (TSH)

**Dopamine**

Dopamine is a derivative of the amino acid tyrosine. Its principal function in the hypothalamus  
is to inhibit the release of prolactin (PRL) from the anterior lobe of the pituitary.

**Ghrelin**

This peptide of 28 amino acids

stimulates the pituitary to release growth hormone (thus acting like GHRH);

stimulates feeding, at least in lab animals.

This second action counteracts the inhibition of feeding by leptin.

Pituitary

Anterior Pituitary

Acidophils

Somatotrophs

**Growth Hormone**

Human growth hormone (also called somatotropin) is a protein of 191 amino acids. The GH-secreting cells are stimulated to synthesize and release GH by the intermittent arrival of growth hormone releasing hormone (GHRH) from the hypothalamus. GH promotes body growth by:

- binding to receptors on the surface of liver cells
- this stimulates them to release insulin-like growth factor-1 (IGF-1; also known as somatomedin)
- IGF-1 acts directly on the ends of the long bones promoting their growth

Mammotrophs

**Prolactin**

Prolactin is a protein of 198 amino acids. During pregnancy it helps in the preparation of the breasts for future milk production. After birth, prolactin promotes the synthesis of milk. Prolactin secretion is

- stimulated by TRH
- repressed by estrogens and dopamine.

Basophils

Corticotrophs

**Adrenocorticotrophic hormone**

ACTH is a peptide of 39 amino acids. ACTH acts on the cells of the adrenal cortex, stimulating them to produce

- glucocorticoids, like cortisol
- mineralocorticoids, like aldosterone
- androgens (male sex hormones, like testosterone)

in the fetus, ACTH stimulates the adrenal cortex to synthesize a precursor of estrogen called dehydroepiandrosterone sulfate (DHEA-S) which helps prepare the mother for giving birth. Production of ACTH depends on the intermittent arrival of corticotropin-releasing hormone (CRH) from the hypothalamus.

Thyrotrophs

**Thyroid-stimulating hormone (TSH)**

TSH (also known as thyrotropin) is a glycoprotein consisting of: a beta chain of 112 amino acids and an alpha chain of 89 amino acids. The alpha chain is identical to that found in two other pituitary hormones, FSH and LH. Thus it is its beta chain that gives TSH its unique properties.

The secretion of TSH is

- stimulated by the arrival of thyrotropin releasing hormone (TRH) from the hypothalamus.
- inhibited by the arrival of somatostatin from the hypothalamus.

As its name suggests, TSH stimulates the thyroid gland to secrete its hormones

- thyroxine (T<sub>4</sub>)
- triiodothyronine (T<sub>3</sub>)

It does this by binding to transmembrane G-protein-coupled receptors (GPCRs) on the surface of the cells of the thyroid.

Gonadotrophs

**Follicle-stimulating hormone (FSH)**

FSH is a heterodimer of

- the same alpha chain found in TSH (and LH)
- a beta chain of 115 amino acids, which gives it its unique properties.

Synthesis and release of FSH is triggered by the arrival from the hypothalamus of gonadotropin-releasing hormone (GnRH). The effect of FSH depends on one's sex

FSH in females

In sexually-mature females, FSH (assisted by LH) acts on the follicle to stimulate it to release estrogens.

FSH in males

In sexually-mature males, FSH acts on spermatogonia stimulating (with the aid of testosterone) the production of sperm.

### Luteinizing hormone (LH)

LH is synthesized within the same pituitary cells as FSH and under the same stimulus (GnRH). It is a heterodimeric glycoprotein consisting of

the same 89-amino acid alpha subunit found in FSH and TSH

a beta chain of 115 amino acids that is responsible for its properties.

The effects of LH also depend on sex.

LH in females

In sexually-mature females, LH

stimulates the follicle to secrete estrogen in the first half of the menstrual cycle

a surge of LH triggers the completion of meiosis I of the egg and its release (ovulation) in the middle of the cycle

stimulates the now-empty follicle to develop into the corpus luteum, which secretes progesterone during the latter half of the menstrual cycle.

LH in males

LH acts on the interstitial cells of the testes stimulating them to synthesize and secrete the male sex hormone, testosterone.

LH in males is also known as interstitial cell stimulating hormone (ICSH).

### Anterior Pituitary Pathology

tumors = prolactinoma, somatotroph adenoma (gigantism, acromegaly), corticotroph adenoma (Cushing's disease)

GTT: glucose normally suppresses GH to zero

Panhypopituitarism

due to apoplexy (infarction), tumor, surgery, infiltrative dz, empty sella, hypothalamic dz, iatrogenic

hypothyroidism (nl TSH, low T4), adrenal insufficiency (low ACTH, low cortisol),

hypogonadism/amenorrhea (low estrogen, LH & FSH), no lactation (low prolactin), diabetes insipidus (low ADH)

GH, levothyroxine, hydrocortisone, estrogen, DdAVP

Sheehan syndrome = apoplexy post-partum (w/ shock, hemorrhage, hypotension); replace glucocorticoids before adding thyroid hormones

Acromegaly

GH-producing pituitary tumor -> constitutively activates Gas -> high cAMP

enlargement of hands/feet, excess sweating, glucose intolerance, hyperglycemia, hypertension, weakness; Dx: high IGF-1 (somatomedin C), abnl glucose tolerance test (pts. need high insulin levels to maintain normal glucose)

octreotide (somatostatin); surgery; radiation

complications = cardio dz, sleep apnea, diabetes, hypertension, colon malignancy, neuromuscular probs

Hyperprolactinemia

pituitary tumor (prolactinoma; often chromophobic); tumor may enlarge w/ exposure to estrogen (BC pills, pregnancy)  
amenorrhea + galactorrhea (mimics pregnancy); prolactin > 200; tumor smaller in women, larger in men; Dx: pregnancy test (negative), then prolactin level  
bromocriptine (D<sub>2</sub> agonist)  
often come back pregnant after Tx; high prolactin levels bad if: big tumor, abnl menses, fertility is issue, galactorrhea is concern

#### Posterior Pituitary

##### Antidiuretic Hormone (ADH) (from SON of hypothalamus)

ADH is a peptide of 9 amino acids. It is also known as arginine vasopressin.  
ADH acts on the collecting ducts of the kidney to facilitate the reabsorption of water into the blood. This it acts to reduce the volume of urine formed (giving it its name of antidiuretic hormone).

##### Oxytocin (from PVN of hypothalamus)

Oxytocin is a peptide of 9 amino acids. Its principal actions are:  
stimulating contractions of the uterus at the time of birth  
stimulating release of milk when the baby begins to suckle  
Oxytocin is often given to prospective mothers to hasten birth.  
Also released by the uterus.

#### Posterior Pituitary Syndromes

##### Diabetes insipidus

inability to concentrate urine; trauma (surgery), tumor, idiopathic, familial, pituitary stalk & hypothalamic lesions  
sudden onset polyuria & polydipsia; hypernatremia; volume depletion -> orthostatic hypotension; low urine osm w/ high serum osm; Dx: water deprivation test (w/ dDAVP) -> low urine osmolality

##### Pituitary DI

ADH not produced  
normal after dDAVP  
dDAVP

##### Nephrogenic DI

ADH doesn't work  
hyposmolar urine even after dDAVP

##### Primary polydipsia

compulsive water drinking due to lesion in thirst center  
can concentrate urine w/ hyperosmolar serum; no change w/ dDAVP  
dDAVP treatment would cause severe hyponatremia & brain damage

##### SIADH

ADH secretion despite water retention & plasma hypotonicity; due to CNS disorder, tumor (paraneoplastic), pulmonary dz, drugs  
hypotonic & hyponatremic plasma, hypertonic urine; Na > 120 -> ASx; Na between 110-120 -> confusion & lethargy; Na < 110 -> convulsions, coma, death; drinking continues despite inability to dilute urine (thirst not shut down)  
acute = furosemide (CPM if too rapid); chronic = treat underlying, water restriction, demeclocycline  
rapid change in [Na] is more important than absolute level; evaluate for heart failure, cirrhosis, nephrotic syndrome, hypothyroidism, cortisol defic, volume depletion

#### Pineal Gland

##### Melatonin

a derivative of the amino acid tryptophan.  
Synthesis and release of melatonin is  
stimulated by darkness and  
inhibited by light.

But even without visual cues, the level of melatonin in the blood rises and falls on a daily (circadian) cycle with peak levels occurring in the wee hours of the morning.

However, this cycle tends to drift in people who are totally blind - often making them sleepy during the day and wide awake at night. Giving melatonin at bedtime has proved helpful in a number of cases.

## Thyroid Gland

### Thyroxine (T<sub>4</sub>)

### Triiodothyronine (T<sub>3</sub>)

T<sub>4</sub> and T<sub>3</sub> are derivatives of the amino acid tyrosine with three (T<sub>3</sub>) or four (T<sub>4</sub>) atoms of iodine. These two hormones have many effects on the body. Among the most prominent of these are:  
an increase in metabolic rate (seen by a rise in the uptake of oxygen)  
an increase in the rate and strength of the heart beat

The cells responsible for the synthesis and release of T<sub>4</sub> and T<sub>3</sub> take up circulating iodine from the blood. This action as well as the synthesis of the hormones is stimulated by the interaction of TSH on transmembrane receptors at the cell surface.

### Calcitonin

Calcitonin is a polypeptide of 32 amino acids. The thyroid cells in which it is synthesized have receptors that bind calcium ions (Ca<sup>2+</sup>) circulating in the blood. These cells monitor the level of circulating Ca<sup>2+</sup>. A rise in its level stimulates the cells to release calcitonin.

bone cells respond by removing Ca<sup>2+</sup> from the blood and storing it in the bone

kidney cells respond by increasing the excretion of Ca<sup>2+</sup>

Both types of cells have surface receptors for calcitonin.

Because it promotes the transfer of Ca<sup>2+</sup> to bones, calcitonin has been examined as a possible treatment for osteoporosis, a weakening of the bones that is a leading cause of hip and other bone fractures in the elderly. Being a polypeptide, calcitonin cannot be given by mouth (it would be digested), and giving by injection is not appealing. However, inhaling calcitonin appears to be an effective way to get therapeutic levels of the hormone into the blood. A synthetic version of calcitonin (trade name = Miacalcin) is now available as a nasal spray.

## Pathology of Thyroid

### Sick euthyroid syndrome

physiologic response to any illness -> inhibits liver 5' deiodinase; TSH levels unresponsive to low T<sub>3</sub>

low total and free T<sub>3</sub>; normal/low TSH (would normally be high if hypothyroid), usu. normal T<sub>4</sub>

TSH is inappropriately normal

### Endemic goiter

at least 10% of population has iodine deficiency; due to 1) cassava (thiocyanate inhibits TPO), 2) glaciers (low iodine in soil), 3) selenium deficient soil (part of active site of 5' deiodinase)

### Endemic cretinism

children born to mothers w/ iodine deficiency

mental retardation, abnormalities of hearing, bone, gait, posture, and short stature

### Hyperthyroidism

nervous, diaphoresis, heat intolerance, palpitations, insomnia, weight loss, fatigue, tachycardia, systolic HTN; goiter, lid lag, rapid relaxation of deep tendon reflexes (DTR), systolic HTN, A-fib

most common cause = Graves' disease

### Graves' disease

autoimmune TSIs (thyroid stimulating immunoglobulins) activate TSH receptor; F>M; onset 30-40; genetic = HLA-DR3; other autoimmune dz common; T-suppressor defect

thyroid thrill/bruit (neck murmur); ophthalmopathy = exophthalmos, peri-orbital

edema, diplopia, dry eyes, corneal ulceration; affects extra-ocular muscles;

dermopathy = pre-tibial myxedema; diffuse thyroid hyperplasia, scalloped colloid, columnar epithelium; Dx: low TSH, high FT<sub>3</sub>/FT<sub>4</sub>, high radioiodide uptake, TSI(+);

also Abs vs. TPO or Tg

anti-thyroid meds = methimazole & PTU (inhibit TPO); b-blockers; iodide;

radioiodide; surgery; artificial tears

atypical presentation in older pts (angina, A-fib, weakness, cachexia); eye Sx due to GAG accumulation behind orbit that inhibits venous drainage; pretreat w/ PTU or methimazole before surgery to prevent thyroid storm

#### Subacute thyroiditis

leakage of T4/T3  
low radioiodide uptake

#### Solitary adenoma

"hot nodule" = benign adenoma; TSH receptor mutation -> constitutively active (cAMP)  
high radioiodide uptake, makes TH, usu. euthyroid; "toxic adenoma" may cause hyperthyroid (if > 1 inch diameter); labs = high T3/T4, low TSH -> rest of thyroid atrophies  
radioiodide; surgery; methimazole or PTU  
hot nodule 100% benign

#### Multinodular goiter

usu. older pts.  
enlarged thyroid, multiple lumps, irregular; usu. euthyroid, no excess TH produced; flat cuboidal epithelium  
radioiodide; surgery; methimazole or PTU  
"toxic" implies autonomous enough to cause hyperthyroid

#### Hypothyroidism

iodine deficiency is most common cause worldwide  
myxedema in adults, cretinism in infants  
secondary hypothyroidism = no TSH produced (monitor w/ T4)

#### Hashimoto's thyroiditis

autoimmune Abs vs. thyroid (anti-TPO, anti-Tg); F>M; genetic = HLA-DR5; risk of other autoimmune dz = type I diabetes, Addison's, pernicious anemia  
fatigue, lethargy, weakness, cold intolerance, slow thinking, depression, dry skin, constipation, fluid retention, hoarseness, irregular menses, mild weight gain, delayed DTR, bradycardia, hypertension; goiter (firm, symmetric, non-tender); labs = high TSH, low FT4; pale tan thyroid, lymphocyte infiltration (germinal centers), Hurthle cells, fibrosis, oncocytic change (pink cytoplasm)  
thyroxine (T4)  
most common cause of non-iatrogenic hypothyroidism in US; high incidence of malignant lymphoma

#### Thyroid nodules

F>M; 95% benign; more malignant in children, elderly, males; often Hx of childhood XRT  
can be hypo- or hyper-thyroid; malignant = hoarseness, adenopathy, rock hard; Dx: fine needle aspiration biopsy  
surgery; T4 (suppress TSH); radioiodine (I-131 if malignant)  
cold nodules (don't concentrate radioiodine) 95% benign, but 90% of nodules are cold

#### Follicular adenoma

benign  
encapsulated; single nodule

#### Thyroid cancer: malignant

##### Papillary

most common; excellent prognosis; RET-PTC translocation; due to childhood radiation exposure  
spreads first to local lymph nodes; optically clear nuclei (Orphan Annie eyes); finger-like papillae; nuclear grooves & pseudoinclusions; psammoma bodies  
surgery; radioiodine  
tumor marker = thyroglobulin; common in children of Chernobyl

##### Follicular

good prognosis; Pax8-PPAR $\gamma$  translocation

spreads first to lung & bone (not nodes); difficult to distinguish from benign nodule

tumor marker = thyroglobulin

#### Anaplastic

poorly differentiated  
no thyroglobulin

#### Medullary

from parafollicular C cells; sporadic or MEN-2; RET point mutations  
amyloid stroma  
surgery  
tumor marker = calcitonin

### Parathyroid Gland

#### Parathyroid Hormone (PTH)

The parathyroid glands are 4 tiny structures embedded in the rear surface of the thyroid gland. They secrete parathyroid hormone (PTH) a polypeptide of 84 amino acids. PTH has three functions, all of which increase the concentration of  $Ca^{2+}$  in the blood. PTH promotes release of  $Ca^{2+}$  from the huge reservoir in the bones. (99% of the calcium in the body is incorporated in our bones.)  
reabsorption of  $Ca^{2+}$  from the fluid in the tubules in the kidneys  
absorption of  $Ca^{2+}$  from the contents of the intestine (this action is mediated by calcitriol, the active form of vitamin D.)

The cells of the parathyroid glands have surface receptors that bind  $Ca^{2+}$  (the same type of receptor is found on the calcitonin-secreting cells of the thyroid and on the calcium absorbing cells of the kidneys). Binding of  $Ca^{2+}$  to this receptor depresses the secretion of PTH and thus leads to a lowering of the concentration of  $Ca^{2+}$  in the blood. Two classes of inherited disorders involving mutant genes encoding the  $Ca^{2+}$  receptor occur:

loss-of-function mutations with the mutant receptor always "off". Patients with this disorder have high levels of  $Ca^{2+}$  in their blood and excrete small amounts of  $Ca^{2+}$  in their urine. This causes hyperparathyroidism.

gain-of-function mutations with the mutant receptor always "on" (as though it had bound  $Ca^{2+}$ ). People with this disorder have low levels of  $Ca^{2+}$  in their blood and excrete large amounts of  $Ca^{2+}$  in their urine. This causes hypoparathyroidism.

#### Parathyroid Pathology and Ion Metabolism Disorders

neuro Sx = lethargy, weakness, disorientation, coma

#### Hypercalcemia

other causes = immobilization, familial hypocalciuric hypercalcemia, thiazides

#### Primary hyperparathyroidism

due to single benign parathyroid adenoma, hyperplasia, MEN syndrome, carcinoma (not oat cell)

ASx, kidney stones, hyposthenuria (Ca-induced diabetes insipidus), renal failure, bone pain, GI Sx, neuro Sx; Dx: high Ca, high PTH, low  $PO_4$ , high Alk-phos, high urine Ca

parathyroidectomy; estrogen therapy

measure urine Ca to exclude familial hypocalciuric hypercalcemia (defect of parathyroid and kidney Ca receptors)

#### Vitamin D intoxication

due to exogenous overdose or granulomatous disease (macrophages have 1 $\alpha$ -hydroxylase) -> activate vit D

kidney stones, renal failure, GI Sx, neuro Sx, no bone probs; Dx: high Ca, low PTH, very high urine Ca

saline infusion, glucocorticoids, treat underlying cause

granulomatous dz includes TB, fungi, sarcoidosis; glucocorticoids antagonize vit D

#### Hypercalcemia of malignancy

due to overproduction of PTHrP (PTH related-protein by squamous cell ca) or bone tumor (multiple myeloma, breast ca -> local cytokines cause resorption)

high Ca; kidney stones, bone pain, Ca-induced nephrogenic diabetes insipidus, volume depletion, rapid onset -> GI & neuro Sx; if severe calcemia (> 15 mg/dl) -> disorientation, coma  
hydrate w/ saline, pamidronate, calcitonin, gallium nitrate, diuretics

#### Hypocalcemia

determine if true hypocalcemia by correcting for low albumin (1 g/dl albumin = 0.8 mg/dl Ca)

##### Hypoparathyroidism

low PTH production  
neuromuscular irritability, twitching, tetany, convulsions; low Ca, high PO<sub>4</sub>, low PTH  
Ca & vit D

##### Pseudo-hypoparathyroidism

end organ resistance to PTH  
neuromuscular irritability, twitching, tetany, convulsions; low Ca, high PO<sub>4</sub>, high PTH  
Ca & vit D

##### Vitamin D deficiency (osteomalacia)

low intake & sunlight, malabsorption, liver disease, renal failure  
bone pain, pathological fractures, low bone density; low PO<sub>4</sub>, high Alk-phos, high PTH, late low Ca  
vit D (1,25 if renal failure)  
aka rickets in children

##### Renal disease

secondary hyperPTH  
low albumin, low Ca, high PO<sub>4</sub>, high creatinine, high glucose

#### Other

##### Parathyroid carcinoma

low grade  
firm irregular mass, adheres to adjacent structures, infiltrative, fibrous

#### Adrenal Gland Cortex

##### Zona Reticularis: Glucocorticoids

###### Cortisol et al.

The glucocorticoids get their name from their effect of raising the level of blood sugar (glucose). One way they do this is by stimulating gluconeogenesis in the liver: the conversion of fat and protein into intermediate metabolites that are ultimately converted into glucose.

The most abundant glucocorticoid is cortisol (also called hydrocortisone). Cortisol and the other glucocorticoids also have a potent anti-inflammatory effect on the body. They depress the immune response, especially cell-mediated immune responses.

For this reason glucocorticoids are widely used in therapy:

to reduce the inflammatory destruction of rheumatoid arthritis and other autoimmune diseases

to prevent the rejection of transplanted organs

to control asthma

##### Zona Glomerulosa: Mineralocorticoids

###### Aldosterone et al.

The mineralocorticoids get their name from their effect on mineral metabolism. The most important of them is the steroid aldosterone.

Aldosterone acts on the kidney promoting the reabsorption of sodium ions (Na<sup>+</sup>) into the blood. Water follows the salt and this helps maintain normal blood pressure.

Aldosterone also

acts on sweat glands to reduce the loss of sodium in perspiration

acts on taste cells to increase the sensitivity of the taste buds to sources of sodium.

The secretion of aldosterone is stimulated by:  
a drop in the level of sodium ions in the blood  
a rise in the level of potassium ions in the blood  
angiotensin II  
ACTH (as is that of cortisol)

Zona Fasciculata: Androgens

Testosterone et al.

The adrenal cortex secretes precursors to androgens such as testosterone.

In sexually-mature males, this source is so much lower than that of the testes that it is probably of little physiological significance. However, excessive production of adrenal androgens can cause premature puberty in young boys.

In females, the adrenal cortex is a major source of androgens. Their hypersecretion may cause some masculinization in adult females, producing a masculine pattern of body hair and cessation of menstruation.

Dehydroepiandrosterone (DHEA)

Stimulates sex drive  
Induces labor

Medulla

Catecholamines

Epinephrine

Norepinephrine

The adrenal medulla consists of masses of neurons that are part of the sympathetic branch of the autonomic nervous system. Instead of releasing their neurotransmitters at a synapse, these neurons release them into the blood. Thus, although part of the nervous system, the adrenal medulla functions as an endocrine gland.

Both catecholamines are derived from the amino acid tyrosine.

Release of epinephrine and norepinephrine is triggered by nervous stimulation in response to physical or mental stress. The hormones bind to adrenergic receptors - transmembrane proteins in the plasma membrane of many cell types.

Some of the effects are:

- increase in the rate and strength of the heartbeat resulting in increased blood pressure
- blood shunted from the skin and viscera to the skeletal muscles, coronary arteries, liver, and brain
- rise in blood sugar
- increased metabolic rate
- bronchi dilate
- pupils dilate
- hair stands on end ("gooseflesh" in humans)
- clotting time of the blood is reduced
- increased ACTH secretion from the anterior lobe of the pituitary.

All of these effects prepare the body to take immediate and vigorous action.

Adrenal Pathology

Hypercortisolism (Cushing's syndrome)

caused physiologically by pregnancy, stress, chronic excessive exercise, malnutrition

truncal obesity, buffalo hump, moon facies, purple striae, tinea versicolor, hyperpigmentation, muscle atrophy (difficulty standing), skin thinning, osteoporosis,

diabetes, acanthosis nigricans (insulin resistance), hypertension, acne, hirsutism (lanugal & androgenous), amenorrhea, impotence, depression, memory loss  
high ACTH causes hyperpigmentation (because POMC precursor includes MSH) and androgen excess (acne, hirsutism, irregular menses); bone breakdown due to PTH

#### Pituitary Cushing's Disease

70%; pituitary adenoma secretes ACTH  
low CRH, high pituitary ACTH, high cortisol; bilateral adrenal hyperplasia; no circadian rhythm; loss of feedback sensitivity; mass lesion -> bitemporal hemianopsia, headache; Dx: inferior petrosal sinus sampling (high ACTH)  
transphenoidal resection; cortisol  
may suppress w/ dexamethasone; ACTH-dependent has detectable ACTH (> 9 pg/ml), independent < 9 pg/ml

#### Ectopic ACTH syndrome

tumor (bronchial carcinoid, oat/small cell lung carcinoma) secretes ACTH -> stimulates adrenal hyperplasia  
low CRH, low pituitary ACTH, high ectopic ACTH, high cortisol; bilateral adrenal hyperplasia; no circadian rhythm  
not suppressed by dexamethasone; not responsive to CRH

#### Ectopic CRH syndrome

tumor secretes CRH  
low hypothalamic CRH, high ectopic CRH, high ACTH, high cortisol; bilateral adrenal hyperplasia; no circadian rhythm

#### ACTH-independent Cushing's syndrome

20%; adrenal adenoma or primary adrenal hyperplasia  
low CRH, low ACTH, high cortisol; unilateral hyperplasia (other adrenal atrophies due to no ACTH); no circadian rhythm  
adrenal resection; cortisol  
familial form = PKA gain-of-function mutation -> bilateral hyperplasia

#### Hyperaldosteronism

hypokalemia + mild hypertension; high aldosterone, high Na, metabolic alkalosis; low K -> muscle weakness, EKG change, polyuria, abnl GTT  
ACE-I, All blockers, MR antagonists, Na-channel blockers  
Primary HA (Conn's syndrome)  
70% adrenal adenoma (glomerulosa), 30% hyperplasia  
low renin; Dx: 24-hr urine aldo (> 10 ug/day) w/ low renin (< ng/ml/hr)  
Secondary HA  
physiologic adaptation to low plasma volume  
high renin

#### Adrenal insufficiency

low cortisol, low aldosterone; hypoglycemia, impaired consciousness, orthostatic hypotension, pigmentation, decr. pubic hair; weakness, fatigue, weight loss, hyponatremia, lethargy, mental slowness

cortisol; 9a-fluorocortisol

#### Primary AI (Addison's)

adrenal defect; due to autoimmune adrenalitis (Addison's), infection, infiltrative dz (TB), vascular, congenital  
high CRH, high ACTH, low cortisol, low aldosterone; hyperpigmentation, vitiligo, hyperkalemia, hypothyroid, hypogonadism; bilateral adrenal atrophy  
infections = TB, fungi, CMV

#### Secondary AI

pituitary or hypothalamic defect; due to genetic dz, vascular, tumor, immune, iatrogenic (steroid use)  
high CRH, low ACTH, low cortisol; growth delay, headache, diabetes insipidus, hypothyroid, hypogonadism; no ACTH -> adrenal atrophy

Acute adrenal insufficiency (adrenal crisis)  
 adrenal hemorrhage, drugs (incr. metabolism (phenytoin, phenobarbital, rifampin) or decr. production (ketoconazole, AG, mitotane) of GCs), sudden steroid therapy withdrawal  
 catecholamine-resistant hypotension, abdominal pain, high K, low Na, hypoglycemia, hyperpigmentation  
 IV cortisone, saline, glucose  
 Waterhouse-Friderichsen syndrome = hemorrhagic necrosis of adrenal cortex (due to meningococcus)

Adrenal tumors  
 remove any mass > 5 cm

Adenoma  
 benign  
 usu. < 5 cm diameter & < 50 g; lipid-filled areas

Carcinoma  
 malignant  
 usu. > 5 cm diameter & > 100 g; no lipid areas

Pheochromocytoma  
 adrenal paraganglioma; may be syndrome if bilateral (MENII, MENIII, von Hippel Lindau, von Recklinghausen, Sturge-Weber)  
 pushes out cortex -> yellow rim; zellballen = cell balls;  
 catecholamine-induced hypertension

Ovary

### Estrogens

a mixture of three estrogens of which 17 $\beta$ -estradiol is the most abundant (and most potent). Estrogens are steroids. They are primarily responsible for the conversion of girls into sexually-mature women.

development of breasts  
 further development of the uterus and vagina  
 broadening of the pelvis  
 growth of pubic and axillary hair  
 increase in adipose (fat) tissue  
 participate in the monthly preparation of the body for a possible pregnancy  
 participate in pregnancy if it occurs

Estrogens also have non-reproductive effects.

They antagonize the effects of the parathyroid hormone, minimizing the loss of calcium from bones and thus helping to keep bones strong.  
 They promote blood clotting.

### Progesterone

See below

Corpus luteum (and Placenta)

### Progesterone

Progesterone is one of the steroid hormones.  
 It is secreted by the corpus luteum and by the placenta and is responsible for preparing the body for pregnancy and, if pregnancy occurs, maintaining it until birth.

Progesterone secretion by the corpus luteum occurs after ovulation and  
 continues the preparation of the endometrium for a possible pregnancy  
 inhibits contraction of the uterus  
 inhibits development of a new follicle

If pregnancy does not occur, secretion wanes toward the end of the menstrual cycle, and menstruation begins.

### Relaxin (from ovary and placenta)

As the time of birth approaches in some animals (e.g., pigs, rats), this polypeptide has been found to:

relax the pubic ligaments  
 soften and enlarge the opening to the cervix

Relaxin is found in pregnant humans but at higher levels early in pregnancy than close to the time of birth. Relaxin promotes angiogenesis, and in humans it probably plays a more important role in the development of the interface between the uterus and the placenta that it does in the birth process.

**Activin**

**Inhibin**

**Follistatin**

These three proteins are synthesized within the follicle. Activins and inhibins bind to follistatin. Activins increase the action of FSH; inhibins, as their name suggests, inhibit it. How important they are in humans remains to be seen. However the important role that activin and follistatin play in the embryonic development of vertebrates justifies mentioning them here.

Trophoblasts (and Placenta)

Syncytiotrophoblasts

**Adrenocorticotrophic hormone (ACTH)**

**Human chorionic gonadotropin**

It is a dimer of

the same alpha subunit (of 89 amino acids) used by TSH, FSH, and LH)  
and

a unique beta subunit (of 148 amino acids).

HCG behaves much like FSH and LH with one crucial exception: it is NOT inhibited by a rising level of progesterone. Thus HCG prevents the deterioration of the corpus luteum at the end of the fourth week and enables pregnancy to continue beyond the end of the normal menstrual cycle.

Because only the implanted trophoblast makes HCG, its early appearance in the urine of pregnant women provides the basis for the most widely used test for pregnancy (which can provide a positive signal even before menstruation would have otherwise begun).

As pregnancy continues, the placenta becomes a major source of progesterone, and its presence is essential to maintain pregnancy

**Human chorionic thyrotropin (hCT)**

**Human chorionic somatomammotropin (hCS) or Human placental lactogen (hPL)**

Cytotrophoblasts

**Corticotropin Releasing Hormone (CRH)**

**Gonadotropin Releasing Hormone (GnRH)**

**Thyrotropin Releasing Hormone (TRH)**

**Somatostatin**

Testes

Androgens (Leydig Cells)

**Testosterone**

The principal androgen (male sex hormone) is testosterone. This steroid is manufactured by the interstitial (Leydig) cells of the testes. Secretion of testosterone increases sharply at puberty and is responsible for the development of the so-called secondary sexual characteristics (e.g., beard) of men.

Testosterone is also essential for the production of sperm.

Production of testosterone is controlled by the release of luteinizing hormone (LH) from the anterior lobe of the pituitary gland, which is in turn controlled by the release of GnRH from the hypothalamus. LH is also called interstitial cell stimulating hormone (ICSH).

Hypothalamus -> GnRH -> Pituitary -> LH ->  
Testes -> Testosterone

The level of testosterone is under negative-feedback control: a rising level of testosterone suppresses the release of GnRH from the hypothalamus. This is exactly parallel to the control of estrogen secretion in females

**Anti-Mullerian Hormone (AMH) (Sertoli Cells)**

Leads to regression of Mullerian structures

Fallopian tubes

Uterus

Upper third of vagina

**Dihydrotestosterone (DHT)**

Converted from testosterone

More potent

Important for development of

Prostate

Urethra

External genitalia

Scrotum

Secondary sex characteristics

**Inhibin**

Acts on anterior lobe of pituitary to inhibit FSH release

Gonadal Pathology

Many things can go wrong with sexual development in both males and females; fortunately rarely. Let's look only at a few that clearly result from the inheritance of single-gene mutations.

Inherited mutations in both copies of the gene encoding the GnRH receptor result in failure to develop at puberty.

Mutations in the gene encoding the LH receptor prevent normal sexual development in both sexes.

Mutations in the gene encoding the FSH receptor block development of the gonads in both males and females.

Mutations in any of the genes encoding the enzymes for synthesis and metabolism of testosterone interfere with normal sexual function in males.

A similar spectrum of disorders in males can be caused by mutations in the genes encoding the androgen receptor.

Pancreas (Islets of Langerhans)

Alpha Cells

**Glucagon**

a polypeptide of 29 amino acids.

Glucagon acts principally on the liver where it stimulates the conversion of glycogen into glucose which is deposited in the blood.

Glucagon secretion is

stimulated by low levels of glucose in the blood and

inhibited by high levels.

The physiological significance of this is that glucagon functions to maintain a steady level of blood sugar level between meals.

Injections of glucagon are sometimes given to diabetics suffering from an insulin reaction in order to speed the return of normal levels of blood sugar.

Beta Cells

**Insulin**

Insulin is a small protein consisting of

an alpha chain of 21 amino acids linked by two disulfide (S-S) bridges to a beta chain of 30 amino acids.

Beta cells have channels in their plasma membrane that serve as glucose detectors. Beta cells secrete insulin in response to a rising level of circulating glucose ("blood sugar"). Insulin affects many organs.

Insulin stimulates liver cells to take up glucose from the blood and convert it into glycogen.

Insulin stimulates skeletal muscle fibers to

take up amino acids from the blood and convert them into protein

take up glucose and convert it into glycogen

Insulin acts on fat (adipose) cells to stimulate the synthesis of fat.

In each case, insulin triggers these effects by binding to the insulin receptor - a transmembrane protein embedded in the plasma membrane of the responding cells.

Taken together, all of these actions result in:

the storage of the soluble nutrients absorbed from the intestine into insoluble, energy-rich products (glycogen, protein, fat)  
a drop in the level of blood sugar

### Amylin

Amylin is secreted in a pattern very similar to that of insulin, i.e. blood levels of amylin rise and fall in response to blood glucose levels.  
Because type 1 diabetics have lost their beta cells, they cannot secrete insulin, C-peptide or amylin.  
Scientists are now actively researching the role of amylin in nondiabetic humans. Amylin appears to control how rapidly food leaves the stomach, which has a large influence on how fast blood sugar levels rise after a meal.  
In a way, amylin controls the transfer of glucose from the gut to the bloodstream, and insulin controls the transfer of glucose from the bloodstream to the body tissues.

### C-peptide

Some C-peptide is released into the blood with insulin  
The role of C-peptide is currently controversial, but some studies have shown that it may aid insulin in lowering glucose levels and administration of C-peptide to IDDM patients has shown amelioration of long-term complications

### Delta Cells

#### Somatostatin

This consists of two polypeptides, one of 14 amino acids (the most active) and one of 28. Somatostatin has a variety of functions. Taken together, they work to reduce the rate at which food is absorbed from the contents of the intestine. Somatostatin is also secreted by the hypothalamus and by the stomach (q.v).

#### Gastrin

See under Stomach.

### F Cells or Gamma Cells

#### Pancreatic polypeptide

No function has yet been found for this peptide of 36 amino acids.

### Periphery of Islets

#### Adrenomedullin

is a potent vasodilatory peptide

### Pancreatic Disorders

#### Islet Cell Tumors

usu. solitary, benign, well-circumscribed  
can also make ectopic hormones  
often infants of diabetic mothers

#### Insulinoma

90% solitary adenoma, 10% malignant  
Whipple's triad (hypoglycemia, neuro Sx, resolution)  
most common functioning islet cell tumor

#### Glucagonoma

rare  
tall cytoplasm

#### VIPoma

rare  
defined by blood vessels  
aka pancreatic cholera

#### Gastrinoma

often malignant  
excess gastrin -> ulcers  
Zollinger-Ellison syndrome

### Diabetes Mellitus

relative or absolute deficiency of insulin; can also be caused by pancreatitis, hemochromatosis, acromegaly (GH), Cushing's (GCs), stress, glucocorticoids, thiazide diuretics, CF, Klinefelter's, Turner's, pregnancy; Sx = chronic

hyperglycemia; polyuria, polydipsia, polyphagia; can lead to ketoacidosis, HONK, retinopathy, nephropathy, neuropathy, macrovascular complications, pregnancy problems, impaired immune system (TB, pneumococcus, thrush, delayed wound healing); Dx = random [glucose] > 200 mg/dl w/ symptoms or 2 fasting [glucose] > 126 mg/dl

#### Type I (IDDM)

autoimmune destruction of b-cells in islets; young onset (<30 y.o.); genetic (HLA-DR3, DR4), 30% twin concordance  
ketosis; small islets, decr. b cells

#### Type II (NIDDM)

decr. sensitivity to insulin (resistance); older onset (>40 y.o.); obesity is major risk Fx; strong heredity, 90% twin concordance  
usu. no ketosis; insulin resistance, abnl insulin secretion & abnl hepatic glucose output; early = postprandial hyperglycemia, later = fasting hyperglycemia

#### Diabetic ketoacidosis (DKA)

due to absence of effective insulin; more common w/ type 1 diabetes than type 2; usu. precipitating event (illness, stress, injury, lack of insulin); ketones = acetoacetate & b-hydroxybutyrate  
low insulin, high stress hormones (epi, NE, glucagon, cortisol, GH) -> incr. glucose output, lipolysis & proteolysis -> incr. ketoacids; Sx = hyperglycemia, polyuria, polydipsia, anion gap acidosis (15-30), volume depletion, electrolyte loss, decr. renal blood flow, prerenal azotemia, hypotension, shock; monitor recovery by anion gap (indicates acid-base status)

IV insulin (shut off ketone production); IV fluids (saline); electrolytes (Na, K, Mg, PO<sub>4</sub>); glucose (prevent hypoglycemia); treat underlying life-threatening; Kussmaul respirations = deep breaths to blow off CO<sub>2</sub> from metabolic acidosis (Juicy Fruit breath); may lead to coma, death; any fever is due to infection, not from DKA itself; give K if kidneys are fxnl (making urine)

#### Hyperosmolar nonketotic coma (HONK)

relative insulin deficiency (but enough to prevent lipolysis); in old, type 2 pts; precipitated by infection, MI, stroke  
extreme hyperglycemia without acidosis; vicious cycle = hyperglycemia -> polyuria -> volume depletion -> hemoconcentration; Sx = CNS impairment, hyperviscosity, thrombosis  
saline, electrolytes, insulin, treat underlying cause

#### Diabetic retinopathy

##### proliferative (PDR) or background (NPDR)

PDR = neovascularization (hypoxia induced GFs); NPDR = microaneurysms, macular edema, exudates, microinfarcts  
#1 cause of blindness in US adults

#### Diabetic nephropathy

Kimmelstiel-Wilson glomerulosclerosis, mesangial thickening, proteinuria (detect w/ urinary microalbumin)  
ACE-I to control BP & diabetes  
#1 cause of renal failure in US

#### Diabetic peripheral neuropathy

usu. stocking/glove distribution (not dermatomal)  
lose vibration, then have paresthesias (burning, pins/needles), then total sensory loss -> skin trauma  
#1 cause of leg amputations in US (nontraumatic)

#### Diabetic autonomic neuropathy

cardiac (incr. HR, arrhythmia, sudden death), vascular (orthostatic hypotension, edema), GI (gastroparesis, diarrhea, constipation), GU (urinary retention, impotence)

#### Macrovascular complications

incr. incidence of gangrene, coronary artery disease (women placed at equal risk), stroke, MI (often without chest pain = silent ischemia)

#### Hypoglycemia

##### Insulin-induced hypoglycemia

triggered by skipped meal, exercise, alcohol, insulin overdose  
autonomic (palpitations, sweating, tremulousness, paresthesia, loss of focus, anxiety) & neuroglycopenic (confusion, disorientation, slurred speech, agitation, LOC, seizures, coma)  
glucose tablets; IM glucagon injection  
patients often eat too much to prevent hypoglycemic episode -> gain weight -> worsens DM

##### Spontaneous (fasting) hypoglycemia

due to insulinoma, drugs/toxins, renal failure, fulminant hepatic failure, sepsis, adrenal insufficiency, hypopituitarism, Addison's  
Whipple's triad = 1) hypoglycemia (glucose < 50 mg/dl), 2) CNS Sx (autonomic, neuroglycopenic), 3) resolves w/ glucose intake; test surreptitious sulfonylurea w/ urine or plasma test  
drugs/toxins = insulin, sulfonylurea, pentamidine, EtOH, hypoglycin, aspirin; may have autoimmune Ab's vs. insulin receptor (extreme resistance)

##### Insulinoma

rare; may be multiple in MEN-1 (also have high PTH, pituitary adenoma)  
Whipple's triad; Dx: 72-hour fast (inappropriately high insulin in presence of hypoglycemia -> low glucose, high insulin, high C-peptide)  
other squamous tumors = sarcoma, hepatoma, adrenal carcinoma, carcinoid -> abnormally form IGF-2 to cause hypoglycemia

##### Post-prandial hypoglycemia

after meals

##### Post-gastrectomy hypoglycemia

rapid food passage stimulates inappropriate insulin  
hypoglycemia 4-6 hrs after meal

##### Reactive hypoglycemia

Whipple's triad 1-4 hrs after meal  
GTT is useless

#### Kidney

##### Erythropoietin

Erythropoietin is a glycoprotein. It acts on the bone marrow to increase the production of red blood cells. Stimuli such as bleeding or moving to high altitudes (where oxygen is scarcer) trigger the release of EPO.

People with failing kidneys can be kept alive by dialysis. But dialysis only cleanses the blood of wastes. Without a source of EPO, these patients suffer from anemia.

Now, thanks to recombinant DNA technology, recombinant human EPO is available to treat these patients. Some of the drugs used to treat AIDS, zidovudine (AZT) for example, cause anemia as a side effect. Recombinant EPO helps AIDS patients cope with this one of the many problems that the disease creates.

Because EPO increases the hematocrit, it enables more oxygen to flow to the skeletal muscles. Some distance runners (and cyclers) have used recombinant EPO to enhance their performance. Although recombinant EPO has exactly the same sequence of amino acids as the natural hormone, the sugars attached by the cells used in the pharmaceutical industry differ from those attached by the cells of the human kidney. This difference can be detected by a test of the athlete's urine.

Recently it has been found that EPO is also synthesized in the brain when oxygen becomes scarce there (e.g., following a stroke), and helps protect neurons from damage. Perhaps recombinant human EPO will turn out to be useful for stroke victims as well.

### Calcitriol

Calcitriol is 1,25[OH]<sub>2</sub> Vitamin D<sub>3</sub>, the active form of vitamin D. It is derived from calciferol (vitamin D<sub>3</sub>) which is synthesized in skin exposed to the ultraviolet rays of the sun

precursors ("vitamin D") ingested in the diet.

Calciferol in the blood is converted into the active vitamin in two steps:

calciferol is converted in the liver into 25[OH] vitamin D<sub>3</sub>

this is carried to the kidneys where it is converted into calcitriol. This final step is promoted by the parathyroid hormone (PTH).

Calcitriol acts on the cells of the intestine to promote the absorption of calcium from the diet. Calcitriol diffuses into cells and, if they contain receptors for it (intestine cells do), it binds to them. The calcitriol receptors are zinc-finger transcription factors. The receptor-ligand complex bind to its response element, the DNA sequence:

5' AGGTCAnnnAGGTCA 3'

This sequence of nucleotides (n can be any nucleotide) is found in the promoters of genes that are turned on by calcitriol. Once the hormone-receptor complex is bound to its response element, other transcription factors are recruited to the promoter and transcription of the gene(s) begins.

Renin (not a hormone, but important in this context)

One of the functions of the kidney is to monitor blood pressure and take corrective action if it should drop. The kidney does this by secreting the proteolytic enzyme renin.

Renin acts on angiotensinogen, a plasma peptide, splitting off a fragment containing 10 amino acids called angiotensin I.

angiotensin I is cleaved by a peptidase secreted by blood vessels called angiotensin converting enzyme (ACE) - producing angiotensin II, which contains 8 amino acids.

angiotensin II

constricts the walls of arterioles closing down capillary beds;

stimulates the proximal tubules in the kidney to reabsorb sodium ions;

stimulates the adrenal cortex to release aldosterone. Aldosterone causes the kidneys to reclaim still more sodium and thus water

increases the strength of the heartbeat;

stimulates the pituitary to release the antidiuretic hormone (ADH, also known as arginine vasopressin).

All of these actions lead to an increase in blood pressure.

Skin

### Calciferol (VitD3)

When ultraviolet radiation strikes the skin, it triggers the conversion of dehydrocholesterol (a cholesterol derivative) into calciferol (vitamin D<sub>3</sub>).

Calciferol travels in the blood to the liver where it is converted into 25[OH] vitamin D<sub>3</sub>.

This compound travels to the kidneys where it is converted into calcitriol (1,25 [OH]<sub>2</sub> vitamin D<sub>3</sub>). This final step is promoted by the parathyroid hormone (PTH)

Although called a vitamin, calciferol and its products fully qualify as hormones because they are

made in certain cells,

carried in the blood,

affect gene transcription in target cells.

Heart

### Atrial-natriuretic peptide (ANP)

### Brain-natriuretic peptide (BNP)

In response to a rise in blood pressure, the heart releases these two peptides:

Both hormones lower blood pressure by

relaxing arterioles

inhibiting the secretion of renin and aldosterone

inhibiting the reabsorption of sodium ions by the kidneys.

The latter two effects reduce the reabsorption of water by the kidneys. So the volume of urine increases as does the amount of sodium excreted in it.

These effects give ANP and BNP their name (natrium = sodium; uresis = urinate). The net effect of these actions is to reduce blood pressure by reducing the volume of blood in the circulatory system.

#### Stomach and Intestine

##### Gastrin

Gastrin is a mixture of several peptides, of which the most active contains 14 amino acids. It is secreted by cells in the stomach and duodenum. It stimulates the exocrine cells of the stomach to secrete gastric juice, a mixture of hydrochloric acid and the proteolytic enzyme pepsin.

##### Secretin

It is a polypeptide of 27 amino acids. It is secreted by cells in the duodenum when they are exposed to the acidic contents of the emptying stomach. It stimulates the exocrine portion of the pancreas to secrete bicarbonate into the pancreatic fluid (thus neutralizing the acidity of the intestinal contents).

##### Cholecystokinin

A mixture of peptides, of which an octapeptide (8 amino acids) is the most active. Like secretin, it is secreted by cells in the duodenum when they are exposed to the acidic contents of the emptying stomach.

It acts

on the gall bladder stimulating it to contract and force its contents of bile into the intestine

on the pancreas stimulating the release of pancreatic digestive enzymes into the pancreatic fluid.

There is some evidence that CCK acts on the brain as a satiety signal (i.e., "that's enough food for now").

##### Somatostatin

This mixture of peptides acts on the stomach where it inhibits the release of gastrin, the duodenum where it inhibits the release of secretin and cholecystokinin, and the pancreas where it inhibits the release of glucagon.

Taken together, all of these actions lead to a reduction in the rate at which nutrients are absorbed from the contents of the intestine.

Somatostatin is also secreted by the hypothalamus and the pancreas.

##### Neuropeptide Y

Neuropeptide Y contains 36 amino acids. It is a potent feeding stimulant and causes increased storage of ingested food as fat.

Neuropeptide Y also blocks the transmission of pain signals to the brain.

#### Other endocrine hormones of the Small Intestine

##### Glucagon

See under Pancreas

##### Serotonin

Synthesized from tryptophan (Trp).

##### Substance P

This peptide (containing 11 amino acids) is released by C fibers. It is associated with intense, persistent, chronic - thus "bad" - pain.

#### Liver

##### Insulin-like Growth Factor

This protein of 70 amino acids was once called somatomedin because it, not growth hormone, is the immediate stimulus for growth of the body.

Growth hormone released from the anterior lobe of the pituitary binds to receptors on the surface of liver cells.

This stimulates the synthesis and release of IGF-1 from them.

Many cells have receptors for IGF-1, especially cells in the bone marrow in the cartilaginous growing regions of the long bones. Binding of IGF-1 to cells with receptors for it stimulates them to move from G<sub>1</sub> of the cell cycle to S phase and on to mitosis.

These are not the same as the Igf-2 receptors whose genes are imprinted.  
The levels of IGF-1 in the blood are highest during the years of puberty which is, of course, a time of rapid growth. Occasionally children are found that have stunted growth because they have inherited mutant genes for the growth hormone (GH) receptor. Recombinant human IGF-1 has been successfully used to treat them.

### Angiotensinogen

This protein is released into the blood where it serves as the precursor for angiotensin. How angiotensin is manufactured, and the role it plays in maintaining blood pressure is described in the discussion of renin.

### Thrombopoietin

Thrombopoietin is a protein of 332 amino acids. It stimulates precursor cells in the bone marrow to differentiate into megakaryocytes. Megakaryocytes generate platelets, essential to blood clotting. A segment of thrombopoietin, manufactured by recombinant DNA technology, is now available for human therapy. It already shows promise in quickly restoring normal platelet counts in patients who have undergone chemotherapy.

Fat

### Leptin

Most of this information is from a rat model and may prove to differ slightly in humans: Leptin is manufactured in fat cells (adipose tissue), and the level of circulating leptin is directly proportional to the total amount of fat in the body.

Leptin acts on receptors in the hypothalamus of the brain where it:  
counteracts the effects of neuropeptide Y (a potent feeding stimulant secreted by cells in the gut and in the hypothalamus);  
counteracts the effects of anandamide (another potent feeding stimulant that binds to the same receptors as THC, the active ingredient of marijuana)  
promotes the effects of alpha-MSH, an appetite suppressant;  
the result: inhibition of food intake.

Thus leptin provides homeostatic control of food intake.

The absence of a functional hormone (or its receptor) leads to uncontrolled food intake and resulting obesity.

In addition to its effect on the hypothalamus, leptin acts directly on the cells of the liver and skeletal muscle where it stimulates the oxidation of fatty acids in the mitochondria. This reduces the storage of fat in those tissues (but not in adipose tissue).

### Resistin

a small protein (114 amino acids)

Resistin causes tissues to be less sensitive to the action of insulin, which is the hallmark of Non Insulin-Dependent Diabetes Mellitus (NIDDM) ["Type 2" diabetes]

Resistin secretion is enhanced in the extra-large fat cells of obese mice. If the same holds true for humans, this might account for the strong association between human obesity and Type 2 diabetes (over 80% of the people with NIDDM are obese).

Systemic Endocrine Syndromes

Multiple endocrine neoplasia syndromes

RET gain-of-function mutations -> tumor or hyperplasia

MEN 1 (Wermer's)

AD

pituitary adenoma, parathyroid (usu. hyperplasia), pancreatic islet cell tumor (gastrinoma, insulinoma); adrenal or thyroid tumors

presents as Zollinger-Ellison, hyperinsulin, pancreatic cholera (VIPoma)

MEN 2A (Sipple's) or 2

AD; mutation of Cys in extracellular RET -> odd number -> intermolecular disulfide bond -> constitutively active tyrosine kinase

parathyroid (usu. hyperplasia), medullary thyroid cancer, bilateral pheochromocytoma

MEN 2B or 3

AD; mutation of intracellular tyrosine kinase domain of RET proto-oncogene -> changed specificity

medullary thyroid cancer, bilateral pheochromocytoma, mucosal neuromas, ganglioneuromas, marfanoid habitus  
no hyperparathyroidism

Polyglandular autoimmune syndromes (Schmidt's)

PGA I

2 of following: adrenal insufficiency, hypoparathyroidism, chronic mucocutaneous candidiasis  
also, dental enamel hypoplasia, ectodermal dystrophy; occasionally hep B, malabsorption, cholelithiasis, pernicious anemia, alopecia, vitiligo, hypogonadism, hypothyroid, IDDM  
affects young people & kids

PGA II

adrenal insufficiency + hypothyroidism or diabetes mellitus  
affects middle aged women

PGA III

hypothyroidism; other autoimmune disorder (but not AI)  
NO adrenal insufficiency  
does not involve adrenal glands

Growth Disorders

Familial short stature

family Hx (small parents); inherited defect in endochondrial ossification (?)  
height < 5th %ile; birth weight < 5 lbs; growth parallel to growth chart; normal annual growth rate; bone age = chronological age; normal puberty onset  
can predict adult height (average of parents + 2.5 inches if male or - 2.5 inches if female)

Constitutional growth delay

family Hx; delayed adolescence  
delayed puberty; delayed bone age; normal annual growth rate; normal predicted adult height; very picky eater

Psychosocial dwarfism

failure to thrive > 2 y.o.; due to poor home environment  
short; immature; indistinct speech; bizarre eating & drinking habits; temper tantrums; enuresis; growth resumption lines on Xray  
put into foster home (return to normal)  
parents may have abnl social behavior

Chronic illness

often Crohn's  
delayed puberty; delayed bone age; recent deceleration of growth rate; microcytic anemia

Growth hormone deficiency

delayed height, weight, and bone age; low IGF-1; fatty face, frontal bossing, mid-facial hypoplasia; Dx: IGF-1, response to insulin & arginine

Turner syndrome

XO karyotype  
short stature, webbed neck, no sexual development, low posterior hairline, facial hypoplasia, lymphedema, cubitus valgus

Fetal alcohol syndrome

low birth weight (< 5 lbs), midfacial hypoplasia, small head, learning disability, social immaturity, VSD (heart murmur), developmental delay

Obesity

high among low SE classes, women, minorities; obese BMI > 28  
incr. risk for CV disease, sleep apnea, HTN, NIDDM, high lipids, endometrial carcinoma, degenerative joint dz, gallstones, gynecologic abnormalities  
decr. intake, incr. expenditure, modify eating, drugs  
BMI = weight/height<sup>2</sup>; normal BMI 23-25, overweight BMI 25-28; mortality increases w/ BMI > 25