Hormones are \textcolor{red}{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 hyposecretion 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
adrenocorticotropic 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

  \textbf{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**

**Adrenocorticotropic 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 ($T_4$)
- triiodothyronine ($T_3$)

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, hypothyroidism (dl 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)
amenorrhoea + galactorrhea (mimics pregnancy); prolactin > 200; tumor smaller in women, larger in men; Dx: pregnancy test (negative), then prolactin level
bromocriptine (Da 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

**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 (T4)**

**Triiodothyronine (T3)**

T₄ and T₃ are derivatives of the amino acid tyrosine with three (T₃) or four (T₄) 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 T₄ and T₃ 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 (Ca²⁺) circulating in the blood. These cells monitor the level of circulating Ca²⁺. A rise in its level stimulates the cells to release calcitonin. Bone cells respond by removing Ca²⁺ from the blood and storing it in the bone. Kidney cells respond by increasing the excretion of Ca²⁺.

Both types of cells have surface receptors for calcitonin. Because it promotes the transfer of Ca²⁺ 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 T₃
- low total and free T₃; normal/low TSH (would normally be high if hypothyroid), usu. normal T₄
- 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; diermopathy = pre-tibial myxedema; diffuse thyroid hyperplasia, scollop colloid, columnar epithelium; Dx: low TSH, high FT3/FT4, 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-PPARg 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.

Hyperparathyroidism
- ASx, kidney stones, hyposthenuria (Ca-induced diabetes insipidus), renal failure, bone pain, GI Sx, neuro Sx; Dx: high Ca, high PTH, low PO4, high Alk-phos, high urine Ca
- parathyroidectomy; estrogen therapy
- measure urine Ca to exclude familial hypocalciuric hypercalcemia (defect of parathyroid and kidney Ca receptors)

Hypercalcemia
- other causes = immobilization, familial hypocalciuric hypercalcemia, thiazides
- Vitamin D intoxication
due to exogenous overdose or granulomatous disease (macrophages have 1a-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

Vitamin D intoxication
- 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 PO4, low PTH
Ca & vit D

Pseudo-hypoparathyroidism
end organ resistance to PTH
neuromuscular irritability, twitching, tetany, convulsions; low Ca, high PO4, 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 PO4, 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 PO4, 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+) 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)**

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

truncal obesity, buffalo hump, moon facies, purple striae, linea 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, AII 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 (increased metabolism (phenytoin, phenobarbital, rifampin) or decreased 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 17β-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 activity 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
  
  Adrenocorticotropic 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.
  - Insulin takes up glucose and converts 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
ketois; 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. ketocids; 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, PO4); glucose (prevent hypoglycemia); treat underlying life-threatening; Kussmal respirations = deep breaths to blow off CO2 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, hypoglcin, aspirin; may have autoimmume 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 the active form of vitamin D. It is derived from calciferol (vitamin D₃) which is synthesized in skin exposed to the ultraviolet rays of the sun. Calciferol in the blood is converted into the active vitamin in two steps: calciferol is converted in the liver into 25[OH] vitamin D₃, 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 D₃). Calciferol travels in the blood to the liver where it is converted into 25[OH] vitamin D₃. This compound travels to the kidneys where it is converted into calcitriol (1,25[OH]₂ vitamin D₃). 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
- 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 G₁ 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.

**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**

- **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 endochondral 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, midfacial 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^2; normal BMI 23-25, overweight BMI 25-28; mortality increases w/ BMI > 25