8. ENDOCRINE PHYSIOLOGY

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PRINCIPLES OF ENDOCRINOLOGY

1. What is a hormone?

An **endocrine** hormone is classically considered a substance produced in small amounts, released into the blood where it is transported to a distant organ to exert its specific action on target tissue equipped with a **receptor** for the hormone. A hormone can also act on neighboring tissue within the same gland (**paracrine**) and can act on the tissue that produced it (**autocrine**). Hormones can also be synthesized and released into the bloodstream by nerves (**neurocrine**).

2. List general functions that hormones regulate.

- **Reproduction**—menstrual cycle, ovulation, spermatogenesis, pregnancy, lactation
- **Growth and development**—sexual differentiation, secondary sex characteristics, growth velocity
- **Maintenance of the internal environment**—extracellular fluid volume, blood pressure, electrolyte balance, and regulation of plasma ions such as calcium and sodium
- **Energy flux**—storage, distribution, and consumption of calories; heat production
- **Behavior**—food and water intake, sexual behavior, mood

3. What is the chemical nature of classic hormones, and where are they produced?

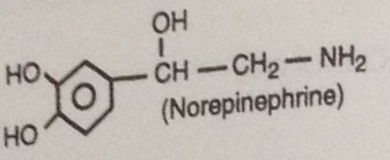
The chemical nature of hormones is determined by the site of synthesis and, in turn, determines the mode of transport in blood, the mechanism of action, and rate of metabolism.

	SITE OF RELEASE	HORMONE
Amines and tyrosine derivatives	Adrenal medulla	Catecholamines (epinephrine, norepinephrine, dopamine)
	Thyroid gland	Triiodothyronine (T_3), thyroxine (T_4)
Steroids	Gonads and placenta	Testosterone, estrogens, progesterone
	Adrenal cortex	Cortisol, aldosterone, adrenal androgens
	Diet/skin/liver/kidney	Secosteroids (vitamin D and its metabolites)
Polypeptides and proteins	Posterior pituitary	Oxytocin, vasopressin
	Hypothalamus	TRH, somatostatin, GnRH, CRH, GHRH
	Anterior pituitary	MSH, ACTH, prolactin, GH
	Gastrointestinal	Gastrin, somatostatin, cholecystokinin, secretin
	Endocrine pancreas	Insulin, glucagon, pancreatic polypeptide
	Placenta	Chorionic somatomammotropin
	Parathyroid/thyroid	PTH, calcitonin
	Many others	Examples: heart (atrial natriuretic peptide), liver (IGF-1)
Glycoproteins	Anterior pituitary	LH, FSH, TSH
	Placenta	hCG

TRH = thyrotropin-releasing hormone, GnRH = gonadotropin-releasing hormone, MSH = melanocyte-stimulating hormone, CRH = corticotropin-releasing hormone, GHRH = growth hormone–releasing hormone, ACTH = adrenocorticotropic hormone, GH= growth hormone, PTH = parathyroid hormone, LH = luteinizing hormone, FSH = follicle-stimulating hormone, TSH = thyroid-stimulating hormone, hCG = human chorionic gonadotropin

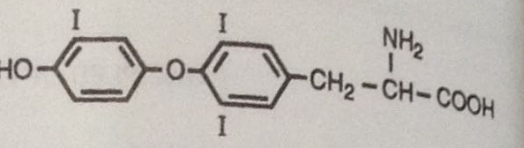
4. What are some examples of different categories of hormones?

Amines



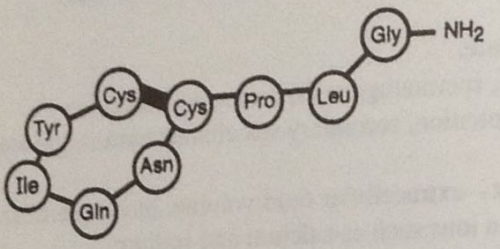
(Norepinephrine)

Thyroid Hormones



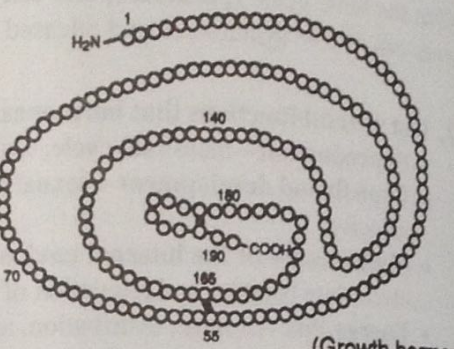
(3,5,3'-triiodothyronine, T_3)

Polypeptides



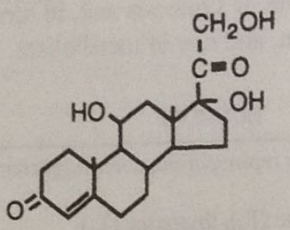
(Oxytocin)

Proteins

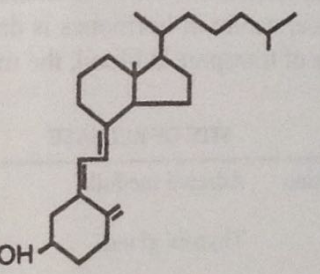


(Growth hormone)

Steroids



(Cortisol)



(Vitamin D3)

Examples of different categories of hormones. In the case of the protein hormone, each circle represents an amino acid, as shown for the polypeptide hormone. The structure of oxytocin is similar to arginine vasopressin. (From Griffin JE, Ojeda SR (eds): Textbook of Endocrine Physiology, 3rd ed. New York, Oxford University Press, 1996, p 7, with permission.)

5. Is there a pattern to the release of hormones?

Hormones are released with a variety of rhythms. Hormones can be released in **circadian rhythm,** such as cortisol, which peaks at 8 A.M. and reaches its nadir at midnight in diurnal animals. Hormones can be released in **ultradian rhythm,** with many regular pulses within a day (e.g., luteinizing hormone [LH]), and even have seasonal rhythms. Hormones can also be released primarily in response to specific stimuli (e.g., suckling-induced prolactin). Pulsatility appears to maintain receptor sensitivity to hormones.

6. What are the general principles of the control of hormone secretion?

The end-product (hormone, metabolite) inhibits the release of the hormone that stimulated the production of the end-product (feedback loop). Most hormones are under **negative feedback** (thermostatic) control. For example, glucagon stimulates glucose production; an increase in plasma glucose shuts off glucagon production.

7. Compare and contrast the general mechanism of action of each class of hormone.

Most hormones work via either a cell membrane receptor, which activates or inhibits a second messenger that alters the function (increases or decreases) of an existent cellular component (e.g., pump), or via an intracellular receptor, which activates specific gene transcription and translation of new protein (synthesis of a new cellular component [e.g., pump]). Some cell membrane hormone receptors also influence gene expression, and some intracellular hormone receptors may act via nongenomic mechanisms.

HORMONE	RECEPTOR LOCATION	SECOND MESSENGER	TIME TO EFFECT
Thyroid	Nuclear	Transcription	Slow
Steroid	Cytoplasmic	Transcription	Slow
Peptide	Cell membrane	cAMP/cGMP	Fast
Catecholamine	Cell membrane	cAMP/cGMP	Fast
Peptide	Cell membrane	IP_2/DAG	Fast

8. List some of the types of cell membrane receptors, and give an example of a hormone ligand.

Seven-transmembrane domain receptor: This classic cell membrane receptor is covered in detail in Chapter 2. The β-adrenergic receptor (catecholamine ligand) is the classic model. These receptors interact with another family of proteins (G-proteins) that mediate changes in adenylate cyclase activity and cyclic adenosine monophosphate (cAMP) production and turn on the classic phosphorylase cascade.

Protein tyrosine kinase activity: These receptors (e.g., epidermal growth factor [EGF] and insulin) catalyze the phosphorylation of tyrosine on intracellular proteins.

Guanylate cyclase-linked receptors: These receptors (e.g., for atrial natriuretic peptide) promote the production of the second messenger cyclic guanosine monophosphate (cGMP).

Cytokine receptor superfamily: Growth hormone (GH) and prolactin are examples of hormones that bind to these receptors, which activate tyrosine phosphorylation despite no apparent homology to known protein kinases.

9. Briefly describe the different second messengers that mediate the action of the cell surface hormone receptors.

Second messengers quickly transduce and amplify the signal generated by the binding of the hormone to the cell surface receptor. Among these second messengers are cAMP, cGMP, the calcium-calmodulin system, and the phosphatidylinositol-diacylglyceride-inositol 1,4,5 triphosphate (IP_3) system. The details of each of these can be found in Chapter 2. Briefly, although they are quite different in their biochemistry, the end result of each is the same in that they quickly act on an intracellular element either to inhibit or to activate some function (e.g., enzyme, pump, membrane potential, calcium release).

10. List and briefly describe some of the types of intracellular hormone receptors.

The intracellular receptors work mostly by altering gene expression. This is why they generally have a slower onset of action than cell membrane receptors, which quickly activate second messengers. **Steroid and thyroid hormones** bind either to a cytoplasmic receptor that is translocated to the nucleus or to nuclear receptors. The binding of steroid to the receptor either liberates the complex from heat-shock proteins (e.g., cortisol) or directly activates the receptor already bound to its respective hormone-responsive elements (HRE) on DNA (e.g., thyroid hormone, estrogen, $1,25(OH)_2D$). Either way, the activated receptor-ligand forms a complex (e.g., homodimer), binds to its HRE, and activates transcription of specific genes (mRNA production). This increase in specific mRNAs results in the synthesis (translation) of specific proteins (e.g., enzyme pumps).

11. List the general features of the metabolism (clearance) of hormones.

1. Some hormones are transported in plasma bound to carrier proteins. Hormones are metabolized from the plasma compartment; usually only the free (unbound) component of the circulating hormone is available for metabolism. It is the unbound hormone that is free to exert a biologic action.

2. Metabolic clearance is inversely proportional to the percent of total hormone circulating in the bound form. Thyroid hormone has a slow metabolic clearance (long half-life) because it circulates > 99.6% bound. Protein binding of a hormone in the plasma compartment protects the hormone from metabolism because only the free hormone is biologically active and available for metabolism.

3. Within a class of hormones, metabolic clearance is also inversely proportional to protein binding in plasma. For example, the steroid cortisol circulates 95% bound and has a slower metabolic clearance than aldosterone, which circulates only 15% bound.

12. Discuss the general principles of endocrine disease.

In general, most disorders that are primarily attributable to hormones result from either their real or apparent underproduction or real or apparent overproduction.

Underproduction:

- **Primary underproduction** is due to loss of the function of the gland producing the active hormone. An example is destruction of both adrenal glands (primary adrenal insufficiency).
- **Secondary underproduction** is due to the loss of the hormone that normally stimulates the gland producing the active hormone. An example of this is hypopituitarism, in which the pituitary fails to produce trophic hormones (e.g., adrenocorticotropic hormone [ACTH]), which maintain normal function of a gland (e.g., adrenal cortex).
- **Apparent underproduction** (target cell insensitivity) is usually due to a receptor defect (mutation) such that, even if the hormone is present, the target cell cannot respond. An example of this is testicular feminization, in which a male genotype (XY) fetus has a mutation in the testosterone receptor and, as a result of loss of androgen activity, develops a female phenotype. Another example is pseudohypoparathyroidism, in which, despite normal or elevated parathyroid hormone (PTH) levels, the target cells for PTH cannot respond.

Overproduction:

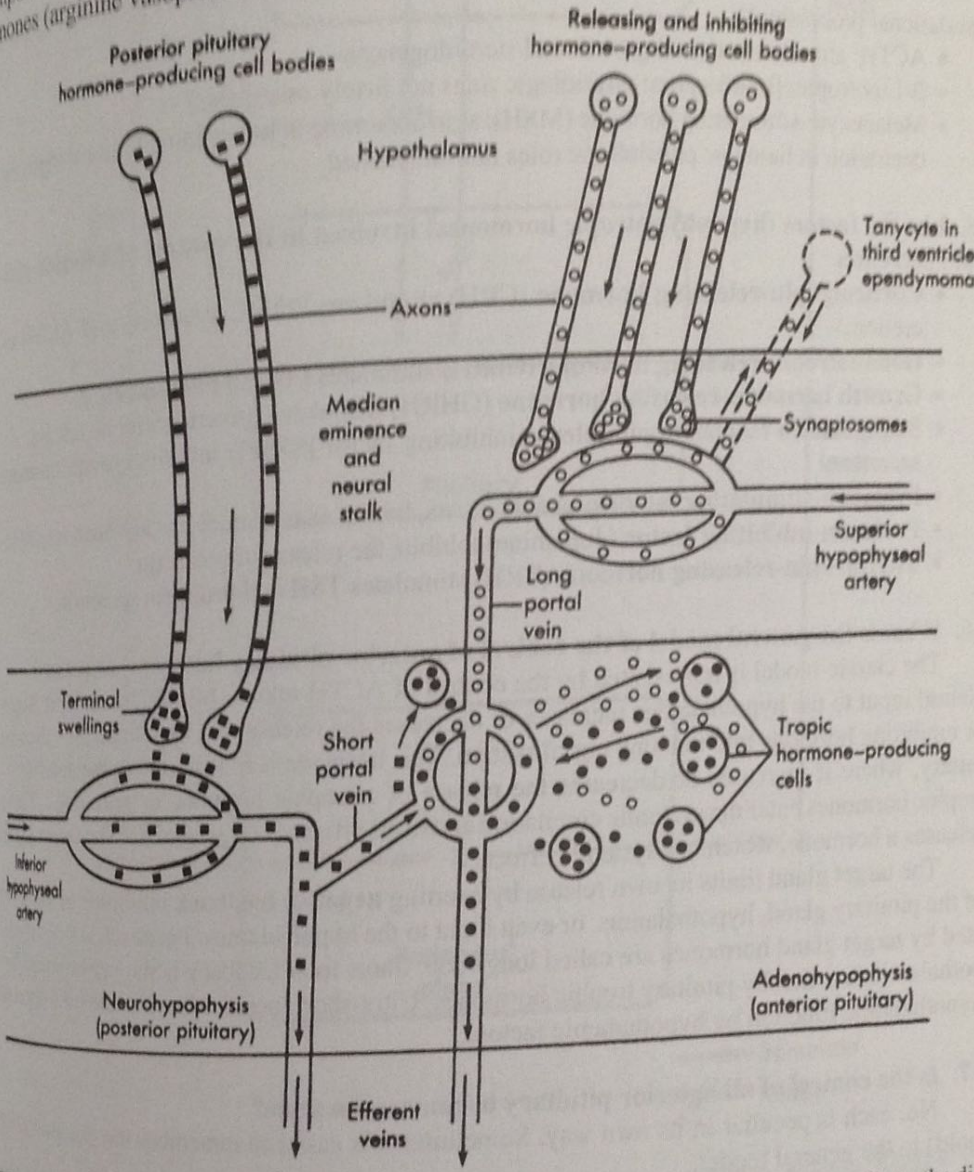
- **Primary overproduction** is usually due to a neoplasm (tumor) arising from a cell population that normally produces the hormone such that the hormone is produced in excess regardless of any endogenous signal to stop its production. An example is an adrenocortical adenoma that produces cortisol even in the absence of ACTH.
- **Secondary overproduction** is due to excess input into the target gland. An example is a tumor arising from normal pituitary cells and producing too much trophic hormone (e.g., ACTH) such that an otherwise normal adrenal cortex is told to produce too much cortisol. Another example is secondary hyperparathyroidism, in which calcium, which inhibits PTH release, is not absorbed properly in the gastrointestinal tract, and PTH release is greatly increased to compensate for it.
- **Apparent overproduction** is due to activation of a receptor or cellular component owing to a mutation. Therefore, the function of the target gland is activated even in the absence of normal hormonal stimulation. An example of an activating mutation is Liddle's syndrome, in which the renal epithelial sodium channel is constitutively activated and mimics the effects of too much aldosterone, even though aldosterone is low.

PITUITARY PHYSIOLOGY

13. Describe the functional anatomy of the hypothalamic-pituitary interface.

The control of anterior and posterior pituitary hormone release is a classic example of **neuroendocrine** systems. The **anterior pituitary** (adenohypophysis, pars distalis) is controlled by hypothalamic releasing or inhibiting (hypophysiotropic) hormones synthesized in parvocellular neurons with cell bodies in nuclei in the hypothalamus (generally medial nuclei such as arcuate and medial

paraventricular). Input to these cell bodies increases or decreases the release of stimulatory (releasing) or inhibitory hormones, which are released from terminals located on capillaries in the median eminence. They enter the long portal blood vessels and are transported to the anterior pituitary, where they stimulate or inhibit the release of hormones from the anterior pituitary. The **posterior pituitary** (neurohypophysis, pars nervosa) releases hormones directly into the blood from axons with magnocellular cell bodies located in the supraoptic and paraventricular (lateral) nuclei of the hypothalamus. Input into these cell bodies causes the increase or decrease in the release of posterior pituitary hormones (arginine vasopressin [AVP] or oxytocin) into capillaries in the posterior pituitary.



The functional anatomy of the hypothalamic-pituitary interface and its blood supply. Arrows indicate the direction of hormone movement. The posterior pituitary has direct arterial blood supply, whereas the anterior pituitary receives most of its blood (containing hypothalamic releasing and inhibiting factors) via portal blood. (From Genuth SM: The endocrine system. In Berne RM, Levy MN (eds): Physiology, 3rd ed. St. Louis, Mosby, 1993, with permission.)

ANTERIOR PITUITARY

14. What are the hormones of the anterior pituitary?

1. **Glycoproteins** (α-subunits identical; β-subunits confer specificity):
   - Thyroid-stimulating hormone (TSH; thyrotropin): stimulates thyroid hormone synthesis and release

- Gonadotropins: LH and follicle-stimulating hormone (FSH)
  Female: stimulates ovarian function and steroidogenesis
  Male: stimulates testicular function and steroidogenesis

2. **Somatomammotropins** (single-peptide chain with disulfide bonds):
- GH (somatotropin): stimulates somatic growth (via insulin-like growth factor I [IGF-1]) and is counterregulatory to insulin
- Prolactin (mammotropin): promotes lactation in females

3. **Proopiomelanocortin (POMC) family** (precursor for small peptides produced by post-translational processing):
- ACTH: stimulates adrenal growth and steroidogenesis
- β-Lipotropin, β-endorphin: physiologic roles not firmly established
- Melanocyte-stimulating hormone (MSH): skin darkening in lower animals and at high concentration in humans; physiologic roles not established

15. List the factors (hypophysiotropic hormones) involved in the control of anterior pituitary secretion.
- **Corticotropin-releasing hormone** (CRH) stimulates POMC synthesis and ACTH secretion.
- **Gonadotropin-releasing hormone** (GnRH) stimulates LH and FSH secretion.
- **Growth hormone–releasing hormone** (GHRH) stimulates growth hormone release.
- **Somatostatin** (somatotropin release-inhibiting factor [SRIF]) inhibits growth hormone secretion.
- **Prolactin-stimulating factor** probably exists, but its exact nature has not been resolved.
- **Prolactin-inhibiting factor** (dopamine) inhibits the release of prolactin.
- **Thyrotropin-releasing hormone** (TRH) stimulates TSH and prolactin secretion.

16. What is the general model of the control of anterior pituitary hormone secretion?

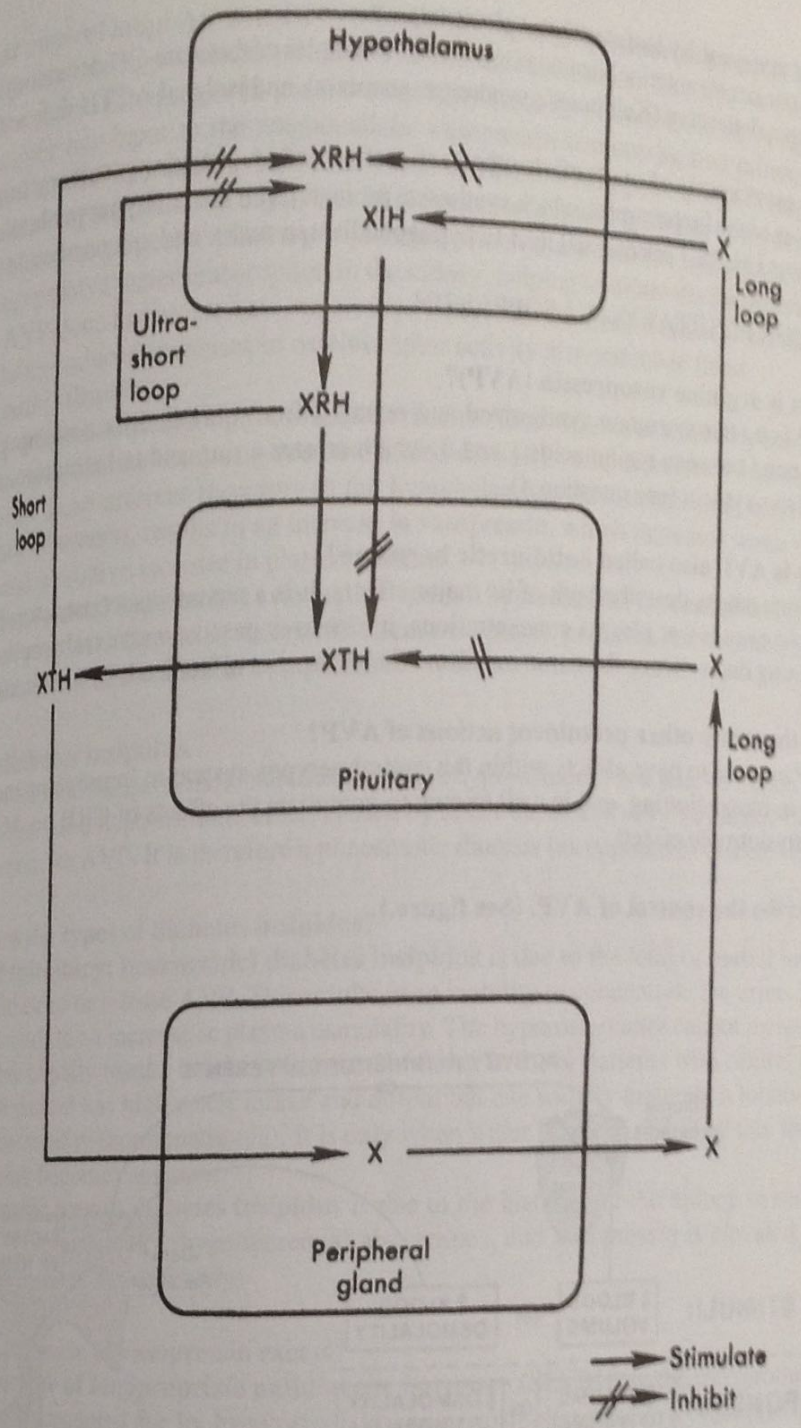
The classic model is represented by the control of ACTH release (see figure on next page). Neural input to the hypothalamus increases or decreases the release of a hypothalamic releasing or inhibiting hormone into the long portal system. This hormone is transported to the anterior pituitary, where it increases or decreases the release of a trophic hormone or hormones. These trophic hormones enter the systemic circulation and exert effects at target glands. The target gland releases a hormone, which has systemic effects.

The target gland limits its own release by exerting **negative feedback** inhibition at the level of the pituitary gland, hypothalamus, or even input to the hypothalamus. Feedback actions mediated by target gland hormones are called long-loop. Short-loop feedback is the inhibition of hypothalamic function by pituitary trophic hormones. Ultra-short loop feedback is the inhibition of hypothalamic function by hypothalamic factors.

17. Is the control of all anterior pituitary hormones the same?

No, each is peculiar in its own way. Sometimes it is easier to remember the exceptions (in **bold**) to the general model:

CRH-ACTH-cortisol	Classic system
GHRH/somatostatin-GH-IGF-I	**Dual (stimulatory [GHRH] and inhibitory [somatostatin]) hypophysiotropic hormones**
TRH-TSH-T_3/T_4	**Majority of negative feedback of thyroid hormone exerted at pituitary (inhibition of TSH)**
GnRH-LH/FSH-testes	**Two pituitary hormones (parallel system) LH and FSH controlled by same hypothalamic factor**
GnRH-LH/FSH-ovaries	**Positive feedback of estrogen on LH during menstrual cycle**
Dopamine-prolactin	**Primarily inhibitory hypophysiotropic control (dopamine inhibition of prolactin release)**



Classic feedforward and feedback regulation of anterior pituitary hormone secretion. Release (XRH) or inhibitory (XIH) hypothalamic hormones access the anterior pituitary via portal veins and either stimulate or inhibit the release of a pituitary tropic hormone (XTH). XTH then acts at target gland to stimulate peripheral gland hormone (X). X inhibits XTH either directly or by inhibiting XRH or stimulated XIH (long-loop negative feedback). XTH may inhibit XRH or stimulate XIH (short-loop negative feedback). It has even been suggested that XRH can inhibit itself (ultrashort-loop negative feedback). (From Genuth SM: The endocrine system. In Berne RM, Levy MN (eds): Physiology, 3rd ed. St. Louis, Mosby, 1993, with permission.)

18. Define hypopituitarism.

Hypopituitarism is a decrease in anterior pituitary function (although posterior pituitary function can be decreased).

19. What is meant by isolated hypopituitarism?

Only one or two anterior hormones are absent. Examples of these are GH deficiency (dwarfism), gonadotropin deficiency (Kallmann's syndrome, anorexia), and isolated ACTH deficiency.

20. Give an example of overactivity (hyperfunction) of an anterior pituitary hormone.

Tumors of the **lactotrophs,** which synthesize prolactin, can lead to **hyperprolactinemia.** This can suppress LH-FSH release and lead to hypogonadism in males and amenorrhea in females.

POSTERIOR PITUITARY—VASOPRESSIN

21. What is arginine vasopressin (AVP)?

AVP is a neurohormone synthesized and released from nerves. It is a nonapeptide with a disulfide bond between amino acids 1 and 6, which creates a ring and tail structure. Its structure is similar to oxytocin (see question 4).

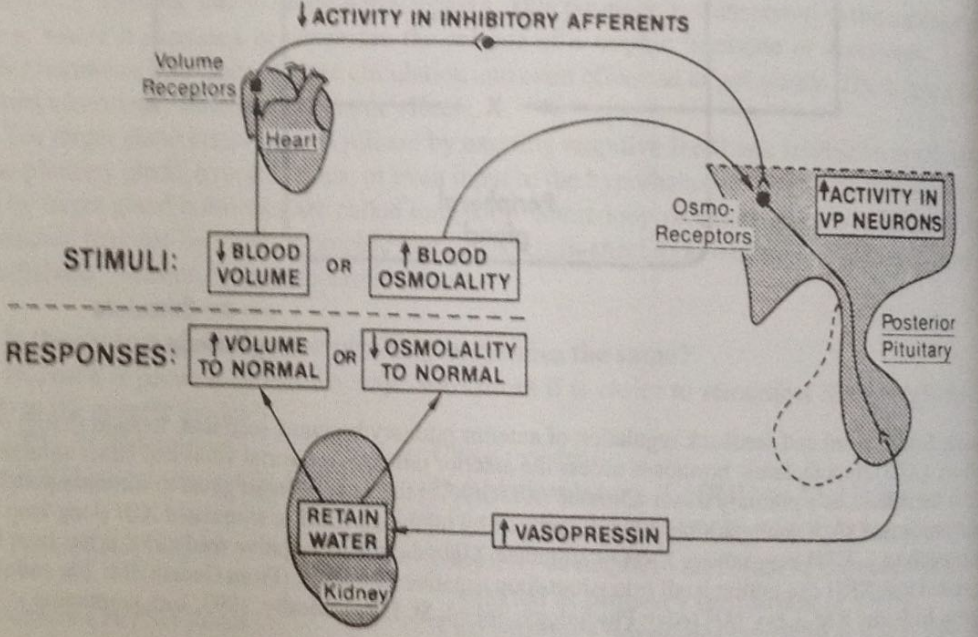
22. Why is AVP also called antidiuretic hormone?

The two names describe both of its major effects. It is a potent vasoconstrictor, hence **vasopressin.** At even lower plasma concentrations, it increases passive water reabsorption in the renal collecting ducts, hence the name **antidiuretic** because its effect leads to a concentrated urine.

23. Are there any other prominent actions of AVP?

AVP appears to have effects within the central nervous system to improve memory, may be involved in blood clotting, and is well known to potentiate the effects of CRH on ACTH release (a hypophysiotropic effect).

24. Describe the control of AVP. (See figure.)



The two major vasopressin control loops. An increase in the osmolality of the blood stimulates vasopressin release, which increases renal passive water reabsorption (retaining the plasma solvent). A decrease in blood volume stimulates vasopressin release via low-pressure baroreceptors in the heart, which increase plasma volume by increasing renal water reabsorption. Although not shown, an increase in osmolality also increases thirst, thereby increasing solvent intake. (From Hedge GA, Colby HD, Goodman RL: Clinical Endocrine Physiology. Philadelphia, W.B. Saunders, 1987, with permission.)

Osmolar control loop: An increase in osmolality is sensed by **osmoreceptors** located in the *portion of the anterior hypothalamus devoid of a blood-brain barrier. This allows these neural structures to sense small changes in plasma osmolality (usually plasma sodium). A signal from the osmoreceptor has input to the magnocellular vasopressin neurons located primarily in the supraoptic (SON) and lateral paraventricular nuclei (PVN) of the hypothalamus. These neurons have long axons that terminate on capillaries in the posterior pituitary, which, when depolarized, release AVP into the posterior pituitary capillaries, which drain into the systemic circulation. AVP increases passive water reabsorption in the kidney, helping to dilute the increase in plasma osmolality. AVP does not create new water; it just prevents the loss of water from the kidney. Hyperosmolality-induced increases in osmoreceptor activity also stimulate thirst.*

Nonosmotic stimuli:

- **Blood volume control loop:** A small decrease in blood volume is sensed by low-pressure baroreceptors in the heart as a decrease in end-diastolic volume/pressure/wall stretch. Input from these afferent receptors to the hypothalamus (via a decrease in activity of inhibitory afferents), results in an increase in vasopressin, which increases water reabsorption, and a relative increase in plasma volume.
- **Others:** Arterial hypotension (via baroreceptors), hypercapnia (via central and peripheral chemoreceptors), hypoxia (via arterial chemoreceptors), pain (via nociception), and nausea all increase the release of vasopressin.

25. Define diabetes insipidus.

Diabetes (siphon/excess urine) insipidus (tasteless/hypo-osmotic) is a state of excess free water excretion (polyuria/hypo-osmotic urine) caused by either the lack of AVP or the inability of the kidney to respond to AVP. It is therefore a nonosmotic diuresis (as opposed to diabetes mellitus).

26. What are the types of diabetes insipidus?

Central (pituitary; neurogenic) diabetes insipidus is due to the total or partial loss of the ability to synthesize or release AVP. This results in an inability to concentrate the urine. The loss of free water leads to an increase in plasma osmolality. The hyperosmolality cannot increase AVP sufficiently but usually results in a large increase in thirst. In many patients with central diabetes insipidus, the patient has high water intake and output but can usually maintain a relatively normal plasma osmolality (normonatremia). It is only when water intake is restricted that the severe hyperosmolality becomes apparent.

Nephrogenic (renal) diabetes insipidus is due to the inability of the kidney to respond to vasopressin. Hyperosmolality (hypernatremia) also ensues, and vasopressin is elevated, but the kidney cannot respond appropriately.

27. Is there a disease of vasopressin excess?

The **syndrome of inappropriate antidiuretic hormone (SIADH)** is the overproduction of vasopressin not accounted for by hyperosmolality or nonosmotic stimuli to vasopressin (e.g., pain, nausea). The overproduction of vasopressin (usually from a pulmonary neoplasm) results in excess water reabsorption, an expansion of plasma volume (hypo-osmolality), and hyponatremia (low plasma sodium).

ADRENAL GLAND

28. Describe the functional zonation of the adrenal gland.

The adrenal gland is composed of layers:

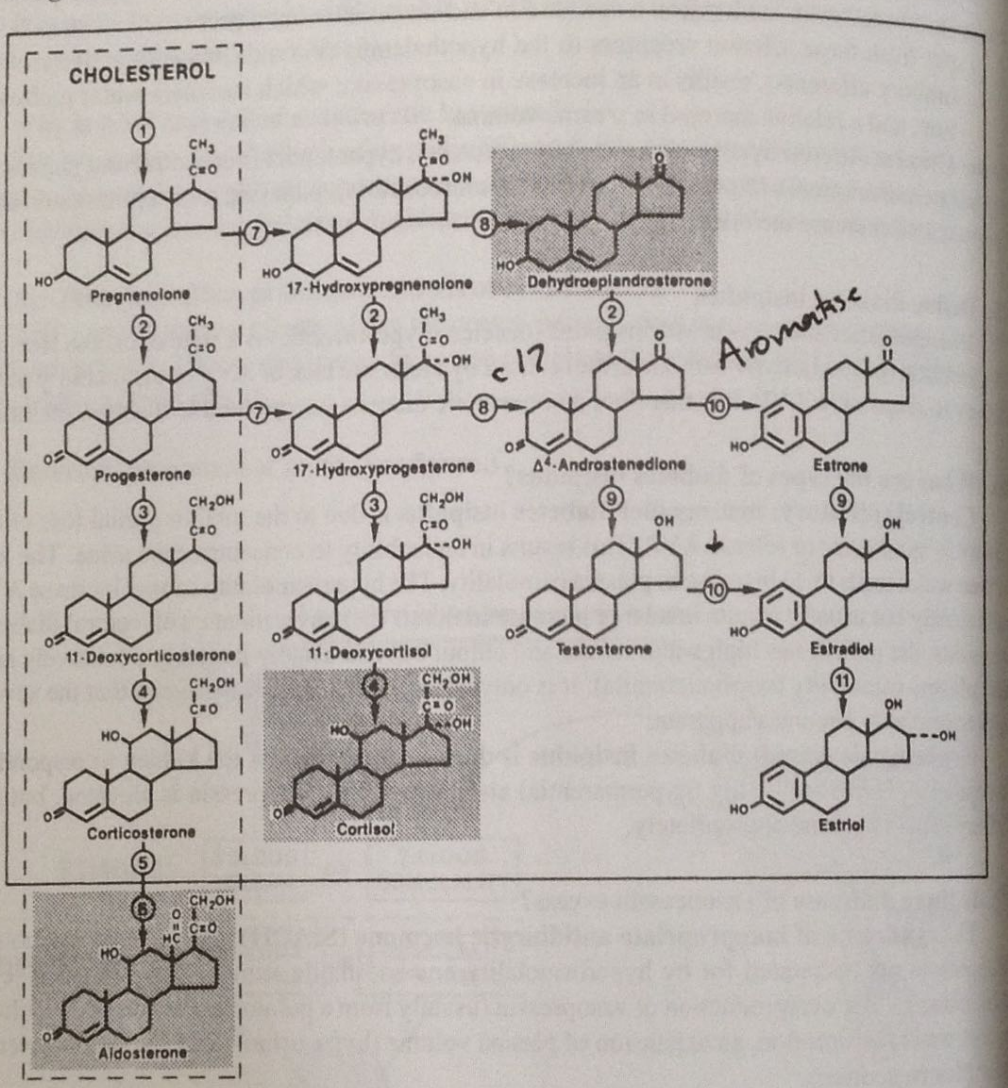
- The outermost layer is the capsule.
- The next layer is the adrenal cortex, which constitutes approximately 90% of the mass of the adrenal gland and synthesizes steroid hormones.
- The innermost layer, the core of the adrenal gland, is the medulla, which is controlled primarily by the autonomic nervous system and secretes catecholamines.

ADRENAL CORTEX

29. Describe the histology of the adrenal cortex.

This is a classic example of functional zonation. The outermost zone is the **zona glomerulosa,** which synthesizes and releases the mineralocorticoid **aldosterone.** Next is the **zona fasciculata,** whose primary secretory product is the glucocorticoid **cortisol.** The innermost zone is the **zona reticularis,** whose primary secretory product is the adrenal androgen **dehydroepiandrosterone** (DHEA). The zonae fasciculata and reticularis are often considered together because they both secrete cortisol and DHEA to some degree.

30. Diagram the synthetic pathway for the adrenal steroids.



Steroidogenic pathways in the zona glomerulosa (dotted lines) that produce aldosterone and the zona fasciculata-reticularis (solid lines) that produce cortisol and adrenal androgens. Major secretory products are shaded. (From Hedge GA, Colby HD, Goodman RL: Clinical Endocrine Physiology. Philadelphia, W.B. Saunders, 1987, with permission.)

Enzymes (abbreviation/gene name) keyed by number to the figure above:

1. Side-chain cleavage (P450scc/*CYP11A1*). Rate-limiting step is cholesterol transport into the mitochondria
2. 3β-Hydroxysteroid dehydrogenase (3β-HSD/*HSD3B*)

3. 21-Hydroxylase (P450c21/*CYP21*)
4. 11β-Hydroxylase (P450c11β/*CYP11B1*) in zona fasciculata (*solid box*)
4–6. Aldosterone synthase (P450c11AS/*CYP11B2*) in the zona glomerulosa (*dotted box*). The zona fasciculata/reticularis does not produce aldosterone under normal conditions.
7. 17α-Hydroxylase (P450c17/*CYP17*) in the zona fasciculata and reticularis only (zona glomerulosa does not produce cortisol)
8. 17,20 Lyase (P450c17/*CYP17*). Steps 7 and 8 are catalyzed by same enzyme. Step 8 is required for steroid to enter the androgen and estrogen pathways.
9. 17-Hydroxysteroid dehydrogenase (17OHSD)
10. Aromatase (P450aro/*CYP19*)
11. 16α-Hydroxylase

31. What is the primary controller of cortisol synthesis?

ACTH from the pituitary gland increases the synthesis of cortisol acutely and maintains adrenocortical size and function chronically. ACTH binds to a specific cell surface receptor, which, via a guanine nucleotide-binding (G) protein, stimulates adenylate cyclase activity. This leads to an increase in cAMP, which stimulates protein kinase A. This leads to an increase in cholesterol transport from the cytosol into the mitochondria, where the first enzyme–side chain cleavage (P450scc) is located. Therefore, the rate-limiting step of steroidogenesis is cholesterol transport into the mitochondria.

32. What is the primary controller of aldosterone synthesis?

The control of aldosterone synthesis involves multiple stimulatory and inhibitory secretagogues. Classically, angiotensin II (Ang II) is used as a model secretagogue for aldosterone. Ang II binds to its receptor on the zona glomerulosa cell, which, via a G protein, activates phospholipase C. Phospholipase C catalyzes the production of the second messengers IP_3 and DAG, which directly (and indirectly by activating release of intracellular calcium) activates cholesterol transport into the mitochondria.

33. Are cortisol and aldosterone the most potent glucocorticoid and mineralocorticoid?

They are the most potent **endogenous** steroids of their class. There are several more potent synthetic steroids, such as the glucocorticoids dexamethasone, prednisone, and triamcinolone and the mineralocorticoid 9α-fluorocortisol. Furthermore, some intermediates of endogenous steroidogenesis have biologic activity, such as corticosterone (both glucocorticoid and mineralocorticoid activity) and deoxycorticosterone (mostly mineralocorticoid activity). The latter can cause hypertension in P450c11β deficiency.

34. How are adrenal steroids transported in the blood?

Steroids circulate in the free (dissolved) form and bind to carrier proteins. The free and bound plasma steroid compartments are in equilibrium. In the case of cortisol, about 95% circulates in the bound form primarily to corticosteroid-binding globulin (CBG), a high-affinity, low-capacity carrier, and albumin, a low-affinity, high-capacity carrier. The **free form** is biologically active and is available for metabolism.

35. List the physiologic effects of cortisol.

Central nervous system	Suppresses CRH and AVP
	Increases food intake
Cardiovascular system	Maintains ability to respond to vasoconstrictors
Liver	Increases gluconeogenesis (glucose synthesis)
Lungs	Necessary for lung maturation and surfactant production in the fetus
Pituitary	Inhibits ACTH synthesis and secretion
Kidney	Increases glomerular filtration rate

	Increases resorption/decreases formation
Bone	Increases protein catabolism (increase in gluconeogenic precursors)
Muscle	Decreases insulin sensitivity (decrease in glucose uptake)
	Immunosuppressive (pharmacologic?)
Immune system	Decreases fibroblast activity and collagen synthesis
Connective tissue	

It is well known that cortisol deficiency is a lethal disorder that must be treated promptly. The exact biologic reason for this is not known, although it is presumed that the ability to maintain blood pressure and volume is the main factor. Some of the effects above are probably relevant only when the hormone is used in pharmacologic doses.

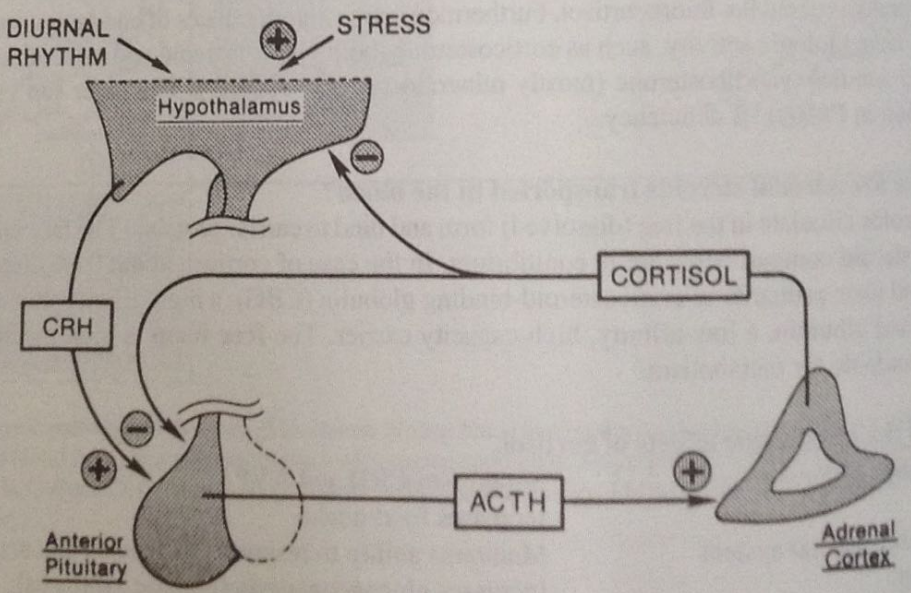
36. Why is cortisol called a glucocorticoid?

One of the long-term effects of cortisol is to increase blood glucose (hyperglycemia). It does this in two general ways: First, cortisol leads to an increase in glucose production in the liver (gluconeogenesis). The liver uses amino acids from muscle and glycerol from fat as gluconeogenic precursors, so, in that sense, cortisol is catabolic. Second, cortisol prevents insulin-mediated glucose uptake in muscle and fat, which prevents glucose from leaving the plasma compartment. The combination of increased gluconeogenesis and decreased insulin-stimulated glucose uptake leads to hyperglycemia. This is thought to be an important mechanism in maintaining plasma glucose levels during a prolonged fast.

37. How is ACTH synthesized?

ACTH is synthesized in pituitary corticotrophs as part of a large precursor molecule, POMC. Posttranslational processing of POMC produces big (22 kilodaltons) ACTH, from which ACTH is produced. POMC is also the precursor for β-LPH, which is further cleaved to γ-LPH and β-endorphin. ACTH contains within it the MSH sequence; hence, when plasma ACTH levels are high (e.g., primary adrenal insufficiency, Nelson's syndrome), skin darkening can occur.

38. Draw the overall control of cortisol secretion.



Regulation of the hypothalamic-pituitary-adrenal (HPA) axis. + indicates that stress stimulates CRH, that CRH stimulates ACTH, and that ACTH stimulates cortisol (feedforward control). − indicates that cortisol inhibits CRH and ACTH release (negative feedback). (From Hedge GA, Colby HD, Goodman RL: Clinical Endocrine Physiology. Philadelphia, W.B. Saunders, 1987, with permission.)

39. Describe the four main elements of the HPA axis.

1. **Neural input into the hypothalamus:** The parvocellular CRH neurons are located primarily in the medial paraventricular neurons. They receive input from a variety of sources, including nociceptive pathways (e.g., pain, burn), limbic system (e.g., anxiety), and other hypothalamic nuclei (e.g., circadian rhythm, hunger, hypoglycemia), and via afferents from the nucleus of the tractus solitarius in the brain stem (hypotension, hypoxia).
2. **CRH** released into the portal circulation stimulates ACTH release.
3. **ACTH** released from the pituitary into the systemic circulation acutely stimulates cortisol synthesis and release. Long-term elevations in ACTH cause adrenal hypertrophy. Conversely, long-term suppression of ACTH (secondary adrenal insufficiency, corticosteroid therapy) leads to adrenal atrophy.
4. **Negative feedback:** Cortisol released from the adrenal gland exerts a variety of systemic effects. In addition, it limits its own release by inhibiting the ACTH sensitivity to CRH (at the pituitary), inhibiting CRH release (at the hypothalamus), and inhibiting input into the hypothalamus (e.g., via the limbic system).

40. Describe the circadian variation in cortisol.

In most humans with a diurnal lifestyle (awake during the day/asleep at night), cortisol peaks at or around 8 A.M. and is at its lowest at around midnight. The increase in cortisol early in the morning may be partly due to the overnight fast during sleeping. This pattern is shifted in humans with consistently nocturnal lifestyles (e.g., third-shift workers).

41. Can one classify the stimuli to the HPA axis?

The general term used to describe these stimuli is **stress.** Stress is difficult to define but can generally be divided into two categories: **neurogenic** (e.g., anxiety, pain, psychological disturbances) and **systemic** (hypotension, hypoglycemia, hypoxia). These categories are arbitrary, and it is often difficult to predict the magnitude of the ACTH response to specific stimuli.

42. Outline the general disorders of the HPA axis.

A. Adrenocortical insufficiency (not enough cortisol)
   1. Primary (loss of adrenal function; e.g., Addison's disease)
   2. Secondary (atrophy of adrenal gland as a result of long-term suppression of ACTH)
B. Cushing's syndrome (glucocorticoid excess)
   1. ACTH-dependent (ACTH induces hypertrophy of adrenal gland)
      a. Cushing's disease (pituitary source of ACTH usually from a microadenoma)
      b. Ectopic ACTH syndrome (nonpituitary source of ACTH; usually from a neoplasm)
   2. ACTH-independent
      a. Adrenal (autonomous secretion from adrenal adenoma or carcinoma)
      b. Iatrogenic/factitious (pharmacologic glucocorticoid therapy)
C. Adrenocortical enzyme deficiencies—congenital adrenal hyperplasia (CAH)
   1. 21-Hydroxylase (virilizing; salt wasting)
   2. 11β-Hydroxylase (hypertension)
   3. 3β-HSD (salt wasting)
   4. 17α-Hydroxylase (hypertension)

43. What are the most common symptoms of primary adrenal insufficiency?

Weakness	Weight loss
Fatigue	Hyperpigmentation
Anorexia	Hypotension

44. What is the cause of adrenal insufficiency?

Primary adrenal insufficiency is usually caused by an autoimmune destruction or by tuberculosis of the adrenal gland. **Secondary adrenal insufficiency** is usually caused by hypopi-

tuitarism. Abrupt withdrawal of long-term exogenous glucocorticoid therapy also leads to secondary adrenal insufficiency because of suppression of the HPA axis (negative feedback).

45. How is the diagnosis of adrenal insufficiency made?

If suspected, a rapid ACTH (cosyntropin) test is performed. If the patient has primary adrenal insufficiency, the cortisol response to exogenous ACTH is low. If the patient has **significant** secondary adrenal insufficiency, the cortisol response to exogenous ACTH is low because of adrenal atrophy owing to long-term loss of tropic action of ACTH. To differentiate between primary and secondary adrenal insufficiency, measurement of plasma ACTH is usually sufficient (ACTH elevated in primary; low or normal in secondary).

The fact that ACTH can be within the normal (reference) range in secondary adrenal insufficiency is an **extremely important** concept that has implications in other consequences of hypopituitarism (e.g., hypogonadotropic hypogonadism, secondary hypothyroidism). The best way to think about it is that if cortisol were low in a normal person, ACTH should be elevated. The fact that the ACTH **is not elevated** means that it is inappropriately low for the low cortisol and that there is something wrong with the hypothalamus, pituitary, or both.

46. What are the general symptoms of Cushing's syndrome (glucocorticoid excess)?

- Obesity (truncal distribution)
- Facial plethora (red cheeks) and moon face
- Hirsutism
- Hypertension (owing to mineralocorticoid action of cortisol)
- Myopathy (muscle weakness)
- Striae (purple stripes on the abdomen because of skin thinning and stretching and easy bruisability)
- Psychological symptoms (usually depression)

47. How does one screen patients to make the diagnosis of spontaneous Cushing's syndrome, and distinguish between ACTH-dependent and independent Cushing's?

One or more of the following is usually found in patients with any form of Cushing's syndrome:

- A 24-hour collection of urine for cortisol is elevated (index of adrenal secretion of cortisol).
- Bedtime salivary cortisol is elevated (due to loss of circadian rhythm; salivary cortisol reflects free [bioactive] plasma cortisol).
- A low dose of dexamethasone given at bedtime indicates that plasma cortisol not fully suppressed in Cushing's syndrome (test of negative feedback).

To distinguish ACTH-dependent from ACTH-independent Cushing's syndrome, the measurement of plasma ACTH by immunometric assay is *usually* sufficient. It is low in ACTH-independent Cushing's syndrome (because of cortisol feedback on a normal pituitary) and within or above the normal range in ACTH-dependent Cushing's syndrome. The logic here is similar to that for the normal ACTH in secondary adrenal insufficiency. Pituitary adenomas used to be normal corticotrophs and retain some responsiveness (albeit diminished) to glucocorticoid feedback. Therefore, although within the normal range, ACTH is inappropriately elevated for the increase in cortisol.

48. Is there a simple way to distinguish between Cushing's disease (pituitary) and ectopic ACTH?

Sometimes it is obvious (big pituitary tumor by magnetic resonance imaging or a lung tumor on radiograph). Occult (radiologically hidden) pituitary and ectopic ACTH-secreting tumors, however, are common. Biochemical testing (e.g., different doses of dexamethasone) is notoriously inaccurate. The only method with sufficient precision involves the measurement of ACTH in the venous outflow from the pituitary (i.e., in the petrosal sinuses) in response to stimulation with exogenous CRH.

49. What is the logic behind the dexamethasone suppression test?

This test was originally designed to diagnose Cushing's syndrome (hypercortisolism). The logic is that a corticotroph adenoma, although arising from a normal corticotroph cell and ex-

pressing the glucocorticoid receptor, has lost sensitivity to cortisol negative feedback. Therefore, low doses of dexamethasone (e.g., 1 mg at bedtime) suppress ACTH and cortisol release in normal subjects but do not suppress cortisol release in patients with any form of Cushing's syndrome. Some ACTH-secreting pituitary adenomas express sufficient glucocorticoid receptor function to exhibit suppression even with low doses of dexamethasone.

This test has also been modified to attempt to differentiate pituitary from ectopic ACTH-dependent Cushing's syndrome. A higher dose of dexamethasone (e.g., 8 mg at bedtime) is used. The logic is that ACTH-secreting pituitary adenomas (Cushing's disease), because they arose from normal corticotrophs and express some glucocorticoid receptor function, diminish ACTH secretion if enough dexamethasone is used. In contrast, ectopic tumors, which did not arise from pituitary corticotrophs, do not express glucocorticoid receptors linked to ACTH secretion. This method also lacks precision because not all pituitary corticotrophs suppress ACTH secretion with high-dose dexamethasone, and some ectopic tumors suppress ACTH secretion with dexamethasone. Therefore, although still widely used, the dexamethasone suppression test lacks sensitivity and specificity and is used with caution.

50. What is congenital adrenal hyperplasia?

Congenital adrenal hyperplasia is caused by a mutation (usually inherited) in a gene for a steroidogenic enzyme leading to a defect (usually partial) in a step of the steroidogenic pathway. In general, the fetal adrenal cannot synthesize adequate cortisol, and the loss of negative feedback inhibition leads to an increase in ACTH. This drives the adrenal to hypertrophy and increases the activity of the enzymes before the enzyme step that is blocked.

51. Describe the consequences of the most common enzyme deficiency, 21-hydroxylase deficiency.

Because 17-OH-progesterone cannot be converted to 11-deoxycortisol (cortisol pathway) *and* progesterone cannot be converted to 11-deoxycorticosterone (aldosterone pathway), both cortisol and aldosterone are deficient. The elevation of ACTH increases production of the precursors, which can be converted to androgens. The excess androgens cause virilization in girls and can lead to ambiguous genitalia in XX fetuses (not sure if phenotype is girl or boy). These children can be salt wasting because of a deficiency in mineralocorticoid production.

52. Why do some inherited enzyme deficiencies cause salt retention and hypertension?

The best example is 11β-hydroxylase deficiency. Because cortisol synthesis is impaired, ACTH is elevated, which drives steroidogenesis and increases production of the precursor to cortisol, 11-deoxycortisol, and the precursor to corticosterone, 11-deoxycorticosterone. Although a weaker mineralocorticoid than aldosterone, 11-deoxycorticosterone has sufficient mineralocorticoid when elevated to increase renal sodium reabsorption and cause hypertension.

53. List the major controllers of aldosterone secretion.

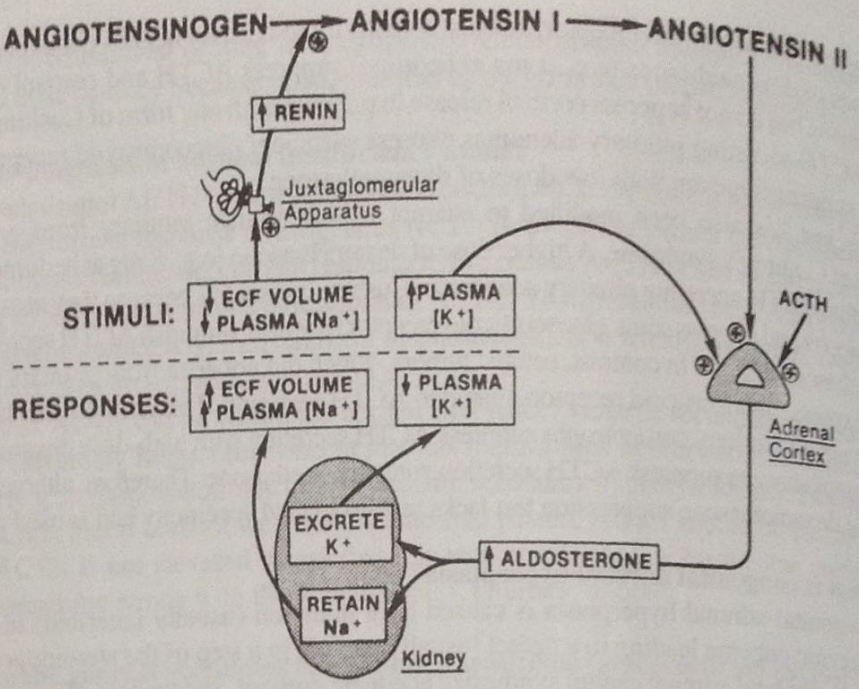
Stimulatory	*Inhibitory*
Ang II	Plasma sodium
ACTH (acutely)	ACTH (chronically)
Plasma potassium	Atrial natriuretic peptide

54. Describe the control of plasma Ang II concentration.

Renin release from the kidney is stimulated by a decrease in plasma sodium and a decrease in extracellular fluid volume, blood volume, and blood pressure. Renin catalyzes the cleavage of Ang II from the substrate angiotensinogen (see figure, top of next page). Angiotensin I is converted to Ang II by the angiotensin-converting enzyme (ACE). Ang II also directly inhibits renin secretion (negative feedback; not shown in figure).

55. How does aldosterone help to prevent increases in plasma potassium (hyperkalemia)?

An increase in plasma potassium directly stimulates aldosterone synthesis and secretion from the adrenal zona glomerulosa. An increase in aldosterone stimulates renal potassium excretion, thereby lowering plasma potassium.



Highly simplified version of the renin-angiotensin-aldosterone system. + indicates that renin increases the conversion of angiotensinogen to angiotensin I and that plasma potassium and Ang II directly stimulate aldosterone release. ACTH is a potent acute stimulator of aldosterone release, but this effect wanes after several days. Notice that plasma potassium forms its own feedback loop independent of the renin-angiotensin system. Not shown is that the conversion of angiotensin I to Ang II is catalyzed by ACE. (From Hedge GA, Colby HD, Goodman RL: Clinical Endocrine Physiology. Philadelphia, W.B. Saunders, 1987, with permission.)

56. What are the other major renal effects of aldosterone?

Aldosterone is called a mineralocorticoid mainly because it increases reabsorption of sodium in the kidney. Therefore, when sodium intake is low, renin secretion is increased, which leads to an increase in plasma Ang II, which stimulates aldosterone secretion. Aldosterone increases sodium reabsorption to restore plasma sodium to normal.

57. List the major disorders of aldosterone production.

Hypoaldosteronism

- Primary (loss of zona glomerulosa function; e.g., Addison's disease)
- Secondary (hyporeninemic hypoaldosteronism; loss of renin secretion from the kidney)

Hyperaldosteronism

- Primary (hyporeninemic): usually caused by a solitary adrenal adenoma (Conn's syndrome) or nodular adrenal hyperplasia
- Secondary (hyperreninemic): usually caused by renal artery stenosis such that the perfusion pressure in the kidney is decreased and the intrarenal baroreceptor stimulates renin release

58. How does one make the biochemical diagnosis of primary hyperaldosteronism?

An increased ratio of plasma aldosterone to plasma renin activity, especially in the presence of hypokalemia (which usually decreases aldosterone secretion) with the appropriate clinical symptoms (e.g., hypertension), suggests an autonomous production of aldosterone.

ADRENAL MEDULLA

59. Why is the adrenal medulla analogous to a postganglionic sympathetic neuron?

The adrenal medulla is derived from neuroectoderm, is innervated by preganglionic sympathetic neurons, and synthesizes and releases catecholamines.

60. Describe the synthesis of adrenal catecholamines.

The relevant cells in the adrenal medulla are called chromaffin cells because they contain storage granules. These cells convert tyrosine to dihydroxyphenylalanine (DOPA) by the regulated enzyme tyrosine hydroxylase. DOPA is converted to dopamine. Dopamine is converted to norepinephrine by the enzyme dopamine-β-hydroxylase. Norepinephrine is converted to epinephrine by phenylethanolamine-*N*-methyltransferase (PNMT).

61. Which of these enzymatic steps are regulated?

The major regulated step is tyrosine hydroxylase, which is inhibited by the products of the pathway (end-product inhibition). Although somewhat controversial, it is also thought the PNMT activity in the adrenal medulla is increased by cortisol release from the adrenal cortex via a paracrine action within the adrenal gland.

62. What are the major effects of catecholamines, and what adrenergic receptor mediates these effects?

Responses of Target Tissues to Catecholamines

TARGET TISSUE	RECEPTOR TYPE	RESPONSE
Liver	β_2	Glycogenolysis, lipolysis, gluconeogenesis
Adipose tissue	β_2	Lipolysis
Skeletal muscle	β_2	Glycogenolysis
Pancreas	α_2	Decreased insulin secretion
	β_2	Increased insulin secretion
Cardiovascular system	β_1	Increased heart rate, increased contractility, increased conduction velocity
	α	Vasoconstriction
	β_2	Vasodilation in skeletal muscle arterioles, coronary arteries, and all veins
Bronchial muscle	β_2	Relaxation
Gastrointestinal tract	β_2	Decreased contractility
	α	Sphincter contraction
Urinary bladder	α	Sphincter contraction
	β_2	Detrusor relaxation
Uterus	α	Contraction
	β_2	Relaxation
Male sex organs	α	Ejaculation, detumescence
	β_2	Erection?
Eye	α_1	Radial muscle contraction
	β_2	Ciliary muscle relaxation
Central nervous system	α	Stimulation
Skin	α	Piloerection, sweat production
Renin secretion	β_1	Stimulation

Adapted from Hedges GA, Colby HD, Goodman RL: Clinical Endocrine Physiology. Philadelphia, W.B. Saunders, 1987.

63. What are the primary stimuli to catecholamine secretion?

Hypoglycemia
Trauma
Hemorrhage
Illness
Hypoxia
Cold exposure

64. Is there a disease of the adrenal medulla?

The best appreciated is pheochromocytoma, which is a catecholamine-secreting tumor. These tumors are usually located within the adrenal gland but can be extra-adrenal (along the sympathetic chain).

65. What are the most common symptoms of pheochromocytoma?

Hypertension
Headache
Excessive perspiration
Palpitations

Absence of all four of these symptoms virtually excludes pheochromocytoma.

THYROID PHYSIOLOGY

66. Describe the functional anatomy of the thyroid gland.

- **Follicles:** formed by cells that synthesize, store (extracellularly), and secrete thyroid hormone
- **Colloid:** central space in the follicle where thyroid hormone is stored as a component of thyroglobulin
- **Parafollicular (C) cells:** synthesize and secrete the hormone calcitonin

67. What are the main thyroid hormones?

- T_4 (3,5,3′,5′-tetraiodo-L-thyronine) is the main secretory product of the thyroid gland.
- T_3 (3,5,3′-triiodo-L-thyronine) can also be produced by the thyroid gland. Most T_3 is produced by monodeiodination of T_4 in peripheral tissue including target cells. Because T_3 is significantly more potent than T_4, T_4 can be considered a circulating prohormone.
- **Reverse T_3** (3,3′,5′-triiodothyronine) is found in the blood, although little if any is secreted by the thyroid. This hormone is essentially devoid of biologic activity and is produced primarily by peripheral monodeiodination of T_4.

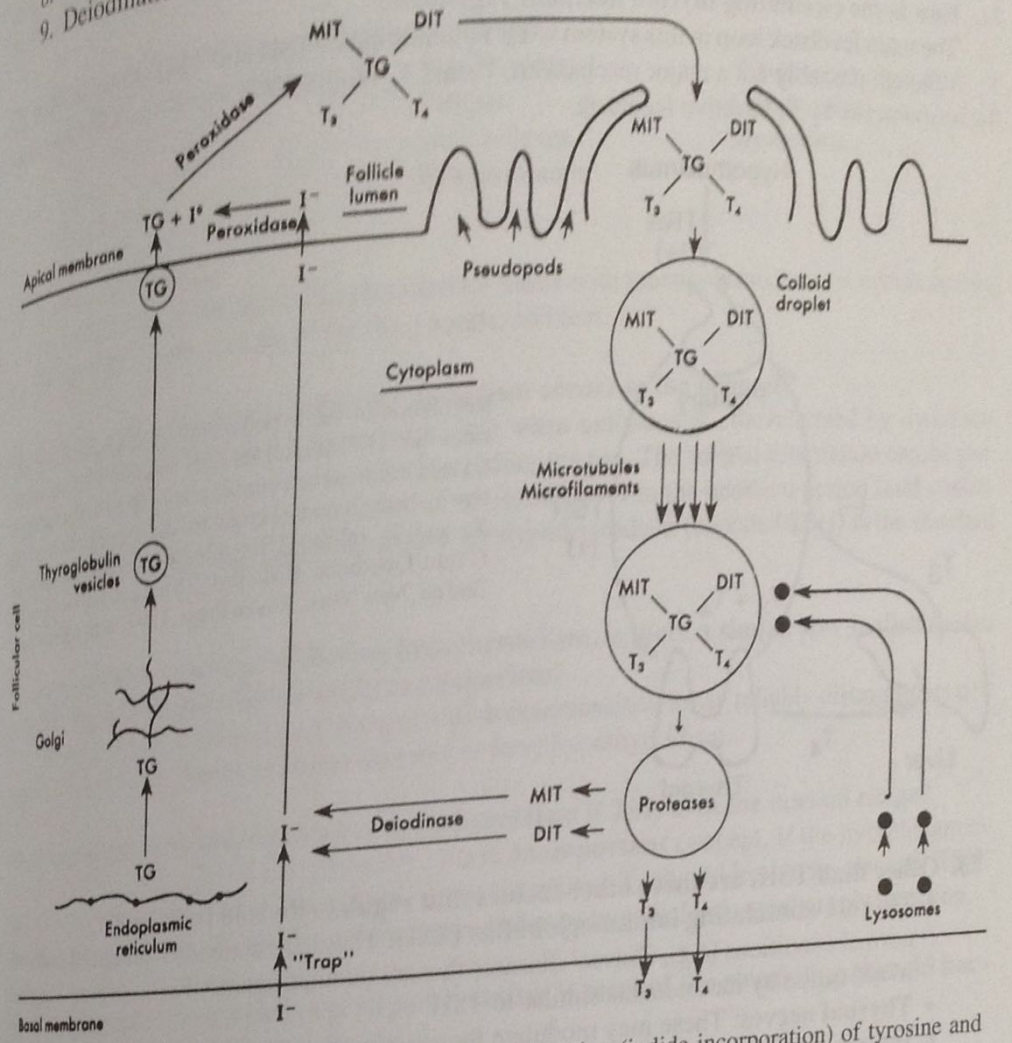
68. What is the source of the iodine used by the thyroid gland to synthesize thyroid hormone?

Organic iodine or inorganic iodide (food supplement) in the diet is absorbed into the blood from the gastrointestinal tract. The follicular cell has an iodide (ionic form of iodine) pump, which traps iodine within the thyroid gland.

69. Describe the synthesis of thyroid hormone.

1. Trapping of iodide—iodide [I^-] pumped from the plasma to the intracellular compartment.
2. Oxidation and organification of iodide (on colloidal side of follicular cell). This is probably the conversion of I^- to I^0 and is catalyzed by the enzyme thyroperoxidase. I^0 is highly reactive and binds quickly to the ring of a tyrosyl residue of thyroglobulin (see later).
3. Exocytosis of thyroglobulin, which has been synthesized within the cell, into follicular lumen.
4. Iodination of tyrosine residues within thyroglobulin. This occurs within the **follicular lumen** and is therefore an extracellular reaction. If one carbon of the tyrosine ring is iodinated, this results in 3-monoiodotyrosine (MIT). If two carbons of the tyrosine ring are iodinated, this results in 3,5 diiodotyrosine (DIT).
5. Coupling of iodotyrosines (**on thyroglobulin molecule**) occurs when MIT and DIT come in contact while still part of the thyroglobulin molecule. If MIT and DIT are coupled, T_3 results. If DIT and DIT are coupled, T_4 results.
6. Endocytosis of thyroglobulin-containing thyroid hormone. If thyroid hormone is needed systemically, TSH from the pituitary is increased and stimulates recovery of thyroglobulin from its storage space in the colloid.

7. Proteolysis of thyroglobulin. The liberation of T_4 and T_3 from thyroglobulin occurs intracellularly.
8. Selective release of T_3 and T_4 from the intracellular to the plasma compartment.
9. Deiodination of MIT and DIT such that iodide and tyrosine can be recycled.



Thyroid hormone biosynthesis and secretion. Notice that iodination (iodide incorporation) of tyrosine and synthesis and storage of thyroid hormone as a component of thyroglobulin (TG) occur extracellularly (in the follicular lumen [colloid]). For detailed description of each step, see text. (From Genuth SM: The endocrine system. In Berne RM, Levy MN (eds): Physiology, 3rd ed. St. Louis, Mosby, 1993, with permission.)

70. Why do the thyroid hormones have such a long half-life?

The half-life of T_4 (6 days) and T_3 (1 day) is long primarily because thyroid hormones circulate bound to carrier proteins. T_4 circulates more than 99.9% bound to thyroid-binding globulin (TBG), transthyretin, and albumin. T_3 is slightly less tightly bound (99.7%) and apparently does not bind appreciably to transthyretin. Because little of the total circulating thyroid hormone is free, little is available for metabolism, hence the long half-life.

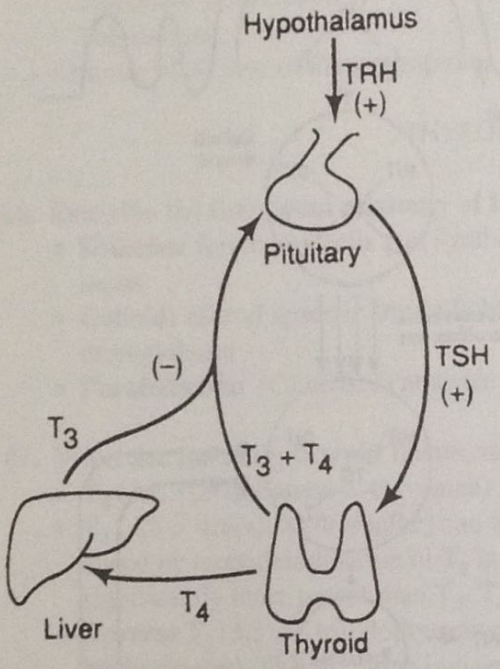
71. List the systemic effects of thyroid hormones.

- **Metabolism:** increase basal metabolic rate and oxygen consumption (and therefore increase minute ventilation, cardiac output, food intake, carbohydrate metabolism, and heat production)
- **Growth and maturation:** required for normal skeletal growth probably by allowing normal effects of IGF-1 on bone and normal GH secretion

- **Central nervous system:** necessary for perinatal maturation and normal reflexes
- **Autonomic nervous system:** increase sympathetic activity
- **Temperature regulation:** increase thermogenesis

72. How is the circulating thyroid hormone regulated?

The main feedback loop in this system is T_4-T_3 inhibition of TSH and TSH stimulation of T_4-T_3. Although probably not a major mechanism, T_3 and T_4 inhibit TRH secretion. TRH increases the set-point for T_4-T_3 negative feedback.



Regulation of the hypothalamic-pituitary axis. + indicates that TRH stimulates TSH and that TSH stimulates thyroid hormone release. T_4 is converted to the more potent T_3 in the liver and target tissue. − indicates that both T_3 and T_4 inhibit TSH release (negative feedback). (From Goodman HM: Basic Medical Endocrinology, 2nd ed. New York, Raven Press, 1994, with permission.)

73. Other than TSH, are there other factors that regulate thyroid function?

- **Thyroid-stimulating immunoglobulins (TSI):** These are antibodies produced under abnormal conditions (e.g., Graves' disease) that are directed against TSH receptors but result in activation by mechanisms similar to TSH.
- **Thyroid nerves:** These may modulate the sensitivity to TSH.
- **Iodine:** Although chronic iodine deficiency leads to a decrease in thyroid hormone and a TSH-mediated increase in thyroid size, an increase in iodine can also decrease thyroid hormone secretion by the paradoxical **Wolff-Chaikoff effect.** This is due to a decrease in the organification of iodide and may be protective against iodine-induced hyperactivity of the thyroid gland. Excess iodine may also decrease the secretion of thyroid hormone possibly by decreasing the sensitivity to TSH.

74. Outline the general disorders of thyroid gland function.

A. Hypothyroidism (too little thyroid hormone)
   1. Primary
      a. Hashimoto's thyroiditis (autoimmune)
      b. Iodine deficiency
   2. Secondary—Hypopituitarism

B. Hyperthyroidism (too much thyroid hormone secretion)
   1. Primary (thyrotoxicosis)
      a. Endogenous (Graves' disease—TSI)
      b. Iatrogenic (overuse of exogenous thyroxine)
   2. Secondary—TSH secreting tumors (very rare)

75. What is a goiter?

A goiter is an enlargement of the thyroid gland. It can be due to **hyperthyroidism** (e.g., TSI in Graves' disease) or **hypothyroidism** (e.g., iodine deficiency causing decreased T_4 production leading to elevated TSH, which induces thyroid hypertrophy).

76. What are the symptoms of hypothyroidism?

- Reduced basal metabolic rate
- Cold intolerance
- Cool, dry skin
- Coarse hair
- Hoarse voice
- Fatigue
- Slow reflexes
- Muscle cramps
- Weight gain
- Constipation
- Myxedema

77. Define myxedema.

An infiltration of the skin and subcutaneous tissue with mucopolysaccharides occurs leading to a puffy appearance, usually of the face, hands, and feet.

78. Is there a specific concern if hypothyroidism occurs in the neonate?

Yes, congenital hypothyroidism (cretinism) when untreated is characterized by dwarfism, mental retardation, and a puffy face with protruding tongue. The mental retardation can be prevented or minimized when thyroid hormone is administered in the neonatal period (and continued throughout life). Testing of all newborns for hypothyroidism (elevated TSH) is the standard of care.

79. If a patient is suspected of having hypothyroidism, is there a simple way to distinguish primary thyroid dysfunction from hypopituitarism?

Measurement of TSH using a third-generation supersensitive assay reliably distinguishes primary (elevated TSH) from secondary (normal or low) hypothyroidism.

80. Why can hypopituitarism lead to hypothyroidism if TSH is in the normal range?

As in secondary adrenal insufficiency, this is an **important** concept. If the hypothalamic-pituitary-thyrotroph function were normal, a low circulating T_4 should lead to an elevated TSH. If TSH is **not elevated,** the low thyroid hormone is due to hypothalamic-pituitary dysfunction.

81. How does one assess functional hypothyroidism if most of the circulating thyroid hormone is bound (not biologically active)?

Measure free T_4.

82. Is there a common condition that causes a discrepancy between free and total T_4?

The most common explanation is a change in circulating TBG concentration. For example, in **pregnancy** (or with **estrogen therapy**), TBG is elevated, which increases total T_4. Because the hypothalamic-pituitary system is normal in most pregnant women, once the new binding sites are saturated, free T_4 is properly regulated and maintained within the normal range.

83. List the symptoms of hyperthyroidism.

- Elevated basal metabolic rate
- Heat intolerance
- Warm skin
- Excessive perspiration
- Weight loss (despite an increase in the intake of food)
- Loss of muscle mass
- Hypertension
- Tachycardia (a sympathomimetic effect)
- Exophthalmos (protruding eyeballs; occurs in Graves' disease)

84. Is there a simple method to diagnose hyperthyroidism?

Because TSH-secreting tumors are exceedingly rare, suppressed TSH is used as a screening test. The current TSH assays available can distinguish normal from suppressed TSH, obviating the need for TRH testing.

85. What are the treatment options for patients with Graves' disease?

- Surgical removal of thyroid gland (thyroidectomy)
- Radioactive iodine administration (ablation)
- Interruption of thyroid hormone secretion with drugs (e.g., methimazole [Tapazole])

86. Summarize the thyroid findings in primary hyperthyroidism, primary hypothyroidism, and pregnancy.

	NORMAL	HYPERTHYROID	HYPOTHYROID	PREGNANT
Total T_4	N	↑	↓	↑
TBG	N	N	N	↑
Free T_4	N	↑	↓	N
TSH	N	↓	↑	N

87. Discuss the thyroid findings in primary hyperthyroidism.

The main defect is excess secretion of T_4 and hence an increase in total and free T_4. TSH is suppressed in primary hyperthyroidism because of negative feedback inhibition by free T_4.

88. Discuss the thyroid findings in primary hypothyroidism.

The main defect is a failure to produce T_4 normally. Therefore, total and free T_4 are decreased. TSH is increased because of the loss of the negative feedback inhibition by free T_4.

89. Discuss the thyroid findings in pregnancy.

The increase in estrogen during pregnancy is probably due to an increase in TBG synthesis in the liver. (Oral contraceptives can cause a similar effect.) Total T_4 is increased because of an increase in the number of available binding sites on TBG. Assuming normal thyroid and pituitary function, free T_4 and TSH levels are regulated and maintained within the normal range. **Hyperthyroidism** may occur during pregnancy and postpartum, and it is extremely important that true endogenous hyperthyroidism be distinguished from a normal elevation of total T_4 during pregnancy because of an increase in TBG.

ENDOCRINE CONTROL OF GROWTH AND DEVELOPMENT

90. Summarize the hormonal regulation of growth.

Prenatal growth is not well understood. It is thought that insulin or insulin-like factors may be involved because women with increased blood glucose (diabetic hyperglycemia) tend to have larger infants (possibly as a result of fetal hyperinsulinemia). Clearly, other unknown factors influence fetal growth. Hormonal control of growth up to about 1 year of age is also not well understood.

Juvenile growth (from age 1 year to puberty) is thought to be influenced by the GH axis (and its intermediates), thyroid hormone, and insulin. Much of the effect of thyroid hormone appears to be due to its maintenance of normal GH secretion.

Puberty is a time of dramatic changes in growth and development. The increase in sex steroid production (androgens in males and estrogens in females) stimulates the pubertal growth spurt. The major mechanism appears to be sex steroid–induced growth hormone secretion, although

many other factors are involved. Sex steroids also terminate the pubertal growth spurt by induction of fusion of the epiphyseal (growth) plates of long bones.

91. Itemize the hormones influencing normal growth.

- **GH** stimulates IGF-1, the major controller of somatic growth.
- **Thyroid hormone** is necessary for normal central nervous system development and for normal action of IGF-1; it stimulates GH secretion.
- **Gonadal steroids** stimulate and terminate pubertal growth spurt. They are necessary for normal GH secretion (particularly androgens).
- **Insulin** stimulates fetal and postnatal growth.
- **Cortisol** inhibits somatic growth by inhibiting GH release and decreasing effects of growth factors on growth plates of bone.

92. Does GH directly increase growth velocity in children?

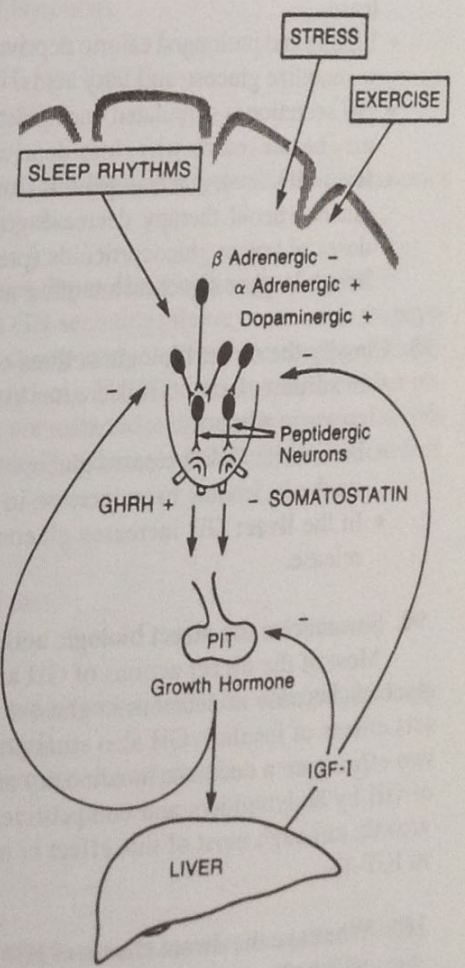
The current theory is that most of the growth-promoting effects of GH are mediated by **IGF-1.** The synthesis and release of IGF-1 from the liver and its local production in GH-target tissues are stimulated by GH. IGF-1 was originally called sulfation factor because it increased incorporation of chondroitin sulfate into bone. It was then called somatomedin C because it mediates the effects of somatotropin (GH). Because somatomedin C was subsequently found to have sequence homology with insulin, the currently accepted name is IGF-1. IGF-1 circulates in the blood bound to insulin-like growth factor binding proteins (IGFBPs).

93. Describe the control of GH secretion.

Hypothalamic control of GH secretion involves stimulatory and inhibitory hypophysiotropic factors. Neurons in the hypothalamus synthesize GHRH, which stimulates GH release, and somatostatin, which inhibits GH. These neurons receive inputs from higher brain centers and stress pathways much like the HPA axis. An increase in GH secretion can be ascribed to an increase in GHRH release or a decrease in somatostatin release. GH then stimulates IGF-1 release, which can inhibit GH release directly at the pituitary, inhibit GHRH release, or stimulate somatostatin release, each of which is a negative feedback loop. It has been suggested that GH can also act as a negative feedback signal within the hypothalamus.

94. Describe the hypothalamic-pituitary-IGF-1 axis.

The figure at right demonstrates regulation of the hypothalamic-pituitary-IGF-1 axis. Notice that GHRH stimulates (+) whereas somatostatin inhibits (−) release of GH from the pituitary. Multiple feedback loops include inhibition of GHRH, stimulation of somatostatin, or glucose-induced inhibition of GH.



(Modified from Reichlin S: Neuroendocrinology. In Wilson JD, Foster DW, Kronenberg H, Larsen PR (eds): Williams Textbook of Endocrinology, 9th ed. Philadelphia, W.B. Saunders, 1998.)

95. List some potential negative feedback loops.

- GHRH stimulates GH, which inhibits GHRH, which decreases GH.
- GHRH stimulates GH, which stimulates IGF-1, which stimulates somatostatin, which inhibits GH release.
- Somatostatin decreases, which increases GH release, which increases IGF-1, which stimulates somatostatin release, which decreases GH release.

96. What central and systemic factors are involved in the control of GH release?

Stimulation of GH	*Inhibition of GH*
Decrease in plasma glucose (hypoglycemia)	Increase in plasma glucose (hyperglycemia)
Decrease in plasma free fatty acids	Increase in plasma free fatty acids
Increase in amino acids (e.g., arginine)	Cortisol (exogenous or endogenous)
Fasting	Pregnancy
Stage 4 (deep) sleep	
Exercise	

97. Place factors involved in the control of GH release into context.

GH has direct effects on intermediate metabolism. It is a counterregulatory hormone to insulin and stimulates glucose production. Therefore, it makes sense that plasma glucose would inhibit GH release because this forms yet another feedback loop: GH stimulates plasma glucose, which inhibits GH release, *or* a decrease in glucose stimulates GH, which increases plasma glucose.

- Because one of the main effects of GH (via IGF-1) is to increase linear growth, it makes sense that ingestion of the building blocks of protein (amino acids) stimulates GH release.
- Fasting and prolonged caloric deprivation require mobilization of endogenous fuel stores to mobilize glucose and fatty acids.
- GH secretion is stimulated during deep sleep. This is extremely important in children and may be one reason why sleep deprivation may lead to short stature.
- It is well known that endogenous Cushing's syndrome (hypercortisolism) and exogenous glucocorticoid therapy decrease growth velocity in children. Children receiving high doses of potent glucocorticoids (prednisone therapy) for rheumatoid arthritis or to prevent transplant rejection are often much shorter than predicted.

98. Classify the direct biologic actions of GH.

- In **adipose tissue:** GH decreases glucose uptake and increases lipolysis, leading to a decrease in adiposity.
- In **muscle:** GH decreases glucose uptake and increases amino acid uptake and protein synthesis, leading to an increase in lean body mass.
- In the **liver:** GH increases gluconeogenesis (glucose secretion) and increases IGF-1 release.

99. Summarize the direct biologic actions of GH.

Most of the **direct** actions of GH are on intermediate metabolism. GH results in hyperglycemia because of decrease in glucose uptake and increase in glucose production (counteracts effects of insulin). GH also stimulates increase in muscle mass. The net results of these two effects are a decrease in adiposity and increase in muscle mass. This explains the abuse of GH by bodybuilders and competitive athletes. GH may also directly increase epiphyseal growth, although most of this effect is mediated by local production of growth factors (such as IGF-1).

100. What are the direct effects of IGF-1?

IGF-1 stimulates an increase in organ size and function. For example, it ensures that as a child grows rapidly, the heart, lungs, kidneys, and other structures grow as well. IGF-1 also has dra-

matic effects on the chondrocytes in bone; it increases transcription, protein synthesis, chondroitin sulfate incorporation, and cell size and number, all of which lead to an increase in linear growth.

101. Briefly outline the pattern of linear growth from conception to adulthood.

A. Fetal growth
1. Peaks at about 4–6 months' gestation
2. Peaks at as high as 12 cm per month

B. Juvenile growth
1. Declines from prenatal peak until about 2 years of age
2. With adequate GH and thyroid hormone levels, continues at a fairly constant rate (about 4–8 cm/year) until the onset of puberty

C. Pubertal growth spurt
1. Stimulated by increased gonadal steroids (which stimulate GH secretion)
2. Usually starts at about 10 years of age in girls and 13 years of age in boys
3. **Variable** between subjects even within the same family
4. Usually peaks at about 12 years of age in girls and 14–15 years of age in boys
5. Most females reach adult height by 15–16 years of age and most males by 17–18 years of age
6. Termination of the pubertal growth spurt caused by gonadal steroid-induced fusion of the epiphyseal (growth) plates of the long bones

102. List the general disorders involving GH.

GH deficiency:
- Hypopituitarism, isolated GH deficiency—leads to short stature in children (dwarfism) and is treated with recombinant human GH injections
- Old age—controversial subject
- GH insensitivity—Laron dwarfism (high GH, low IGF-1)

GH excess—GH-secreting pituitary adenoma:
- Childhood—gigantism
- Postpubertal—acromegaly (acral enlargement, soft tissue overgrowth, insulin resistance leading to hyperglycemia and hyperinsulinemia)

103. Why does GH excess have two different names depending on the age of onset?

Although the cause is the same (almost always a GH-secreting pituitary adenoma), the physical appearance is quite different. GH excess before puberty leads to greatly increased growth velocity and a greatly increased final adult height (**gigantism**). If GH excess commences after pubertal fusion of the epiphyseal plates, linear growth is not restarted and final adult height does not change. **Acromegaly** (from the Greek *akron* ["extremity"] and *megas* ["large"]) is characterized by connective tissue proliferation.

104. List some of the features of acromegaly.
- Soft tissue swelling, particularly in hands and feet
- Skin thickening
- Increased sweating
- Bony changes (cortical thickening, osteophyte proliferation, mandible enlargement leading to a protrusion of the lower jaw [prognathism])
- Nerve entrapment (owing to bone and connective tissue overgrowth)
- Organomegaly (large liver and kidneys)
- Insulin resistance

105. How does one diagnose GH deficiency?

Because of the episodic nature of GH secretion, a single plasma measurement is not particularly helpful. Usually, some kind of stimulation test is performed, such as an arginine infusion or a GHRH infusion, or a sleep study to measure GH during stage 4 sleep.

106. How does one diagnose acromegaly?

Measurement of several elevated plasma IGF-1 levels is probably the most common current approach. Comparison of photographs from different ages is often helpful.

107. What is the treatment for acromegaly?

- Pituitary surgery to remove the GH-secreting tumor
- Treatment with somatostatin analogue
- Radiation therapy of the pituitary

ENDOCRINE PANCREAS

108. Describe the anatomy of the endocrine pancreas.

The pancreas is both an exocrine (secretes digestive enzymes into the gastrointestinal tract) and an endocrine organ. The endocrine component of the pancreas consists of several million clusters (islets) of cells called the **islets of Langerhans.**

109. What are the *major* hormones secreted by the islets and from what cell type?

- **Insulin** is secreted by B cells (also known as β cells)—approximately 75% of islet
- **Glucagon** is secreted by A cells (also known as α cells)
- **Somatostatin** is secreted by D cells (also known as δ cells)

110. What is the major secretory product of the islets of Langerhans, and how is it synthesized?

The protein insulin, the **storage hormone,** is synthesized as a prohormone called **proinsulin.** Posttranslational cleavage of proinsulin produces insulin and C-peptide (connecting). Although C-peptide has minimal, if any, biologic activity, its measurement is generally used as a marker for islet cell function because it is released with insulin.

111. List the major components of intermediate metabolism under endocrine control.

Glucose production	Glycogenolysis (breakdown of glycogen to glucose)
	Gluconeogenesis (synthesis of new glucose from precursors)
Glucose consumption	Glycolysis (burning of glucose for energy production)
Fat storage	Lipogenesis
Fat breakdown	Lipolysis
Ketone production	Ketogenesis (oxidation of fatty acids to ketone bodies)

112. Categorize the effects of insulin.

Generally, insulin promotes the storage (**anabolic effect**) of circulating sugar, amino acids, and fat *and* prevents the breakdown (**anticatabolic effect**) of these stores.

	ANABOLIC	ANTICATABOLIC
Effect on liver	Increases glycogen storage, synthesis of very low-density lipoproteins (VLDL), glycolysis	Inhibits glycogenolysis, ketogenesis, glucogenesis
Effect on muscle	Increases amino acid uptake and protein synthesis and increases glucose transport and glycogen synthesis	Inhibits glycogen phosphorylase
Effects on fat	Increases glucose uptake and triglyceride storage	Inhibits lipolysis

113. In question 112, why was hepatic glycolysis (glucose consumption) listed as anabolic?

The main effect of insulin within the hepatocyte is to increase glucose uptake and then to store it as efficiently as possible. Therefore, one of the goals of insulin is to maintain free intra-

cellular glucose concentration within the hepatocyte as low as possible. If glucose cannot be stored quickly enough, the hepatocyte has no other option but to burn the glucose (glycolysis). Because this process is linked to glucose uptake, it is considered anabolic.

114. If one had to pick one primary effect of insulin, what would it be?

Insulin increases glucose uptake and leads to a decrease in blood glucose (plasma glucose).

115. How is the release of insulin controlled?

Factors that directly stimulate insulin release:

- Food metabolites (glucose, amino acids, fatty acids, ketones)
- Gastrointestinal hormones (increase sensitivity of B cell to glucose)
- Glucagon
- Acetylcholine

Factors that indirectly increase insulin release:

- Counterregulatory hormones (cortisol and GH induce peripheral resistance to insulin leading to increases in blood glucose [which stimulates insulin release])

Factors that inhibit insulin release:

- Somatostatin (paracrine effect, which may prevent insulin overshoot)
- Catecholamines (epinephrine and norepinephrine)

116. Describe the effects of glucagon.

Glucagon opposes (counterregulates) insulin and is therefore catabolic. The main role of glucagon is to prevent hypoglycemia by stimulating hepatic glycogenolysis and gluconeogenesis Glucagon also promotes the conversion of circulating free fatty acids to ketoacids.

117. Are the factors that regulate glucagon secretion basically the opposite of those that regulate insulin?

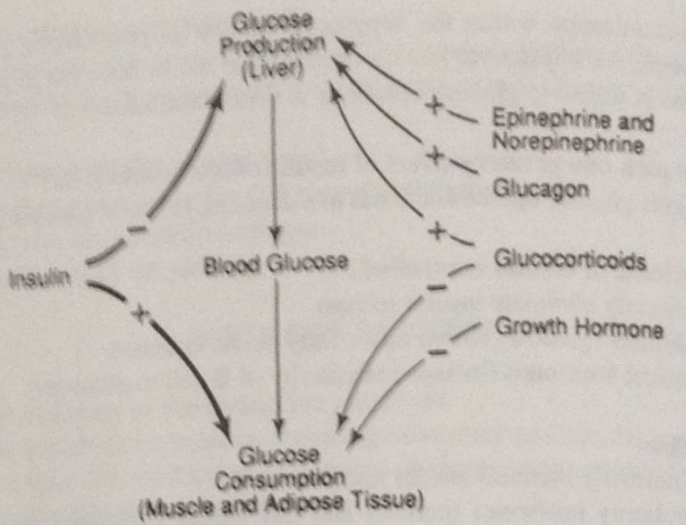
Yes, with notable exceptions. Glucose, ketones, and free fatty acids all inhibit glucagon release, as one would expect. Amino acids, however, actually stimulate glucagon release. A way to remember this is to consider a carnivore in the wild. The hyena can ingest up to 30% of its body weight when it eats, for example, a zebra. This represents a huge protein (and potassium) load. As the metabolites of protein digestion (amino acids) are absorbed (without concomitant glucose absorption), massive insulin release would lead to hypoglycemia and, possibly, loss of consciousness. Therefore, amino acid stimulation of glucagon makes sense to counteract the hypoglycemic effect of insulin when consuming a protein meal. Glucagon also increases amino acid uptake in the liver (for gluconeogenesis), so it makes sense that glucagon is stimulated by amino acids.

118. What is the derivation of the name *somatostatin* as it refers to an islet cell hormone?

The 14-amino-acid peptide somatostatin was first identified as a neurohormone in the hypothalamus that inhibits GH (somatotropin) release—hence the name somatostatin. The identical hormone was subsequently identified from the D cells of the islets of Langerhans and found to inhibit both insulin and glucagon release.

119. Describe the hormonal maintenance of blood glucose.

At one end of the spectrum is a state of total glucose consumption (**fed state**), and at the other end is a state of total glucose production (**fasted state**). Insulin and the counterregulatory hormones regulate the balance between glucose consumption and glucose production. In the fed state, insulin is stimulated and promotes glucose uptake in muscle and adipose tissue (storage). In the fasted state, insulin is low, allowing catabolism. Furthermore, the counterregulatory hormones (GH, cortisol, glucagon, and catecholamines) are elevated in the fasted state, which (1) decreases glucose uptake (decreases insulin sensitivity in muscle and fat) and (2) increases hepatic glucose production (gluconeogenesis).



Integration of the regulatory (insulin) and couterregulatory hormones. In the fasted state (upward), insulin is low, which uninhibits glucose production; and the counterregulatory hormones are elevated, which stimulates glucose production (net increase in gluconeogenesis). In fed state (downward), insulin, the storage hormone, is increased, which inhibits glucose production while encouraging glucose intake (consumption). The counter-regulatory hormones are inhibited in the fed state, which unstimulates glucose production. (From Goodman HM: Basic Medical Endocrinology, 2nd ed. Philadelphia, Lippincott-Raven, 1994, with permission.)

120. What is the insulin-to-glucagon ratio?

In the normal individual, this reflects degree of fed versus fasted state. If the individual is in the fed state, the insulin-to-glucagon ratio is high, which induces anabolic enzymes and inhibits catabolic enzymes. If the individual is in the fasted state, the insulin-to-glucagon ratio is low, and catabolic enzyme activity predominates.

121. Describe the pattern of glucose, glucagon, and insulin during a typical day in a normal person.

A mixed meal (carbohydrate, protein, fat) increases glucose. Insulin increases in response, which stimulates glucose uptake and lowers blood glucose. After some meals, insulin levels actually decline while blood glucose is still elevated. This decrease in insulin may be due to paracrine actions of somatostatin within the islet cells and probably prevents too large a decrease in glucose after a meal (reactive hypoglycemia). That is, if insulin stayed high for too long, glucose would continue to decrease from its peak after a meal to below baseline. The attenuation of the insulin response after a meal allows plasma glucose to normalize gradually without going significantly below basal levels.

122. What is the flow of fuel during a prolonged fast, and what hormones are responsible?

In a prolonged fast, insulin is low, and the counterregulatory hormones are increased. Hepatic gluconeogenesis is the prime source of glucose (180 g/day), which is consumed by the central nervous system (which does not require insulin to maintain glucose uptake); blood cells; and, to some extent, muscle, heart, kidney, and other organs. The substrate for hepatic gluconeogenesis is supplied by cortisol-induced muscle catabolism, which can break down as much as 75 g of protein a day, thus supplying amino acids to the liver to be used in glucose synthesis. GH-induced and catecholamine-induced lipolysis supplies glycerol for hepatic gluconeogenesis and fatty acids. These fatty acids can be used by the heart, kidney, and muscle for fuel and are also converted to ketones in the liver.

123. What would be the consequence of either an inability to secrete insulin or an inability to respond properly to circulating insulin?

Diabetes mellitus (too much sweet urine):

- Type 1: the absence of insulin itself
- Type 2: a resistance to insulin action

Either form can result in a failure in glucose uptake leading to hyperglycemia and a glucose-induced (osmotic) diuresis.

124. Characterize the two forms of diabetes mellitus.

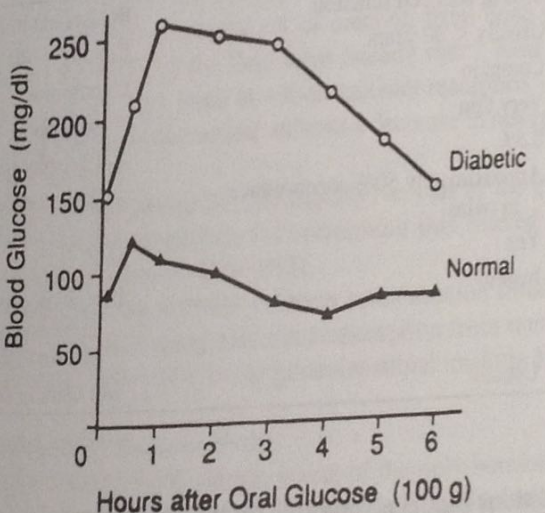
Type 1 diabetes mellitus (T1DM) has also been called juvenile-onset or insulin-dependent (IDDM) diabetes mellitus because its onset is usually (but not always) manifest before adulthood. It results from the autoimmune destruction of the B cells of the islets that normally produce insulin. (Other islet cell types can also be destroyed.) Without insulin, blood glucose is elevated, and, paradoxically, gluconeogenesis and fat breakdown continue. Therefore, although there is excess fuel (glucose, fatty acids, amino acids) available in the plasma compartment, the lack of an insulin signal prevents their uptake. This is why T1DM can be considered "tissue starvation in the face of plenty."

Type 2 diabetes mellitus (T2DM) has also been called adult-onset or non–insulin-dependent (NIDDM) diabetes mellitus because it usually occurs after puberty and is not due to a lack of insulin, at least early in the onset of the syndrome. NIDDM is currently thought to be an inadequate definition at best or a confusing one at worst because type 2 diabetes mellitus can be treated with pharmacologic doses of insulin under certain circumstances. Although the pathogenesis of T2DM is complicated, it generally can be considered a syndrome of severe insulin resistance. That is, the insulin-dependent glucose transporter has a decreased sensitivity to insulin, particularly in skeletal muscle and fat. Therefore, although the insulin signal is present, the response to it is inadequate, and glucose uptake is decreased.

125. Define diabetes mellitus.

Diabetes mellitus is generally defined as fasting hyperglycemia and an exaggerated plasma glucose response to oral glucose that is unexplained by other factors.

126. Discuss an example of diabetes mellitus as formally defined.



Typical oral glucose tolerance test in normal and diabetic subjects. The diabetic subject has fasting (0 hour) hyperglycemia. The normal subject responds to an oral glucose load by increasing insulin, which lowers blood glucose to (but usually not below) control. The diabetic subject's response to an oral glucose load is characterized by hyperglycemia because of a failure to release insulin (type 1 diabetes mellitus) or the failure to respond adequately to the insulin released (type 2 diabetes mellitus). (From Goodman HM: Basic Medical Endocrinology, 2nd ed. Philadelphia, Lippincott-Raven, 1994, with permission.)

127. How is T1DM treated?

Insulin therapy is the mainstay of treatment. Various preparations of insulin are available with different pharmacokinetics, such that the patient can fairly accurately duplicate a normal pattern of insulin action during the day. Nothing substitutes for a normal endocrine pancreas as of yet; so, eventually, most type 1 diabetics exhibit morbidity from the disease.

128. What happens if insulin therapy is not given to a patient with type 1 diabetes?

Carbohydrate. Glucose transport and glycogen synthesis are decreased, while glycogenolysis and gluconeogenesis are maintained. This leads to hyperglycemia, glucosuria, polyuria (osmotic diuresis), dehydration, and a failure of the circulatory system to maintain systemic perfusion.

Lipid. Lipogenesis is decreased, and lipolysis is increased. This leads to hyperlipemia. Insulin is not present to inhibit conversion of fatty acids to ketones, so ketonemia and ketonuria occur. This leads to severe metabolic acidosis.

Protein. A decrease in amino acid uptake and protein synthesis and an increase in protein degradation lead to increased amino acids in the blood and urine. This is manifest as a negative nitrogen balance.

The end result is the patient loses large quantities of calories, amino acids, water, and bicarbonate in the urine. This is manifest as extreme weight loss, weakness, hyperglycemic shock, coma, severe acidosis, and, if not treated, death.

129. What is the pathogenesis of type 2 diabetes mellitus?

The first defect is probably a decrease in the sensitivity to insulin (insulin resistance), which appears to be an inherited propensity. If this occurs without weight gain, the islet cell can usually compensate by increasing insulin secretion. If the patient gains weight and insulin resistance worsens, the islet cell response is inadequate, and hyperglycemia occurs. Eventually the insulin response to hyperglycemia wanes, and the symptoms worsen. There is usually adequate insulin secretion to prevent ketogenesis in the liver, although there is not sufficient insulin to shut off hepatic gluconeogenesis.

130. Compare and contrast type 1 and type 2 diabetes mellitus.

	TYPE 1 DIABETES MELLITUS	TYPE 2 DIABETES MELLITUS
Pathogenesis	Loss of islet cell function	Resistance to insulin
Age of onset	Usually < 30 years	Usually > 40 years
Ketoacidosis	Common	Uncommon
Body weight	Very thin	> 80% obese
Prevalence	0.5%	2–4% (may be higher)
Genetics	Approximately 50% concordance in twins	> 95% concordance in twins
Autoimmune	Yes	No
Treatment	Insulin	Diet, hypoglycemia agents, appetite suppression, weight loss, exercise, insulin (sometimes)
Symptomatic	Usually	Not usually (at least, at first)

131. List other conditions that can resemble diabetes mellitus.

Secondary diabetes

- Pancreatic disease
- Excess in the counterregulatory hormones such as GH (acromegaly), cortisol (Cushing's syndrome), catecholamines (pheochromocytoma)
- Drugs

Syndrome X (also known as syndrome of insulin resistance, subclinical diabetes, or the metabolic syndrome)

Gestational diabetes

- Glucose intolerance (hyperglycemia) usually only manifest during pregnancy. It is probably due to placental hormones (e.g., human chorionic somatomammotropin, placental steroids).

HORMONAL CONTROL OF CALCIUM HOMEOSTASIS

132. Why is calcium flux so tightly regulated?

Calcium is an extremely important cation in many intracellular and extracellular processes. **Extracellular** calcium is necessary for normal mineralization of bone, blood clotting, and plasma membrane function. **Intracellular** calcium is necessary for a large number of processes, including skeletal and cardiac muscle function; the secretion of hormones, neurotransmitters, and digestive enzymes; normal action potentials and retinal function; maintenance of transport of ions across membranes; regulation of enzyme function; and cell growth and division.

133. In what form does calcium circulate in the plasma?

- Bound to protein (primarily albumin)
- In the free ionized state

134. Describe daily calcium balance.

The extracellular fluid (including plasma) is the central compartment with which all other compartments exchange calcium. The other important compartments and their hormonal controllers are as follows:

Gastrointestinal tract. This is the primary site of calcium **absorption.** For example, out of 1000 mg of dietary calcium, about 400 mg (40%) is absorbed. The absorption of calcium in the gastrointestinal tract is stimulated by $1,25(OH)_2D$, the biologically active component of the vitamin D pathway. Production of $1,25(OH)_2D$ is stimulated by PTH. About 300 mg (out of 1000 mg/day) of calcium is lost from the extracellular fluid compartment to the gastrointestinal tract via secretions. Therefore, the typical net calcium absorption per day is about 10% of the calcium intake, although this can be changed dramatically by vitamin D excess or deficiency.

Bone. Bone is the primary storage site for calcium (approximately 1 kg; ~99% of total body calcium). Calcium in bone is actively exchanged with the plasma compartment. Bone accretion (formation) is an ongoing process. Reclamation of calcium from bone is a process called **resorption** and is stimulated by PTH. In the long term (steady state), bone formation and resorption are generally in equilibrium. Any state in which calcium resorption is increased without an increase in formation or formation is decreased without a decrease in resorption ultimately results in loss of bone (e.g., osteoporosis).

Kidney. Calcium is filtered (about 10,000 mg/day) as part of the glomerular filtrate. The kidney has developed efficient mechanisms for reclaiming this filtered calcium from tubular fluid—**reabsorption**—which is stimulated by PTH.

Therefore, PTH increases extracellular calcium concentration directly by increasing calcium resorption from bone and increasing calcium reabsorption from renal tubular fluid and indirectly by increasing calcium absorption in the gastrointestinal tract via $1,25(OH)_2D$.

135. How is the secretion of PTH controlled?

PTH, produced by the parathyroid glands, is one of the only hormones whose secretion is inhibited by an increase in extracellular calcium. In a simple feedback loop, a decrease in plasma calcium results in an increase in PTH, which increases bone resorption, calcium reabsorption, and calcium absorption (via $1,25(OH)_2D$), all acting to restore plasma calcium. The converse is also true in that an increase in plasma calcium suppresses PTH release, which decreases the resorption, reabsorption, and absorption (via $1,25(OH)_2D$) of calcium, allowing plasma calcium to decrease. PTH is the most important acute controller of plasma calcium.

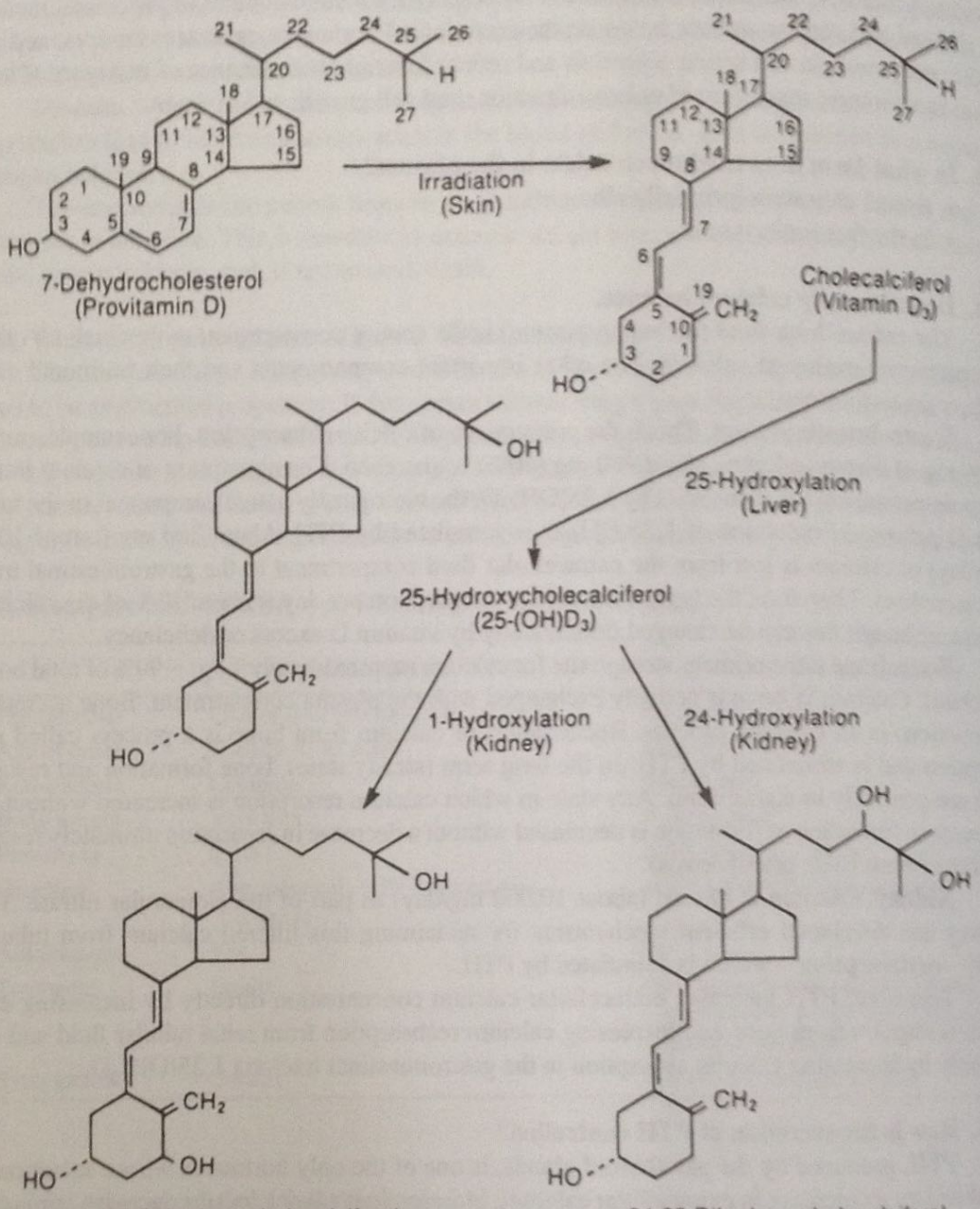
136. How do the parathyroid cells detect small changes in extracellular (plasma) calcium?

These cells express a receptor with an extracellular calcium-sensing component and a 7-transmembrane spanning domain; the receptor is G-protein coupled. This receptor acts via phospholipase-C and also by inhibiting adenylate cyclase. Parathyroid hormone is one of the few whose secretion is **inhibited** by an increase in calcium.

137. Other than PTH and $1,25(OH)_2D$, is there another hormonal controller of plasma calcium?

Calcitonin, produced by the parafollicular cells of the thyroid gland, inhibits bone resorption.

138. Describe the pathway that produces $1,25(OH)_2D$.



The endogenous vitamin D steroidogenic pathway. Conversion of vitamin D to 25(OH)D in the liver is relatively unregulated while activation of 25(OH)D to $1,25(OH)_2D$ in the kidney is highly regulated (e.g., stimulated by PTH). Vitamin D can also be obtained in the diet as cholecalciferol (animal vitamin D_3) or ergocalciferol (plant vitamin D_2). (From Griffin JE, Ojeda SR (eds): Textbook of Endocrine Physiology, 3rd ed. New York, Oxford University Press, 1996, with permission.)

1. The vitamin D (calciferol) pathway is a steroidogenic pathway catalyzed by a series of cytochrome P-450 enzymes. There are two forms of vitamin D in the diet: animal vitamin D_3 (cholecalciferol) and plant vitamin D_2 (ergocalciferol). In addition, vitamin D_3 can be liberated from the skin from 7-dehydrocholesterol via the action of ultraviolet light.

2. Once vitamin D_2 or D_3 reaches the plasma compartment, it is converted to 25(OH)D by the action of 25-hydroxylase enzyme in the liver. This is a relatively unregulated step, although elevated $1,25(OH)_2D$ is thought to inhibit this step (end-product inhibition). In physiologic concentrations, 25(OH)D has little biologic activity, whereas it may have calciotropic effects when elevated.

3. 25(OH)D is activated to the active form, $1,25(OH)_2D$, by 1-hydroxylase enzyme located in the kidney. The activity of 1-hydroxylase is increased by PTH and inhibited by plasma phosphate and $1,25(OH)_2D$ (end-product inhibition). 25(OH)D can also be inactivated to $24,25(OH)_2D$ by 24-hydroxylase in the kidney.

139. What is the best method to assess the activity of the vitamin D pathway?

Measurement of serum $1,25(OH)_2D$, the active component of the pathway.

140. What is the best method to assess vitamin D intake and stores?

Measurement of serum 25(OH)D because it reflects the summation of vitamin D from dietary and skin sources available for activation to $1,25(OH)_2D$.

141. Summarize the actions of the major calcium-regulating hormones.

HORMONE	SITE	ACTION
Parathyroid hormone	Bone	↑ Calcium and phosphate resorption
	Kidney	↑ Calcium reabsorption
		↓ Phosphate reabsorption
		↑ Conversion of 25(OH)D to $1,25(OH)_2D$
Calcitonin	Bone	↓ Calcium and phosphate resorption
	Kidney	↓ Calcium and phosphate reabsorption
Vitamin D [$1,25(OH)_2D$]	Bone	Maintains calcium transport system
	Gastrointestinal tract	↑ Calcium and phosphate absorption

142. Discuss other hormones that affect bone and calcium metabolism.

Gonadal steroids. Androgens and estrogens are necessary for the pubertal growth spurt and closure of the epiphyseal (growth) plates in bone and, therefore, before adulthood, favor bone formation. In the adult, estrogen decreases bone resorption (probably PTH-mediated) and therefore protects bone density. Loss of estrogen at menopause (or loss of testosterone in men because of hypogonadism) is characterized by a loss of bone mineral density (osteoporosis).

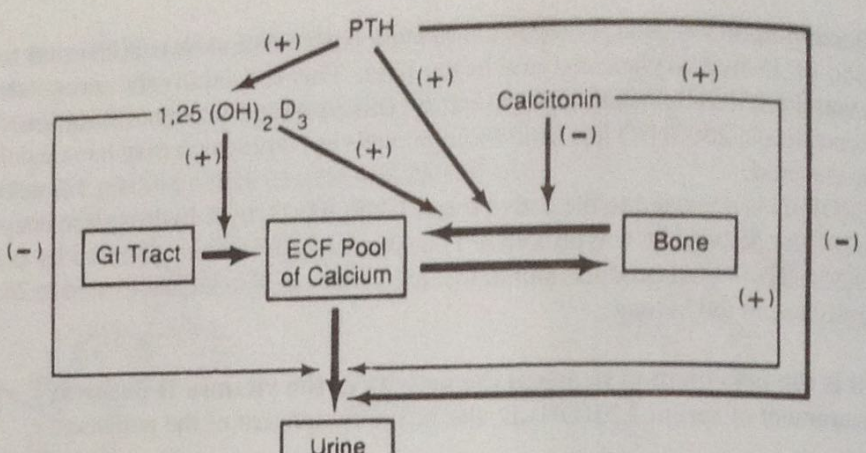
Glucocorticoids. Although cortisol is necessary for normal skeletal growth, cortisol in excess produces severe osteoporosis. There are several mechanisms for glucocorticoid-induced osteoporosis, including hypercalciuria and an inhibition of $1,25(OH)_2D$-mediated calcium absorption in the gastrointestinal tract. The resultant secondary hyperparathyroidism accelerates bone resorption. Furthermore, cortisol in excess appears to inhibit osteoblastic bone formation directly. Finally, excess glucocorticoid may induce secondary hypogonadism.

Thyroid hormone. Lack of adequate thyroid hormone delays ossification of bone growth centers and can retard bone development in children. Excess thyroid hormone may cause increased bone resorption.

GH. GH stimulates IGF-1, which increases bone formation.

143. Describe the overall regulation of calcium balance.

In the steady state, calcium intake should roughly equal calcium loss via the gastrointestinal tract and the urine. Calcium absorption is increased by $1,25(OH)_2D$, whose production is increased by PTH. PTH also increases calcium resorption from bone and calcium reabsorption from the urine. If plasma calcium is high, calcitonin may decrease bone resorption.



Integration of the hormonal regulation of calcium balance. PTH increases plasma (ECF) calcium by increasing bone resorption, increasing reabsorption of calcium in the kidney, and by increasing renal production of $1,25(OH)_2D$, which stimulates gastrointestinal absorption of calcium. Although calcitonin does decrease bone resorption at pathophysiologic concentrations and with pharmacologic doses, its physiologic role is minor. (From Goodman HM: Basic Medical Endocrinology, 2nd ed. Philadelphia, Lippincott-Raven, 1994, with permission.)

144. Briefly explain phosphate balance.

Phosphate resorption in the gastrointestinal tract accompanies calcium and is increased by $1,25(OH)_2D$. Phosphate resorption also accompanies calcium and is increased by PTH. The main difference between calcium and phosphate balance occurs in the kidney, where PTH **increases** phosphate excretion. This is why patients with elevated PTH have hypercalcemia and hypophosphatemia—they reclaim calcium from the urine while allowing phosphate to be excreted.

145. Discuss the pathogenesis of PTH-dependent hypercalcemia.

PTH-dependent hypercalcemia is defined as **primary hyperparathyroidism** and is usually due to a parathyroid adenoma. These tumors produce intact PTH in excess and are not suppressed by small increases in plasma calcium (as opposed to normal PTH-producing cells). Therefore, plasma calcium increases but fails to shut off PTH adequately. This increases calcium (and phosphate) resorption from bone, increases calcium reabsorption and decreases phosphate reabsorption in the kidney, and increases $1,25(OH)_2D$ production from the kidney to increase calcium absorption in the gastrointestinal tract. The result is hypercalcemia without a suppression of PTH or with frankly elevated PTH, hypophosphatemia (owing to the phosphaturic effects of PTH), and hypercalciuria.

146. Explain why a patient with elevated PTH has hypercalciuria if PTH increases renal calcium reabsorption.

When plasma calcium is elevated, the filtered load of calcium in the kidney increases. Although PTH does increase tubular calcium reabsorption of calcium, the filtered load of calcium may exceed the renal reabsorptive capacity, and calcium spills into the urine.

147. What are PTH-independent causes of hypercalcemia?

- Vitamin D intoxication
- PTH-related peptide (PTHrP) secretion from a malignancy

148. Discuss the pathogenesis of vitamin D intoxication.

Hypercalcemia is not necessarily due to an elevation in $1,25(OH)_2D$ but may be due to small but significant biologic activity of 25(OH)D, and that elevated 25(OH)D (index of increased vitamin D stores) may displace $1,25(OH)_2D$ from its plasma carrier protein, increasing its free, bio-

logic activity. The increase in gastrointestinal absorption of calcium increases plasma calcium and suppresses PTH. This allows increased calcium excretion and results in marked hypercalciuria.

149. Discuss the endocrine causes of hypocalcemia.

A loss of parathyroid gland function leads to **primary hypoparathyroidism.** Lack of PTH results in a failure to increase $1,25(OH)_2D$ and a decrease in gastrointestinal absorption of calcium. In addition, the lack of PTH activity in the kidney prevents the renal response to hypocalcemia to increase calcium reabsorption. Also, without PTH to inhibit phosphate reabsorption, hyperphosphatemia may ensue.

Hypocalcemia may also result from a failure to take in adequate vitamin D (**rickets** in children; **osteomalacia** in adults).

Gastrointestinal malabsorption of calcium and vitamin D may also lead to hypocalcemia. This is called **secondary hyperparathyroidism** because PTH is elevated in response to hypocalcemia. This increases calcium resorption from bone and calcium reabsorption in the kidney in an attempt to restore plasma calcium. Secondary hyperparathyroidism is also often a consequence of renal failure because of the inability to generate $1,25(OH)_2D$ and, perhaps, a loss of renal calcium reabsorptive capacity.

150. List the symptoms of hypocalcemia.

- Neurologic: peripheral (tetany) and central (seizures) nerve
- Cardiovascular: abnormal electrocardiogram (prolonged Q-T interval)

151. How can one distinguish between hypercalcemia caused by a PTH-secreting adenoma and hypercalcemia caused by PTHrP?

The best way is to measure intact PTH. Although PTH and PTHrP have sequence homology, most currently used assays for intact PTH do not measure PTHrP. PTH does not have to be above the reference range to suggest primary hyperparathyroidism. PTHrP-induced hypercalcemia should suppress intact (normal) PTH.

152. How can one distinguish between vitamin D intoxication and hypercalcemia of malignancy caused by PTHrP since they both have suppressed intact PTH?

Assays for PTHrP provide accurate results. Furthermore, patients with vitamin D intoxication usually have elevated 25(OH)D levels (an index of vitamin D stores). Measurement of nephrogenous (urinary) cAMP has been done in the past because this is an index of PTH **activity** and is increased by both intact PTH and PTHrP.

FEMALE REPRODUCTION (EXCEPT FOR PREGNANCY AND LACTATION)

153. Discuss the factors controlling fetal sexual differentiation.

Under most circumstances, genotype (genetic sex) and phenotype (sexual characteristics) are the same. That is, an XX conceptus develops into a female baby and an XY conceptus develops into a male baby. The presence of a Y-chromosome (H-Y antigen) induces development of testes, whereas the absence of a Y-chromosome (no H-Y antigen) allows the development of ovaries. The testes secrete testosterone, which induces development of the male reproductive tract from the wolffian ducts. Testosterone is also converted to dihydrotestosterone (DHT) by 5α-reductase in target tissue, which induces development of male genitalia. In addition, the testes secrete müllerian-inhibiting factor (MIF), which causes regression of the müllerian ducts. The absence of testes, and hence the absence of testosterone, DHT, and MIF, allows wolffian ducts to regress, the development of female genitalia, and the formation of the female reproductive tract from the müllerian ducts.

154. Can the histology of the ovary give insight into its function?

Yes.

Oogonia. The number of germ cells (potential oocytes) peaks at approximately 6 million at

about 6 months of gestational age and decreases thereafter via a process called **atresia.** By menopause (approximately 50 years of age), almost no viable germ cells remain.

Primary follicles. These have the potential to start maturation.

Maturing follicles. These begin to develop intrafollicular fluid and proliferating steroidogenic cells (theca and granulosa cells).

Graafian follicle. The dominant follicle is filled with fluid and contains a mature oocyte ready for ovulation. It produces large amounts of estrogen and is primed to produce large amounts of progesterone after ovulation.

Corpus luteum. This develops from the ruptured follicle after ovulation. It is full of steroidogenic cells, which produce large amounts of progesterone (and estrogen, to a lesser extent).

Atretic follicle. This is a follicle whose oocyte was not ovulated but regressed during maturation (nondominant follicle).

Retrogressive corpus luteum. If conception does not occur, the corpus luteum "dies."

155. List the general female endocrine changes throughout life.

- HCG (from trophoblast and placenta) and fetal FSH and LH stimulate development of ovarian germ cells.
- LH and FSH burst approximately 4 months postpartum (sexual differentiation of the brain?).
- Adrenarche—increase in adrenal androgens at about 8 years of age.
- At onset of puberty (8–10 years old), GnRH pulses from hypothalamus increase, which stimulates LH and FSH and increases ovarian function.
- Increase in ovarian steroids induces development of secondary sex characteristics.
- Menstrual cycles (menarche) start at approximately 12 years of age.
- In addition to development of secondary sex characteristics, pubertal estrogens stimulate growth spurt (assuming presence of adequate GH).
- Estrogens also stop growth spurt by causing fusion of epiphyseal plates in bone.
- At menopause (at approximately 50 years of age), ovaries stop producing steroids. This leads to the absence of menses as well as other physiologic (hot flashes) and psychological changes. Lack of steroid negative feedback leads to an increase in FSH and LH.

156. How are ovarian steroids synthesized?

The pathway is essentially the same as that outlined in the adrenal cortex section, particularly with respect to progesterone production. After 17-hydroxylation and androgen production, androstenedione is converted to estrone, and testosterone is converted to estradiol by the enzyme aromatase. It is generally believed that this process requires the two follicular cell types—theca and granulosa cells—to work in what has been called the "two-cell hypothesis of ovarian steroidogenesis" (see figure, next page).

The **theca cell** expresses primarily LH receptors. LH stimulates steroidogenesis and large amounts of androgen production. The theca cell is relatively devoid of aromatase activity.

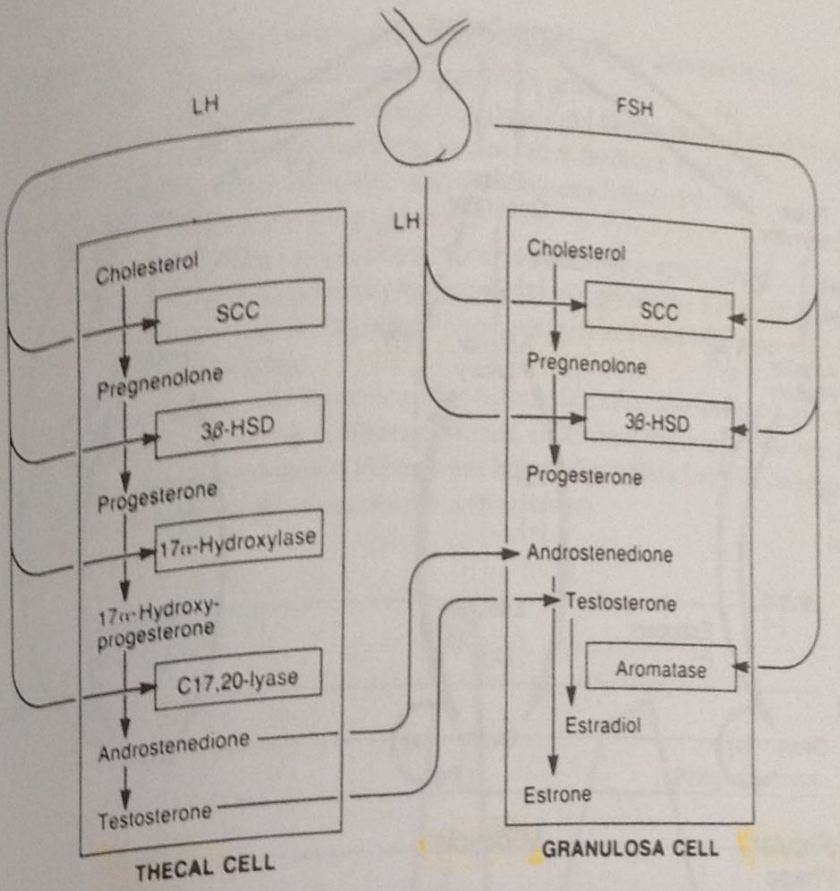
Androgens diffuse through the basal lamina into the **granulosa cell.** The granulosa cell expresses primarily FSH receptors, although it can express LH receptors just before ovulation. Androgens from the theca cell are aromatized to estrogens primarily in the granulosa cell.

157. Since the gonadal hormones are steroids, do they circulate bound to carrier proteins similar to cortisol?

Estradiol and estrone, because they have undergone the 17,20 lyase reaction, do not resemble cortisol very much and therefore do not bind to CBG. There is another carrier protein called sex hormone–binding globulin (SHBG) that carries estradiol (approximately 38%). Progesterone does circulate bound to CBG (approximately 18%).

158. If progesterone only binds about 18% to CBG and estradiol only binds about 38% to SHBG, do these gonadal steroids circulate mostly in the free form?

No, because they are bound significantly by plasma albumin, with estradiol having about 60% binding with albumin, and progesterone about 80% binding with albumin. Therefore, estra-



The two-cell hypothesis of ovarian steroidogenesis. LH primarily stimulates theca cell production of androgens, which diffuse into the granulosa cell where they are converted to estrogens by FSH-stimulated aromatase activity. Granulosa cells also produce progesterone but do not have adequate enzymatic machinery to convert progesterone to androgens. (From Griffin JE, Ojeda SR (eds): Textbook of Endocrine Physiology, 3rd ed. New York, Oxford University Press, 1996, with permission.)

diol and progesterone circulate approximately 2% free, with about 98% percent bound to carrier proteins or albumin.

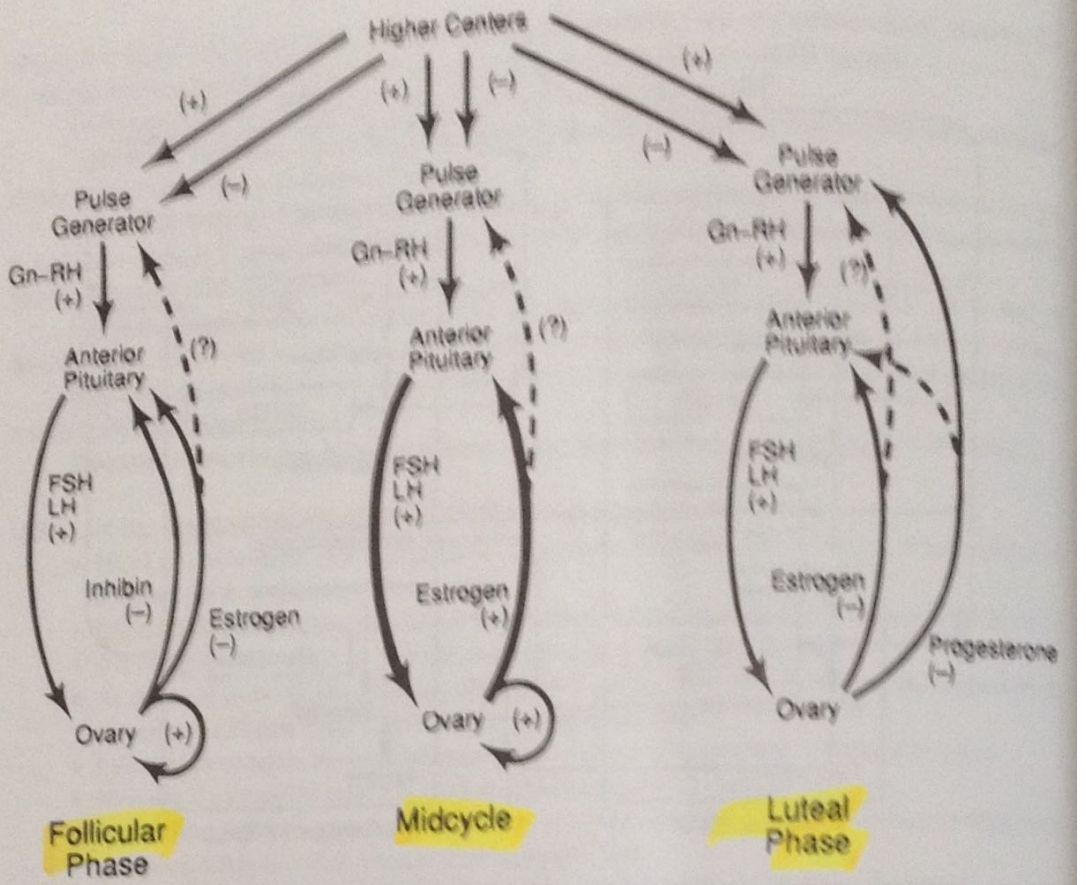
159. Do the ovaries produce peptide hormones?

Relaxin: relaxes pelvic ligaments
Inhibin: selective inhibition of FSH
Activins: selective stimulation of FSH

160. How is the hypothalamic-pituitary-ovarian control system similar to and different from the HPA axis?

In the prepubertal and postmenopausal state, they are similar. Increases in GnRH pulses from the hypothalamus stimulate the secretion of the pituitary gonadotropins LH and FSH. These two hormones stimulate ovarian steroidogenesis, which, via negative feedback, decreases the secretion of GnRH and LH and FSH. Therefore, if ovarian steroids are deficient, LH and FSH are increased (hypergonadotropic hypogonadism analogous to primary adrenal insufficiency); and if hypopituitarism exists, LH and FSH are inappropriately low (analogous to secondary adrenal insufficiency).

Between menarche and menopause, there are quite a few differences. The ovaries produce a second hormone, called inhibin, which inhibits the release of FSH. Therefore, there are parallel negative feedback pathways: gonadal steroids inhibiting LH and inhibin inhibiting FSH. Another major difference is the existence of **positive feedback.** During a specific time (midcycle) in the menstrual cycle, estrogen actually stimulates LH and FSH release. This results in a surge in gonadotropins, which stimulates ovulation. (See figure, next page.)



The hypothalamic-pituitary-ovarian system at different phases of the menstrual cycle. +, stimulation; −, inhibition. Dashed lines indicate hypothetical relationships. Line thickness indicates the intensity of stimulation. (From Goodman HM: Basic Medical Endocrinology, 2nd ed. Philadelphia, Lippincott-Raven, 1994, with permission.)

161. Outline a typical menstrual cycle.

Because this is truly a cycle, **day 1** is somewhat arbitrary. Because the major physical sign is the onset of menses, however, this is considered day 1.

Follicular phase: The emergence of the dominant follicle.

1. Menses are induced by decreases in estrogen and progesterone.
2. Increase in FSH on day 28 is induced by loss of steroid negative feedback. Increase in FSH on day 28 promotes the maturation of 6–12 primary follicles.
3. Increase in FSH on day 28 followed by LH on days 2–5 increases estrogen production.
4. One (usually) follicle becomes dominant and increases estrogen production. This estrogen inhibits FSH secretion by negative feedback. Estrogen concentration may correlate with the size of the dominant follicle.
5. The nondominant follicles cannot survive the decrease in FSH and undergo atresia. The dominant follicle survives this decrease in FSH because it has increased expression of LH and FSH receptors.
6. The system shifts from negative to positive feedback so that the large increase in estrogen from the dominant follicle induces the LH surge. ↑ estrogen causes ↑ LH causes ↑ estrogen causes ↑ LH.
7. Preovulatory increase in progesterone potentiates estrogen positive feedback on LH.
8. LH surge (and FSH surge) occurs, with the ratio of LH to FSH increasing dramatically. This induces resumption of meiosis in the oocyte of the dominant follicle.
9. FSH surge induces LH receptors on granulosa cells to prepare the follicle for transformation into the corpus luteum.

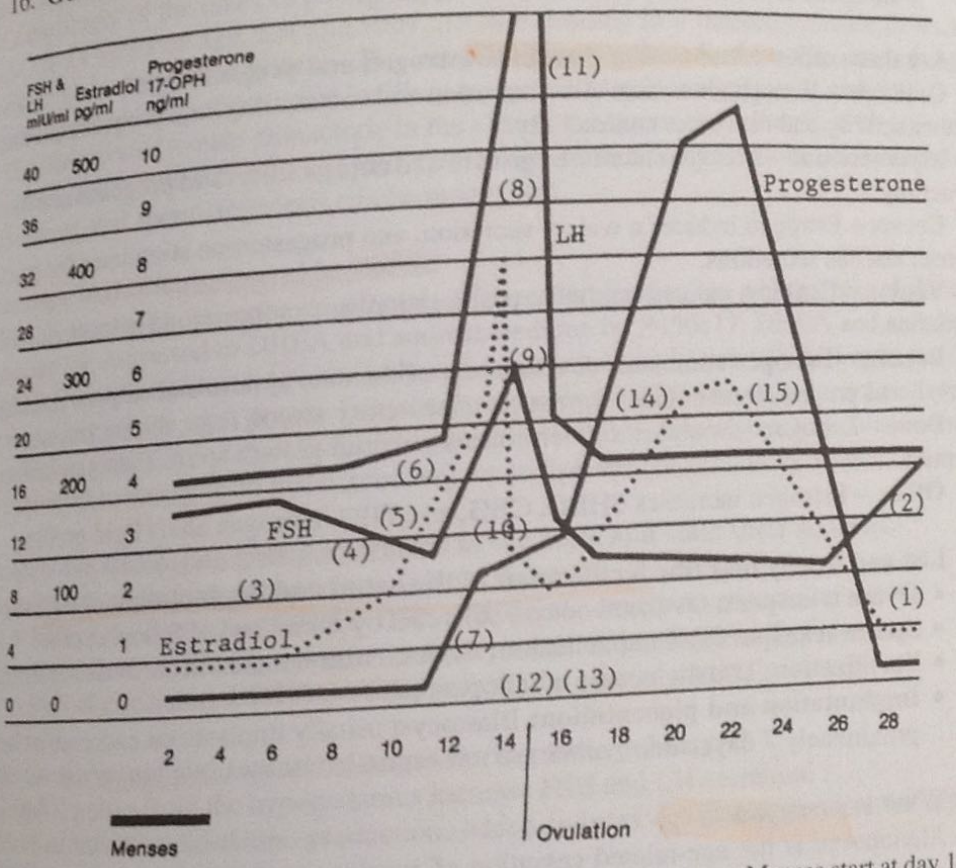
10. Estrogen starts to decrease as LH reaches its peak. This is hypothesized to be due to down-regulation of the LH receptor on the theca/granulosa cells.
11. The loss of estrogen positive feedback stimulation of LH terminates the LH surge. The increasing ratio of progesterone to estrogen may be a negative feedback signal.

Ovulation: The expulsion of the ovum from the dominant follicle.

12. Ovulation occurs owing to prior LH surge.

Luteal phase: Progesterone (and estrogen) secretion from the corpus luteum.

13. Corpus luteum is formed primarily by granulosa cells primed by LH and FSH surge.
14. Corpus luteum secretion of progesterone and estrogen increases; the process is dependent on low (but adequate) LH levels.
15. Progesterone and estrogen decrease owing to finite life of corpus luteum in the absence of significant gonadotropin levels. (If fertilization occurs, HCG from the trophoblast rescues the corpus luteum and prevents menstruation.) The corpus luteum dies unless fertilization occurs and HCG production from the trophoblast rescues the corpus luteum.
16. Go to step 1.



Idealized human menstrual cycle. Days of the cycle are shown across the bottom. Menses start at day 1; ovulation usually occurs around day 15. Each step is identified numerically in the text. (Adapted from Speroff L, Glass RH, Kase NG: Clinical Gynecologic Endocrinology and Infertility. Baltimore, Williams & Wilkins, 1983.)

162. Describe the proliferation of granulosa cells during follicular development.

As the dominant follicle grows, it secretes more and more estrogen despite decreases in FSH in the early follicular phase. Local estradiol production within the dominant follicle increases the expression of FSH receptors. Positive feedback of estrogen from the dominant follicle stimulates FSH release, which induces LH receptor expression on granulosa cells. By the later follicular phase (just before ovulation), the granulosa cells of the dominant follicle have increased greatly in number and express FSH and LH receptors in great number.

163. How do changes in the endometrium of the uterus correlate with the phases of the menstrual cycle?

The **endometrial cycle** is in synchrony with the menstrual cycle and is a hallmark of the extraovarian actions of gonadal steroids.

- **Proliferative phase** occurs during the follicular phase of the menstrual cycle. Estrogen stimulates the growth of the epithelial and stromal layers. The thickness of the endometrium increases, and the uterine glands increase in size. The spiral arteries, which are the primary blood supply for the endometrium, elongate.
- **Secretory phase** occurs during the luteal phase of the menstrual cycle and prepares the endometrium for implantation of the conceptus. Progesterone stimulates secretory activity of the uterine glands, and glycogen production increases. The stroma becomes edematous, and the spiral arteries coil.
- **Menstrual phase** correlates with the end of the luteal phase of the menstrual cycle. The loss of gonadal steroid secretion from the corpus luteum induces vasoconstriction (spasm?) of the spiral arteries and necrosis of the endometrium. The endometrial lining is sloughed off in the form of menstrual bleeding.

164. Are there other extraovarian actions of estrogen and progesterone?

Oviducts—Estrogen increases cilia formation and contractility, and progesterone increases secretory activity and decreases contractility.

Myometrium—Estrogen increases growth and contractility, and progesterone decreases contractility.

Cervix—Estrogen induces a watery secretion, and progesterone stimulates the production of dense, viscous secretions.

Vagina—Estrogen induces epithelial proliferation, and progesterone induces epithelial differentiation.

Breasts—Estrogen stimulates development of the duct system and adipose tissue (e.g., at puberty), and progesterone induces formation of secretory alveoli (e.g., during pregnancy).

Bone—Estrogen stimulates *and* terminates pubertal growth spurt. Estrogen inhibits bone resorption.

Other—Estrogen increases SHBG, CBG, and TBG. Estrogen alters lipid profile.

165. List and briefly describe fertilization of the ovum and implantation of the conceptus.

- **Ovum transport:** Ovulated oocyte collected by fibrial end of fallopian tube
- **Sperm transport and capacitation:** Contact with female tract activates sperm function
- **Fertilization:** Usually occurs in fallopian tube
- **Implantation and placentation:** Blastocyst usually implants on endometrial lining approximately 7 days after ovulation

166. What is menopause?

Menopause is the age-related cessation of regular menses during the female climacteric when reproductive cyclicity gradually disappears. Usually, menstrual cycles become irregular before they completely stop. Menopause is characterized by a loss of ovarian function probably as a result of exhaustion of available follicles lost because of atresia. Because of the decrease in estrogen production from the ovary, LH and FSH increase owing to loss of negative feedback. In that sense, menopause can be defined as **hypergonadotropic hypogonadism.**

167. What is amenorrhea?

- **Primary amenorrhea:** the failure to have menarche (the onset of menstrual cycles at puberty). It is currently believed that the failure to have normal menstrual cycles by the age of 16 should be evaluated.
- **Secondary amenorrhea:** the premature cessation of normal menstrual cycles. Causes include pregnancy, hyperprolactinemia, premature menopause, excessive exercise, and weight loss.
- **Oligomenorrhea:** irregular menstrual cycles.

MALE REPRODUCTION

168. In the male (XY genotype), is there a relationship between gonadal function and physiologic changes throughout life?

As opposed to the female, the development of a male phenotype requires a signal from the developing gonads. The secretion of müllerian inhibitory factor (MIF) induces regression of the müllerian ducts and allows the wolffian ducts to develop into the internal male genitalia. The secretion of testosterone from the fetal testes induces somatic sex differentiation and the male phenotype. If testosterone is absent or if there is resistance to the action of testosterone (testicular feminization), a female (external) phenotype develops.

After parturition, LH and FSH increase at about 6 months of age (analogous to a similar event in females). The subsequent increase in testicular steroidogenesis and androgen secretion may result in the sexual differentiation of the brain.

Adequate testosterone secretion is necessary before puberty to maintain normal growth. Adrenarche (increase in adrenal androgens), which usually occurs at approximately 8 years of age, is a harbinger of the onset of puberty.

At 10–14 years of age, LH and FSH increase, leading to a marked increase in testicular steroidogenesis and spermatogenesis. The increase in testosterone leads to the outward signs of male puberty (deepening of the voice, axillary and pubic hair, increased sweat glands).

The existence of a male climacteric in the elderly is a controversial topic. Although testosterone secretion decreases as men age into their forties to sixties, this may not represent clinical hypogonadism, and spermatogenesis can be maintained.

169. Summarize testicular steroidogenesis.

This is essentially the same as adrenal androgen production, in which pregnenolone and progesterone are converted to DHEA and androstenedione by P450c17. DHEA and androstenedione can be converted to testosterone. Although testosterone is the primary androgen produced by the testes, it is not the most potent. Dihydrotestosterone (DHT) is produced from testosterone by 5α-reductase primarily in target tissue (peripheral activation). In addition, testicular androgens can be converted to estrogens in males primarily by peripheral conversion by aromatase.

170. Review the circulating gonadal steroids in the male and state their sources.

- > 95% of circulating **testosterone** is from the testes.
- > 80% of the circulating **DHT** is from peripheral conversion of testosterone.
- > 80–90% of circulating **estrogen** is from peripheral conversion of precursors.
- > 90% of circulating **DHEA** (sulfate) is from the adrenal cortex.

171. List the hormonal and somatic changes during male puberty.

1. GnRH pulses from the hypothalamus increase FSH and LH secretion.
2. LH stimulates testosterone production, which induces development of secondary sex characteristics.
3. FSH stimulates spermatogenesis.
4. ACTH (or some other pituitary factor) increases adrenal androgen production (adrenarche).
5. GH maintains linear growth.
6. Testosterone enhances the secretion of GH and initiates the pubertal growth spurt. Testosterone then causes epiphyseal fusion (termination of the pubertal growth spurt).

172. What is the significance of the pulsatility of GnRH release from the hypothalamus?

One of the hallmarks of the gonadotropin control system in males and females is pulsatility. LH in males is usually released in pulses with about a 90-minute frequency, although this is variable between and within subjects and by time of day (and even seasons of the year). GnRH pulses are necessary to maintain LH pulses. Constantly high levels of GnRH, although stimulating LH at first, lead to down-regulation of pituitary gonadotrophs and a decrease in LH. This is the basis for using GnRH analogs to induce hypogonadotropic hypogonadism in men with testosterone-sensitive prostate cancer.

173. Describe the overall regulation of testicular function.

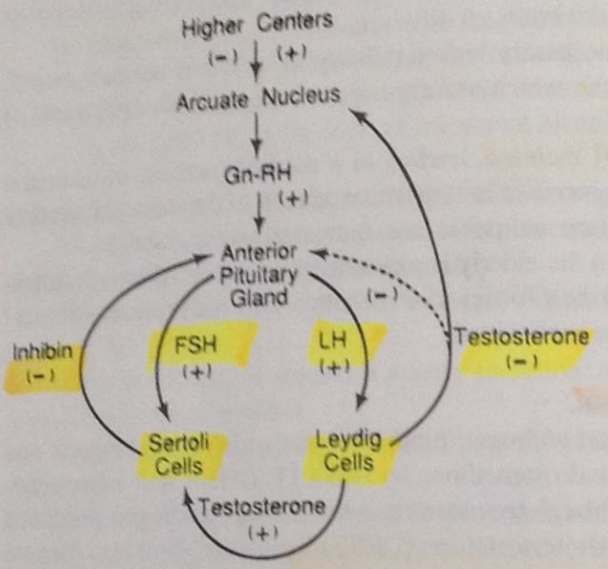
The hypothalamic-pituitary-testicular (HPT) axis is, for the most part, similar to the HPA axis.

1. Neural input into the brain regulates the release of pulses of GnRH from the hypothalamus into the long portal veins, which drain into the anterior pituitary. GnRH pulses stimulate LH and FSH release.

2. LH stimulates steroidogenesis (testosterone production) from the Leydig (interstitial) cells in the testes.

3. FSH stimulates Sertoli cells (in concert with local testosterone) to increase spermatogenesis, androgen binding protein (a local factor), and inhibin production.

4. **Negative feedback:** Testosterone inhibits GnRH and LH release. Inhibin decreases FSH release.



HPT axis. + indicates that GnRH stimulates FSH and LH, that FSH stimulates Sertoli cells while LH stimulates Leydig cells, and that Leydig cells stimulate Sertoli cells (paracrine). − indicates that inhibin produced from Sertoli cells inhibits FSH release while testosterone inhibits GnRH release (negative feedback). Direct inhibition of LH by testosterone has not been firmly established (dotted line). (From Goodman HM: Basic Medical Endocrinology, 2nd ed. Philadelphia, Lippincott-Raven, 1994, with permission.)

174. What is the main difference between the HPT and HPA axes?

The testes produce two negative feedback signals: Testosterone inhibits LH (and FSH); inhibin inhibits FSH release.

175. Categorize the actions of FSH and LH on the testes.

LH stimulates steroidogenesis (testosterone synthesis and release) from the Leydig (interstitial) cells. Although LH was named for its luteinizing action in the female, its effect in males (increase in androgen) is analogous. In fact, in the past, LH has been called interstitial cell-stimulating hormone.

FSH stimulates androgen binding protein from Sertoli cells into the lumen of the seminiferous tubule. Androgen binding protein acts as a local testosterone sink, which dramatically increases the local concentration of testosterone that is necessary for sperm maturation. FSH also stimulates spermatogenesis. (See figure, next page.)

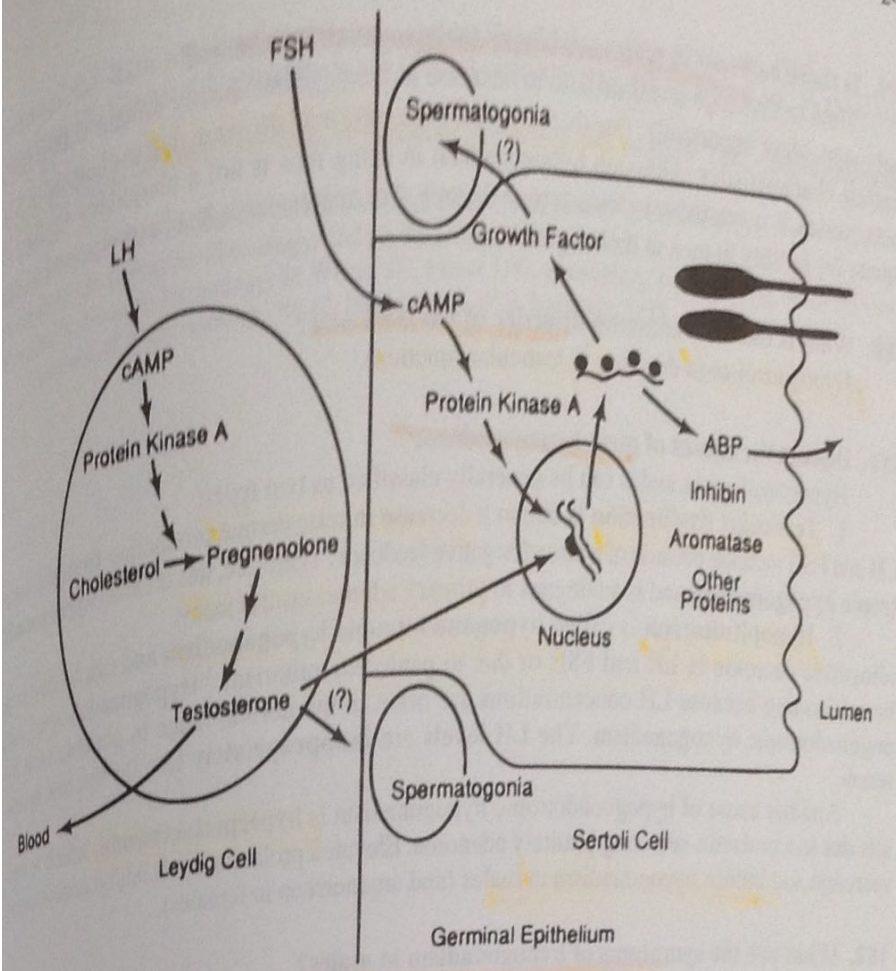
176. Why are LH and FSH necessary?

LH is necessary to stimulate testosterone, which has systemic effects and local effects. FSH stimulates spermatogenesis and increases local testosterone concentration by increasing androgen binding protein release from Sertoli cells into tubular lumens.

177. What are the major actions of androgens?

Fetal development: Testosterone stimulates internal genitalia and testosterone metabolite (DHT) stimulates external genitalia.

Puberty: Testosterone and DHT increase secondary sex characteristics (musculature, lar-



Control of testicular steroidogenesis and spermatogenesis. LH stimulates testosterone production, which exerts actions on target organs via the blood and exerts actions on the Sertoli cell via diffusion (paracrine effect). FSH stimulates Sertoli cells directly to increase androgen binding protein (ABP) production which acts as a testosterone "sink," increasing the testosterone concentration in the fluid bathing the developing sperm. (From Goodman HM: Basic Medical Endocrinology, 2nd ed. Philadelphia, Lippincott-Raven, 1994, with permission.)

ynx, sexual hair, sebaceous glands), spermatogenesis, and prostatic secretion. Androgens also stimulate the pubertal growth spurt (with adequate GH) and terminate the pubertal growth spurt by inducing closure of epiphyseal plates.

Adulthood: Actions include maintenance of normal skeleton, libido, spermatogenesis, and the other secondary sex characteristics.

178. Outline the profile of male puberty.

AGE (YEARS)	PHYSIOLOGIC CHANGES
About 8	Adrenal androgens (DHEA and androstenedione) induce subtle increases in secondary sex characteristics (e.g., light mustache).
About 9–10	GnRH pulses increase, which stimulates LH and FSH release. This stimulates testicular growth and increases in testosterone.
About 12	The pubertal increase in pubic and axillary hair starts followed by an increase in penile growth.
13	The pubertal growth spurt has usually started with a peak growth velocity at about age 14–15 years.
About 16	The growth spurt starts to wane.
18	Final adult height is usually achieved (although growth until age 20 is not uncommon).

179. Is there an event in males analogous to menopause in females?

Total testosterone levels do tend to decrease as men age but usually remain within the normal range. More importantly, free (bioactive) testosterone may decrease due to changes in SHBG binding characteristics. Although hypogonadism in aging men is not a ubiquitous finding (like menopause), it is amenable to testosterone therapy. Spermatogenesis has been reported to be adequate for fertility in men in their eighties.

180. What is the most common disorder of the HPT axis?

Hypogonadism (a decrease in testicular function).

181. Discuss the causes of male hypogonadism.

Hypogonadism in males can be generally classified as two types:

1. **Testicular dysfunction** is due to a decrease in testosterone production from the testes. LH and FSH increase because of a loss of negative feedback. Therefore, this is called **hypergonadotropic hypogonadism** and is analogous to primary adrenal insufficiency.

2. **Hypopituitarism** is called **hypogonadotropic hypogonadism** and can be due to an idiopathic decrease in LH and FSH or due to panhypopituitarism. "Hypogonadotropic" may be misleading because LH concentrations are often in the normal range in patients with hypogonadotropic hypogonadism. The LH levels are **inappropriately** low for the low testosterone.

Another cause of hypogonadotropic hypogonadism is **hyperprolactinemia,** which is usually due to a prolactin-secreting pituitary adenoma. Elevated prolactin levels inhibit gonadotropin secretion and induce hypogonadism in males (and amenorrhea in females).

182. What are the symptoms of hypogonadism in males?

Symptoms depend on the age of onset.

- Androgen deficiency or insensitivity to androgens in **early fetal development** leads to varying degrees of ambiguity of the genitalia and male pseudohermaphroditism.
- **Prepubertal** androgen deficiency leads to limited secondary sex characteristics and eunuchoid skeletal proportions because, even though there is no androgen-mediated pubertal growth spurt, there is also failure to close the epiphyseal plates and the long bones continue to grow. Therefore, the arm span of these individuals is longer than a typical man.
- Androgen deficiency **after puberty** usually results in decreased libido, impotence, and low energy levels. If androgen deficiency continues for longer periods of time, there can be a decrease in facial or body hair.

183. What is the most common cause of male hypogonadism?

Klinefelter syndrome, which occurs in about 0.2% of male births.

184. Describe the genotype and phenotype of Klinefelter syndrome.

The most common genotype is XXY (an extra X chromosome). An XXY genotype usually results from meiotic nondisjunction during gametogenesis. The phenotype usually appears at puberty and includes increased lower-to-upper body segment ratio, gynecomastia, small penis, and sparse upper body hair. The testes do not develop normally and are usually small and fibrotic. The decreased testosterone production usually leads to elevated LH and FSH concentrations.

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