Endocrine Control of Growth and Metabolism

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Disorders of hormone action will be more common causes of endocrinopathy than states of hormone deficiency and excess combined.
— Jean D. Wilson,
Endocrinology: Survival as a Discipline in the 21st Century?

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In 1998 Mark McGwire made news when he hit 70 home runs, surpassing the single-season home run record Roger Maris established in 1961. McGwire also created a firestorm of controversy when he admitted to taking androstenedione, a performance-enhancing steroid prohormone banned by the International Olympic Committee and other groups but not by professional baseball. As a result of the controversy, Congress passed the Anabolic Steroids Act of 2004, which made androstenedione and some other steroid prohormones controlled substances available only by prescription.

What is this prohormone, and why is it so controversial? You will learn more about androstenedione in this chapter as we discuss the hormones that play a role in long-term regulation of metabolism and growth. In normal individuals, these hormones can be difficult to study because their effects are subtle and their interactions with one another complex. As a result, much of what we know about endocrinology comes from studying pathological conditions in which a hormone is either oversecreted or undersecreted. In recent years, however, advances in molecular biology and the use of transgenic animal models have enabled scientists to learn more about hormone action at the cellular level.

**Review of Endocrine Principles**

Before we delve into the different hormones, let’s do a quick review of some basic principles and patterns of endocrinology.

1. **The hypothalamic-pituitary control system.** Several of the hormones described in this chapter are controlled by hypothalamic and anterior pituitary (adenohypophyseal) trophic hormones.

**RUNNING PROBLEM**

**Hyperparathyroidism**

“Broken bones, kidney stones, abdominal groans, and psychic moans.” Medical students memorize this saying when they learn about hyperparathyroidism, a disease in which parathyroid glands (see Fig. 23.12) work overtime and produce excess parathyroid hormone (PTH). Dr. Adiaha Spinks suddenly recalls the saying as she examines Prof. Bob Magruder, who has arrived at her office in pain from a kidney stone lodged in his ureter. When questioned about his symptoms, Prof. Magruder also mentions pain in his shin bones, muscle weakness, stomach upset, and a vague feeling of depression. “I thought it was all just the stress of getting my book published,” he says. To Dr. Spinks, however, Prof. Magruder’s combination of symptoms sounds suspiciously like he might be suffering from hyperparathyroidism.

2. **Feedback patterns.** The negative feedback signal for simple endocrine pathways is the systemic response to the hormone. For example, insulin secretion shuts off when blood glucose concentrations decrease. In complex pathways using the hypothalamic-pituitary control system, the feedback signal may be the hormone itself. In pathological states, endocrine cells may not respond appropriately to feedback signals.

3. **Hormone receptors.** Hormone receptors may be on the cell surface or inside the cell.

4. **Cellular responses.** In general, hormone target cells respond by altering existing proteins or by making new proteins. The historical distinctions between the actions of peptide and steroid hormones are no longer valid. Some steroid hormones exert rapid, nongenomic effects, and some peptide hormones alter transcription and translation.

5. **Modulation of target cell response.** The amount of active hormone available to the cell and the number and activity of target cell receptors determine the magnitude...
of target cell response. Cells may up-regulate or down-regulate their receptors to alter their response. Cells that do not have hormone receptors are nonresponsive.

6 Endocrine pathologies. Endocrine pathologies result from (a) excess hormone secretion, (b) inadequate hormone secretion, and (c) abnormal target cell response to the hormone. It now appears that failure of the target cell to respond appropriately to its hormone is a major cause of endocrine disorders.

In the following sections we first examine adrenal corticosteroids and thyroid hormones, two groups of hormones that influence long-term metabolism. We then consider the endocrine control of growth.

Adrenal Glucocorticoids

The paired adrenal glands sit on top of the kidneys like little caps (Fig. 23.1). Each adrenal gland, like the pituitary gland, is two embryologically distinct tissues that merged during development. This complex organ secretes multiple hormones, both neurotransmitters and classic hormones. The adrenal medulla occupies a little over a quarter of the inner mass and is composed of modified sympathetic ganglia that secrete catecholamines (mostly epinephrine) to mediate rapid responses in fight-or-flight situations. The adrenal cortex forms the outer three-quarters of the gland and secretes a variety of steroid hormones.

The Adrenal Cortex Secretes Steroid Hormones

The adrenal cortex secretes three major types of steroid hormones: aldosterone (sometimes called a mineralocorticoid because of its effect on the minerals sodium and potassium), glucocorticoids, and sex hormones. Histologically, the adrenal cortex is divided into three layers, or zones (Fig. 23.1a). The outer zona glomerulosa secretes only aldosterone. The inner zona reticularis secretes mostly androgens, the sex hormones dominant in men. The middle zona fasciculata secretes mostly glucocorticoids, named for their ability to increase plasma glucose concentrations. Cortisol is the main glucocorticoid secreted by the adrenal cortex.

The generalized synthesis pathway for steroid hormones is shown in Figure 23.1b. All steroid hormones begin with cholesterol, which is modified by multiple enzymes to end up as aldosterone, glucocorticoids, or sex steroids (androgens as well as estrogens and progesterone, the dominant sex hormones in females). The pathways are the same in the adrenal cortex, gonads, and placenta, but what differs from tissue to tissue is the distribution of enzymes that catalyze the different reactions. For example, the enzyme that makes aldosterone is found in only one of the three adrenal cortex zones.

This chapter opened with the story of baseball player Mark McGwire and his controversial use of the supplement androstenedione. Figure 23.1b shows that this prohormone is one intermediate in the synthesis of testosterone and dihydrotestosterone. One androstenedione precursor, dehydroepiandrosterone (DHEA), is used as a dietary supplement. In the United States, purchase of DHEA is not regulated, despite the fact that this substance is metabolically converted to androstenedione and testosterone, both controlled substances whose use is widely banned by sports associations.

The close structural similarity among steroid hormones means that the binding sites on their receptors are also similar, leading to crossover effects when one steroid binds to the receptor for a related molecule. For example, mineralocorticoid receptors (MRs) for aldosterone are found in the distal nephron. MRs also bind and respond to cortisol, which may be 100 times more concentrated in the blood than aldosterone. What is to keep cortisol from binding to an MR and influencing Na⁺ and K⁺ excretion? It turns out that renal tubule cells with MRs have an enzyme (11β-hydroxysteroid dehydrogenase) that converts cortisol to a less active form with low specificity for the MR. By inactivating cortisol, these cells normally prevent crossover effects from cortisol. However, crossover activity and the structural similarities of steroid hormones mean that in many endocrine disorders, patients may experience symptoms related to more than one hormone.

Cortisol Secretion Is Controlled by ACTH

The control pathway for cortisol secretion is known as the hypothalamic-pituitary-adrenal (HPA) pathway (Fig. 23.2a). The HPA pathway begins with hypothalamic corticotropin-releasing hormone (CRH), which is secreted into the hypothalamic-hypophyseal portal system and transported to the anterior pituitary. CRH stimulates release of adrenocorticotropic hormone (ACTH or corticotropin) from the anterior pituitary. ACTH in turn acts on the adrenal cortex to promote synthesis and release of cortisol. Cortisol then acts as a negative feedback signal, inhibiting ACTH and CRH secretion.

Cortisol secretion is continuous and has a strong diurnal rhythm (Fig. 23.2c). Secretion normally peaks in the morning and diminishes during the night. Cortisol secretion also increases with stress.

Cortisol is a typical steroid hormone and is synthesized on demand. Once synthesized, it diffuses out of

Endocrine Control of Growth and Metabolism
THE ADRENAL GLAND

(a) The paired adrenal glands sit on top of the kidneys. Each region secretes different hormones.

(b) Synthesis pathways for steroid hormones

All steroid hormones are synthesized from cholesterol. The blank boxes represent intermediate compounds whose names have been omitted for simplicity. Each step is catalyzed by an enzyme, but only two enzymes are shown in the figure.

FIGURE QUESTIONS
1. A baby is born with a genetic mutation that results in a deficiency of the enzyme 21-hydroxylase. Based on the role of this enzyme in the pathway illustrated, what symptoms might you predict in the baby?
2. Would men or women have more aromatase activity?

KEY
DHEA = dehydroepiandrosterone

adrenal cells into the plasma, where most of it is transported by a carrier protein, corticosteroid-binding globulin (CBG or transcortin). Unbound hormone is free to diffuse into target cells.

All nucleated cells of the body have cytoplasmic glucocorticoid receptors. The hormone-receptor complex enters the nucleus, binds to DNA with the aid of a hormone-response element, and alters gene expression, transcription, and translation. In general, a tissue's response to glucocorticoid hormones is not evident for 60–90 minutes. However, cortisol's negative feedback effect on ACTH secretion occurs within minutes.
Pro-opiomelanocortin (POMC) + ACTH γ-lipotropin β-endorphin Fragments

α-MSH
γ-MSH Fragment
Melanin synthesis
Immune response
Food intake

THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) PATHWAY

(a) The control of cortisol secretion

CRH (hypothalamus) → ACTH (anterior pituitary) → Cortisol (adrenal cortex)

CRH
ACTH
Cortisol

Adrenal cortex
Anterior pituitary
Hypothalamus

Circadian rhythm
Stress

(b) The properties of cortisol

CORTISOL

Origin
Adrenal cortex

Chemical nature
Steroid

Biosynthesis
From cholesterol; made on demand; not stored

Transport in the circulation
On corticosteroid-binding globulin (made in liver)

Half-life
60–90 min

Factors affecting release
Circadian rhythm of tonic secretion; stress enhances release

Control pathway
CRH (hypothalamus) → ACTH (anterior pituitary) → cortisol (adrenal cortex)

Target cells or tissues
Most tissues

Target receptor
Intracellular

Whole body or tissue reaction
↑ Plasma [glucose]; ↓ immune activity; permissive for glucagon and catecholamines

Action at cellular level
↑ Gluconeogenesis and glycogenolysis; ↓ protein catabolism. Blocks cytokine production by immune cells

Action at molecular level
Initiates transcription, translation, and new protein synthesis

Feedback regulation
Negative feedback to anterior pituitary and hypothalamus

(c) The circadian rhythm of cortisol secretion

Plasma cortisol concentration

Noon  6 PM  Midnight  6 AM  Noon

(d) Post-translational processing of POMC creates a variety of active peptides.

FIGURE QUESTION
What do the following abbreviations stand for? ACTH, CRH, MSH
Cortisol Is Essential for Life

Adrenal glucocorticoids are sometimes called the body’s stress hormones because of their role in the mediation of long-term stress. Adrenal catecholamines, particularly epinephrine, are responsible for rapid metabolic responses needed in fight-or-flight situations.

Cortisol is essential for life. Animals whose adrenal glands have been removed die if exposed to any significant environmental stress. The most important metabolic effect of cortisol is its protective effect against hypoglycemia. When blood glucose decreases, the normal response is secretion of pancreatic glucagon, which promotes gluconeogenesis and glycogen breakdown. In the absence of cortisol, however, glucagon is unable to respond adequately to a hypoglycemic challenge. Because cortisol is required for full glucagon and catecholamine activity, it is said to have a permissive effect on those hormones.

Cortisol receptors are found in every tissue of the body, but for many targets we do not fully understand the physiological actions of cortisol. However, we can speculate on these actions based on tissue responses to high levels (pharmacological doses) of cortisol administered for therapeutic reasons or associated with hypersecretion.

All the metabolic effects of cortisol are directed at preventing hypoglycemia. Overall, cortisol is catabolic (Fig. 23.2a, b).

1. **Cortisol promotes gluconeogenesis** in the liver. Some glucose produced in the liver is released into the blood, and the rest is stored as glycogen. As a result, cortisol increases blood glucose concentrations.

2. **Cortisol causes the breakdown of skeletal muscle proteins** to provide a substrate for gluconeogenesis.

### Concept Check

**Answers: End of Chapter**

3. What do the abbreviations HPA and CBG stand for? If there is an alternate name for each term, what is it?

4. You are mountain-biking in Canada and encounter a bear, which chases you up a tree. Is your stress response mediated by cortisol? Explain.

5. The illegal use of anabolic steroids by bodybuilders and athletes periodically receives much attention. Do these illegal steroids include cortisol? Explain.

### Cortisol Is a Useful Therapeutic Drug

Cortisol suppresses the immune system by preventing cytokine release and antibody production by white blood cells. It also inhibits the inflammatory response by decreasing leukocyte mobility and migration. These immunosuppressant effects of cortisol make it a useful drug for treating a variety of conditions, including bee stings, poison ivy, and pollen allergies. Cortisol also helps prevent rejection of transplanted organs. However, glucocorticoids also have potentially serious side effects because of their metabolic actions. Once nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, were developed, the use of glucocorticoids for treating minor inflammatory problems was discontinued.

Exogenous administration of glucocorticoids has a negative feedback effect on the anterior pituitary and may shut down ACTH production. Without ACTH stimulation, the adrenal cells that produce cortisol atrophy. For this reason, it is essential that patients taking steroids taper their dose gradually, giving the pituitary and adrenal glands a chance to recover, rather than stopping the drug abruptly.
Cortisol Pathologies Result from Too Much or Too Little Hormone

The most common HPA pathologies result from hormone deficiency and hormone excess. Abnormal tissue responsiveness is an uncommon cause of adrenal steroid disorders.

**Hypercortisolism** Excess cortisol in the body is called hypercortisolism. It can arise from hormone-secreting tumors or from exogenous administration of the hormone. Cortisol therapy with high doses for more than a week has the potential to cause hypercortisolism—also known as Cushing’s syndrome, after Dr. Harvey Cushing, who first described the condition in 1932.

Most signs of hypercortisolism can be predicted from the normal actions of the hormone. Excess gluconeogenesis causes hyperglycemia, which mimics diabetes. Muscle protein breakdown and lipolysis cause tissue wasting. Paradoxically, excess cortisol deposits extra fat in the trunk and face, perhaps in part because of increased appetite and food intake. The classic appearance of patients with hypercortisolism is thin arms and legs, obesity in the trunk, and a “moon face” with plump cheeks (Fig. 23.3). CNS effects of too much cortisol include initial mood elevation followed by depression, as well as difficulty with learning and memory.

Hypercortisolism has three common causes:

1. **An adrenal tumor that autonomously secretes cortisol.** These tumors are not under the control of pituitary ACTH. This condition is an instance of primary hypercortisolism.

2. **A pituitary tumor that autonomously secretes ACTH.** Excess ACTH prompts the adrenal gland to oversecrete cortisol (secondary hypercortisolism). The tumor does not respond to negative feedback. This condition is also called Cushing’s disease because it was the actual disease described by Dr. Cushing. (Hypercortisolism from any cause is called Cushing’s syndrome.)

3. **Iatrogenic (physician-caused) hypercortisolism** occurs secondary to cortisol therapy for some other condition.

**Hypocortisolism** Hyposecretion pathologies are far less common than Cushing’s syndrome. Addison’s disease is hyposecretion of all adrenal steroid hormones, usually following autoimmune destruction of the adrenal cortex. Hereditary defects in the enzymes needed for adrenal steroid production cause several related syndromes (see the question in Fig. 23.1). These inherited disorders are often marked by excess androgen secretion because substrate that cannot be made into cortisol or aldosterone is converted to androgens. In newborn girls, excess androgens cause masculinization of the external genitalia, a condition called adrenogenital syndrome.

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**CRH and ACTH Have Additional Physiological Functions**

In recent years, research interest has shifted away from glucocorticoids to CRH and ACTH, the trophic hormones of the HPA pathway. Both peptides are now known to belong to larger families of related molecules, with multiple receptor types found...
in numerous tissues. Experiments with knockout mice lacking a particular receptor have revealed some of the physiological functions of peptides related to CRH and ACTH.

Two interesting findings of this research are that cytokines secreted by the immune system can stimulate the HPA pathway and that immune cells have receptors for ACTH and CRH. The association between stress and immune function appears to be mediated through CRH and ACTH, and this association provides one explanation for mind-body interactions in which mental state influences physiological function.

**CRH Family** The CRH family includes CRH and a related brain neuropeptide called urocortin. In addition to its involvement in inflammation and the immune response, CRH is known to decrease food intake and has been associated with signals that mark the onset of labor in pregnant women. Additional evidence links CRH to anxiety, depression, and other mood disorders.

**POMC and Melanocortins** CRH acting on the anterior pituitary stimulates secretion of ACTH. ACTH is synthesized from a large glycoprotein called pro-opiomelanocortin (POMC, pronounced pom-see). POMC undergoes post-translational processing to produce a variety of biologically active peptides in addition to ACTH (Fig. 23.2d). In the pituitary, POMC products include β-endorphin, an endogenous opioid that binds to receptors that block pain perception.

Processing of POMC in nonpituitary tissues creates additional peptides, such as melanocyte-stimulating hormone (MSH). α-MSH is produced in the brain, where it inhibits food intake, and in the skin, where it acts on melanocytes. Melanocytes contain pigments called melanins that influence skin color in humans and coat color in rodents (see the Emerging Concepts box).

POMC-producing neurons in the hypothalamus are being studied for their role in food intake, energy balance, and thermoregulation. Recent investigations indicate that the action of nicotine on POMC neurons explains why smoking decreases food intake, for example. Other research suggests that POMC neurons may respond to changes in blood glucose and possibly participate in the glucostat mechanism influencing food intake.

The MSH hormones plus ACTH have been given the family name melanocortins. Five melanocortin receptors (MCRs) have been identified. MC2R responds only to ACTH and is the adrenal cortex receptor. MC1R is found in skin melanocytes and responds equally to α-MSH and ACTH. When ACTH is elevated in Addison’s disease, the action of ACTH on MC1R leads to increased melanin production and the apparent “tan,” or skin darkening, characteristic of this disorder.

**Thyroid Hormones**

The thyroid gland is a butterfly-shaped gland that lies across the trachea at the base of the throat, just below the larynx (Fig. 23.4a). It is one of the larger endocrine glands, weighing 15–20 g. The thyroid gland has two distinct endocrine cell types: C (“clear”) cells, which secrete a calcium-regulating hormone called calcitonin, and follicular cells, which secrete thyroid hormone. Calcitonin is discussed with calcium homeostasis.

**Thyroid Hormones Contain Iodine** Thyroid hormones, like glucocorticoids, have long-term effects on metabolism. Unlike glucocorticoids, however, thyroid hormones are not essential for life. They are essential for normal growth and development in children, however, and infants born with thyroid deficiency will be developmentally delayed unless treated promptly. Because of the importance of thyroid hormones in children, the United States and Canada test all newborns for thyroid deficiency.

Thyroid hormones are amines derived from the amino acid tyrosine, and they are unusual because they contain the element iodine (Fig. 23.4c). Currently, thyroid hormones are the only known use for iodine in the body, although a few other tissues also concentrate this mineral.

Synthesis of thyroid hormones takes place in the thyroid follicles (also called acini), spherical structures whose walls are
(a) The thyroid gland is a butterfly-shaped gland, located just below the larynx. It secretes thyroid hormones and calcitonin.

(b) Section of thyroid gland. Thyroid hormone synthesis takes place in the colloid of the thyroid follicle.

(c) Thyroid hormones are made from iodine and tyrosine.

**THYROID HORMONE SYNTHESIS**

1. Identify the apical and basolateral membranes of the follicular cell.
2. What kind of transport brings I⁻ into follicular cells?
3. How does thyroglobulin get into the colloid?
4. How does the cell take thyroglobulin back in?
5. How do T₃ and T₄ leave the cell?

**FIGURE QUESTIONS**

1. A Na⁺-I⁻ symporter brings I⁻ into the cell. The pendrin transporter moves I⁻ into the colloid.
2. Follicular cell synthesizes enzymes and thyroglobulin for colloid.
3. Thyroglobulin is taken back into the cell in vesicles.
4. Intracellular enzymes separate T₃ and T₄ from the protein.
5. Free T₃ and T₄ enter the circulation.

**KEY**

- MIT = monoiodotyrosine
- DIT = diiodotyrosine
- T₃ = triiodothyronine
- T₄ = thyroxine
a single layer of epithelial cells (Fig. 23.4b). The hollow center of each follicle is filled with a sticky glycoprotein mixture called colloid. The colloid holds a 2–3 month supply of thyroid hormones at any one time.

The follicular cells surrounding the colloid manufacture a glycoprotein called thyroglobulin and enzymes for thyroid hormone synthesis (Fig. 23.4c (1)). These proteins are packaged into vesicles, then secreted into the center of the follicle. Follicular cells also actively concentrate dietary iodide, I⁻, using the sodium-iodide symporter (NIS) (2). I⁻ transport into the colloid is mediated by an anion transporter known as pendrin (SLC26A4).

As I⁻ enters the colloid, the enzyme thyroid peroxidase removes an electron from the iodide ion and adds iodine to tyrosine on the thyroglobulin molecule (3). The addition of one iodine to tyrosine creates moniodotyrosine (MIT). The addition of a second iodine creates diiodotyrosine (DIT). MIT and DIT then undergo coupling reactions. One MIT and one DIT combine to create the thyroid hormone triiodothyronine, or T₃. (Note the change from tyrosine to thyronine in the name.) Two DIT couple to form tetraiodothyronine (T₄, also known as thyroxine). At this point, the hormones are still attached to thyroglobulin.

When hormone synthesis is complete, the thyroglobulin–T₃/T₄ complex is taken back into the follicular cells in vesicles (4). There intracellular enzymes free the hormones T₃ and T₄ from the thyroglobulin protein (5). For many years scientists believed that the lipophilic nature of T₃ and T₄ allowed the hormones to diffuse out of the follicular cells and into the plasma, but current evidence indicates that the thyroid hormones move across cell membranes by protein carriers (6). Transporters for thyroid gland export of T₃ and T₄ have not been identified. Target tissue uptake transporters include an amino acid transporter (MCT8) and one member of the organic anion transporter (OAT) family.

T₃ and T₄ have limited solubility in plasma because they are lipophilic molecules. As a result, thyroid hormones bind to plasma proteins, such as thyroid-binding globulin (TBG). Most thyroid hormone in the plasma is in the form of T₄, and for years it was thought that T₄ was the active hormone. However, we now know that T₃ is three to five times more active biologically, and that it is the active hormone in target cells.

Target cells make about 85% of active T₃ by using enzymes called deiodinases to remove an iodine from T₄. Target tissue activation of the hormone adds another layer of control because individual target tissues can alter their exposure to active thyroid hormone by regulating their tissue deiodinase synthesis.

Thyroid receptors, with multiple isoforms, are in the nucleus of target cells. Hormone binding initiates transcription, translation, and synthesis of new proteins.

**TSH Controls the Thyroid Gland**

The control of thyroid hormone secretion follows the typical hypothalamic-pituitary-peripheral endocrine gland pattern (Fig. 23.5). Thyrotropin-releasing hormone (TRH) from the hypothalamus controls secretion of the anterior pituitary hormone thyrotropin, also known as thyroid-stimulating hormone (TSH). TSH in turns acts on the thyroid gland to promote hormone synthesis. The thyroid hormones normally act as a negative feedback signal to prevent oversecretion.

Thyroid hormones are not essential for life, but they do affect the quality of life if over- or under-secreted. Patients with thyroid excess or deficiency may experience decreased tolerance to heat or cold and mood disturbances, in addition to other symptoms.

The main function of thyroid hormones in adults is to provide substrates for oxidative metabolism. Thyroid hormones are thermogenic and increase oxygen consumption in most tissues. The exact mechanism is unclear but is at least partly related to changes in ion transport across the cell and mitochondrial membranes. Thyroid hormones also interact with other hormones to modulate protein, carbohydrate, and fat metabolism.

In children, thyroid hormones are necessary for full expression of growth hormone, which means they are essential for normal growth and development, especially of the nervous system. In the first few years after birth, myelin and synapse formation requires T₃ and T₄. Cytological studies suggest that thyroid hormones regulate microtubule assembly, which is an essential part of neuronal growth. Thyroid hormone is also necessary for proper bone growth.

The actions of thyroid hormones are most observable in people who secrete too much or too little hormone. Physiological effects that are subtle in normal people often become exaggerated in patients with endocrine disorders.

**Thyroid Pathologies Affect Quality of Life**

Problems with thyroid hormone secretion can arise either in the thyroid gland or along the control pathway depicted in Figure 23.5. The trophic action of TSH on the thyroid gland

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**RUNNING PROBLEM**

Elevated blood Ca²⁺ leads to high Ca²⁺ concentrations in the kidney filtrate. Calcium-based kidney stones occur when calcium phosphate or calcium oxalate crystals form and aggregate with organic material in the lumen of the kidney tubule. Once Prof. Magruder’s kidney stone passes into the urine, Dr. Spinks sends it for a chemical analysis.

Q3: Only free Ca²⁺ in the blood filters into Bowman’s capsule at the nephron. A significant portion of plasma Ca²⁺ cannot be filtered. Use what you have learned about filtration at the glomerulus to speculate on why some plasma Ca²⁺ cannot filter.
causes enlargement, or **hypertrophy**, of follicular cells. In pathological conditions with elevated TSH levels, the thyroid gland will enlarge, a condition known as a **goiter**. A large goiter can weigh hundreds of grams and almost encircle the neck (Fig. 23.6a).

Goiters are the result of excess TSH stimulation of the thyroid gland. Simply knowing that someone has a goiter does not tell you what the pathology is, however. Let’s see how both hypothyroidism and hyperthyroidism can be associated with goiter.

**Hyperthyroidism**  A person whose thyroid gland secretes too much hormone suffers from **hyperthyroidism**. Excess thyroid hormone causes changes in metabolism, the nervous system, and the heart.

1. **Hyperthyroidism** increases oxygen consumption and metabolic heat production. Because of the internal heat generated, these patients have warm, sweaty skin and may complain of being intolerant of heat.

2. Excess thyroid hormone increases protein catabolism and may cause muscle weakness. Patients often report weight loss.

3. The effects of excess thyroid hormone on the nervous system include hyperexcitable reflexes and psychological disturbances ranging from irritability and insomnia to psychosis. The mechanism for psychological disturbances is unclear, but morphological changes in the hippocampus and effects on β-adrenergic receptors have been suggested.

4. Thyroid hormones are known to influence β-adrenergic receptors in the heart, and these effects are exaggerated with hypersecretion. A common sign of hyperthyroidism is rapid heartbeat and increased force of contraction due to up-regulation of β₁-receptors on the myocardium.
Deficient thyroid hormone secretion in infancy causes cretinism, a condition marked by decreased mental capacity.

The primary cardiovascular change in hypothyroidism is bradycardia (slow heart rate).

Primary hypothyroidism is most commonly caused by a lack of iodine in the diet. Without iodine, the thyroid gland cannot make thyroid hormones (Fig. 23.7a). Low levels of T3 and T4 in the blood mean no negative feedback to the hypothalamus and anterior pituitary. In the absence of negative feedback, TSH secretion rises dramatically, and TSH stimulation enlarges the thyroid gland (goiter). Despite hypertrophy, the gland cannot obtain iodine to make hormone, so the patient remains hypothyroid. These patients exhibit the previously described signs of hypothyroidism. The goiter shown in the photograph of Figure 23.6a is probably due to iodine deficiency.

Therapy for thyroid disorders depends on the cause of the problem. Hypothyroidism is treated with oral thyroxine (T4). Hyperthyroidism can be treated by surgical removal of all or part of the gland, by destruction of thyroid cells with radioactive iodine, or by drugs that block either hormone synthesis (thiourea drugs) or peripheral conversion of T4 to T3 (propylthiouracil).

Hypothyroidism

Deficient thyroid hormone secretion in infancy causes cretinism, a condition marked by decreased mental capacity.

Primary hypothyroidism is most commonly caused by a lack of iodine in the diet. Without iodine, the thyroid gland cannot make thyroid hormones (Fig. 23.7b). Low levels of T3 and T4 in the blood mean no negative feedback to the hypothalamus and anterior pituitary. In the absence of negative feedback, TSH secretion rises dramatically, and TSH stimulation enlarges the thyroid gland (goiter). Despite hypertrophy, the gland cannot obtain iodine to make hormone, so the patient remains hypothyroid. These patients exhibit the previously described signs of hypothyroidism. The goiter shown in the photograph of Figure 23.6a is probably due to iodine deficiency.

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Hypothyroidism

Decreased thyroid hormone secretion slows metabolic rate and oxygen consumption. Patients become intolerant of cold because they are generating less internal heat.

Hypothyroidism decreases protein synthesis. In adults, this causes brittle nails, thinning hair, and dry, thin skin. Hypothyroidism also causes accumulation of mucopolysaccharides under the skin. These molecules attract water and cause the puffy appearance of myxedema (Fig. 23.6b). Hypothyroid children have slow bone and tissue growth and are shorter than normal for their age.

Nervous system changes in adults include slowed reflexes, slow speech and thought processes, and feelings of fatigue.

9. A woman who had her thyroid gland removed because of cancer was given pills containing only T4. Why was this less active form of the hormone an effective treatment for her hypothyroidism?

10. Why would excessive production of thyroid hormone, which uncouples mitochondrial ATP production and proton transport, cause a person to become intolerant of heat?
but essential amino acids must come from dietary sources. Among the minerals, calcium in particular is needed for proper bone formation.

3 Absence of chronic stress. Cortisol from the adrenal cortex is released in times of stress and has significant catabolic effects that inhibit growth. Children who are subjected to stressful environments may exhibit a condition known as failure to thrive that is marked by abnormally slow growth.

4 Genetics. Each human's potential adult size is genetically determined at conception.

Growth Hormone Is Anabolic

Growth hormone (GH or somatotropin) is released throughout life, although its biggest role is in children. Peak GH secretion occurs during the teenage years. The stimuli for growth hormone release are complex and not well
Endocrine Control of Growth and Metabolism

**New Growth Charts**

When you were growing up, did your family mark your growth each year on a special wall chart? Monitoring growth is an important part of health care for children and adolescents, particularly as we see a growing problem with childhood obesity in the United States. In 2000 the U.S. Centers for Disease Control and Prevention (CDC) issued new growth charts for the first time since 1977. In 2006 they recommended that clinicians use an international chart from the World Health Organization for children under two years of age. The old charts were based on 1929–1979 data from mostly bottle-fed, middle-class white children. We now know that breast-fed babies grow more rapidly than bottle-fed infants in the first two months, then more slowly for the remainder of the first year. We also have data showing that babies in lower socioeconomic groups grow more slowly. The new charts take these differences into account and also include body mass index (BMI) information up to age 20. To see the new charts and learn more about monitoring growth in infants and children, visit the CDC web site at www.cdc.gov/growthcharts.

understood, but they include circulating nutrients, stress, and other hormones interacting with a daily rhythm of secretion (Fig. 23.8).

The stimuli for GH secretion are integrated in the hypothalamus, which secretes two neuropeptides into the hypothalamic-hypophyseal portal system: growth hormone-releasing hormone (GHRH) and growth hormone-inhibiting hormone, better known as somatostatin (SS). On a daily basis, pulses of GHRH from the hypothalamus stimulate GH release. In adults, the largest pulse of GH release occurs in the first two hours of sleep. It is speculated that GHRH has sleep-inducing properties, but the role of GH in sleep cycles is unclear.

GH is secreted by cells in the anterior pituitary. It is a typical peptide hormone in most respects, except that nearly half the GH in blood is bound to a plasma growth hormone-binding protein. The binding protein protects plasma GH from being filtered into the urine and extends its half-life by 12 minutes. Researchers have hypothesized that genetic determination of binding protein concentration plays a role in determining adult height.

The target tissues for GH include both endocrine and non-endocrine cells. GH acts as a trophic hormone to stimulate secretion of insulin-like growth factors (IGFs; formerly called somatomedins) from the liver and other tissues. IGFs have a negative feedback effect on growth hormone secretion by acting on the anterior pituitary and on the hypothalamus. IGFs act in concert with growth hormone to stimulate bone and soft tissue growth (Fig. 23.8).

Metabolically, growth hormone and IGFs are anabolic for proteins and promote protein synthesis, an essential part of tissue growth. Growth hormone also acts with IGFs to stimulate bone growth. IGFs are responsible for cartilage growth. GH increases plasma fatty acid and glucose concentrations by promoting fat breakdown and hepatic glucose output.

**Concept Check**

11. Which pituitary hormone in addition to GH has two hypothalamic factors that regulate its release?

**Growth Hormone Is Essential for Normal Growth**

The disorders that reflect the actions of growth hormone are most obvious in children. Severe growth hormone deficiency in childhood leads to dwarfism, which can result from a problem either with growth hormone synthesis or with defective GH receptors. Unfortunately, neither bovine nor porcine growth hormone is effective as replacement therapy, as only primate growth hormone is active in humans. Prior to 1985, when genetically engineered human growth hormone became available, donated human pituitaries harvested at autopsy were the only source of growth hormone. Fortunately, severe growth hormone deficiency is relatively rare. At the opposite extreme, oversecretion of growth hormone in children leads to gigantism.

Once bone growth stops in late adolescence, growth hormone cannot further increase height. GH and IGFs can continue to act on cartilage and soft tissues, however. Adults with excessive secretion of growth hormone develop a condition known as acromegaly, characterized by lengthening of the jaw, coarsening of facial features, and growth of hands and feet (Fig. 23.9). Andre the Giant, a French wrestler who also had a role in the classic movie *The Princess Bride*, exhibited signs of both gigantism (he grew to 7′4″ tall) and acromegaly before his death at age 47.

**Genetically Engineered hGH Raises Ethical Questions**

When genetically engineered human growth hormone (hGH) became available in the mid-1980s, the medical profession was faced with a dilemma. Obviously the hormone should be used to treat children who would otherwise be dwarfs, but what about children with only partial GH deficiency or genetically short children with normal GH secretion levels? This question is complicated by the difficulty of accurately identifying children with partial growth hormone deficiency. And what about
children whose parents want them to be taller? Should these healthy children be given the hormone?

In 2003 the U.S. Food and Drug Administration approved use of a recombinant human growth hormone for treating children with non-GH-deficient short stature, defined as being more than 2.25 standard deviations below the mean height for their age and sex. (This means children in the bottom 1% of their age-sex group.) In clinical trials, daily injections of the drug for two years resulted in an average height increase of 1.3” (3.3 cm). According to a 2006 analysis in a pediatric medicine journal, the cost for this treatment was more than $52,000 per inch of height gained. Side effects reported during hGH studies include glucose intolerance and pancreatitis (inflammation of the pancreas). Long-term risks associated with hGH treatment are unknown, and parents must be made aware that hGH therapy has the potential to create psychological problems in children if the results are less than optimum.
Tissue and Bone Growth

Growth can be divided into two general areas: soft tissue growth and bone growth. In children, bone growth is usually assessed by measuring height, and tissue growth by measuring weight. Multiple hormones have direct or permissive effects on growth. In addition, we are just beginning to understand how paracrine growth factors interact with classic hormones to influence tissue development and differentiation.

Tissue Growth Requires Hormones and Paracrine

Soft tissue growth requires adequate amounts of growth hormone, thyroid hormone, and insulin. Growth hormone and IGFs are required for tissue protein synthesis and cell division. Under the influence of these hormones, cells undergo both hypertrophy (increased cell size) and hyperplasia (increased cell number).

Thyroid hormones play a permissive role in growth and contribute directly to nervous system development. At the target tissue level, thyroid hormone interacts synergistically with growth hormone in protein synthesis and nervous system development. Children with untreated hypothyroidism (cretinism) do not grow to normal height even if they secrete normal amounts of growth hormone.

Insulin supports tissue growth by stimulating protein synthesis and providing energy in the form of glucose. Because insulin is permissive for growth hormone, insulin-deficient children fail to grow normally even though they may have normal concentrations of growth and thyroid hormones.

Bone Growth Requires Adequate Dietary Calcium

Bone growth, like soft tissue development, requires the proper hormones and adequate amounts of protein and calcium. Bone contains calcified extracellular matrix formed when calcium phosphate crystals precipitate and attach to a collagenous lattice support. The most common form of calcium phosphate is hydroxyapatite, \( \text{Ca}_10(\text{PO}_4)_6(\text{OH})_2 \).

Although the large amount of inorganic matrix in bone makes some people think of it as nonliving, bone is a dynamic tissue, constantly being formed and broken down, or resorbed. Spaces in the collagen-calcium matrix are occupied by living cells that are well supplied with oxygen and nutrients by blood vessels that run through adjacent channels (Fig. 23.10c).

Bones generally have two layers: an outer layer of dense compact bone and an inner layer of spongy trabecular bone. In some bones, a central cavity is filled with bone marrow. Compact bone provides strength and is thickest where support is needed (such as in the long bones of the legs) or where muscles attach. Trabecular bone is less sturdy and has open, cell-filled spaces between struts of calcified lattice.

Bones grow when matrix is deposited faster than it is resorbed. Specialized bone-forming cells called osteoblasts produce enzymes and osteoid, a mixture of collagen and other proteins to which hydroxyapatite binds. Recent research has found two other proteins, osteocalcin and osteonecin, that appear to aid in deposition of the calcified matrix.

Bone diameter increases when matrix deposits on the outer surface of the bone. Linear growth of long bones occurs at specialized regions called epiphyseal plates, located at each end of the bone shaft (diaphysis) (Fig. 23.10b). The side of the plate closer to the end (epiphysis) of the bone contains continuously dividing columns of chondrocytes, collagen-producing cells of cartilage. As the collagen layer thickens, the older cartilage calcifies and older chondrocytes degenerate, leaving spaces that osteoblasts invade. The osteoblasts then lay down bone matrix on top of the cartilage base.

As new bone is added at the ends, the shaft lengthens. Long bone growth continues as long as the epiphyseal plate is active. When osteoblasts complete their work, they revert to a less active form known as osteocytes.

Growth of long bone is under the influence of growth hormone and the insulin-like growth factors. In the absence of these hormones, normal bone growth does not occur. Long bone growth is also influenced by steroid sex hormones. The growth spurt of adolescent boys used to be attributed solely to increased androgen production but it now appears that estrogens play a significant role in pubertal bone growth in both sexes.

In all adolescents, the sex hormones eventually inactivate the epiphyseal plate so that long bones no longer grow. Because the epiphyseal plates of various bones close in a regular, ordered sequence, X-rays that show which plates are open and which have closed can be used to calculate a child’s “bone age.”

Linear bone growth ceases in adults, but bones are dynamic tissues that undergo continual remodeling throughout life. The resorption or breakdown of bone is controlled by osteoclasts, large, mobile, multinucleate cells derived from hematopoietic stem cells. Osteoclasts are responsible for dissolving bone.

Osteoclasts attach around their periphery to a section of matrix, much like a suction cup (Fig. 23.10c). The central region of the osteoclast secretes hydrochloric acid with the aid of carbonic anhydrase and an H\(^{+}\)-ATPase. Osteoclasts also secrete protease enzymes that work at low pH. The combination of acid and enzymes dissolves the calcified hydroxyapatite matrix and its collagen support. Ca\(^{2+}\) from hydroxyapatite becomes part of the ionized Ca\(^{2+}\) pool and can enter the blood.

Bone mass in the body is another example of mass balance. In children, bone deposition exceeds bone resorption, and bone mass increases. In young adults up to about age 30, deposition and resorption are balanced. From age 30 on, resorption begins to exceed deposition, with concurrent loss of bone from the skeleton. Bone loss and osteoporosis are discussed in more detail at the end of this chapter.
Bone

(a) Composition of bone

Bone is composed largely of calcified extracellular matrix.

- Compact bone is dense and used for support.
- Spongy bone or trabecular bone forms a calcified lattice.

(b) Bone growth

Chondrocytes form cartilage. Osteoblasts create calcium phosphate crystals to replace cartilage.

- Epiphyseal plate is the site of bone growth.

(c) Bone resorption

Osteoclasts are responsible for bone resorption. Osteoclasts secrete acid and enzymes that dissolve calcium phosphate in bone.

These photographs dramatically illustrate why people with osteoporosis have a high incidence of bone fractures.
### Concept Check

1. Which hormones are essential for normal growth and development?
2. Why don’t adults with growth hormone hypersecretion grow taller?

---

## Calcium Balance

Most calcium in the body—99%, or nearly 2.5 pounds—is found in the bones. This pool is relatively stable, however, so it is the body’s small fraction of nonbone calcium that is most critical to physiological functioning (Fig. 23.11). As you have learned, Ca\(^{2+}\) has several physiological functions:

1. **Ca\(^{2+}\) is an important signal molecule.** The movement of Ca\(^{2+}\) from one body compartment to another creates Ca\(^{2+}\) signals. Calcium entering the cytoplasm initiates exocytosis of synaptic and secretory vesicles, contraction in muscle fibers, or altered activity of enzymes and transporters. Removal of Ca\(^{2+}\) from the cytoplasm requires active transport.

2. **Ca\(^{2+}\) is part of the intercellular cement that holds cells together at tight junctions.**

3. **Ca\(^{2+}\) is a cofactor in the coagulation cascade.** Although Ca\(^{2+}\) is essential for blood coagulation, body Ca\(^{2+}\) concentrations never decrease to the point at which coagulation is inhibited. However, removal of Ca\(^{2+}\) from a blood sample will prevent the specimen from clotting in the test tube.

4. **Plasma Ca\(^{2+}\) concentrations affect the excitability of neurons.** This function of Ca\(^{2+}\) has not been introduced before in this text, but it is the function that is most obvious in Ca\(^{2+}\)-related disorders. If plasma Ca\(^{2+}\) falls too low (hypocalcemia), neuronal permeability to Na\(^+\) increases, neurons depolarize, and the nervous system becomes hyperexcitable. In its most extreme form, hypocalcemia causes sustained contraction (tetany) of the respiratory muscles, resulting in asphyxiation. Hypercalcemia has the opposite effect, depressing neuromuscular activity.

### Plasma Calcium Is Closely Regulated

Because calcium is critical to so many physiological functions, the body’s plasma Ca\(^{2+}\) concentration is very closely regulated. Calcium homeostasis follows the principle of mass balance:

\[
\text{Total body calcium} = \text{intake} - \text{output}
\]

1. **Total body** Ca\(^{2+}\) is all the calcium in the body, distributed among three compartments (Fig. 23.11):

   a. **Extracellular fluid.** Ionized Ca\(^{2+}\) is concentrated in the ECF. In the plasma, nearly half the Ca\(^{2+}\) is bound to plasma proteins and other molecules. The unbound Ca\(^{2+}\) is free to diffuse across membranes through open Ca\(^{2+}\) channels. Total plasma Ca\(^{2+}\) concentration is about 2.5 mM.

   - **Location**
   - **Function**
     - **Extracellular matrix**
       - Ca\(^{2+}\) is bound to plasma proteins and other molecules. The unbound Ca\(^{2+}\) is free to diffuse across membranes through open Ca\(^{2+}\) channels. Total plasma Ca\(^{2+}\) concentration is about 2.5 mM.
     - **Extracellular fluid**
       - Ca\(^{2+}\) is free to diffuse across membranes through open Ca\(^{2+}\) channels. Total plasma Ca\(^{2+}\) concentration is about 2.5 mM.
     - **Intracellular**
       - Ca\(^{2+}\) is bound to plasma proteins and other molecules. The unbound Ca\(^{2+}\) is free to diffuse across membranes through open Ca\(^{2+}\) channels. Total plasma Ca\(^{2+}\) concentration is about 2.5 mM.
b. **Intracellular Ca\(^{2+}\)**. The concentration of free Ca\(^{2+}\) in the cytosol is about 0.001 mM. In addition, Ca\(^{2+}\) is concentrated inside mitochondria and the sarcoplasmic reticulum. Electrochemical gradients favor movement of Ca\(^{2+}\) into the cytosol when Ca\(^{2+}\) channels open.

c. **Extracellular matrix (bone)**. Bone is the largest Ca\(^{2+}\) reservoir in the body, with most bone Ca\(^{2+}\) in the form of hydroxyapatite crystals. Bone Ca\(^{2+}\) forms a reservoir that can be tapped to maintain plasma Ca\(^{2+}\) homeostasis. Usually only a small fraction of bone Ca\(^{2+}\) is ionized and readily exchangeable, and this pool remains in equilibrium with Ca\(^{2+}\) in the interstitial fluid.

2. **Intake** is the Ca\(^{2+}\) ingested in the diet and absorbed in the small intestine. Only about one-third of ingested Ca\(^{2+}\) is absorbed, and unlike organic nutrients, Ca\(^{2+}\) absorption is hormonally regulated. Many people do not eat enough Ca\(^{2+}\)-containing foods, however, and intake may not match output.

Intestinal calcium absorption is apparently both transcellular and paracellular (between the cells). Transcellular transport is accomplished by entry into the enterocyte through apical Ca\(^{2+}\) channels (TRPV6, also called ECaC) and exit through basolateral Na\(^{+}\)-Ca\(^{2+}\) exchanger (NCX) and Ca\(^{2+}\)-ATPase transporters.

3. **Output**, or Ca\(^{2+}\) loss from the body, occurs primarily through the kidneys, with a small amount excreted in feces. Ionized Ca\(^{2+}\) is freely filtered at the glomerulus and then reabsorbed along the length of the nephron. Hormonally regulated reabsorption takes place only in the distal nephron and uses transporters similar to those found in the intestine. There is no paracellular transport in the kidney.

**Concept Check**

14. What does hypercalcemia do to neuronal membrane potential, and why does that effect depress neuromuscular excitability?

15. Draw a picture of a distal tubule cell and label apical and basolateral membranes, lumen, and ECF. Use the description of intestinal Ca\(^{2+}\) absorption in list item 2 (Intake) to draw the appropriate transporters.

16. Describe the renal transport of Ca\(^{2+}\) from the tubule lumen to the ECF as active, passive, facilitated diffusion, and so on.

**Three Hormones Control Calcium Balance**

Three hormones regulate the movement of Ca\(^{2+}\) between bone, kidney, and intestine: parathyroid hormone, calcitriol (vitamin D\(_3\)), and calcitonin (Fig. 23.11). Of these, parathyroid hormone and calcitriol are the most important in adult humans.

The **parathyroid glands**, which secrete parathyroid hormone (para-, alongside of), were discovered in the 1890s by physiologists studying the role of the thyroid gland. These scientists noticed that if they removed all of the thyroid gland from dogs and cats, the animals died in a few days. In contrast, rabbits died only if the little parathyroid “glandules” alongside the thyroid were removed. The scientists then looked for parathyroid glands in dogs and cats and found them tucked away behind the larger thyroid gland. If the parathyroid glands were left behind when the thyroid was surgically removed, the animals lived. The scientists concluded that the parathyroids contained a substance that was essential for life, although the thyroid gland did not. That essential substance was parathyroid hormone.

**Parathyroid Hormone**

Four small parathyroid glands lie on the dorsal surface of the thyroid gland (Fig. 23.12). They secrete **parathyroid hormone** (PTH, also called **parathormone**), a peptide whose main function is to increase plasma Ca\(^{2+}\) concentrations. The stimulus for PTH release is a decrease in plasma Ca\(^{2+}\), monitored by a cell membrane Ca\(^{2+}\)-sensing receptor (CaSR). The CaSR, a G protein–coupled receptor, was the first membrane receptor identified whose ligand was an ion rather than an organic molecule.

PTH acts on bone, kidney, and intestine to increase plasma Ca\(^{2+}\) concentrations (Fig. 23.12). Increased plasma Ca\(^{2+}\) acts as negative feedback and shuts off PTH secretion. Parathyroid hormone raises plasma Ca\(^{2+}\) in three ways:

1. **PTH mobilizes calcium from bone**. Increased bone resorption by osteoclasts takes about 12 hours to become measurable. Curiously, although osteoclasts are responsible for dissolving the calcified matrix and would be logical targets for PTH, they do not have PTH receptors. Instead, PTH effects are mediated by a collection of paracines, including osteoprotegerin (OPG) and an osteoclast differentiation factor called **RANKL**. These paracrine factors
Calcitriol  Intestinal absorption of calcium is enhanced by the action of a hormone known as 1,25-dihydroxycholecalciferol (1,25(OH)₂D₃), also known as calcitriol or vitamin D₃ (Fig. 23.13). The body makes calcitriol from vitamin D that has been obtained through diet or made in the skin by the action of sunlight on precursors made from acetyl CoA. People who live above 37 degrees of latitude north or below 37 degrees south do not get enough sunlight to make adequate vitamin D except in the summer, and they should consider taking vitamin supplements.

Vitamin D is modified in two steps—first in the liver, then in the kidneys—to make vitamin D₃, or calcitriol. Calcitriol is the primary hormone responsible for enhancing Ca²⁺ uptake from the small intestine. In addition, calcitriol facilitates renal reabsorption of Ca²⁺ and helps mobilize Ca²⁺ out of bone.

The production of calcitriol is regulated at the kidney by the action of PTH. Decreased plasma Ca²⁺ increases PTH secretion, which stimulates calcitriol synthesis. Intestinal and
Endocrine Control of Growth and Metabolism

Fig. 23.13

renal absorption of Ca\(^{2+}\) raises blood Ca\(^{2+}\), turning off PTH in a negative feedback loop that decreases calcitriol synthesis.

Prolactin, the hormone responsible for milk production in breast-feeding (lactating) women, also stimulates calcitriol synthesis. This action ensures maximal absorption of Ca\(^{2+}\) from the diet at a time when metabolic demands for calcium are high.

**Calcitonin**

The third hormone involved with calcium metabolism is calcitonin, a peptide produced by the C cells of the thyroid gland (Tbl. 23.1). Its actions are opposite to those of parathyroid hormone. Calcitonin is released when plasma Ca\(^{2+}\) increases. Experiments in animals have shown that calcitonin decreases bone resorption and increases renal calcium excretion.

Calcitonin apparently plays only a minor role in daily calcium balance in adult humans. Patients whose thyroid glands have been removed show no disturbance in calcium balance, and people with thyroid tumors that secrete large amounts of calcitonin also show no ill effects.

Calcitonin has been used medically to treat patients with Paget’s disease, a genetically linked condition in which osteoclasts are overactive and bone is weakened by resorption. Calcitonin in these patients stabilizes the abnormal bone loss, leading scientists to speculate that this hormone is most important during childhood growth, when net bone deposition is needed, and during pregnancy and lactation, when the mother’s body must supply calcium for both herself and her child.

**Calcium and Phosphate Homeostasis Are Linked**

Phosphate homeostasis is closely linked to calcium homeostasis. Phosphate is the second key ingredient in the hydroxyapatite of bone, \(\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2\), and most phosphate in the body is found in bone. However, phosphates have other significant physiological roles, including energy transfer and
Phosphate homeostasis parallels that of Ca\(^{2+}\). Phosphate is absorbed in the intestines, filtered and reabsorbed in the kidneys, and divided between bone, ECF, and intracellular compartments. Vitamin D\(_3\) enhances intestinal absorption of phosphate. Renal excretion is affected by both PTH (which promotes phosphate excretion) and vitamin D\(_3\) (which promotes phosphate reabsorption).

### Table 23.1

<table>
<thead>
<tr>
<th><strong>Cell of origin</strong></th>
<th><strong>C cells of thyroid gland (parafollicular cells)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical nature</td>
<td>32-amino acid peptide</td>
</tr>
<tr>
<td>Biosynthesis</td>
<td>Typical peptide</td>
</tr>
<tr>
<td>Transport in the circulation</td>
<td>Dissolved in plasma</td>
</tr>
<tr>
<td>Half-life</td>
<td>(&lt;10) minutes</td>
</tr>
<tr>
<td>Factors affecting release</td>
<td>(\uparrow) Plasma [Ca(^{2+})]</td>
</tr>
<tr>
<td>Target cells or tissues</td>
<td>Bone and kidney</td>
</tr>
<tr>
<td>Target receptor</td>
<td>G protein–coupled membrane receptor</td>
</tr>
<tr>
<td>Whole body or tissue action</td>
<td>Prevents bone resorption. Enhances kidney excretion</td>
</tr>
<tr>
<td>Action at molecular level</td>
<td>Signal transduction pathways appear to vary during cell cycle</td>
</tr>
<tr>
<td>Other information</td>
<td>Experimentally decreases plasma Ca(^{2+}) but has little apparent physiological effect in adult humans. Possible effect on skeletal development; possible protection of bone Ca(^{2+}) stores during pregnancy and lactation</td>
</tr>
</tbody>
</table>

### Running Problem

The results of Prof. Magruder’s last test confirm that he has hyperparathyroidism. He goes on a low-calcium diet, avoiding milk, cheese, and other dairy products, but several months later he returns to the emergency room with another painful kidney stone. Dr. Spinks sends him to an endocrinologist, who recommends surgical removal of the overactive parathyroid glands. “We can’t tell which of the parathyroid glands is most active,” the specialist says, “and we’d like to leave you with some parathyroid hormone of your own. So I will take out all four glands, but we’ll reimplant two of them in the muscle of your forearm. In many patients, the implanted glands secrete just enough PTH to maintain calcium homeostasis. And if they secrete too much PTH, it is much easier to take them out of your arm than do major surgery on your neck again.”

**Q5:** Why can’t Prof. Magruder simply take replacement PTH by mouth? (Hint: PTH is a peptide hormone.)

---

**Osteoporosis Is a Disease of Bone Loss**

One of the best-known pathologies of bone function is *osteoporosis*, a metabolic disorder in which bone resorption exceeds bone deposition. The result is fragile, weakened bones that are more easily fractured (Fig. 23.10c). Most bone resorption takes place in spongy trabecular bone, particularly in the vertebrae, hips, and wrists.

Osteoporosis is most common in women after menopause, when estrogen concentrations fall. However, older men also...
develop osteoporosis. Bone loss and small fractures and compression in the spinal column lead to kyphosis (hump-back), the stooped, hunchback appearance that is characteristic of advanced osteoporosis in the elderly. Osteoporosis is a complex disease with genetic and environmental components. Risk factors include small, thin body type; postmenopausal age; smoking; and low dietary Ca\(^{2+}\) intake.

For many years estrogen or estrogen/progesterone hormone replacement therapy (HRT) was used to prevent osteoporosis. However, estrogen therapy alone increases the risk of endometrial and possibly other cancers, and some studies suggest that combined estrogen/progesterone HRT might increase risk of heart attacks and strokes. A selective estrogen receptor modulator (SERM) called raloxifene has been used to treat osteoporosis.

The most effective drugs for preventing or treating osteoporosis act more directly on bone metabolism. They include bisphosphonates, which induce osteoclast apoptosis and suppress bone resorption, and teriparatide, a PTH derivative, which stimulates formation of new bone. Teriparatide consists of the first 34 amino acids of the 84-amino acid PTH molecule and must be injected rather than taken orally. Currently clinical studies are investigating whether some combination of bisphosphonates and teriparatide is more effective in combating osteoporosis than either drug alone.

To avoid osteoporosis in later years, young women need to maintain adequate dietary calcium intake and perform weight-bearing exercises, such as running or aerobics, which increase bone density. Loss of bone mass begins by age 30, long before people think they are at risk, and many women suffer from low bone mass (osteopenia) before they are aware of a problem. Bone mass testing can help with early diagnosis of osteopenia.

### Hyperparathyroidism

Prof. Magruder had the surgery, and the implanted glands produced an adequate amount of PTH. He must have his plasma Ca\(^{2+}\) levels checked regularly for the rest of his life to ensure that the glands continue to function adequately. To learn more about hyperparathyroidism, see this article in *The American Family Physician*, www.aafp.org/afp/20040115/333.html.

Check your understanding of this running problem by comparing your answers with the information in the summary table.

<table>
<thead>
<tr>
<th>Question</th>
<th>Facts</th>
<th>Integration and Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What role does Ca(^{2+}) play in the normal functioning of muscles and neurons?</td>
<td>Calcium triggers neurotransmitter release and uncovers the myosin-binding sites on muscle actin filaments.</td>
<td>Muscle weakness in hyperparathyroidism is the opposite of what you would predict from knowing the role of Ca(^{2+}) in muscles and neurons. However, calcium also affects the Na(^{+}) permeability of neurons, and it is this effect that leads to muscle weakness and CNS effects.</td>
</tr>
<tr>
<td>2. What is the technical term for &quot;elevated levels of calcium in the blood&quot;?</td>
<td>Prefix for elevated levels: hyper-. Suffix for &quot;in the blood&quot;: -emia.</td>
<td>Hypercalcemia is the technical term for elevated levels of calcium in the blood.</td>
</tr>
<tr>
<td>3. Speculate on why some plasma Ca(^{2+}) cannot filter into Bowman’s capsule.</td>
<td>Filtration at the glomerulus is a selective process that excludes blood cells and most plasma proteins.</td>
<td>A significant amount of plasma Ca(^{2+}) is bound to plasma proteins and therefore cannot filter.</td>
</tr>
<tr>
<td>4. What one test could definitively prove that Prof. Magruder has hyperparathyroidism?</td>
<td>Hyperparathyroidism is a condition in which excessive amounts of PTH are secreted.</td>
<td>A test for the amount of PTH in the blood would confirm the diagnosis of hyperparathyroidism.</td>
</tr>
<tr>
<td>5. Why can’t Prof. Magruder simply take replacement PTH by mouth?</td>
<td>PTH is a peptide hormone.</td>
<td>Ingested peptides are digested by proteolytic enzymes. This means PTH taken orally cannot be absorbed intact into the body and consequently will not be effective.</td>
</tr>
</tbody>
</table>
Endocrine Control of Growth and Metabolism

and communication across membranes are also essential to hormone activity. In many instances, such as calcium and phosphate homeostasis, the principle of mass balance is the focus of homeostatic regulation.

Review of Endocrine Principles

1. Basic components of endocrine pathways include hormone receptors, feedback loops, and cellular responses.

Adrenal Glucocorticoids

2. The adrenal cortex secretes glucocorticoids, sex steroids, and aldosterone. (Fig. 23.1)
3. Cortisol secretion is controlled by hypothalamic CRH and ACTH from the pituitary. Cortisol is the feedback signal. Cortisol is a typical steroid hormone in its synthesis, secretion, transport, and action. (Fig. 23.2)
4. Cortisol is catabolic and essential for life. It promotes gluconeogenesis, breakdown of skeletal muscle proteins and adipose tissue, Ca\(^{2+}\) excretion, and suppression of the immune system.
5. Hypercortisolism usually results from a tumor or therapeutic administration of the hormone. Addison's disease is hyposecretion of all adrenal steroids.
6. CRH and the melancortins have physiological actions in addition to cortisol release. (Fig. 23.2d)

Thyroid Hormones

7. The thyroid follicle has a hollow center filled with colloid containing thyroglobulin and enzymes. (Fig. 23.4b)
8. Thyroid hormones are made from tyrosine and iodine. Triiodothyronine (thyroxine, T\(_3\)) is converted in target tissues to the more active hormone triiodothyronine (T\(_3\)). (Fig. 23.4)
9. Thyroid hormones are not essential for life, but they influence metabolic rate as well as protein, carbohydrate, and fat metabolism.
10. Thyroid hormone secretion is controlled by thyrotropin (thyroid-stimulating hormone, TSH) and thyrotropin-releasing hormone (TRH). (Fig. 23.5)

Growth Hormone

11. Normal growth requires growth hormone, thyroid hormones, insulin, and sex hormones at puberty. Growth also requires adequate diet and absence of chronic stress.
12. Growth hormone is secreted by the anterior pituitary and stimulates secretion of insulin-like growth factors (IGFs) from the liver and other tissues. These hormones promote bone and soft tissue growth. (Fig. 23.8)
13. Secretion of growth hormone is controlled by growth hormone-releasing hormone (GHRH) and growth hormone–inhibiting hormone (somatostatin). (Fig. 23.8)

Tissue and Bone Growth

14. Bone is composed of hydroxyapatite crystals attached to a collag enous support. Bone is a dynamic tissue with living cells.
15. Osteoblasts synthesize bone. Long bone growth occurs at epiphyseal plates, where chondrocytes produce cartilage. (Fig. 23.10)

Calcium Balance

16. Calcium acts as an intracellular signal for second messenger pathways, exocytosis, and muscle contraction. It also plays a role in cell junctions, coagulation, and neural function.
17. Ca\(^{2+}\) homeostasis balances dietary intake, urinary output, and distribution of Ca\(^{2+}\) among bone, cells, and the ECF. (Fig. 23.11)
18. Decreased plasma Ca\(^{2+}\) stimulates parathyroid hormone (PTH) secretion by the parathyroid glands. (Fig. 23.12)
19. PTH promotes Ca\(^{2+}\) resorption from bone, enhances renal Ca\(^{2+}\) reabsorption, and increases intestinal Ca\(^{2+}\) absorption through its effect on calcitriol. (Fig. 23.12)
20. Calcitonin from the thyroid gland plays only a minor role in daily calcium balance in adult humans. (Tbl. 23.1)

Questions

Level One Reviewing Facts and Terms

1. Name the zones of the adrenal cortex and the primary hormones secreted in each zone.

2. For (a) cortisol, (b) growth hormone, (c) parathyroid hormone, and (d) T\(_3\) and T\(_4\), draw the full control pathway and show feedback where appropriate. Do not use abbreviations.
3. List four conditions that are necessary for people to achieve their full growth. Include five specific hormones known to exert an effect on growth.
4. Name the thyroid hormones. Which one has the highest activity? How and where is most of it produced?
5. Define each of the following terms and explain its physiological significance:
   (a) melanocortins  
   (b) osteoporosis  
   (c) hydroxyapatite  
   (d) mineralocorticoid  
6. List seven functions of calcium in the body.
7. Make a table showing the effects of cortisol, thyroid hormones, growth hormone, insulin, and glucagon on protein, carbohydrate, and lipid metabolism.

**Level Two  Reviewing Concepts**

8. Mapping exercise: Create a reflex map with feedback loops for each of the following situations:
   (a) Hypercortisolism from an adrenal tumor  
   (b) Hypercortisolism from a pituitary tumor  
   (c) Hyperthyroidism from a hormone-secreting thyroid tumor  
   (d) Hypothyroidism from a pituitary problem that decreases TSH synthesis  
9. Define, compare, and contrast or relate the terms in each set:
   (a) cortisol, glucocorticoids, ACTH, CRH  
   (b) thyroid, C cell, follicle, colloid  
   (c) thyroglobulin, tyrosine, iodide, TBG, deiodinase, TSH, TRH  
   (d) somatotropin, IGF, GHRH, somatostatin, growth hormone–binding protein  
   (e) gigantism, acromegaly, dwarfism  
   (f) hyperplasia, hypertrophy  
   (g) osteoblast, osteoclast, chondrocyte, osteocyte  
   (h) vitamin D, calcitriol, 1,25-dihydroxycholecalciferol, calcitonin, estrogen, PTH  
10. Based on what you know about the cellular mechanism of action for T3, would you expect to see tissue response to this hormone within a few minutes or in more than an hour?
11. If average plasma $[\text{Ca}^{2+}]$ is 2.5 mmol/L, what is the concentration in mEq/L?
12. Osteoclasts make acid (H$^+$) from CO$_2$ and H$_2$O. They secrete the acid at their apical membrane and put bicarbonate into the ECF. Draw an osteoclast and diagram this process, including enzymes and the appropriate transporters on each membrane. How many different transporters can you think of that could be used to reabsorb bicarbonate?

**Level Three  Problem Solving**

13. Diabetic patients who have surgery, become sick, or are under other physiological stress are told to monitor their blood sugar carefully because they may need to increase their insulin dose temporarily. What is the physiological explanation behind this advice?
14. One diagnostic test to determine the cause of hypercortisolism is a dexamethasone suppression test. Dexamethasone blocks secretion of ACTH by the pituitary. The following table shows the results from two patients given a dexamethasone suppression test.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before Test</th>
<th>After Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>B</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

Can you tell from these results where the patients’ pathologies originate? Explain for each patient.
15. When blood test results came back last week, someone in the office spilled a cup of coffee on them, smearing the patient names and some of the numbers. One report shows elevated TSH levels, but the thyroid levels are so low they are unreadable. You have three charts waiting for test results on thyroid hormone levels. Your tentative diagnoses, based on physical findings and symptoms, for those three patients are:
   Mr. A: primary hypothyroidism  
   Ms. B: primary hyperthyroidism  
   Ms. C: secondary hyperthyroidism  
   (a) Can you tell whose results are on the smeared report, based on the TSH results and the tentative diagnosis?
   (b) Can you rule out any of the three people based on those same criteria? Explain.
16. The following graph shows the results of a study done in Boston that compared blood vitamin D levels during summer and winter. Boston is located at 42 degrees north latitude, and weak sunlight in winter there does not allow skin synthesis of vitamin D. (Data from Am J Med 112: 659–662, 2002 Jun 1)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Subjects with vitamin D insufficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–29</td>
<td>End of winter</td>
</tr>
<tr>
<td>30–39</td>
<td>End of winter</td>
</tr>
<tr>
<td>40–49</td>
<td>End of winter</td>
</tr>
<tr>
<td>50+</td>
<td>End of winter</td>
</tr>
</tbody>
</table>

(a) Summarize the results shown in the graph. How many variables are shown in the graph that you must address in your summary?
(b) Based on what you know, how could you explain the results of the study?
(c) Would taking a multivitamin supplement affect the results?

**Level Four  Quantitative Problems**

17. Filterable plasma $\text{Ca}^{2+}$ is about 5 mg/L. Assume a man has a GFR of 125 mL of plasma filtered per minute.
   (a) How much $\text{Ca}^{2+}$ does he filter in a day?
   (b) Net dietary $\text{Ca}^{2+}$ intake is 170 mg/day. To remain in $\text{Ca}^{2+}$ balance, how much $\text{Ca}^{2+}$ must he excrete?
   (c) What percentage of filtered $\text{Ca}^{2+}$ is reabsorbed by the kidney tubule?
Endocrine Control of Growth and Metabolism

Answers

Answers to Concept Check Questions

1. The medulla secretes catecholamines (epinephrine, norepinephrine), and the cortex secretes aldosterone, glucocorticoids, and sex hormones.

2. Androstenedione is a prohormone for testosterone. Testosterone is anabolic for skeletal muscle, which might give an athlete a strength advantage.

3. HPA = hypothalamic-pituitary-adrenal. CBG = corticosteroid-binding globulin or transcortin.

4. This immediate stress response is too rapid to be mediated by cortisol and must be a fight-or-flight response mediated by the sympathetic nervous system and catecholamines.

5. No, because cortisol is catabolic on muscle proteins.

6. Primary and iatrogenic hypercortisolism: ACTH is lower than normal because of negative feedback. Secondary hypercortisolism: ACTH is higher because of the ACTH-secreting tumor.

7. Addison’s disease: high ACTH due to reduced corticosteroid production and lack of negative feedback.

8. ACTH is secreted during stress. If the stress is a physical one caused by an injury, the endogenous opioid β-endorphin can decrease pain and help the person continue functioning.

9. In peripheral tissues T₃ is converted to T₄, which is the more active form of the hormone.

10. When mitochondria are uncoupled, energy normally captured in ATP is released as heat. This raises the person’s body temperature and causes heat intolerance.

11. Prolactin also has two hypothalamic factors that regulate its release.

12. Normal growth and development require growth hormone, thyroid hormone, insulin, and insulin-like growth factors.

13. Adults who hyperscrotecte growth hormone do not grow taller because their epiphyseal plates have closed.

14. Hypercalcemia hyperpolarizes the membrane potential, which makes it harder for the neuron to fire an action potential.

15. The figure should resemble.

16. The Na⁺-Ca²⁺ exchanger is a secondary active transporter, and the Ca²⁺-ATPase is an active transporter.

17. ATP and phosphocreatine store energy in high-energy phosphate bonds.

18. A kinase transfers a phosphate group from one substrate to another. A phosphatase removes a phosphate group, and a phosphorylase adds one.

Answers to Figure Questions

Figure 23.1: 1. A baby born with deficient 21-hydroxylase would have low aldosterone and cortisol levels and an excess of sex steroids, particularly androgens. Low cortisol would decrease the child’s ability to respond to stress. Excess androgen would cause masculinization in female infants. 2. Women, who synthesize more estrogens, would have more aromatase.

Figure 23.2: ACTH = adrenocorticotropic hormone or corticotropin. CRH = corticotropin-releasing hormone. MSH = melanocystimulating hormone.

Figure 23.3: 1. The apical membrane faces the colloid, and the basolateral membrane faces the ECF. 2. I⁻ comes into the cell by secondary active transport (co-transport with Na⁺), 3 and 4. Thyroglobulin moves between colloid and cytoplasm by exocytosis and endocytosis. 5. Thyroid hormones leave the cell by an unknown membrane transporter.

Figure 23.4: A pituitary tumor hypersecreting TSH would cause hyperthyroidism and an enlarged thyroid gland. The pathway would show decreased TRH resulting from short-loop negative feedback from TSH to the hypothalamus, increased TSH caused by the tumor, elevated thyroid hormones, but no negative feedback from the thyroid hormones to the anterior pituitary because the tumor does not respond to feedback signals.

Answers to Review Questions

Level One Reviewing Facts and Terms

1. Zona glomerulosa (aldosterone), zona fasciculata (glucocorticoids), zona reticularis (sex steroids, primarily androgens).

2. (a) corticotropin releasing hormone (hypothalamus) → adrenocorticotropic hormone (anterior pituitary) → cortisol (adrenal cortex) feeds back to inhibit secretion of both CRH and ACTH. (b) growth hormone releasing hormone and somatostatin (hypothalamus) → growth hormone (anterior pituitary) (c) decreased blood Ca²⁺ → parathyroid hormone (parathyroid glands) → increases blood Ca²⁺ by increasing reabsorption of bone, among other effects → negative feedback inhibits secretion of PTH. (d) Thyrotropin releasing hormone (hypothalamus) → thyroid stimulating hormone (thyrotropin) (anterior pituitary) → triiodothyronine (T₃) and thyroxine (T₄) (thyroid gland) → negative feedback to hypothalamus and anterior pituitary.

3. Conditions: adequate diet, absence of chronic stress, and adequate amounts of thyroid and growth hormones. Other important hormones: insulin, IGFs (somatomedins), and sex hormones at puberty.

4. Triiodothyronine (T₃) and tetraiodothyronine (T₄ or thyroxine). T₃ is the more active; most of it is made from T₄ in peripheral tissues.

5. (a) Include ACTH (cortisol secretion) and MSH (not significant in humans). (b) Bone loss that occurs when bone reabsorption exceeds bone deposition. (c) The inorganic portion of bone matrix, mostly calcium salts. (d) Steroid hormones that regulate minerals, i.e., aldosterone. (e) Spongy bone, with an
open latticework. (f) Pro-opiomelanocortin, inactive precursor to ACTH and other molecules. (g) Growth zones in long bones, comprised of cartilage.

6. Functions: blood clotting, cardiac muscle excitability and contraction, skeletal and smooth muscle contraction, second messenger systems, exocytosis, tight junctions, strength of bones and teeth.

7. In this table, A indicates anabolism, C indicates catabolism. CHO = carbohydrate

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>PROTEIN</th>
<th>CHO</th>
<th>FAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>C (skeletal muscle)</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Thyroid</td>
<td>A (children), C (adults)</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>GH</td>
<td>A</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Insulin</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Glucagon</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

**Level Two Reviewing Concepts**

8. (d) TRH high, TSH low, thyroid hormones low.

9. (a) Hypothalamic CRH stimulates anterior pituitary secretion of ACTH, which stimulates adrenal cortex ( zona fasciculata) secretion of glucocorticoids such as cortisol. (b) Thyroid gland follicle cells secrete colloid from which thyroid hormones are produced; C cells secrete calcitonin. (c) Thyroid hormone synthesis is controlled by TSH, whose release is controlled by TRH. In the thyroid gland, tyrosine and iodine combine on thyroglobulin to make thyroid hormones. Thyroid-binding globulin (TBG) carries thyroid hormones in the blood. Target cell deiodinase removes iodine from T4 to make T3. (d) Growth hormone releasing hormone (GHRH) stimulates anterior pituitary secretion of growth hormone (GH or somatotropin). Somatostatin (GHIF) inhibits production of GH. Growth hormone binding protein binds about half the GH in the blood. Insulin-like growth factors (IGFs) from the liver act with GH to promote growth. (e) Dwarfism results from severe GH deficiency in childhood. Gigantism results from hypersecretion of GH during childhood. Acromegaly is lengthening of jaw and growth in hands and feet, caused by hypersecretion of GH in adults. (f) Hyperplasia—increased cell number. Hypertrophy—increased cell size. (g) Osteoblasts—bone cells that secrete organic bone matrix. Osteocytes—inactive form of osteoblasts. Osteoclasts—cartilage cells. Osteoclasts—bone-destroying cells. (h) PTH increases blood Ca^{2+} by stimulating bone and renal reabsorption, and intestinal absorption of Ca^{2+}. Calcitriol (1,25-dihydroxycholecalciferol) is a vitamin D derivative that mediates PTH effect on intestinal absorption of Ca^{2+}. Calcitonin decreases bone reabsorption of Ca^{2+}. Estrogen promotes bone deposition.

10. Thyroid hormones have intracellular receptors, so you expect 60–90 minute onset of action. However, effects on metabolic rate are apparent within a few minutes and are thought to be related to changes in ion transport across cell and mitochondrial membranes.

11. Equivalent = ion’s molarity × the number of charges/ion. Ca^{2+} = 2.5 mmole × 2 = 5 mEq.

12. See Figure 23.10c. The cell uses carbonic anhydrase to make H^{+} from CO_{2} + H_{2}O. Apical membrane: H^{+}-ATPase secretes H^{+}; basolateral membrane secretes HCO_{3}^{-} with Cl-HCO_{3} antiporter. Could also be Na-HCO_{3} symporter.

**Level Three Problem Solving**

13. Physiological stress stimulates secretion of cortisol, which increases blood glucose. Increased insulin opposes this effect.

14. Normal response: dexamethasone → ACTH suppression → decrease in cortisol. Patient A: no response to dexamethasone suggests there is adrenal hypersecretion that is insensitive to ACTH. Patient B: dexamethasone decreases cortisol, suggesting that the problem is in the pituitary.

15. Mr. A—elevated TSH. Ms. B—low TSH. Ms. C—elevated TSH. (a) Not possible to determine if the lab slip has the results of Mr. A or Ms. C without knowing the thyroid hormone levels. (b) Ms. B can be ruled out, because her TSH would be low if the tentative diagnosis is correct.

16. (a) People in all age groups showed vitamin D insufficiency at the end of winter. Deficiency was most pronounced in the 18–29 age group and least pronounced in the 50+ age group. At the end of summer, fewer subjects were deficient in vitamin D. Variables: season when blood collected, age group, and % of people with vitamin D insufficiency. (b) Energy from the sun is required for precursors in the skin to be converted to vitamin D. Days are shorter in the winter, and at northern latitudes like Boston, people spend less time outside during the winter. This explains the difference between the two seasons. Fewer than half the people tested were deficient, however, suggesting that most people consumed enough vitamin D. The biggest seasonal difference was in the 18–29 age group, who probably spent more time outside in the summer than members of other groups. (c) Taking multivitamin supplements containing vitamin D should reduce vitamin D insufficiency.

**Level Four Quantitative Problems**

17. (a) 5 mg Ca^{2+}/L plasma × 125 mL plasma filtered/min × 1440 min/day = 900 mg Ca^{2+} filtered/day (b) To remain in Ca^{2+} balance, he must excrete 170 mg/day. (c) 900 mg filtered—170 mg excreted = 730 mg reabsorbed. 730/900 = 81%.

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