In contrast to the other pituitary hormones, which stimulate specific target glands, GH has multiple effects throughout the body.

- **Promotion of linear growth.** GH stimulates the epiphyseal cartilage or growth plates of the long bones. Under the influence of GH, the chondrocytes in the growth plate are stimulated, leading to proliferation of these cells and deposition of new cartilage, followed by conversion of this cartilage to bone. This process elongates the shaft of the long bones. By late adolescence, when there is no remaining epiphyseal cartilage and the shafts have fused with the epiphysis, GH can no longer cause lengthening of the long bones. Because GH also increases osteoblastic activity, total bone mass is increased by GH even after epiphyseal closure.

- **Promotion of protein deposition in tissues.** GH is a protein anabolic hormone and produces a positive nitrogen balance. It increases amino acid uptake in most cells and the synthesis of amino acids into proteins.

- **Promotion of fat utilization for energy.** GH causes the mobilization of fatty acids from adipose tissue and the preferential utilization of free fatty acids for energy. This action of GH, together with its protein anabolic effect, produces an increase in lean body mass. Because GH increases plasma levels of free fatty acids and ketoacids, it is ketogenic.

- **Impairment of carbohydrate utilization for energy.** GH decreases the uptake and utilization of glucose by many insulin-sensitive cells, such as muscle and adipose tissue. As a result, blood glucose concentration tends to rise and insulin secretion increases to compensate for the GH-induced insulin resistance; thus GH is diabetogenic.

GH secretion is under the influence of both a hypothalamic releasing (GHRH) hormone and a hypothalamic inhibiting hormone (somatostatin). High plasma levels of somatomedin C decrease GH release by increasing secretion of somatostatin from the hypothalamus and acting directly on the pituitary to decrease responsiveness to GHRH.

GH secretion is highest during puberty and decreases in adult life. This may be partially responsible for the decline in lean body mass and increase in adipose mass that are characteristic of senescence. There are three general categories of stimuli that increase GH secretion:

- Fasting, chronic protein deprivation, or other conditions in which there is an acute fall in plasma levels of metabolic substrates such as glucose and free fatty acids.
- Increased plasma levels of amino acids, such as occur after a protein meal.
- Exercise and stressful stimuli, such as pain and fever.
many areas of high water permeability. Then, in the absence of ADH, the entire process reverses. Thus, this process temporarily provides many new pores that allow free diffusion of water from the tubular fluid through the tubular epithelial cells and into the renal interstitial fluid. Water is then absorbed from the collecting tubules and ducts by osmosis.

Regulation:

**Osmotic Regulation.** When a concentrated electrolyte solution is injected into the artery that supplies the hypothalamus, the ADH neurons in the supraoptic and paraventricular nuclei immediately transmit impulses into the posterior pituitary to release large quantities of ADH into the circulating blood, sometimes increasing the ADH secretion to as high as 20 times normal. Conversely, injection of a dilute solution into this artery causes inactivity of the impulses and therefore almost total stoppage of ADH secretion. Thus, the concentration of ADH in the body fluids can change from small amounts to large amounts, or vice versa.

When the extracellular fluid becomes too concentrated, fluid is pulled by osmosis out of an osmoreceptor cell, decreasing its size and initiating appropriate nerve signals in the hypothalamus to cause additional ADH secretion. Conversely, when the extracellular fluid becomes too dilute, water moves by osmosis in the opposite direction, into the cell, and this decreases the signal for ADH secretion.

**Vasoconstrictor and pressor effects of ADH, and increased ADH secretion caused by low blood volume.** Whereas minute concentrations of ADH cause increased water conservation by the kidneys, higher concentrations of ADH have a potent effect of constricting the arterioles throughout the body and therefore increasing the arterial pressure. For this reason, ADH has another name, vasopressin.

One of the stimuli for causing intense ADH secretion is decreased blood volume. This occurs especially strongly when the blood volume decreases 15 to 25% or more; the secretory rate then sometimes rises to as high as 50 times normal. The cause of this is the following. The atria have stretch receptors that are excited by overfilling. When excited, they send signals to the brain to inhibit ADH secretion. Conversely, when the receptors are unexcited as a result of underfilling, the opposite occurs, with greatly increased ADH secretion. Decreased stretch of the baroreceptors of the carotid, aortic, and pulmonary regions also stimulates ADH secretion.

**Oxytocin**

**Oxytocin causes contraction of the pregnant uterus.** The hormone oxytocin stimulates contraction of the pregnant uterus, especially toward the end of gestation.
regulated by thyroid-stimulating hormone. TSH secretion from the pituitary gland is increased by the hypophysiotropic hormone thyrotropin-releasing hormone (TRH) and is inhibited in a negative feedback fashion by circulating T4 and T3. Although some feedback occurs at the hypothalamus by influencing TRH secretion, the predominant feedback occurs at the level of the pituitary. Because T4 is deiodinated to T3 in the pituitary gland, T3 appears to be the final effector that mediates the negative feedback.

TSH promotes the synthesis and secretion of thyroid hormones.
- Binding of TSH to its receptors on the cell membrane of the thyroid gland activates adenylyl cyclase so that cyclic AMP mediates some of the actions of TSH. An immediate effect of TSH is to promote endocytosis of colloid, proteolysis of thyroglobulin, and release of T4 and T3 into the circulation.

TSH has chronic effects to promote growth of the thyroid gland.
- The chronic effects of TSH include increased blood flow to the thyroid gland and induction of hypertrophy and hyperplasia of the follicular cells. With prolonged TSH stimulation, the thyroid enlarges, and a goiter occurs. In the absence of TSH, there is marked atrophy of the gland.
Parathyroid hormone.

Parathyroid hormone provides a powerful mechanism for controlling extracellular calcium and phosphate concentrations by regulating intestinal reabsorption, renal excretion, and exchange between the extracellular fluid and bone of these ions. Excess activity of the parathyroid gland causes rapid absorption of calcium salts from the bones, with resultant hypercalcemia in the extracellular fluid; conversely, hypofunction of the parathyroid glands causes hypocalcemia.

Physiologic Anatomy of the Parathyroid Glands.

There are four parathyroid glands in humans; they are located immediately behind the thyroid gland—one behind each of the upper and each of the lower poles of the thyroid. The parathyroid gland contains mainly chief cells and oxyphil cells, but oxyphil cells are absent in many animals and in young humans. The chief cells secrete most, if not all, of the PTH. The function of the oxyphil cells is not certain, but they are believed to be modified or depleted chief cells that no longer secrete hormone.

Effect of parathyroid hormone on calcium and phosphate concentrations in the extracellular fluid.

Parathyroid hormone secretion increases in response to reduction in extracellular calcium concentration.

- The hormone is formed in the chief cells of the parathyroid glands located immediately behind the thyroid gland. The rate of formation of PTH is strongly regulated by the ECF calcium ion concentration; small decreases in the concentration of the ion result in large increases in the rate of PTH formation. If the reduction below the normal level of calcium concentration persists, the parathyroid glands hypertrophy, as occurs with pregnancy and disease states such as rickets that are characterized by inadequate calcium absorption from the gastrointestinal tract.

Increases in PTH concentration decrease renal calcium excretion.
Cortisol exerts its effects by first interacting with intracellular receptors in target cells. Because cortisol is lipid soluble, it can easily diffuse through the cell membrane.

Once inside the cell, cortisol binds with its protein receptor in the cytoplasm, and the hormone-receptor complex then interacts with specific regulatory DNA sequences, called glucocorticoid response elements, to induce or repress gene transcription.

Glucocorticoids increase or decrease transcription of many genes to alter synthesis of mRNA for the proteins that mediate their multiple physiologic effects.

Regulation of cortisol secretion by adrenocorticotropic hormone from the pituitary gland.

ACTH stimulates cortisol secretion.
- The secretion of cortisol is under the control of the hypothalamic-pituitary, corticotropin-releasing hormone (CRH)-ACTH axis. The release of ACTH from the pituitary is dependent on the hypophysiotropic hormone CRH.
- Once ACTH is secreted into the blood, it has a rapid effect on the zona fasciculata, to increase the secretion of cortisol. This effect of ACTH is achieved by increasing the conversion of cholesterol to pregnenolone and is mediated via the second messenger cyclic AMP.
- Under conditions of chronic ACTH excess, such as with Cushing’s syndrome, there are sustained increases in the secretion of cortisol and adrenal androgens.
- Blood levels of free (unbound) cortisol are controlled in a negative feedback fashion. Increased plasma levels of cortisol decrease ACTH secretion through a direct effect on the pituitary as well as indirect inhibition of CRH release from the hypothalamus.

Stress increases ACTH secretion.
- Physical and mental stressors stimulate the neuroendocrine cells of the hypothalamus to secrete CRH; as a result, there is increased ACTH secretion, which stimulates release of cortisol.
amounts of aldosterone, resulting in hypertension and hypokalemia; usually hypertension is relatively mild because there is only a small increase in extracellular fluid volume resulting from sodium escape. The hypertension and hypokalemia are exacerbated by increased sodium intake. Because of expansion of the extracellular fluid volume and the rise in arterial pressure, plasma renin activity is suppressed. The potassium depletion in Conn’s syndrome decreases the concentrating ability of the kidneys, leading to polyuria, and causes muscle weakness and metabolic alkalosis.

Impaired secretion of adrenocortical hormones occurs in Addison’s disease. Destruction of the adrenal cortex can result from autoimmune disease, tuberculosis, or cancer. These processes leads to a progressive reduction in glucocorticoid and mineralocorticoid function. As a result of the decreased cortisol secretion, there is a compensatory increase in ACTH secretion, which produces hyperpigmentation. Symptoms of Addison’s disease include the following.

- Mineralocorticoid Deficiency
  - Excessive loss of sodium, hypovolemia, hypotension, and increased plasma renin activity.
  - Excessive potassium retention and hyperkalemia.
  - Mild acidosis.

- Glucocorticoid Deficiency
  - Abnormal carbohydrate, fat, and protein metabolism resulting in muscle weakness, fasting hypoglycemia, and impaired utilization of fats for energy.
  - Loss of appetite and weight loss.
  - Poor tolerance to stress. The inability to secrete increased amounts of cortisol during stress leads to an Addisonian crisis.
Conversely, too little testosterone allows the hypothalamus to secrete large amounts of GnRH, with a corresponding increase in anterior pituitary LH and FSH secretion and consequent increase in testicular testosterone secretion.

**Regulation of spermatogenesis by FSH and Testosterone.**

FSH binds with specific FSH receptors attached to the Sertoli cells in the seminiferous tubules. This causes these cells to grow and secrete various spermatogenic substances. Simultaneously, testosterone diffusing into the seminiferous tubules from the Leydig cells in the interstitial spaces also has a strong tropic effect on spermatogenesis. To initiate spermatogenesis, both FSH and testosterone are necessary.

**Negative Feedback Control of Seminiferous Tubule Activity—Role of the Hormone Inhibin.**

- When the seminiferous tubules fail to produce sperm, secretion of FSH by the anterior pituitary gland increases markedly. Conversely, when spermatogenesis proceeds too rapidly, pituitary secretion of FSH diminishes. The cause of this negative feedback effect on the anterior pituitary is believed to be secretion by the Sertoli cells of another hormone called inhibin. This hormone has a strong direct effect on the anterior pituitary gland to inhibit the secretion of FSH and a slight effect on the hypothalamus to inhibit secretion of GnRH.
- Inhibin is a glycoprotein. Its potent inhibitory feedback effect on the anterior pituitary gland provides an important negative feedback mechanism for control of spermatogenesis, operating simultaneously with and in parallel to the negative feedback mechanism for control of testosterone secretion.