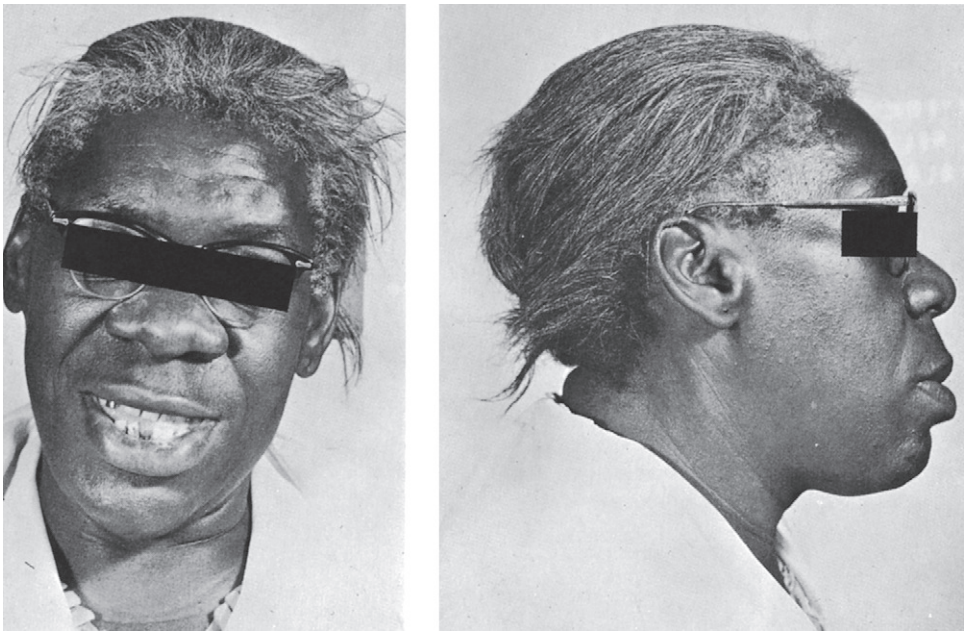

Figure 75–8

Acromegalic patient.

Acromegaly. If an acidophilic tumor occurs after adolescence—that is, after the epiphyses of the long bones have fused with the shafts—the person cannot grow taller, but the bones can become thicker and the soft tissues can continue to grow. This condition, shown in Figure 75–8, is known as *acromegaly.* Enlargement is especially marked in the bones of the hands and feet and in the *membranous bones,* including the cranium, nose, bosses on the forehead, supraorbital ridges, lower jawbone, and portions of the vertebrae, because their growth does not cease at adolescence. Consequently, the lower jaw protrudes forward, sometimes as much as half an inch, the forehead slants forward because of excess development of the supraorbital ridges, the nose increases to as much as twice normal size, the feet require size 14 or larger shoes, and the fingers become extremely thickened so that the hands are almost twice normal size. In addition to these effects, changes in the vertebrae ordinarily cause a hunched back, which is known clinically as *kyphosis.* Finally, many soft tissue organs, such as the tongue, the liver, and especially the kidneys, become greatly enlarged.

Possible Role of Decreased Growth Hormone Secretion in Causing Changes Associated with Aging

In people who have lost the ability to secrete growth hormone, some features of the aging process accelerate. For instance, a 50-year-old person who has been without growth hormone for many years may have the appearance of a person aged 65. The aged appearance seems to result mainly from decreased protein deposition in most tissues of the body and increased fat deposition in its place. The physical and physiological effects are increased wrinkling of the skin, diminished rates of function of some of the organs, and diminished muscle mass and strength.

As one ages, the average plasma concentration of growth hormone in an otherwise normal person changes approximately as follows:

	ng/ml
5 to 20 years	6
20 to 40 years	3
40 to 70 years	1.6

Thus, it is highly possible that some of the normal aging effects result from diminished growth hormone secretion. In fact, multiple tests of growth hormone therapy in older people have demonstrated three important effects that suggest antiaging actions: (1) increased protein deposition in the body, especially in the muscles; (2) decreased fat deposits; and (3) a feeling of increased energy.

Posterior Pituitary Gland and Its Relation to the Hypothalamus

The *posterior pituitary gland,* also called the *neurohypophysis,* is composed mainly of glial-like cells called *pituicytes.* The pituicytes do not secrete hormones; they act simply as a supporting structure for large numbers of *terminal nerve fibers* and *terminal nerve endings* from nerve tracts that originate in the *supraoptic* and *paraventricular nuclei* of the hypothalamus, as shown in Figure 75–9. These tracts pass to the neurohypophysis through the *pituitary stalk* (hypophysial stalk). The nerve endings are bulbous knobs that contain many secretory granules. These endings lie on the surfaces of capillaries, where they secrete two posterior pituitary hormones: (1) *antidiuretic hormone* (ADH), also called *vasopressin,* and (2) *oxytocin.*

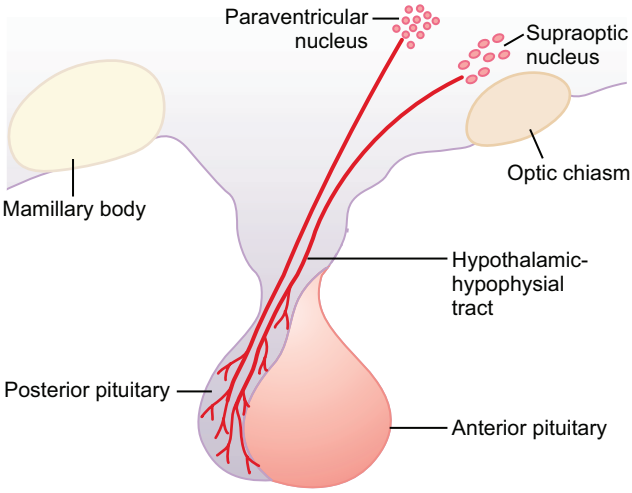

Figure 75–9

Hypothalamic control of the posterior pituitary.

If the pituitary stalk is cut above the pituitary gland but the entire hypothalamus is left intact, the posterior pituitary hormones continue to be secreted normally, after a transient decrease for a few days; they are then secreted by the cut ends of the fibers within the hypothalamus and not by the nerve endings in the posterior pituitary. The reason for this is that the hormones are initially synthesized in the cell bodies of the supraoptic and paraventricular nuclei and are then transported in combination with "carrier" proteins called *neurophysins* down to the nerve endings in the posterior pituitary gland, requiring several days to reach the gland.

ADH is formed primarily in the supraoptic nuclei, whereas oxytocin is formed primarily in the paraventricular nuclei. Each of these nuclei can synthesize about one sixth as much of the second hormone as of its primary hormone.

When nerve impulses are transmitted downward along the fibers from the supraoptic or paraventricular nuclei, the hormone is immediately released from the secretory granules in the nerve endings by the usual secretory mechanism of *exocytosis* and is absorbed into adjacent capillaries. Both the neurophysin and the hormone are secreted together, but because they are only loosely bound to each other, the hormone separates almost immediately. The neurophysin has no known function after leaving the nerve terminals.

Chemical Structures of ADH and Oxytocin

Both oxytocin and ADH (vasopressin) are polypeptides, each containing nine amino acids. Their amino acid sequences are the following:

Vasopressin: Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-$GlyNH_2$

Oxytocin: Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-$GlyNH_2$

Note that these two hormones are almost identical except that in vasopressin, phenylalanine and arginine replace isoleucine and leucine of the oxytocin molecule. The similarity of the molecules explains their partial functional similarities.

Physiological Functions of ADH

The injection of extremely minute quantities of ADH—as small as 2 nanograms—can cause decreased excretion of water by the kidneys (antidiuresis). This antidiuretic effect is discussed in detail in Chapter 28. Briefly, in the absence of ADH, the collecting tubules and ducts become almost impermeable to water, which prevents significant reabsorption of water and therefore allows extreme loss of water into the urine, also causing extreme dilution of the urine. Conversely, in the presence of ADH, the permeability of the collecting ducts and tubules to water increases greatly and allows most of the water to be reabsorbed as the tubular fluid passes through these ducts, thereby conserving water in the body and producing very concentrated urine.

The precise mechanism by which ADH acts on the collecting ducts to increase their permeability is only partially known. Without ADH, the luminal membranes of the tubular epithelial cells of the collecting ducts are almost impermeable to water. However, immediately inside the cell membrane are a large number of special vesicles that have highly water-permeable pores called *aquaporins.* When ADH acts on the cell, it first combines with membrane receptors that activate adenylyl cyclase and cause the formation of cAMP inside the tubular cell cytoplasm. This causes phosphorylation of elements in the special vesicles, which then causes the vesicles to insert into the apical cell membranes, thus providing many areas of high water permeability. All this occurs within 5 to 10 minutes. Then, in the absence of ADH, the entire process reverses in another 5 to 10 minutes. 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, as explained in Chapter 28 in relation to the urine-concentrating mechanism of the kidneys.

Regulation of ADH Production

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 cessation of the impulses and therefore almost total cessation of ADH secretion. Thus, the concentration of ADH in the body fluids can change from small amounts to large amounts, or vice versa, in only a few minutes.

The precise way that the osmotic concentration of the extracellular fluid controls ADH secretion is not clear. Yet somewhere in or near the hypothalamus are modified neuron receptors called *osmoreceptors.* When the extracellular fluid becomes too concentrated, fluid is pulled by osmosis out of the 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. Although some researchers place these osmoreceptors in the hypothalamus itself (possibly even in the supraoptic nuclei), others believe that they are located in the *organum vasculosum,* a highly vascular structure in the anteroventral wall of the third ventricle.

Regardless of the mechanism, concentrated body fluids stimulate the supraoptic nuclei, whereas dilute body fluids inhibit them. A feedback control system is available to control the total osmotic pressure of the body fluids.

Further details on the role of ADH in controlling renal function and body fluid osmolality are presented in Chapter 28.

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 per cent 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. For further details about this blood volume-pressure feedback mechanism, refer to Chapter 28.

Oxytocic Hormone

Oxytocin Causes Contraction of the Pregnant Uterus. The hormone *oxytocin,* in accordance with its name, powerfully stimulates contraction of the pregnant uterus, especially toward the end of gestation. Therefore, many obstetricians believe that this hormone is at least partially responsible for causing birth of the baby. This is supported by the following facts: (1) In a hypophysectomized animal, the duration of labor is prolonged, indicating a possible effect of oxytocin during delivery. (2) The amount of oxytocin in the plasma increases during labor, especially during the last stage. (3) Stimulation of the cervix in a pregnant animal elicits nervous signals that pass to the hypothalamus and cause increased secretion of oxytocin. These effects and this possible mechanism for aiding in the birth process are discussed in much more detail in Chapter 82.

Oxytocin Aids in Milk Ejection by the Breasts. Oxytocin also plays an especially important role in lactation—a role that is far better understood than its role in delivery. In lactation, oxytocin causes milk to be expressed from the alveoli into the ducts of the breast so that the baby can obtain it by suckling.

This mechanism works as follows: The suckling stimulus on the nipple of the breast causes signals to be transmitted through sensory nerves to the oxytocin neurons in the paraventricular and supraoptic nuclei in the hypothalamus, which causes release of oxytocin by the posterior pituitary gland. The oxytocin is then carried by the blood to the breasts, where it causes contraction of *myoepithelial cells* that lie outside of and form a latticework surrounding the alveoli of the mammary glands. In less than a minute after the beginning of suckling, milk begins to flow. This mechanism is called *milk letdown* or *milk ejection.* It is discussed further in Chapter 82 in relation to the physiology of lactation.

References

Antunes-Rodrigues J, de Castro M, Elias LL, et al: Neuroendocrine control of body fluid metabolism. Physiol Rev 84:169, 2004.

Besser GM, Thorner MO: Comprehensive Clinical Endocrinology, 3rd ed. Philadelphia: Mosby, Elsevier Science Limited, 2002.

Burbach JP, Luckman SM, Murphy D, Gainer H: Gene regulation in the magnocellular hypothalamo-neurohypophysial system. Physiol Rev 81:1197, 2001.

Butler AA, Le Roith D: Control of growth by the somatropic axis: growth hormone and the insulin-like growth factors have related and independent roles. Annu Rev Physiol 63:141, 2001.

Cummings DE, Merriam GR: Growth hormone therapy in adults. Annu Rev Med 54:513, 2003.

Dattani M, Preece M: Growth hormone deficiency and related disorders: insights into causation, diagnosis, and treatment. Lancet 363:1977, 2004.

Dunn AJ, Swiergiel AH, Palamarchouk V: Brain circuits involved in corticotropin-releasing factor–norepinephrine interactions during stress. Ann N Y Acad Sci 1018:25, 2004.

Edmondson SR, Thumiger SP, Werther GA, Wraight CJ: Epidermal homeostasis: the role of the growth hormone and insulin-like growth factor systems. Endocr Rev 24:737, 2003.

Eugster EA, Pescovitz OH: Gigantism. J Clin Endocrinol Metab 84:4379, 1999.

Freeman ME, Kanyicska B, Lerant A, Nagy G: Prolactin: structure, function, and regulation of secretion. Physiol Rev 80:1523, 2000.

Gimpl G, Fahrenholz F: The oxytocin receptor system: structure, function, and regulation. Physiol Rev 81:629, 2001.