take place if the tissue contains cells capable of dividing; thus increasing the number of cells. It can be physiologic or pathologic.

Physiologic Hyperplasia

Physiologic hyperplasia due to the action of hormones or growth factors occurs in several circumstances: when there is a need to increase functional capacity of hormone sensitive organs; when there is need for compensatory increase after damage or resection. Hormonal hyperplasia is well illustrated by the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy, usually accompanied by enlargement (hypertrophy) of the glandular epithelial cells. The classic illustration of compensatory hyperplasia comes from the study of liver regeneration. In individuals who donate one lobe of the liver for transplantation, the remaining cells proliferate so that the organ soon grows back to its original size. Experimental models of partial hepatectomy have been very useful for defining the mechanisms that stimulate regeneration of the liver (Chapter 3). Marrow is remarkable in its capacity to undergo rapid hyperplasia in response to a deficiency of terminally differentiated blood cells. For example, in the setting of an acute bleed or premature breakdown of red cells (hemolysis), feedback loops involving the growth factor erythropoietin are activated that stimulate the growth of red cell progenitors, allowing red cell production to increase as much as 8-fold. The regulation of hematopoiesis is discussed further in Chapter 13.

Pathologic Hyperplasia

Most forms of pathologic hyperplasia are caused by excessive or inappropriate actions of hormones or growth factors acting on target cells. Endometrial hyperplasia is an example of abnormal hormone-induced hyperplasia. Normally, after a menstrual period there is a rapid burst of proliferative activity in the endometrium that is stimulated by pituitary hormones and ovarian estrogen. It is brought to a halt by the rising levels of progesterone, usually about 10 to 14 days before the end of the menstrual period. In some instances, however, the balance between estrogen and progesterone is disturbed, resulting in absolute or relative increases in the amount of estrogen, with consequent hyperplasia of the endometrial glands. This form of pathologic hyperplasia is a common cause of abnormal menstrual bleeding. Benign prostatic hyperplasia is another common example of pathologic hyperplasia induced in responses to hormonal stimulation by androgens. Although these forms of pathologic hyperplasias are abnormal, the process remains controlled and the hyperplasia regresses if the hormonal stimulation is eliminated. As is discussed in Chapter 7, in cancer the growth control mechanisms become deregulated or ineffective because of genetic aberrations, that drive unrestrained proliferation. *Thus, while hyperplasia is distinct from cancer, pathologic hyperplasia constitutes a fertile soil in which cancerous proliferations may eventually arise*. For instance, patients with hyperplasia of the endometrium are at increased risk for developing endometrial cancer (Chapter 22).

Hyperplasia is a characteristic response to certain *viral infections*, such as papillomaviruses, which cause skin warts and several mucosal lesions composed of masses of hyperplastic epithelium. Here, the viruses make factors that interfere with host proteins that regulate cell proliferation. Like other forms of hyperplasia, some of these virally induced proliferations are also precursors to cancer (Chapter 7).

Mechanisms of Hyperplasia

Hyperplasia is the result of growth factor-driven proliferation of mature cells and, in some cases, by increased output of new cells from tissue stem cells. For instance, after partial hepatectomy growth factors are produced in the liver that engage receptors on the surviving cells and activate signaling pathways that stimulate cell proliferation. But if the proliferative capacity of the liver cells is compromised, as in some forms of hepatitis causing cell injury, hepatocytes can instead regenerate from intrahepatic stem cells. The roles of growth factors and stem cells in cellular replication and tissue hyperplasia are discussed in more detail in Chapter 3.

Atrophy

Atrophy is defined as a reduction in the size of an organ or tissue due to a decrease in cell size and number. Atrophy can be physiologic or pathologic. *Physiologic atrophy* is common during normal development. Some embryonic structures, such as the notochord and thyroglossal duct, undergo atrophy during fetal development. The decrease in the size of the uterus that occurs shortly after parturition is another form of physiologic atrophy.

Pathologic atrophy has several causes and it can be local or generalized. The common causes of atrophy are the following:

- *Decreased workload (atrophy of disuse).* When a fractured bone is immobilized in a plaster cast or when a patient is restricted to complete bed rest, skeletal muscle atrophy rapidly ensues. The initial decrease in cell size is reversible once activity is resumed. With more prolonged disuse, skeletal muscle fibers decrease in number (due to apoptosis) as well as in size; muscle atrophy can be accompanied by increased bone resorption, leading to osteoporosis of disuse.
- *Loss of innervation (denervation atrophy).* The normal metabolism and function of skeletal muscle are dependent on its nerve supply. Damage to the nerves leads to atrophy of the muscle fibers supplied by those nerves (Chapter 27).
- *Diminished blood supply.* A gradual decrease in blood supply (ischemia) to a tissue as a result of slowly developing arterial occlusive disease results in atrophy of the tissue. In late adult life, the brain may undergo progressive atrophy, mainly because of reduced blood supply as a result of atherosclerosis (Fig. 2-5). This is called *senile atrophy,* which also affects the heart.
- *Inadequate nutrition.* Profound protein-calorie malnutrition (marasmus) is associated with the utilization of skeletal muscle proteins as a source of energy after other reserves such as adipose stores have been depleted. This results in marked muscle wasting *(cachexia;* Chapter 9*)*. Cachexia is also seen in patients with chronic inflammatory diseases and cancer. In the former, chronic overproduction of the inflammatory cytokine tumor necrosis factor (TNF) is thought to be responsible for appetite