PATHOLOGIC BASIS OF DISEASE

Atrophy

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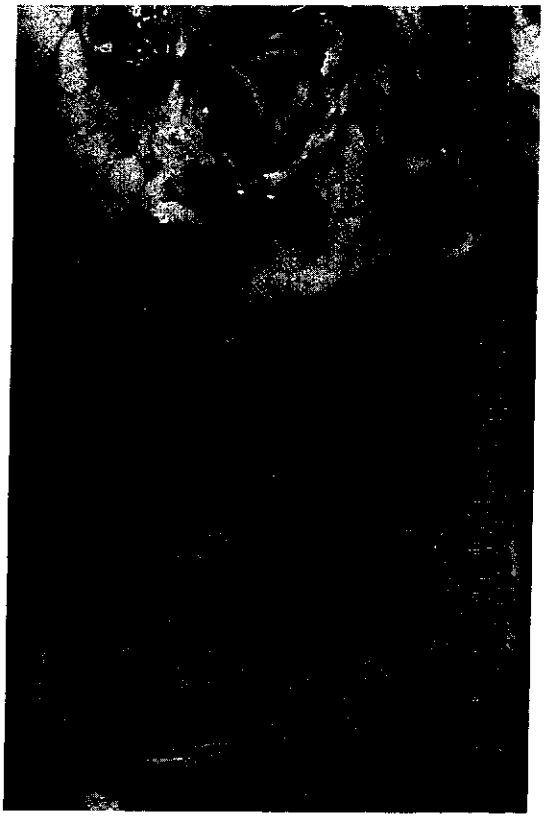

Figure 1–5. *Aortic stenosis with resultant myocardial hypertrophy. The narrowed valvular lumen is viewed from above, and the myocardial thickening is illustrated in the cross section of the ventricles (normal thickness of left ventricle is 1.2 to 1.4 cm.).*

not well understood, but it has been proposed that enlargement in striated muscle cell size is not accompanied by a commensurate increase in the oxidative and phosphorylative capabilities of the mitochondria. The mitochondria of hypertrophied cells may be more numerous than in normal cells, but they appear to have inadequate cristae, the ultimate source of oxidative respiration. Presumably, then, at some point in cellular enlargement, the limiting factor becomes the energy-generating mechanisms within the cell and, when an imbalance occurs, cardiac failure ensues.

ATROPHY

Shrinkage in the size of a cell by loss of cell substance is known as atrophy. It is another form of adaptive response. When a sufficient number of cells are involved, the entire tissue or organ diminishes in size—becomes atrophic. Such diminution of cell and organ size may affect many organs but occurs principally in skeletal muscle, the heart, secondary sex organs and brain. *The apparent causes of such atrophy are decreased workload, loss of innervation, diminished blood supply, inadequate nutrition or loss of endocrine stimulation* (Fig. 1–6). When a limb is immobilized in a plaster cast or muscles become paralyzed from loss of their innervation, as in poliomyelitis, atrophy of cells ensues (Fig. 1–7). In late adult life, the brain undergoes progressive atrophy, presumably as arteriosclerosis narrows its blood supply, and the gonads shrink with depletion of their endocrine stimulation (Figs. 1–8 and 1–9). In classic pathology, it was traditional to call such atrophy physiologic and to dignify the various circumstances in which pathologic atrophy might be encountered with such terms as disuse atrophy, neurogenic atrophy, vascular atrophy and endocrine atrophy. The fundamental cellular change is identical in all, representing a retreat by the cell to a smaller size at which survival is still possible within its constricted world. By bringing into balance cell volume and lower levels of blood supply, nutrition or trophic stimulation, a new equilibrium is achieved.

Atrophy represents a reduction in the

Figure 1–6. *Atrophic pancreas. The externally secreting acinar glands have atrophied, and only the islets remain in fat and fibrous tissue.*

Figure 1–7
liomyelitis. Cor vening denerva cross striations

Figure 1–8.
B. *Normal brain*

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Figure 1–7. *Atrophic striated muscle cells in poliomyelitis. Contrast large normal cells with the intervening denervated shrunken cells which have indistinct cross striations.*

structural components of the cell. Fewer myofilaments, mitochondria and less endoplasmic reticulum are presumably present. But the most striking intracellular alteration is an increased number of autophagic vacuoles. As mentioned earlier, many of these autophagic vacuoles become converted to residual bodies containing lipofuscin pigment. The concurrence of atrophy and accumulation of lipofuscin is recognized by the term *brown atrophy.* The heart in the aged individual may weigh only 200 to 250 gm. and be dark brown in color—the so-called brown atrophy of the heart. The atrophic shrunken liver may likewise undergo brown atrophy. Obviously, atrophy may progress to the point where cells are injured and die. If the blood supply is inadequate even to maintain the life of shrunken cells, injury and cell death may supervene. The adaptive capability of the cell is limited and, when exceeded, is followed by more ominous consequences.

HYPERPLASIA

Just as enlargement of cells (hypertrophy) represents a response to increased functional demand, cells capable of mitotic division may divide when stressed or stimulated to increased activity. In this way, the load is shared among a greater number. *Hyperplasia comprises, then, an*

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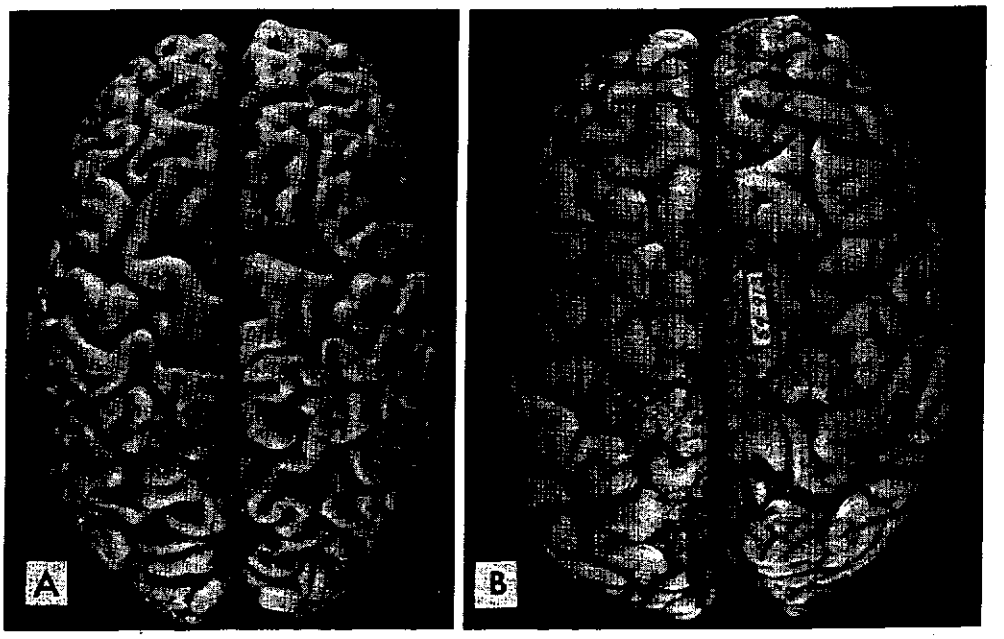

Figure 1–8. A, *Physiologic atrophy of the brain in an 82-year-old male. The meninges have been stripped.* B. *Normal brain of 35-year-old male.*

appear to be continuous with invaginations of the cell membrane. In effect, the T system is an extension of the interstitial fluid space across the muscle cell. This anatomic detail provides a possible mechanism by which contraction stimuli, initiated at the cell membrane, may spread rapidly across the entire cell, contacting all myofilaments (Nelson and Benson, 1963).

In addition to these structural specializations, the muscle cell often contains lipid droplets, glycogen particles and lipofuscin granules. The lipofuscin is found in increased quantity in the advanced years of life and, as elsewhere, presumably represents a "wear and tear" metabolic residuum (p. 47). In cardiac muscle, the lipofuscin residual bodies are characteristically located at the nuclear poles.

As is well known, the muscle cell is the mover of the body. Its single purpose is contraction which involves the conversion of chemical energy to kinetic energy. ATP is the major source of the chemical energy, and the contractile proteins of the myofilaments, actin and myosin, are the mediators of this transformation of chemical energy. Muscle shortening, according to Huxley (1965), occurs by the sliding of the thin filaments between the thick filaments toward the center of the sarcomere. Since the thin filaments are attached to the Z line at both ends of the sarcomere, a sliding motion toward the central A band causes shortening of the sarcomere, and it is the summation of shortening of all sarcomeres which constitutes contraction of the entire muscle cell.

Muscular contraction is now conceived of as an electrochemical reaction triggered by the release of acetylcholine at the myoneural junction. Involved in such contraction is an energy-consuming interaction between the tadpole-shaped myosin molecule and the reversibly globular-fibrillar actin molecule. The precise sequence of events following acetylcholine release is still a controversial issue and beyond our scope. It is enough to simply indicate that release of acetylcholine results in a flux of sodium and potassium ions along the membrane and through the T system of tubules, transiently depolarizing the membranes. Depolarization is associated with an influx of sodium into the cell, while muscle cell relaxation and repolarization involve an outflow of potassium. The energy consumed in muscular contraction is largely derived from the hydrolysis of ATP by calcium-activated ATPase. Recently, it has been found that in addition to actin and myosin, myofilaments contain two additional proteins, tropomyosin and troponin, which inhibit interaction of actin and myosin and so block contraction. This inhibition is overcome by calcium ions. Further details on the mec... excitation-contraction coupling may ... in Sandow (1965).

PATHOLOGY

Disorders of skeletal muscle (myo... occur in a variety of systemic diseases o... in certain primary muscular disorders... eral, these myopathies comprise a ... small and peripheral area of patholo... tice. To recount all the conditions in ... skeletal muscles may be affected wo... listing a large percentage of all the ... that have already been presented. F... ple, in staphylococcic infections, subc... abscesses may secondarily involve ... muscle fibers, and hematogenous ... nation of staphylococci may produce ... foci of suppurative infection within ... cles. Muscular involvement is a prom... ture of scleroderma and dermat... Muscle cell injury is encountered ... fever. Patients who are long confined ... who sustain a fracture with immobiliz... an extremity may suffer disuse atro... muscles. And so the skeletal muscle ... seat of numerous morphologic chan... great variety of states.

The present consideration of ... disease will be largely limited to a disc... of the basic reactions of muscle to ... forms of injury. The number of these ... logic reactions is limited because the ... reaction may be produced by a variety ... ogies. Thus, atrophy of muscle occurs ... mobilization of an extremity, follow... vation and in severe malnutrition. To ... the meaning of one of these reactions ... and thus establish a pathogenetic mec... and a clinical diagnosis of muscular dis... is necessary to: (1) identify the basic pat... muscle injury, (2) determine the distribu... muscle involvement and (3) ascertain the ... istence of other organ involvements and ... ble etiologic mechanisms. A simplified ... cation of the basic morphologic pat... muscle injury follows, indicating some ... more common conditions evoking such ... (Table 31–1). Following this overview, ... the more important reaction patterns ... few specific muscle diseases are discus... greater detail.

MUSCULAR ATROPHY

Atrophic shrinkage, death and disa... ance of muscle cells comprise basic ... patterns to many forms of adverse in...

TABLE 31–1. CLASSIF... MYOPATHIE...

Dysvoluminal Myopathies
A. Atrophy
1. Poliomyelitis (or any oth...
2. Disuse
3. Cachexia
4. Senility
5. Hyperthyroidism
6. Panhypopituitarism
B. Hypoplasia
1. Amyotonia congenita
C. Hypertrophy
1. Myotonia congenita
2. Hypothyroidism
3. Hyperpituitarism
4. Overuse

The major anatomic char... olves alteration in size of m... lume reflects augmentation ... ils and sarcoplasm.
II. Myopathies Associated wit...
A. Primary muscular dystr...
B. Specific infections (tric...
C. Corticosteroid myopath...
D. Polymyositis and derm...
E. Polymyopathy of Mey...
Characteristic of all of the ... uscle cells. Usually the whol... nes of altered sarcoplasm m... ed sarcomeres. In the foc... nerally a leukocytic infiltrat... d. lymphocytes. Sarcolem... runken and pyknotic or ... mber. In later stages, thin ... regeneration occurs. If en... fibrosis may result.
III. Myopathies Associated ...
Alterations
A. Familial periodic pa...
B. Hyperaldosteronism
In these conditions, th... dropic vacuoles, reflectin...
C. McArdle's phospho...
D. Pompe's disease
These two disorders ... seases in which abnorm... pear within lysosomes.
E. Central core myo...
ber contains condensed m...
F. Rod-body myop...
yosin-like bodies lie bene...
G. Myotonic dystro...
ripheral zones of sarc... inelles and isolated myo... ndles which encircle th... brils.
IV. Functional Myopathi...
A. Myasthenia gravi...
B. Thyroid myopath...
C. Tetanus
D. Addison's diseas...
Morphologic exami... uctural alteration in t... sorders. Occasionally, ... tes (lymphorrhages) ... distinctive and are ofte...

TABLE 31–1. CLASSIFICATION OF MYOPATHIES

voluminal Myopathies
Atrophy
1. Poliomyelitis (or any other form of denervation)
2. Disuse
3. Cachexia
4. Senility
5. Hyperthyroidism
6. Panhypopituitarism
Hypoplasia
1. Amyotonia congenita
Hypertrophy
1. Myotonia congenita
2. Hypothyroidism
3. Hyperpituitarism
4. Overuse
e major anatomic change in these myopathies alteration in size of muscle fibers. The altered reflects augmentation or diminution of myo- nd sarcoplasm.

opathies Associated with Muscle Cell Necrosis
Primary muscular dystrophies
Specific infections (trichinosis and toxoplasmosis)
Corticosteroid myopathy
Polymyositis and dermatomyositis
Polymyopathy of Meyer-Betz with myoglobinuria
aracteristic of all of these myopathies is necrosis of ells. Usually the whole fiber is not involved, and altered sarcoplasm may be juxtaposed with pre- arcomeres. In the focus of muscle injury, there is y a leukocytic infiltrate principally of neutrophils mphocytes. Sarcolemmal nuclei may appear n and pyknotic or enlarged and increased in In later stages, thin new fibers can be identified eration occurs. If entire fibers are destroyed, foci is may result.

opathies Associated with Distinctive Intracellular erations
Familial periodic paralysis
Hyperaldosteronism
hese conditions, the muscle cells contain small c vacuoles, reflecting the accumulation of water.
McArdle's phosphorylase deficiency
Pompe's disease
ese two disorders represent glycogen storage s in which abnormal accumulations of glycogen within lysosomes.
Central core myopathy—The inner part of the ains condensed myofibrils.
Rod-body myopathy—Rod-shaped packets of ike bodies lie beneath the sarcolemma.
Myotonic dystrophy—The main features are eral zones of sarcoplasm containing various or- and isolated myofilaments, some of which form which encircle the longitudinally oriented myo-

nctional Myopathies
Myasthenia gravis
Thyroid myopathies
Tetanus
Addison's disease with contractions
rphologic examination of muscle may reveal no al alteration in neurons or muscle fibers in these rs. Occasionally, intercellular infiltrates of lympho- lymphorrhages) are found, but these are non- ive and are often absent.

Atrophy consists essentially of progressive **loss of myofilaments, shrinkage of muscle cells by resorption of sarcoplasm followed later by fibrous replacement of collapsed sarcolemmal sheaths.** The individual myocytes show a progressive dimunition in their diameters. The striations are preserved for a long time, but eventually become less distinct. The sarcolemmal or muscle nuclei may appear to increase in number as the fibers lose substance. Eventually, in atrophy, the myocyte shrinks to almost a hollow tube with preservation of only the sarcolemmal nuclei. Up to this stage, there is little increase in the interstitial connective tissue and little evidence of inflammatory reaction. However, the cell may die and be replaced by fibrous tissue and, at this time, a scant lymphocytic interstitial infiltrate appears.

Frequently, in the later stages, golden yellow perinuclear lipochrome pigment becomes apparent within the partially atrophic muscle cells, a change that has already been described as **brown atrophy** (p. 47). The distribution of these atrophic cells is frequently of considerable help in differentiating, for example, disuse, vascular or denervation atrophy from the regressive alterations encountered in the muscular dystrophies. In the pure atrophic process, there is little inflammatory reaction and little evidence of acute necrosis of muscle cells. In general, the atrophic changes tend to affect bundles of cells or whole muscles rather than the random spotty distribution characteristic of the dystrophies to be described.

These alterations, when sufficiently marked, cause shrinkage and flabbiness of the entire muscle mass. Under certain circumstances, as when the atrophy is caused by focal loss of nerve supply, the unaffected adjacent fibers may undergo compensatory hypertrophy and there may be no appreciable loss of muscle mass. The muscle loses its normal red-brown, meaty color and becomes yellow to brown depending upon the amount of deposition of lipochrome pigment. In far advanced cases, the replacement fibrosis imparts a pale gray, fibrous quality to the shrunken muscle.

Causes. The causes of muscular atrophy are legion and vary from the generalized skeletal atrophy encountered in old age to minute foci of atrophy that may affect only a single motor neuromuscular unit when a peripheral nerve fiber is cut. The atrophy of *advanced age* usually produces moderate diminution in the muscle mass without destruction of muscle cells. In this condition, all the muscle fibers tend to be affected equally. *Chronic malnutrition* may produce the same changes. Muscular atrophy which is fairly diffuse throughout the body is also seen in *panhypopituitarism*. *Ischemia* is an important cause of muscle atrophy and may, in fact, underlie the generalized atro-