The presence of perifascicular atrophy is diagnostic of DM, even in the absence of inflammation.

In PM there is no perifascicular atrophy and the blood vessels are normal. The endomysial infiltrates are mostly within the fascicles surrounding individual healthy myofibers, resulting in phagocytosis and necrosis. With chronic disease there is increased connective tissue formation and reaction with alkaline phosphatase stains.

The histologic hallmarks of IBM include basophilic granular inclusions distributed around the edge of slittlike vacuoles, so-called rimmed vacuoles (Fig. 3); angulated or round fibers, scattered or in small groups; eosinophilic cytoplasmic inclusions; primary endomysial inflammation with T cells invading muscle fibers in a pattern identical to, but often more severe than, those seen in PM; and tiny deposits of Congo red or crystal violet-positive amyloid in or adjacent to vacuoles. The amyloid, seen in approximately 80% of our patients, immunoreacts with β-amyloid protein, the type sequenced from the amyloid fibrils of blood vessels of patients with Alzheimer's disease (18–20). Characteristic filamentous inclusions seen by electron microscopy in the cytoplasm or in myonuclei and prominence in the vicinity of the rimmed vacuoles are also a hallmark. Although the demonstration of filaments by electron microscopy was at one time essential to the diagnosis of IBM, it is no longer necessary when all of the characteristic light microscopic features, including the amyloid deposits, are present. Furthermore, the filamentous inclusions are not specific for IBM but can be seen in other vacuolar myopathies. The cytoplasmic tubulofilaments within the vacuolated muscle fibers immunoreact strongly with tau, ubiquitin, chromatin, and prion (18). Finally, abnormal mitochondria are seen as ragged red fibers that are often negative with cytochrome oxidase and contain mitochondrial DNA deletions (21).

IMMUNE-MEDIATED MECHANISMS
Presence of Autoantibodies

Various autoantibodies against nuclear and cytoplasmic antigens are found in up to 20% of patients with inflammatory myopathy (1–3,8,22). Antibodies to cytoplasmic antigens are directed against cytoplasmic ribonucleoproteins that are involved in RNA translation and protein synthesis. They include antibodies against various synthetases, translation factors, and proteins of the signal-recognition particles. The antibody directed against the histidyl-transfer RNA synthetase, called anti-Jo-1, accounts for 75% of all the anti-synthetases, and it is diagnostically useful because up to 80% of patients with anti-Jo-1 antibodies have interstitial lung disease. In general, they may not be specific because they are directed against ubiquitous targets and may represent epiphenomena without pathogenic significance; they occur in PM, DM, and IBM despite their clinical and immunopathologic differences; and they are almost always associated with interstitial lung disease even in patients who do not have active myositis.

Immunopathology of Dermatomyositis

It has been repeatedly shown that the primary antigenic targets in DM are components of the vascular endothelium of the endomysial blood vessels and the capillaries (23,24). The earliest pathologic alterations are changes in the endothelial cells consisting of pale and swollen cytoplasm with microvacuoles and undulating tubules in the smooth endoplasmic reticulum, followed by obliteration, microvesSEL necrosis, and thrombosis (24). The microvascular alterations occur early in the disease and are mediated by C5b-9membranolytic attack complex (MAC), deposited along capillaries before the onset of inflammatory or structural changes in the muscle fibers (25). Using an in vitro assay system that measures C3 consumption by sensitized erythrocytes on the basis of radiolabeled anti-C3 antibodies (26), it is also known that patients with active, but not chronic, DM have a very high uptake of C3 in the serum. MAC and the active fragments of the early complement components C3b and C4b are also increased in the sera of patients using a radioimmunoassay (26).

Sequentially, the disease begins when putative antibodies are directed against endothelial cells of the endomy- sium (27) that activate the C3 component of the complement that forms C3b and C4b fragments and leads to formation and deposition of MAC on endomysial microvessels. The deposition of MAC leads to osmotic lysis of endothelial cells with capillary necrosis, perivascular inflammation, ischemia, and muscle fiber destruction resembling microinfarction. Perifascicular atrophy, seen more often in chronic stages, is a reflection of distal endofascicular hypoperfusion. Finally, there is marked reduction in the number of capillaries per muscle fiber with dilatation of the remaining capillaries in an effort to compensate for the impaired perfusion.

Putative anti-endothelial cell antibodies that fix complement can be detected by an ELISA using human umbilical vein endothelial cells as antigen (28); however, characterization of the pathogenicity of these antibodies has not yet been performed. The presence of systemic features, with involvement of myocardium, pericardium, lungs, and the gut, suggests that the MAC-mediated microvascular injury may be more widespread and that the target antigen may be a ubiquitous component of the blood vessel endothelium. The activation of complement by putative anti-endothelial cell antibodies is believed to be responsible for the induction of cytokines (29) that in turn upregulate the expression of vascular and intercellular adhesion molecules (ICAM) type 1 on endothelial cells (30) and facilitate the exit of activated lymphoid cells to the perimysial and endomysial spaces.
Immunophenotypic analysis of the lymphocytic infiltrates in the muscle biopsies of patients with DM demonstrates a predominance of B cells and CD4+ cells in perimysial and perivascular regions, supporting a humoral-immune mediated process, as described above (4,31,32). In the perifascicular areas, however, the infiltrates contain mainly CD8+ cells and macrophages and invade major histocompatibility complex class I (MHC-I)–antigen-expressing muscle fibers, a sign of coexisting T-cell–mediated and MHC-I–restricted cytotoxic processes.

Immunopathology of Polymyositis and Inclusion Body Myositis

Cytotoxic T Cells

In PM and IBM, there is evidence of primarily antigen-directed cytotoxicity mediated by cytotoxic T cells (4,31,32). This is supported by the presence of CD8+ cells, which along with macrophages, initially surround healthy MHC-I class expressing nonnecrotic muscle fibers that eventually invade and destroy. The T cells are activated, as evidenced by their expression of ICAM-1 and MHC-I and -II antigens on their surface, and exert a cytotoxic effect against muscle fibers as supported by the following:

1. Cell lines established from muscle biopsies of PM patients exerted cytotoxicity to autologous myotubes in vitro (33).
2. With immunoelectron microscopy, CD8+ cells and macrophages send spikelike processes into nonnecrotic muscle fibers, which traverse the basal lamina and focally displace or compress the muscle fibers (31).
3. Cytotoxic autoinvasive CD8+ T cells contain perforin and granzyme granules (34) directed against the surface of myofibers and, upon release, they induce cell destruction.
4. On the basis of T-cell receptor analysis, there is clonal expansion of T cells with a restricted usage of the T-cell receptor variable region of certain T-cell receptor gene families, notably Va1, Vb15, and Vb6. This suggests that the T cell response is driven by a muscle-specific antigen (35,36).
5. The cytotoxicity mediated by the CD8+ cells appears to be antigen-specific because, in addition to clonal expansion of certain T-cell receptor gene families described above, the T cells invade muscle fibers expressing MHC-I class antigen, a prerequisite for antigen recognition by the CD8+ cells. MHC-I class antigen is not present on normal muscle fibers but is ubiquitous to the sarcolemma of the muscle fibers in patients with PM and IBM (37). MHC-I expression is probably upregulated by cytokines secreted by activated T cells, macrophages, and viruses in a setting of a viral infection. The nature of these antigenic peptides bound by the MHC-I for presentation to the CD8+ cells still remains unknown. It is believed that such antigens are probably endogenous sarcolemmal or cytoplasmic self proteins synthesized within the myofibers. The possibility of endogenous viral peptides appears unlikely because several laboratories have failed to amplify viruses within the muscle fibers not only in PM patients with a putative viral infection (38,39), but also in patients with classic PM associated with human immunodeficiency virus (HIV) type 1 or human T-cell lymphotropic virus type 1 (HTLV-I) infection (40,41).
6. In three rare cases, gamma/delta T cells or natural killer cells were the main participating cells in the myocytotoxicity of PM and IBM (42,43).

Cytokines and Adhesion Molecules

The T-cell–derived cytokines and interleukins (IL): IL-2, IL-4, IL-5; interferon-β; the macrophage-derived cytokines IL-1, IL-6, and tumor necrosis factor-α; and cytokines that are either T-cell– or macrophage-derived such as granulocyte-macrophage colony-stimulating factor and transforming growth factor-β can be amplified with the reverse transcriptase polymerase chain reaction (PCR) method in the muscles of patients with PM, DM, and IBM (44–46). The adhesion molecules and their receptors, ICAM-1, vascular cellular adhesion molecule type 1, and their respective ligands, integrins 1 and 2, are also upregulated on the endothelial cells or the infiltrating T cells in patients with PM, DM, and IBM and may facilitate the adhesion, penetration, and exit of activated T cells through the endothelial cell wall (32,44–46).

Association with Viral Infections

Coxsackie, influenza, paramyxoviruses, cytomegalovirus, Epstein Barr virus, and other viruses have been indirectly associated with chronic and acute myositis (47,48). The phenomenon of molecular mimicry has been proposed with the coxsakievirus because of structural homology between the Jo-1 and the genomic RNA of an animal picornavirus, the encephalomyocarditis virus. Sensitive PCR studies, however, have repeatedly failed to confirm the presence of such viruses in the muscle biopsies of patients we studied, suggesting that it is unlikely, although not impossible, for them to be replicated in the muscles of patients with PM, DM, and IBM (38,39).

The best evidence of a viral connection in PM and IBM is with retroviruses that were associated with PM in monkeys infected with the simian immunodeficiency virus (49,50) and in humans infected with HIV and HTLV-I (51,52). In HIV-positive patients, an inflammatory myopathy, HIV-PM, occurs as the first clinical indication of HIV infection or concurrent with other mani-
festations of AIDS (51,53,54). HIV seroconversion may coincide with myoglobinuria and acute myalgia, suggesting that myotropism for HIV may be symptomatic early in the infection. In addition, HTLV-I does not only cause a myeloneuropathy, referred to as tropical spastic paraparesis, but also PM, which may coexist with tropical spastic paraparesis or may be the only clinical manifestation of HTLV-I infection (52–54). IBM also occurs with HIV or HTLV-I infection (55). Using either in situ hybridization, PCR, immunocytochemistry, or electron microscopy, we did not detect viral antigens within the myofibers of these patients’ muscle but only in occasional endomysial macrophages. (40,41,54,55). We interpreted these observations to suggest that in HIV-1 and HTLV-I PM and IBM, there is no evidence of persistent infection of the muscle fiber by the virus or viral replication within the muscle. The predominant endomysial cell in HIV-1 and HTLV-I PM and IBM are CD8+ non–viral-specific, cytotoxic T cells that along with macrophages invade or surround MHC-I–antigen-expressing necrotic muscle fibers. We proposed that a T-cell–mediated and MHC-I–restricted cytotoxic process was a common pathogenetic mechanism in both retroviral negative and retroviral-positive PM and IBM, but in the latter, viral-induced cytokines might have triggered the process by breaking tolerance.

Role of Nonimmune Factors in Sporadic Inclusion Body Myositis

In IBM, the presence of amyloid-positive deposits within some of the vacuolated muscle fibers and the finding of abnormal mitochondria have generated reasonable concerns that, in addition to the autoimmune components mentioned earlier, there is also a degenerative process. The amyloid deposits in IBM are accompanied by all of the other proteins seen in the β-amyloid of Alzheimer disease, including β-amyloid precursor protein, chymotrypsin, apolipoprotein E, and phosphorylated tau. Whether these deposits are secondarily related to the chronicity of the disease or are generated de novo and contribute to disease pathogenesis is unclear. The same can be said for mitochondrial abnormalities and mitochondrial DNA deletions that were observed in up to 70% of IBM muscles. Although such mitochondrial changes are more frequently seen in IBM than in normal aging, it is unclear if they are primary or secondary or if they are enhanced by the upregulated cytokines.

TREATMENT

Because the specific target antigens in DM, PM, and IBM are unknown, currently proposed forms of immunosuppressive therapy such as prednisone do not selectively target autoreactive T cells or the complement-mediated process on the intramuscular blood vessels. Instead, they induce nonselective immunosuppression or immunomodulation. Further, many of these therapies are empirical and mostly uncontrolled.

The goal of therapy in inflammatory myopathy is to improve muscle strength and thereby improve overall function in activities of daily living. When strength improves, the serum CK also tends to fall, but the reverse is not always true because most immunosuppressive therapies can result in decrease of serum muscle enzymes without necessarily improving muscle strength. Unfortunately, this has been misinterpreted as chemical improvement and has formed the basis for the common habit of chasing or treating the CK level instead of the muscle weakness, a practice that has led to a prolonged use of unnecessary immunosuppressive drugs and erroneous assessment of their efficacy. It is prudent to discontinue these nonspecific immunosuppressive drugs if after an adequate trial there has been only a reduction in the serum CK and not an objective improvement in muscle strength (1–3,56–59). Agents used in the treatment of PM and DM follow.

Corticosteroids, including prednisone, are the first-line agents. Its actions are unclear, but it may exert a beneficial effect by inhibiting recruitment and migration of lymphocytes to the areas of muscle inflammation and interfering with the production of lymphokines. Its effect on lymphokine IL-1 may be important because IL-1 is myotoxic (60) and is secreted by the activated macrophages that invade the muscle fibers. Steroid-induced suppression of ICAM-1 may also be relevant because downregulation of ICAM-1 can prevent the trafficking of lymphocytes across the endothelial cell wall toward the muscle fibers.

Because the effectiveness and relative safety of prednisone therapy will determine the future need for stronger immunosuppressive drugs, our preference has been to start with high dosages, such as 80 to 100 mg/day. After an initial period of 3 to 4 weeks, it is tapered over a 10-week period by reducing the alternate off-day dose by 10 mg/wk, or faster if necessary because of side effects, though the latter carries a greater risk of breakthrough of disease. If improvement occurs and there are no serious side effects, the dose can be gradually reduced by 5 to 10 mg every 3 to 4 weeks until the lowest possible dose that controls the disease is reached. If by the time the dose has been tapered to 80 to 100 mg alternating with 0 mg, approximately 14 weeks after initiating therapy (and there is no increase in muscle strength), the patient may then be considered unresponsive to prednisone, and tapering is accelerated while the next in line immunosuppressive drug is started (56–59).

Although almost all patients with bona fide PM or DM respond to steroids to some extent and for some period of time, a number of them fail to respond or become steroid resistant. The decision to start a nonsteroidal immunosuppressive drug in PM or DM is based on the need for