Inflammatory and toxic myopathies

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The major advances in the immunopathogenesis and treatment of inflammatory myopathies, and the main criteria that distinguish polymyositis (PM) from dermatomyositis (DM) or inclusion-body myositis (IBM) are presented. The origin and implications of the amyloid and ubiquitin deposits found within the vacuolated fibers of patients with IBM are considered. The pathogenesis of human immunodeficiency virus (HIV) and human T-cell lymphotrophic virus (HTLV)-1-associated PM is presented, and the role of retroviruses in triggering PM, even in the absence of detectable viral genome within the muscle fibers, is discussed. In addition, three toxic myopathies with distinct morphologic, biochemical, or molecular characteristics, caused by zidovudine [azidothymidine (AZT) myopathyl, the cholesterol-lowering-agent myopathy (CLAM), and the combination of blocking agents with corticosteroids are presented.

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Introduction

Clinical, histopathologic, immunologic, and therapeutic criteria emerging over the past 5 years have distinguished three major groups of inflammatory myopathies: polymyositis (PM), dermatomyositis (DM), and inclusion-body myositis (IBM). Diverse or opposing views among diagnosticians of different disciplines, as well as common errors in the definition, diagnosis, histology, immunopathology, and management of patients with these diseases prompted a recent review by Dalakas [1••]. This review introduced new clinical and diagnostic criteria to supercede the criteria proposed 17 years ago [2]. In the old criteria, the main diagnostic features - proximal muscle weakness, myopathic findings on the electromyogram, elevated creatine kinase levels, and muscle biopsy findings - had equal diagnostic weight, and the diagnosis of 'PM' was acceptable even without a diagnostic muscle biopsy. Consequently, IBM was overlooked, and non-inflammatory myopathies were often erroneously diagnosed as PM. The review discussed the clinical findings of OM, PM, and IBM as well as overlapping syndromes, immunopathogenetic mechanisms, the role of viruses, and therapy. Here, I shall therefore present only the background information necessary for discussion of new information represented in 1991-1992. I shall discuss three recently identified toxic myopathies that are sometimes considered inflammatory myopathies; these disorders are related to the use of azidothymidine (AZD; zidovudine), cholesterol-lowering agents, or the combined use of neuromuscular blocking agents and corticosteroids.

Inflammatory myopathies

Dermatomyositis

OM is clinically distinct because of the characteristic rash; it is also immunpathologically unique because there is a complement-mediated intramuscular microangiography. Early in the disease, the CSb-9 membranolytic attack complex (MAC) is activated by antibodies bound to microvascular components [1 •• ,3,4]. The MAC deposits may allow osmotic leakage from the endothelial cell, resulting in lysis and destruction of intramuscular capillaries. The loss of capillaries then leads to ischemia, muscle fiber destruction with patterns resembling microinfarcts, inflammation, and finally perifasicular atrophy. These changes are seen not only in the classic fonn of DM, but also in the so-called 'amyopathic OM' (DM sine myositis). Euwer and Southeimer [5•] described six

Abbreviations

AIDS--acquired immune deficiency syndrome; AZT--azidothymidine (zidovudine); CLAM---cholesterol-lowering-agent myopathy; DM-dermatomyositis; HIV-human immunodeficiency virus; HMG-CoA-3-hydroxy-3-methylglutaryl coenzyme A; HTLV-human T-cell lymphotrophic virus; IBM-inclusion-body myositis; MAC-membranolytic attack complex; MHC-major histocompatibility complex; MRI-magnetic resonance imaging; mRNA-messenger RNA; mtDNA-mitochondrial DNA; PM-polymyositis.

patients with amyopathic OM who had normal strength up to 2 years from the time skin lesions appeared, and suggested that amyopathic OM is a subset of OM affecting onlv the skin. Otero *et cd* l6], however. challenged this vie after studying muscle biopsies of seven OM patients with normal muscle strength. The biopsies revealed subclinical myositis with histologic and immunopathologic characteristics identical to those of typical OM. They concluded that OM is a single disease with identical immunopathology affecting both skin and muscle, but to a varying degree among patients.

Anti endothelial cell antibodies were found in the sernm of eight out of 18 patients with OM. including six with interstitial lung disease [7•]. It is not known whether these antibodies resulted from the iVIAC-mediated capilla1y destruction, or were primary, inititiating the immune-mediated microangiopathy.

Polymyositis

Polymyositis is still a diagnosis of exclusion; no unique clinical criteria have been identified [I•• j. Observations in the past few years. however, suggest that most patients with an initial diagnosis of PM who have not responded to any form of immunotherapy most likely have **IBM** or ·something else·. In **PM,** the primary effector T cells surrounding or invading healthy muscle fibers are cytotoxic CDS+ T cells that recognize heretofore unidentified muscle antigens in the context of major histocompatibility complex (MHC) class I expression 1l •• ,8,9]. These lymphocytes seem to be cytotoxic and recognize muscle auto-antigens. as supported by the cytotoxic effect noted in cocultures of autologous myotubes with T-cell lines derived from the endomysial inflammatory cells [1O••]. Although most of the cos+ T cells use the ***ex/*** **T** cell receptor for antigen recognition, CD4 - and CDS - y */8* cytotoxic **T** cells can also mediate muscle fiber injury [11].

Emslie-Smith and Engel [12••] described a new necrotiz ing myopathy in three patients. The histologic hallmark was a microangiopathy characterized by 'pipestem' with no other histologic or clinical signs suggestive of DM. None of the three patients responded to immunotherapies. This unique immune-mediated microangiopathy differs from PM, DM, or IBM, and emphasizes the need to search for immune markers in the muscle biopsies of patients with unusual histologic features.

The incidence of cancer is apparently increased in patients with DM, but not PM or IBM [13] (for a review see Dalakas [1 ••]). This view was recently challenged by Sigurgeirsson *et al.* [14•] in a retrospective study of patients with PM or DM identified from a national registry of Swedish patients who had been admitted to hospitals between 1963 and 1983. Compared with cancer patients from the Swedish cancer registry, there was an increased association with cancer for both PM and DM. These disquieting results can be attributed to several methodological problems: undocumented diagnosis, incomplete chart review (only 1 patient's chart was reviewed out of 10 patients included in the study), inclusion for analysis at least 30% of patients with a diagnosis that did not satisfy even the reviewers' criteria for PM, grouping of children and adults, and use of population statistics rather than matched controls or patients with other neuromuscular diseases.

Inclusion-body myositis

Distinct clinical signs and ymptoms may point to the suspicion of IBM in a patient with presumed PM who has not responded to immunotherapies. The signs include: weakness of distal limb muscles, including the hand and feet, and, commonly, weakness of the deep finger flexors; asvmmetric weakness, with marked wasting of selected m 1scle groups; and earlv onset of dysphagia. The diagnosis of IBM relies on muscle biopsy findings of rimmed vacuoles, eosinophilic cytoplasmic inclusions with 15 to 18 nm filaments, small angulated fibers. and endomysial inflammation characterized by CDS+ cytotoxic T cells surrounding MHCI antigen-expressing muscle fibers. Although these changes imply a T-cell-mediated cytotoxic process identical to that seen in PM [1••,8,9], patients with IBM are notoriously resistant to all therapies. Rare cases can be familial. with autosomal dominant inheritance in some families [15•].

Some histologic features of IBM, specifically the rimmed vacuoles and microfilamentous inclusions. are also found in Welander's distal myopathy, a dominantly inherited muscle disease of late onset / 16]. Lindberg *et al* [17•], therefore, compared patients with Welander's distal myopathv and patients with non-familial IBM matched for age. They concluded that the Welander syndrome is less disabling and differs from IBM by the absence of endomysial inflammation and the sparing of proximal muscles.

Of much interest are the amyloid filamentous deposits within muscle fibers of IBM patients. With Congo-red staining ,\,lendell *et al.* [18••] found, green bi-refringed amyloid deposits adjacent to the vacuoles, in locations that corresponded to the IBM filaments. Askanas *et al.* [19••] found that the amyloid-positive material within the vacuoles reacted with antibodies to the -amyloid protein, the protein sequenced from the amyloid deposited in the blood vessels of patients with Alzheimer's disease. The vacuolated muscle fibers also reacted with antibodies to ubiquitin, which.was immunolocalized to the cytoplasmic tubulofilaments [20•]. Beta-amyloid-positive fibrils also co-localized with ubiquitin.

These observations may stimulate a change in attention from immunopathic to degenerative etiologies of IBM, but they also raise several questions. Ubiquitin, a 76 amino acid protein is present in the cytoplasm of all eukaryotic cells; it also has a proteolytic function that leads to non lysosomal degradation of abnormal or short-lived cellular proteins [2 I]. Ubiquitinated neurofilaments associated with abnormal degradation of cytoskeletal proteins have been found in areas of tissue damage in other chronic neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. If normal cellular components are inappropriately ubiquitinated, resulting in

aggregates of non-functional proteins, inclusion bodies can be generated [22]. Ubiquinated fibers, found not only in the vacuoles of IBM but also in the autophagic vacuoles of oculopharyngeal muscular dystrophy, distal myopathy, and hereditary vacuolar myopathy [20•], may represent non-specific degradation products associated with autophagia. Because both amyloid deposits and ubiquinated material have been associated with autophagic vacuoles, they might have a common origin and, as suggested by Mendell *et al* [18••], may result from modification of normal proteins within an acidic degradative vacuole. A_<; for the origin of amyloid, analogy should also be drawn to dystrophic an1yloidosis, an amyloid formation seen with local complications of chronic tissue damage, as in chronic cardiac valvular disease [23].

Viruses and inflammatory myopathies

Several viruses, especially enteroviruses, have been linked to the pathogenesis of inflammatory myopathies, because many members of the picornaviridae family can cause myopathy in laboratory animals. The association of these viruses with the human disease, however, is circumstantial, unconvincing, and unconfirmed [1••]. A possible seasonal pattern in the onset of inflammatory myopathies has been interpreted as an indirect sign of environmental (viral) cause [24]. Using a sensitive and specific method based on the polymerase chain reaction, Leff *et al.* [25••] searched for nucleic acid sequences from Coxsackie virus, mumps virus, encephalomyocarditis virus, adenoviruses, human T-cell lymphotrophic virus (HTLV) types I and II, and human immunodeficiency virus (HIV) in the RNA extracted from muscle biopsy specimens of 44 patients with PM, DM, or IBM. No viral sequences were detected in any of the muscles. It is therefore unlikely that these or closely related viruses persisted in the muscles, or provided a continuing stimulus for disease progression in these patients.

Retroviruses and inflammatory myopathies

Five different retroviruses have been linked to inflammatory myopathies: HIV, HTLV-1, simian retrovirus type I, simian immunodeficiency virus, and the human foamy retrovirus [1••,26,27].

The immunopathogenesis of HIV-associated PM was studied by Illa *et al.* [28..], Lamperth *et al* [29], and Leon-Monzon and Dalakas [30•] in biopsies of 21 patients by means of immunocytochemistry, *in situ* hybridization, and the polymerase chain reaction using specific HIV antibodies, probes, and primers. Viral antigens were found in occasional interstitial mononuclear cells next to the muscle fibers, but not within the muscle fibers themselves. Similar findings were noted by Hantai *et al* [31•] in the muscle biopsies from seven patients. In a quantitative analysis of lymphocyte subsets Illa *et al* [28••] found that the predominant endomysial cells were **COS+** cells and macrophages that invaded or surrounded healthy and MHC-I antigen-expressing muscle fibers. HIV-associated PM therefore is not related to direct infection of the muscle fibers by the virus, but rather is the result of a T cell-mediated and MHC-1-restricted cytotoxic process triggered by the virus [28••].

A similar mechanism was suggested for the PM of HTLV-1 infection in a study of six patients by Dalakas *et al* [32•]. They found HTLV-1 expression in only occasional endomysial lymphoid cells and not within the muscle fibers. Like HIV-PM, the muscle fiber injury in HTLV-1-PM was initiated by CD_8+ cytotoxic T cells in the context of MHC-I expression by muscle fibers. Because the immunopathologic characteristics of PM in retrovirus-positive patients are identical to those of the PM in retrovirus-negative patients, we suggested that retroviruses may be leading candidates in the viral cause of inflammatory myopathies. In a persistent viral infection, activated cytotoxic T cells can lead to myositis by exposing, via lymphokines or cytokines released by the endomysial lymphoid cells infected with HIV or HTLV-I, normally hidden or newly surfacing antigens against which there is no self-tolerance. The endomysial inflammation may then become self-sustaining if it cannot be down-regulated by the host. Molecular antigenic mimicry may also be a mechanism of self-sensitization because some anti-ribonucleoproteins react with polypeptides encoded by the *gag* gene of retroviruses [33].

Human myoblasts and myotubes resist infection and transfection with intact HIV or HIV proviral DNA construct, not only with the virus alone but also with HIV-infected lymphocytes [34•]. Like mature muscle, myotubes lack the CD4 receptor, which explains the resistance of muscle to direct infection by the virus.

The human foamy retrovirus, although not pathogenic in humans, was associated with a destructive myopathy in transgenic mice carrying the *be!* region of the retrovirus [35••]. The transgene was expressed in the striated muscle, and viral RNA was present in the viable muscle fibers.

In addition to an immune-related inflammatory myopathy, some HIV-positive patients have had myoglobinuria, myasthenia gravis, or pyomyositis. Previously rare in Europe or North America. Pyomyositis is now occurring with increasing frequency in patients with the acquired immune deficiency syndrome (AIDS) [1••]. Two recent studies [36•,37•] described 11 new patients with pyomyositis, caused by gram-negative bacteria in one, and by *Staphylococcus aureus* in the others. Pyomyositis begins with low-grade fever, even without leukocytosis, and localized muscle pain, and swelling. Ultrasonography, magnetic resonance imaging (MRI), or computerized tomography reveals an enhancing lesion, often with a fluid density. The common colonization of HIV-positive patients with S. *aureus,* and the reduced chemotaxis and bactericidal activity of their neutrophils against S. *aureus,* may be responsible for the bacterial infection of the muscle [36•].

Numerous iron granules (muscle siderosis) were found in the muscle fibers, endothelial cells, and macrophages in 21 of 41 AIDS patients with myopathy [38•]. Muscle siderosis may be caused by dysfunction of macrophages, which in the late stage of HIV infection may be incapable

of removing the iron granules produced hy the degradation of myoglobin [38•].

Muscle imaging and inflammatory myopathies

In the past *2* years or so, the ust:> of MRI, especially with a fat-suppressing imaging technique, has been advocated for the diagnosis and follow-up of patients with inflammatory myopathies [39•-42•]. This expensive procedure, however, is unnecessary to determine if a patient with PM or OM has improved, and its accuracy and validity in differentiating PM or OM from a non-inflammato1y myopathy are questionable. The only clinically useful indication for muscle MRI is in the evaluation of HIV-associated focal PM, which led to the diagnosis in six out of 13 patients with AIDS [3•]. The characteristic radiologic sign was that of muscle abscess with a rim of increased signal intensitv corresponding to margins between clrainable pus and edematous tissue. The subcutaneous tissues appeared nom1al. Sparing the subcutaneous tissues was considered a useful radiologic sign to distinguish pyomyositis from diffuse soft-tissue swellings related to other conditions, such as lymphodema, venous thrombosis, cellulitis, or lymphoma, where both the muscle and the subcutaneous tissues are involved.

Treatment

Treatment of the inflammatory myopathies with corticosteroids, and the use of non-steroidal immunosuppresive drugs for their 'steroid-sparing' effect were discussed in the recent review by Dalakas [1••], who stressed the need for controlled therapeutic studies separately for PM, DM, and IBM. The first double-blind controlled therapeutic trial in PM and OM patients using plasma exchange and leukopheresis was conducted by Miller *et al* [44••] in 39 patients randomized to receive 12 treatments, over a I-month period, of plasmapheresis, leukopheresis, or sham pheresis. Plasmapheresis and leukopheresis were ineffective, and the results were conclusive for patients with chronic and severe disease. This study was important because it should terminate the uncontrolled use of this expensive and risky procedure.

Cyclosporin was effective in an uncontrolled study of three patients with PM refractory to conventional therapy and one patient with DM [45•], but the conclusion that it may be considered as a first-line agent in the management of PM and OM is premature without a controlled study.

High-close intravenous immunoglobulin, 2 g/kg/month, was effective in two uncontrolled trials in patients with PM or DM. In one trial, [46•] five patients with juvenile OM improved during a 9-month course of intravenous immunoglobulin, allowing steroids to be reduced or discontinued. In the other trial, 14 patients with chronic PM and six patients with DM had been unresponsive to previous therapies [47•]. Intravenous immunoglobulin, given in conjunction with prednisone, methotrexate, or plasmapheresis for a mean of 4 months, resulted in marked clinical improvements in 15 out of the 20 patients. Although its mode of action is unclear, intravenous immunoglobulin appears to he a promising new agent for both PM and DM. It is safe, and well tolerated, but expensive, and a controlled study is required to document efficacy. Separate studies for PM, OM, and IBM are now underway at the National Institutes of Health.

Cricopharyngeal myotomy improved the dysphagia in two patients with IBM [48•,49•]. When weakness of pharyngeal muscles is severe the generated hypopharyngeal pressure may be insufficient to trigger reflex relaxation of the cricopharyngeal muscle. By eliminating the zone of elevated pressure between the pharynx and the esophagus, myotomy can produce more efficient swallowing, and should therefore be considered in selected patients with IBM.

Toxic myopathies

Azidothymidine myopathy

The challenge of distinguishing the HIV-associated primary myopathy from that resulting from the use of AZT, now called zidovudine, has been resolved by identifying the unique histologic and biochemical features present only in AZT-treated patients (50]. The unique histologic features found in AZT myopathy are 'ragged red fibers' that imply structural mitochondrial abnormalities, subsarcolemmal or central accumulations of red granular material and longitudinal or circumferential 'red-rimmed cracks' that are seen with the trichrome stain, as well as pale granular degeneration, rods, endomysial inflammation, and increased neutral fat that are attributed to impaired mitochondrial control of fatty acid use. These morphologic features characterize what we now call the 'AZT fiber'.

Electron microscopic study of muscle biopsies from patients with HIV myopathy, who had never received AZT, and from patients with AZT myopathy confirmed the presence of ultrastructurally abnormal mitochondria only in the AZT groups (51••].

The clinical features of AZT myopathy are those of a genetic myopathy, characterized by proximal limb weakness, myalgia predominantly in the thighs and calves, fatigue, myopathic changes on the electromyogram, and hyperCKemia, which often worsens with exercise. In a follow-up of 20 patients with AZT-myopathy (52•], myalgia resolved, strength improved or became normal, and spontaneous activity on the EMG decreased or clisappeared 4 to 6 weeks after AZT was discontinued. Jay *et al.* [53] found that weight loss and elevation of semm lactate levels may herald the onset of AZT myopathy. AZT can cause myopathy not only at the originally recommended high doses, but also with the lower doses currently recommended by the USA Food and Dmg Administration (53].

With detailed histochemical and electromicroscopic studies, Mhiri *et al* [54••] also concluded that mitochondrial myopathy is caused by AZT and not HIV. They found reduced activity of mitochondrial enzymes in muscles,

incl ding succinate-cytochrome c reductase (respiratoty cham complex II and III) and cytochrome c oxidase (res piratoty chain complex IV). In contrast, there was normal activity of the citrate synthase, an enzvme encoded by nuclear DNA.

In a definitive study, Arnaudo *et al.* [55••] demonstrated, by means of Southern blotting, that AZT reduces the muscle content of mitochondrial DNA (mtDNA), a condition called depletion. Nine AZT-treated patients with myopathy had as much as 78% reduction of muscle mtDNA compared v.ith normal nuclear DNA. A repeat muscle biopsy in one patient showed that the depletion was reversible with discontinuation of the drug. AZT, a DNA chain terminator, causes mitochondrial myopathy by inhibiting the y-DNA polymerase of the mitochondrial matrix, resulting in termination of the mtDNA chain.

In a subsequent study [51••], the depletion of mtDNA was confirmed by immunocytochemistty using antibodies to single- and double-stranded DNA, in serial sections stained first with trichrome and then with anti-DNA antibodies. The immunostainable mtDNA was dramatically reduced in the muscles of AZT-treated patients. By contrast, within the ragged red fibers of patients with mitochondrial encephalomyopathies, where there is proliferation of mitochondria that show mutations or deletions in mtDNA, the staining was increased, reflecting normal mtDNA content. In AZT-myopathy, the mitochondria also proliferate, but have fewer mtDNA copies per organelle, resulting in a shortage of energy within the cell and severe destruction of the muscle fiber.

The structurally abnormal mitochondria in the muscles of AZT-treated patients are impaired in oxidative metabolism, as shown by depression and delayed recovety of phosphocreatine on *in uiuo* 3lp magnetic resonance spectroscopy [56••]. Soueidan *et al.* [57] found vety early depletion of phosphocreatine, even in patients who had normal strength and normal muscle histology on light microscopy; abnormal mitochondria were seen only with electron microscopy.

AZT causes mitochondrial myopathy not only in HIV infection but also in normal rats and human muscle cultures. Lamperth *et al* [58•] found that normal human myotubes, 19 days after AZT treatment, exhibited abnormal mitochondria characterized by proliferation, enlargement, abnormal cristae, and electron-dense deposits in the matrix. Similarly, Herzberg *et al* [59•] showed marked inhibition of myotube proliferation with reduction of the mitochondrial-encoded cytochrome c oxidase. When healthy rats were treated intraperitoneally with AZT, the animals lost weight and developed hyperCKemia, lacticacidemia, hyperglycemia, and abnormal mitochondria in skeletal and cardiac muscles, but not in liver [58••]. Muscles had the highest concentration of AZT. On the basis of oxygen consumption and respiratoty activity, muscle mitochondria isolated from the AZT-treated rats had a decrease in state three of the respiration and were uncoupled. Lewis *et al* [60••,61••] found structural abnormalities in the heart and skeletal muscle mitochondria in rats fed AZT. There was depletion of muscle mtDNA, depression of cytochrome b messenger RNA (mRNA) (but not of sarcomeric or cytosolic mRNA or of mRNA-encoded nuclear polypeptides), and decreased synthesis of mitochondrial polypeptides.

AZT is a unique muscle mitochondrial toxin, causing depletion of muscle mtDNA, which results in myopathy. Some severe myopathies in childhood are characterized by depletion of mtDNA [62]; AZT may therefore serve as a model toxin for the study of molecular events in some mitochondrial encephalomyopathies.

Cholesterol-lowering-agent myopathy

Several cholesterol- or lipid-lowering drugs have been implicated in causing an often reversible myopathy characterized by proximal limb weakness, myalgia, elevation of creatine kinase levels, and myopathic changes on the electromyogram consisting of fibrillation potentials and myotonic or complex repetitive discharges [63-66]. Muscle biopsy usually shows non-specific changes or type II muscle fiber atrophy. Rarely, there are necrotic fibers without inflammation (66]. The implicated cholesterol-lowering agents include: fibric acid derivatives, such as fenofibrate, clofibrate, gemfibrozil (Lopid), and bezafibrate; nicotinic acid (niacin); dizacholesterol; and the 3-hydroxy-3-methylglutatyl coenzyme A (HMG-CoA) reductase inhibitors, such as lovastatin (Mevacor), simvastatin (Zocor), and pravastatin (Pravachol).

Cholesterol-lowering-agent myopathy (CLAM) was recently reviewed by London *et al* [67••], who presented an additional case and proposed that the early development of myotonic discharges and myopathic symptomatology may be caused by an increase in muscle 'membrane fluidity', the freedom of motion within the phospholipid membrane bi-layer (68]. Because cholesterol is the major sterol constituent of muscle membranes, reduction of the normal cholesterol pool available for membrane synthesis can increase membrane fluidity. This may result in unstable sarcolemma, myotonic discharges, and increased levels of sarcoplasmic enzymes or myoglobinuria [67••].

Although a transient increase in serum creatine kinase levels is common after treatment with lovastatin, the drug has been associated with clinically overt myopathic symptoms in fewer than 1% of the patients treated. Combined drug use increases the risk of myopathy. When cyclosporin is co-administered with lovastatin to patients with a heart or kidney transplant and hyperlipidemia, the incidence of myopathy with hyperCKemia or myoglobinuria may increase by as much as 30%. These figures may, however, be viewed cautiously, because when cyclosporin is administered alone, there have been cases of histologically proven and reversible myopathy [69,70•].

Four different HMG-CoA-reductase inhibitors (lovastatin, simvastatin, pravastatin, and L647318), produced in Sprague-Dawley rats a dose-related myocytotoxicity documented histologically [71• j. The myopathy was potentiated by clyclosporin. Doses of the HMG-CoA reductase inhibitors that did not produce muscle toxicity when given alone increased the incidence of myopathy by 75 and 100% when co-administered with c.yclosporin [71•].

Blocking agent-corticosteroid myopathy

Patients 'with prolonged paralvsis induced ,vith non de· polarizing blocking agents, such as pancuroniurn, may manifest an acute myopathv. ;\lost of these patients have received high closes of corticosteroids to treat status asthmaticus [72] or some other systemic illness for which artificial paralysis was induced to secure an aggressive pulmonary toilette, as revie,ved by Danon and Carpenter [73••]. The combination of blocking agents and corticosteroids has been consistentlv implicated in the development of this myopathv, which can be called blocking agent-conicosteroicl myopatlw. The clinical presentation is rather typical and characterized by severe generalized quadric paresis. muscle wasting, normal or moderately elevatecl creatine kinase levels, and rnyopathic changes on the electromyogram. The weakness usually improves, but slowly. We have seen three cases of blocking agent-corticosteroid rnyopathy at the National Institutes of Health in the past 3 years, and at least 20 cases have been reported [73•• J. Muscle biopsy shows severe morphologic abnormalities characterized by central empty areas, like autolvsis, but without signs of necrosis, inflammation, or phagocytosis (Fig. 1). With adenosine triphosphate (ATP Jase staining, striking areas of central pallor are seen in many fibers (Fig. 2 *).*

The histologic hallmark of blocking agent-corticosteroid myopathy is selective and extensive loss of thick myofilaments with preservation of the thin myofiJaments and Z

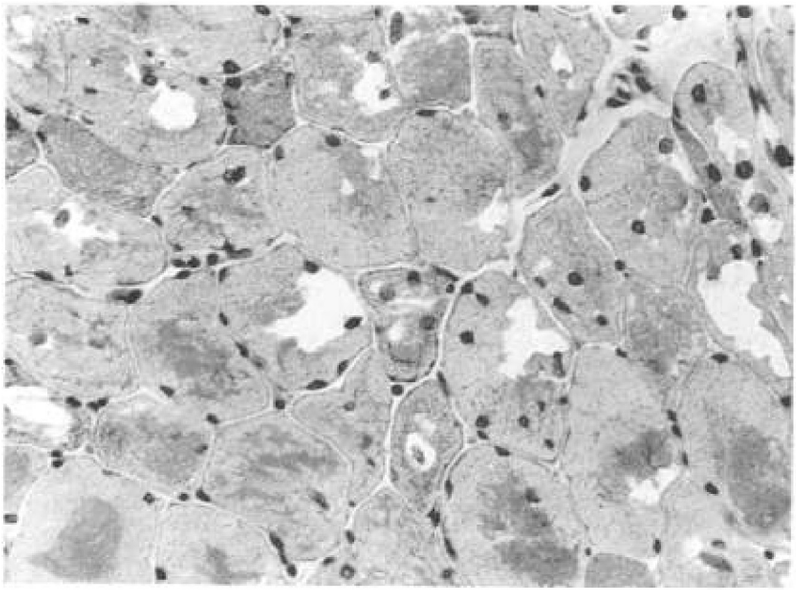

Fig. 1. Transverse section of a muscle biopsy from one of our patients with blocking agent-corticosteroid myopathy. Trichrome staining shows large, irregular, unstained empty areas without an associated cellular reaction corresponding to focal loss of myofibrils. Some fibers have dark smudgy areas, probably representing accumulations of disorganized myofilaments or Z-disc streaming lx 680).

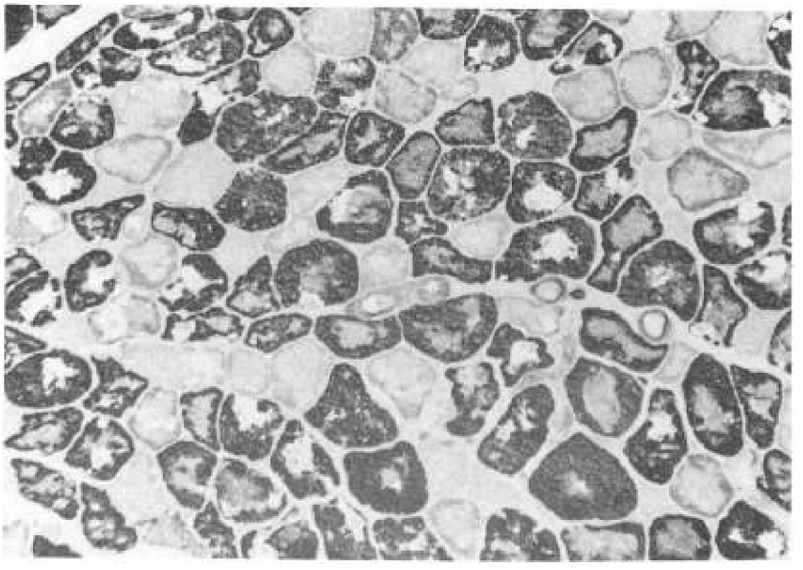

Fig. 2. Muscle biopsy from one of our patients with blocking agent-corticosteroid myopathy. Adenosine triphosphate IATP)ase staining (pH 9.4) shows central or irregular and patchy areas of extensive loss of filaments in both fiber types I x 425).

discs [73••]. These changes resemble those observed in denervated rats treated with high doses of steroids [74]. High doses of steroids should, therefore be used with caution in patients receiving paralytic agents for prolonged periods.

Acute external ophthalmoplegia has also been seen in blocking agent-corticosteroid myopathy [75•]. In these cases, a differential diagnosis should include myasthenia gravis, Guillain-Barre syndrome (Miller-Fisher variant), Wernicke's encephalopathy, and phenytoin intoxication.

Conclusion

Advances in immunocytochemistry, immunology, and molecular virology have increased our understanding of the immunopathogenesis of inflammatory myopathies. Recent observations suggest that retroviruses appear to be the most promising candidate viruses capable of triggering an inflammatory myopathy. The cellular mechanisms of myotoxicity related to AZT, the cholesterol-lowering drugs and the combination of blocking agents with steroids, have been defined. Awareness of myocytotoxicity of these drugs has began to have and impact on medical therapeutics.

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