Inclusion-body myositis
Clinical, diagnostic, and pathologic aspects

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Abstract—The diagnostic aspects of sporadic inclusion-body myositis (s-IBM), and a few comments on our own approach to its treatment, are presented to foster the goals of this symposium, which was organized to provoke new ideas concerning the cause and treatment of this currently unsolvable disease. s-IBM is the most common, progressive, debilitating muscle disease beginning in persons over age 50 years, and it is more common in men. Diagnostic parameters reviewed are clinical, muscle-biopsy histochemistry, electrophysiologic and CSF evaluations. Overall, the degenerative phenomena in s-IBM muscle fibers seem to be the major cause of the progressive, unstoppable weakness, rather than the lymphocytic inflammation. Available treatments are of only slight, temporary benefit for only some s-IBM patients, indicating a desperate need for definitive therapies.

This article is focusing on clinical, diagnostic and pathologic features of sporadic inclusion-body myositis (s-IBM). New findings of the molecular pathology and concepts of the molecular pathogenesis are described in an accompanying article by Askanas and Engel. Immunologic and viral considerations, including potential treatments, are discussed by Dalakas. Treatment approaches by others, including various therapeutic trials, are reviewed by Griggs.

s-IBM is the most common progressive muscle disease of persons over age 50 years. Because s-IBM muscle contains lymphocytic inflammatory cells, it has been considered an inflammatory myopathy, together with polymyositis (PM) and dermatomyositis (DM). But in contrast to PM and DM patients, s-IBM patients as a group respond poorly to antidysimmune treatment, and there is mounting evidence that mechanisms other than a dysimmune inflammatory aspect play the key role in s-IBM pathogenesis.

The term hereditary inclusion-body myopathies (h-IBMs) designates hereditary muscle diseases with pathology resembling that of s-IBM, but usually lacking lymphocytic inflammation, hence “myopathy” vs “myositis.” However, a few, especially older, h-IBM patients have some degree of inflammation (our unpublished observations). The h-IBMs are only briefly mentioned here, and are more detailed in a recent review and elsewhere.

s-IBM clinical features. Typical s-IBM. Typical s-IBM usually begins after age 50 years and occurs predominantly in men. Muscle weakness is both distal and proximal (figure 1). In the lower limbs, the quadriceps is prominently involved, as is gluteus maximus, and foot-drop is common. In the upper limbs, the greatest weakness is in finger flexors and extensors; biceps and triceps are moderately to prominently involved. Curiously and highly characteristically, the flexor digitorum profundus (FDP) (which flexes the distal phalanges) is much weaker than the flexor digitorum sublimus (FDS) (which flexes the proximal phalanges at the metacarpal-phalangeal joints) (personal observations), even though the FDS is located immediately adjacent, superficially, to the FDP. The reason for the remarkable susceptibility/resistance of different muscles is not known, but if discovered could be a clue to preventing and treating s-IBM.

The progressive course of s-IBM leads slowly to severe disability. Finger functions can become very impaired, such as for manipulating pens, keys, buttons, and zippers, pulling handles, and firmly grasping handshakes. Arising from a chair becomes difficult. Walking becomes more precarious. Sudden falls, sometimes resulting in major injury to the skull or other bones, can occur, even from walking on minimally-irregular ground or from other minor imbalances outside or in the home, due to weakness of quadriceps and gluteus muscles depriving the patient of automatic posture maintenance. A foot-drop can increase the likelihood of tripping. Dysphagia can occur, usually caused by upper esophageal constriction that often can be symptomatically improved, for several months to years, by bougie...
dilation per a GI or ENT physician. Respiratory-muscle weakness can sometimes eventuate. Among sporadic “inflammatory-myopathy” patients, the specific degenerative accumulations of proteins\(^1,8,9,15\) occur only in s-IBM, not in PM or DM.\(^1\) Most older patients with lymphocytic myositis have s-IBM. Patients over age 50 years with what can be considered “pure PM” are rare (but we have found they can respond well to single-dose alternate-day prednisone). Infrequently, DM begins over age 50 years and is sometimes associated with a remote neoplasm.

Late-juvenile s-IBM. Late-juvenile s-IBM (LJ-sIBM) is a rare form of s-IBM recently described in three young unrelated males who have muscle weakness distribution similar to that of s-IBM, including prominent quadriceps weakness, but age at onset in two patients was in the late teens and at age 20 in one.\(^16\) Their muscle biopsies had features of s-IBM, including vacuolated muscle fibers, lymphocytic infiltration and accumulations of IBM-characteristic proteins.\(^16\) However, there were also some pathologic aspects similar to h-IBM, namely: only infrequent congophilia (in intracellular plaquettes); and their phosphorylated-tau (p-tau) was mostly in straight tubulofilaments rather than in PHF configuration and it lacked some of the p-tau epitopes typical of s-IBM.\(^16\) One patient biopsied at age 30 had muscle blood-vessel amyloid (never seen in typical s-IBM) that was not immunopositive for A\(\beta\) or transthyretin, or \(\kappa\) or \(\lambda\) light-chains.\(^16\) Another patient’s fingers have remained strong through age 42. The earlier onset of LJ-sIBM may be based on yet-unknown susceptibility genes, possibly ones related to aging phenomena in muscle fibers.\(^16\) Their atypical features may be related to a “youthful” cellular milieu.

**Associations with other systemic disorders.**

Transfthretin gene mutation and s-IBM. A 70-year-old African-American man had both s-IBM and cardiac amyloidosis, the latter identified clinically by the Tc\(^{99}\)-MDP (methyl diphosphonate) whole-body bone-scan modified for soft-tissue views.\(^17\) He was homozygous for the *transfthretin (TTR)* Val122Ile mutation.\(^18\) In addition to the pathologic features typical of s-IBM, there were unique aspects, which included: a) congophilic deposits co-immunoreactive for both TTR and A\(\beta\) within vacuolated muscle fibers (TTR is never present in ordinary s-IBM); and b) prominent blood-vessel congophilic amyloid, co-immunoreactive for both TTR and amyloid-\(\beta\) (A\(\beta\)) (neither occurring in blood-vessels of ordinary s-IBM).

The TTR Val122Ile mutation, as in our patient, is the most common cause of late-onset cardiac amyloidosis among African-Americans.\(^19\) Our patient’s mutant-TTR might be a facilitating factor, promoting the amyloid-fibrillogenesis of A\(\beta\) within his muscle fibers and in muscle blood vessels. In other systems, non-mutant TTR can protectively sequester A\(\beta\), prevent amyloid fibril formation in vitro, and mitigate A\(\beta\)-cytotoxicity in vivo.\(^20\) We have proposed that if our patient’s cardiac amyloidosis, muscle blood-vessel amyloidosis, and s-IBM all relate to his TTR mutation, that would make it a susceptibility-gene mutation.\(^18,21\) By extension, perhaps mutations or polymorphisms of other yet-unknown susceptibility gene-products—congenital, or induced by viral, environmental or aging factors—may be promoting the s-IBM in many, if not all, other s-IBM patients. If the TTR Val122Ile mutation was a susceptibility factor in our patient, it probably had existed since conception, but his muscle weakness did not develop until after age 60 years. This would reemphasize the importance of an aging, or virally/environmentally-modified cellular milieu for developing s-IBM.

**HTLV-1 seropositivity and s-IBM.** HTLV-1 seropositivity was present in a few s-IBM patients, raising suspicion that this retrovirus may be a rare cause of s-IBM.\(^2,6,22,23\) This would support our hypothesis that s-IBM may have a viral basis of its pathogenesis.\(^2,7,8,9,22,23\) In one patient, we immunocytochemically detected HTLV-1 p19 antigen within the s-IBM muscle fibers.\(^23\) Others have found HTLV-1 antigen in the muscle biopsy only within macrophages.\(^2,24\) A recent s-IBM patient with associated HTLV-1 myelopathy reportedly had HTLV-1 proviral DNA and viral mRNA transcripts in the inflammatory cells infiltrating muscle.\(^25\) Based on our successful treatment of HTLV-1 myelopathy with immunosuppression,\(^26\) this might be interesting to try in HTLV-1 s-IBM.

**Postpolio syndromes and s-IBM.** In a few postpolio patients, s-IBM has been described,\(^2,22,77\) raising

Figure 1. s-IBM patient who has typical prominent weakness and atrophy of quadriceps and finger flexors.
the possibility that their decades-old virus infection was, in some manner, related to their subsequently developing s-IBM.

**Neuropathy.** In s-IBM, a neuropathy component have been recognized by ourselves, and by others. Our own studies indicate that it often is of dysschwannian type (see below).

**Others.** Rare associations of s-IBM with other syndromes have been reviewed.

**Light and electron microscopic pathology.**

**Vacuoles.** Several to numerous muscle fibers, each containing one or a few vacuoles, are typically present in a given 10-μm thick cross-section. Many of the vacuoles appear to be lysosomal, having their periphery positive with acid-phosphatase and panesterase, and dark-reddish (indicating lipoprotein membranous material) on the Engel-version rapid trichrome (E-trichrome) (figure 2A and B).

Often s-IBM vacuoles do not have a conspicuous reddish rim, which may be indicating broken lysosomes or focal microhydrolyses from spilled lysosomal hydrolytic enzymes. Within the vacuole there is often insoluble reddish or greenish-gray material, (i.e., membranous or proteinaceous material, respectively).

Engorged and accumulated secondary lysosomes (autophagosomes) are one of two major findings in s-IBM that reflect muscle-fiber damage from probable indigestibilities (the other being accumulated misfolded/unfolded proteins and inclusions of multiprotein-aggregates suggesting abnormality of the ER-ubiquitin-proteasome protein-disposing system). Ultrastructurally, collections of lysosomal autophagosomes containing undigested/unhydrolysed intracellular debris are a common feature of vacuolated s-IBM muscle fibers. The lysosomal debris appears as myelin-like whors (sometimes looking like "cabbage bodies"), osmophilically-dark amorphous material, and other forms. The autophagosomal membrane is often broken, and its unbounded contents spilled into cytoplasmic foci, producing little collections of the undigested cellular garbage. Soluble acid-hydrolytic enzymes, including proteases, glycosidases, phosphatases, and phospholipases, leaking from engorged or broken lysosomes can damage nearby cellular organelles, presumably causing a vacuolar microfocal "endodissolution," adding to the woes of the s-IBM muscle fiber. Autophagosomes normally hydrolyze unwanted, damaged, or "spent" molecules brought to them by endosomes that had engulfed abnormal cellular contents, such as mitochondria and other membranous structures containing macromolecules damaged by oxidative stress and toxic oligomers. Molecules difficult to digest in aggresomes are also brought to lysosomes. "Protease-resistant" amyloidic structures, such as PHFs and fibrils, if on the lysosomes' menu, are not being adequately devoured in s-IBM. Denervation increases muscle-fiber lysosomal activity. The cause, or causes, of the abnormal lysosomal autophagosomes in s-IBM is not known. Possibilities include: a) inability to manage a normal supply of substrate due to defective lysosomal enzymes, perhaps inactivated...
by a muscle-fiber endogenous cytotoxin, such as Aβ, or an exogenous agent originating in the body or outside (known exogenous lysosomal toxins include chloroquin, hydroxychloroquin, amiodarone, doxyribicin, aminoglycoside antibiotics, a product in some leukemias, and a diet low in vitamin E and selenium);30 b) oversupply of substrate to normally-functioning lysosomes, such as an excessive amount of damaged mitochondria or other cellular elements; c) late-late expression of a lysosomal-enzyme genetic defect; and d) a combination of these. An important contribution of autophagia in AD pathogenesis has recently been emphasized.31,78

Multiple or single foci of amyloid. Multiple or single foci of amyloid as identified by Congo-red florescence visualized through Texas-red filters32 (Askanas technique, figure 2C) are evident within about 60% to 80% of the s-IBM vacuolated muscle fibers, sometimes within vacuoles but mostly in their nonvacuolated regions. This fluorescence-enhanced Congo-red technique32 is the best and most sensitive for highlighting amyloid inclusions, which sometimes are very small or few. Crystal-violet metachromatically-red staining (figure 2E) can also show amyloid deposits, more conveniently but somewhat less precisely. Thioflavin-T fluorescence also identifies amyloid deposits. The least precise, most difficult to interpret and least satisfactory, but widely-used, amyloid-seeking method is Congo-red visualized in polarized light. We consider that the “congophilia” reported in the abnormal regions of myofibrillar myopathy is not true amyloid because it is not positive with crystal-violet or thioflavin-T; we have noted for many years that hyper-contracted regions of even normal muscle fibers can be apple-green “congo philic” in polarized light.

Regarding definitions, amyloid is a general term referring simply to a β-pleated-sheet configuration of certain protein molecules that are homogeneously-aggregated (“birds of a feather flocked together”), by hydrophobic bonding, due to their having become abnormally unfolded/misfolded. Various proteins have the propensity to form amyloid, which is protease-resistant. In s-IBM, true fluorescence-enhanced congophilia is a property of inclusions containing Aβ, p-tau, and possibly other protein aggregates.

Sometimes authors confuse amyloid with amyloid-β. Amyloid-β (Aβ) is one specific protein (figure 2D), an undesirably increased, putatively toxic, proteolytic product of AβPP (amyloid-β precursor protein), which can be assembled into polymeric β-pleated sheet amyloid, but also has the tendency to form invisible toxic oligomers within s-IBM muscle fibers.1,33,37,52 A similar invisible toxic mechanism, called “para-sparafucile” phenomenon,79 based on “amyloid-precursor molecules” acting extracellularly, was suggested, in 1979, in systemic amyloidoses to explain symmetric distal polyneuropathy without detectable amyloid deposited diffusely in affected nerves (“perhaps these amyloid precursor molecules invisible on electron microscopy also may have a selective affinity for exposed molecule ‘receptors’ of plasmalemma of certain cells, and by binding there damage cell function”).79

Phosphorylated tau. Phosphorylated tau (p-tau) collections are evident light-microscopically as squiggly inclusions (figure 2F, and ultrastructurally as paired-helical filaments (figure 3A) in s-IBM muscle fibers when immunostained with several antibodies against various epitopes of p-tau (figure 3B).34,35

Tau is a microtubule-associated protein, and in skeletal muscle fibers it is probably associated with the rather abundant tubulin-containing microtubular network. It might also be in nuclei because PHFs can be in nuclei, especially in some h-IBM patients.1 The pathologically-increased phosphorylation of tau produces p-tau (by unconfirmed mechanisms, but which might be provoked by excessive intracellular Aβ, in both s-IBM and AD). This probably is the cause of p-tau dissociating more readily from microtubules and aggregating into the s-IBM paired 15-21 nm-diameter p-tau-containing filaments of the congophilic PHFs35,36 (which are essentially identical to PHFs composing the neurofibrillary tangles in AD neurons). In s-IBM muscle fibers, PHFs containing p-tau can be seen in vacuolated regions, and even more so in otherwise normal-appearing regions, the latter suggesting they can be an early abnormality. In some settings,40 soluble p-tau, presumably mono/oligomeric, is cytotoxic, and PHF-tau inhibits the proteasome—possibly these p-tau toxicities are also occurring in s-IBM.

Ultrastructural components containing Aβ are detained.1,37 The combination of p-tau-positive PHFs and Aβ-positive collections is virtually diagnostic for s-IBM, the only exceptions being the various forms of the h-IBMs and autosomal-dominant oculopharyngeal muscular dystrophy (OPMD),74 the latter due to
mutation of PABPN1 (polyadenylate-binding protein nuclear-1) gene. In fact, we think OPMD can be classified as a form of h-IBM (Table 1).

In s-IBM, intranuclear inclusions of p-tau-positive 15-21 nm diameter “tubulofilaments” in favorable sections are sometimes seen to be PHFs like those in the cytoplasm. These nuclear PHFs are sparse, present in only 2% to 4% of s-IBM nuclei. However, immunostaining with anti-tau antibodies can identify more nuclei having incompletely assembled p-tau immunopositive PHFs in s-IBM nuclei (our unpublished observations). In some forms of h-IBM, such as with mutant valosin-containing-peptide, intranuclear p-tau-positive PHFs can be frequent. Other proteins increased in s-IBM muscle fibers. An intriguing aspect of the s-IBM muscle-fiber molecular phenotype is the remarkable similarity of accumulated proteins within muscle fibers to those accumulated in the AD brain. These nuclear PHFs are sparse, present in only 2% to 4% of s-IBM nuclei. However, immunostaining with anti-tau antibodies can identify more nuclei having incompletely assembled p-tau immunopositive PHFs in s-IBM nuclei (our unpublished observations). In some forms of h-IBM, such as with mutant valosin-containing-peptide, intranuclear p-tau-positive PHFs can be frequent.

Other proteins increased in s-IBM muscle fibers. An intriguing aspect of the s-IBM muscle-fiber molecular phenotype is the remarkable similarity of accumulated proteins within muscle fibers to those accumulated in the AD brain. Previously, one difference was thought to be that cellular prion protein (PrP C) and PrP C-mRNA are accumulated in s-IBM muscle fibers but not in AD brain. However, PrP C has recently been reported over-expressed in AD frontal cortical neurons. We suggest that might reflect a pathologic aspect or a valiantly-attempted “reparative/regenerative” aspect of the AD neurons, because in normal human muscle PrP C is increased in regenerative muscle fibers and at normal neuromuscular junctions.

Regenerating normal muscle fibers accumulate, presumably because they are essential, many of the same proteins accumulated in s-IBM muscle fibers, including AβPP. In s-IBM fibers, some of these proteins may be there because they are part of an earnest but frustrated regenerative effort, and some may be trapped there by a pathologic “aggregator.” Proteins accumulated at the postsynaptic region of normal human neuromuscular junctions (NMJs) include many of those accumulated in s-IBM muscle fibers. We have proposed that phenomena of “junctionalization,” “extrajunctionalization,” and a putative “junctionalizing master-gene” may be involved. In normal muscle fibers, during generation and regeneration in vivo, various proteins and their mRNAs are expressed along the length of the fiber. As a result of motor-innervation, in normal maturing fibers some of the proteins, termed “junctional proteins,” and their mRNAs become increased at the postsynaptic region of the NMJs and suppressed everywhere in the fiber, a process we have termed junctionalization of the muscle fiber. A number of the “s-IBM proteins” aberrantly accumulated in nonjunctional regions of s-IBM muscle fibers, such as AβPP/Aβ and nicotinic ACh receptors, are in normal innervated mature human muscle fibers, morphologically identifiable only at the NMJ postsynaptic region. P-tau, which is abnormally-phosphorylated in s-IBM, is not accumu-

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<th>Type</th>
<th>Gene/linkage</th>
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<tr>
<td>Autosomal recessive (AR-IBM)</td>
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<tr>
<td>Quadriceps spared</td>
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<td>Persian (Iranian) Jews</td>
<td>GNE</td>
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<tr>
<td>Persian (Iranian) Jews, pseudodominant (presumably from two-allele x one-allele intermarriage)</td>
<td>GNE</td>
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<td>Others</td>
<td>GNE</td>
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<td>Quadriceps not spared</td>
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<tr>
<td>French-Canadian family, with central nervous system abnormality</td>
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<td>Others</td>
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<td>Autosomal dominant (AD-IBM)</td>
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<td>Swedish</td>
<td>Myosin heavy-chain IIa</td>
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<td>Finnish “tibial muscular dystrophy”</td>
<td>Titin</td>
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<td>Chicago family</td>
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<tr>
<td>Pennsylvania family, and others</td>
<td>VCP</td>
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<td>Denver family</td>
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<td>Los Angeles Mexican family</td>
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<td>Oculopharyngeal muscular dystrophy (OPMD)</td>
<td>PABPN1</td>
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<td>Others</td>
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GNE = UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase; VCP, valosin-containing-peptide; PABPN1 = polyadenylate-binding protein nuclear-1.
lated at normal NMJs. Normal junctionalization is under the control of presynaptically-released peptides that activate postsynaptic metabotropic receptors to effect an orchestrated muscle-fiber response. There is also a retrograde trophic influence of myogenic factors to metabotropic receptors on the motor-axonal tip, abnormality of which could contribute to the s-IBM NMJ abnormalities. In s-IBM muscle fibers, there may be pathologic “extrajunctionalization,” partly related to normal attempts of the stricken fibers to regenerate, and driven by ectopic extrajunctional unrestrained expression of “junctional genes.” A pathologically-unrestrained normal junctional master gene (JMG) has been hypothesized, whose product might act directly or indirectly as a transcription factor activating genes for some of the “s-IBM-proteins.” A normal JMG, or a specific “s-IBM-master-gene,” might itself be activated by an adjacent-inserted viral gene (insertional mutagenesis), a viral gene-product, or possibly indirectly via microRNAs. In s-IBM possibly only some nuclei of individual multinucleated muscle fibers are affected. A deranged JMG might also fail to properly form and maintain the junctional postsynaptic region. The more-dispersed “junctional” proteins might meet a dispersed intracellular “aggregator,” such as oligomeric Aβ, α-synuclein, or possibly p-tau, and those encounters could account for the wider distribution within s-IBM fibers in the form of the aggregates/inclusions.

Mitochondrial abnormalities. Mitochondrial abnormalities (reviewed by Oldfors, this issue) include ragged-red fibers on the E-trichrome stain, cytochrome-c-oxidase (Cox) negative muscle fibers, and possibly unstudied enzyme defects. These can be accompanied by multiple mitochondrial DNA deletions. All are more common in s-IBM than expected for the patient’s age. In s-IBM we find that the Cox-negative muscle-fibers can be of moderate number or many. With their electron-transport generation of ATP blocked, those fibers must be surviving on anaerobic glycolysis in their Cox-negative segments or on ATP diffusing from their Cox-normal segments, but probably with impaired vitality and impending doom.

Small angular muscle fibers. Small angular muscle fibers, presumably denervated, are evident on the E-trichrome stains, and are often but not always histochemically dark with the NADH-tetrazolium-reductase and pan-esterase reactions. They are indistinguishable from those in ordinary denervation diseases, and generally are considered indicative of “recent denervation” (our preferred term). They are a characteristic feature of s-IBM muscle biopsies and probably contribute significantly to the clinical weakness. These fibers seem to gradually atrophy and, as in ordinary denervation, when very atrophic they may show “apoptoid” features but not ordinary apoptosis.

In s-IBM the denervation of muscle fibers might be “neurogenous” or “myogenous.” Denervations of any type can produce EMG fibrillations and positive waves. “Myogenous deinervation” (our preferred term), is, in general, caused by a postaxonal synaptic “malreceptivity” of the muscle-fiber that impairs its responding to the neurogenic trophic influences, producing small angular muscle fibers accompanied by fibrillations and, assuming random involvement, a BSAP EMG pattern. “Established reinnervation,” histochemically in the form of muscle-fiber type-grouping indicating motor-unit densification and enlargement, is only slight in s-IBM, and less than expected from the amount of recent denervation in the same patient. Perhaps this is because of difficulty reinnervating s-IBM muscle fibers. Note that cultured human muscle fibers experimentally overexpressing AβPP/Aβ cannot become innervated when co-cultured with fetal rat spinal cord; whereas control muscle fibers can, and when innervated they neurogenically twitch.

Atrophic nonangular muscle fibers. Atrophic nonangular muscle fibers are also present. Some of these, too, might be denervated, or be atrophic from myogenic endodissolution caused by various lytic mechanisms within muscle fibers.

Regen-degen muscle fibers. Regen-degen muscle fibers, showing nonspecific aspects of regeneration and degeneration (having lighter, reddish-blue cytoplasm, and large nuclei and nucleoli), are occasionally present, but fewer than expected from the accompanying evidence of active muscle fiber damage and lymphocytic inflammatory cells. Necrotizing/phagocytotic muscle fibers are infrequently found in s-IBM biopsies.

Absent or very faint alkaline phosphatase staining of perimysial connective tissue. In s-IBM, perimysial connective tissue, even in regions of active disease, lacks the typically-vigorous alkaline phosphatase (AP)-positivity (which we attribute to fibroblasts) that is seen in DM and PM (figure 2G and H). Interestingly, subacute changes in recovering post-ischemic human muscle also can have vigorous alkaline-phosphatase-positive connective-tissue. The regen-degen muscle fibers, as ones present in PM, DM, and other myopathies, are often slightly to moderately alkaline-phosphatase-positive, but in s-IBM those positive fibers seem to be less numerous and less positive.

Diagnostic criteria of s-IBM muscle biopsies. According to the above, to diagnose s-IBM and to help distinguish it from polymyositis, we recommend the following stainings on 10-μm sections of a fresh-frozen muscle biopsy: 1. Engel-version rapid trichrome method to visualize vacuoles and mononuclear-cell inflammation (figure 2A and B) as well as muscle-fiber atrophy, and any regen-degen and necrotizing/phagocytosed fibers. 2. Fluorescence-enhanced Congo-red to detect β-pleated-sheet amyloid inclusions (figure 2C). If fluorescence microscopy is not available, crystal-violet can be used for showing amyloid (figure 2E). 3. SMI-31 antibody staining...
to identify p-tau$^{34,35}$ (figure 2F). Monoclonal SMI-31 antibody, originally made to react with phosphorylation-related neurofilament heavy-chain, recognizes p-tau of PHFs within s-IBM muscle fibers and AD brain.$^{34,35,60}$ This antibody, which can be used in a very high dilution (1:1000), is highly specific and economic. If SMI-31 antibody is not available, antiubiquitin antibody can be used to react with both p-tau and Aβ deposits within s-IBM muscle fibers. These stains together differentiate s-IBM from polymyositis and dermatomyositis, which do not have intrafiber congoophilic or ubiquitin-positive deposits.$^{61,62}$ 4. Alkaline phosphatase staining for absent or only very faint perimysial positivity (figure 2G and H). 5. Amyloid-β immuno-staining is also useful in uncertain cases (figure 2D). Even though, in our opinion, SMI immunostaining usually eliminates the need for electron-microscopic evaluation, in an occasional case ultrastructural confirmation of the presence of PHFs is useful. In this situation, we recommend our technique utilizing fresh-frozen sections adhered to the bottom of petri dishes.$^{63}$

**Clinical electrophysiology of s-IBM.** 1. The EMG is abnormal but not diagnostic. A. Evidence of “recent denervation” in the form of few to many fibrillations and positive waves, is usually present, and that sometimes confuses the diagnosis. The denervation can be neurogenic or myogenic. B. There are usually small motor-unit potentials, called BSAPs (brief, small, abundant potentials) and BSAPPs (polyphasic BSAPs).$^{64,65}$ BSAPs and BSAPPs do not define a myopathy, contrary to the nearly-ubiquitous misconceptions and writings—they simply identify “motor-unit fractionation,” meaning reduction of the number of activatable muscle fibers in a motor unit.$^{64,65}$ BSAPs can occur in neuropathic disorders involving distal axonal twigs, in neuromuscular-junction disorders (e.g., myasthenia gravis), as well as in various myopathies.$^{64,65}$ C. There can be some established-reinnervation, evidenced as enlarged and prolonged motor-units, but generally less, by EMG or muscle-biopsy histochemistry, than one might expect from the amount of recent-denervation and the disease chronicity.

2. Nerve conduction velocities (NCVs) in some s-IBM patients we have found to be abnormally slow and reflect a dysschwannian ("demyelinating") polyneuropathy. When present in an s-IBM patient, this pattern strongly suggests a component of dysimmune neuropathy, viz. a CIDP (chronic immune dyschwannian polyneuropathy, our preferred term to emphasize the cell that is the dysimmune victim and which must be therapeutically protected).$^{66,67}$ This likelihood is enhanced in a patient if the CSF protein is elevated above the normal of 45 mg/dL, and if there are serum markers of dysimmunity, such as a monoclonal antibody, free light-chains, circulating immune complexes, or tissue-, cell-, or protein-specific antibodies. Note that a reduced CMAP (compound motor action potential) amplitude cannot be used to distinguish between a “dysneuronal”$^{66,67}$ ("axonal") neuropathic and a myopathic aspect.

**Hereditary inclusion-body myopathies.** The hereditary inclusion-body myopathies (h-IBMs) encompass several autosomal-recessive and autosomal-dominant syndromes of progressive muscle weakness with various clinical presentations, and the mutations in different genes indicate that the h-IBMs are polygenetic disorders (table) (reviewed in$^{11}$ and$^{12}$). However, the unusual constellations of proteins constituting the inclusions in abnormal muscle fibers are very similar in s-IBM and h-IBM.$^{11}$ The genetic defect is known in some, but in none has the crucial molecular pathogenic mechanism or a therapeutic correction been discovered. The best studied is the GNE gene (UDP-N-acetylglucosamine 2-epimerase/N acetylmannosamine kinase), which is mutated in an autosomal-recessive quadriceps-sparing h-IBM.$^{12,68,69}$

More recently discovered, and of special interest related to s-IBM,$^{3}$ is the valosin-containing-peptide gene mutation in an autosomal-dominant form of h-IBM.$^{70}$

**Treatment: A personal view.** General comments. A broad review of published therapeutic trials in s-IBM is presented by Griggs$^{3}$ in this issue. The following comments represent strictly a personal view of treating s-IBM patients, based on n-of-1’s. At best, some current treatments are of only slight benefit for only some s-IBM patients, and none permanently reverses, or even stops, their on-going slow progression of weakness. A good treatment of s-IBM should produce increased strength, because muscle fibers (cells) can repair and regenerate. The overall difficulty is that in sIBM the regenerative fibers seem to not get a chance for sustained, effective re-maturation, probably because they become afflicted by the basic degenerative process. (This raises an unanswered question of possible cell-to-cell extracellular transfer of myotoxic molecules.)

**Corticosteroid.** Even though the majority of s-IBM patients do not respond to corticosteroid therapy (see Griggs$^{3}$ this issue), some of our patients with s-IBM definitely have benefitted, to some degree, from treatment with a corticosteroid such as single-dose alternate-day (SDAD) prednisone. Endurance of limb-strength in those responsive patients can clearly be improved, repeatedly proven by increased weakness and fatigability when the dose was lowered below a level critical for the given patient, such as 44, 38, 30, 27, 18, or 14 mg SDAD prednisone. Evaluation of endurance is often overlooked clinically and in trials, but should not be, because even detailed quantitative strength-testing can miss improvement in endurance, often the first parameter of subjective muscle function to improve. Several s-IBM patients have preferred continuing the slight prednisone benefit to their rather modest prednisone side effects. The underlying progressive muscle weakness is not stopped, and whether the process may be
somewhat slowed is not known. In a few of our patients, swallowing difficulty has been improved by prednisone. The pertinent therapeutic mechanism of prednisone in s-IBM is not known. It could be by stabilizing muscle-fiber abnormal lysosomes (a known effect of a corticosteroid), preventing other degenerative phenomena (including modulating gene expression), ameliorating a coexisting dysimmune neuropathy or myogenously dysinnervation, or inhibiting macrophages and/or cytotoxic T-cells in the muscle. (Corticosteroid treatment can prevent lymphocytes from appearing in muscle biopsies, but that does not prove clinical efficacy—only improved, or long-term-maintained, muscle function does.)

IV immunoglobulin G. Some slight benefit can be achieved in some patients, and may be related especially to the CIDP (chronic immune dyschwan-nian polyneuropathy) component demonstrable in them. In some patients, swallowing difficulty can be improved.7 However, IV immunoglobulin G (IVIG) does not stop the underlying progression.

Depo-testosterone. Sometimes a male with s-IBM can obtain increased strength/endurance from depo-testosterone 100-150 mg IM weekly, assuming the prostate/PSA status allows it, there is no diabetes or prediabetes, and no concurrent corticosteroid treatment (W.K. Engel and R. Albo, personal observations).

Self-locking knee brace. To help prevent the sudden loss of knee locking ability due to severe quadriiceps weakness, and resultant often-injuries falls, a self-locking knee brace on the side with the weaker quadriceps has been very effective in number of our s-IBM patients. It should not be combined into a heavy one-piece long-leg brace with a drop-foot brace. The latter, if necessary, must be light-weight and improve, not impair, walking, or else the brace will not be used.

“Cocktail Royal.” As speculative cytoprotection since 1997, one 73-year-old man has been taking for 8 years our empiric combination. It consists of daily high-doses: L-carnitine 900 mg 5x, Co-Q10 100 mg 4x, B-1 100 mg, B-2 100 mg, B-6 100 mg, E 1000 mg 3x, and s.q. B-12 1 mg. (He also is taking allopurinol 300 mg, since a single attack of acute gout at age 30). On the Cocktail Royal there was initial slight improvement (“no more feeling like I was going to fall, and ability to do more with my hands, opening pull-handles of the dryer, frig and car with the fingers of only one hand instead of two”), and no progression (“no more downhill at all”) for the 8 years to date. Whether his response is unique is not known. A recent study reported that CoQ10 counteracted brain mitochondrial alterations induced by Aβ.72

Other treatment possibilities. Is anti-dysimmune treatment likely to be successful in s-IBM? Cytotoxic T-cell inflammation is an observed component of s-IBM muscle-fiber pathology. Unanswered questions include: Is lymphocyte-instigated muscle-fiber damage quantitatively significant and a worthwhile therapeutic target? Are there myodestructive T-cells, and some B-cells, pathologically programmed to attack normal muscle fibers, or are they reacting to abnormal, “foreignized” muscle fibers already possessing morphologically-invisible unique-degenerative, ± “hidden-viral,” features of s-IBM? Are the macrophages visualized between and invading s-IBM muscle fibers initiating myotoxic, quantitatively significant, and a worthy therapeutic target? New anti-dysimmune drugs are continually being introduced, but whether they will be beneficial in s-IBM remains uncertain. The overall failure of various forms of immunosuppression therapy, including methotrexate, azathioprine and corticosteroid, to stop s-IBM progression suggests (although others might not agree) that a dysimmune mechanism is neither paramount nor of major significance in caus-ing the gradually-increasing weakness, compared to the degenerative phenomena that have been de-tailed.1 In s-IBM, the mononuclear inflammatory cells are similar to those in PM, being mainly clonally-expanded CD8+ auto-invasive T-cells and some macrophages.2,4-6 The difference in their treat-ability may relate to the myodegenerative aspects of s-IBM. The cause of the lymphocytic mononuclear-cell inflammation in typical s-IBM is not known. Although the T-cell response is considered to be is antigen-driven,2,4-6 a responsible antigen is not known.

Can intracellular amyloid and other inclusions in s-IBM muscle fibers be dissolved? Although they appear permanently indigestible, they might not be—for example, amyloid storage material can gradually disappear, presumably by proteolysis, after dis-continuing a provoking chloroquin therapy,30 as can amyloid in rat liver achieved after stopping experimen-tal feeding of amyloid-producing casein.

Can formation of putatively-toxic oligomers be prevented or their disposal be enhanced? This is briefly considered in reference 1.

Drugs to be developed: General comment. Better treatment is certainly needed. To know the unknown at the very top of the pathogenic cascade would sharpen the therapeutic focus. Drugs must, of course, be safe, target the muscle fibers, and not damage other organs. Drugs for s-IBM should be easier to develop than ones for AD, because they would not have to cross the blood-brain barrier. For both, they would need to effect benefit intracellularly. Molecular-pathologic data manifesting potential opportunities upon which one might develop definitive therapies are presented in various articles of this issue. Conceptually possible types of new drugs to correct or prevent the various molecular abnormalities now identified within s-IBM muscle fibers have been summarized.1

Suppressing a selected mRNA by exogenous mRNA-interference (RNAi) (discussed by Paulson73) seems attractive, for example, to knock-down the overexpressed AβPP. But that could be a problem because a normal amount AβPP may be essential for function of cellular membranes, postsynaptic junc-
tions, and regeneration of muscle fibers. Possibly knocking-down selected promoting or inhibiting factors in muscle might eventually be beneficial.

MicroRNAs. MicroRNAs (miRNAs) are 18-24 nucleotide-long regulatory molecules, naturally produced by cells, that modulate the stability or translational efficiency of target mRNAs, thereby influencing normal growth and development to achieve and maintain cellular differentiation.\(^4\),\(^5\),\(^6\) Each miRNA targets a number of different mRNAs, and miRNAs themselves are regulated by other genes. A possible therapeutic role of miRNAs in preventing s-IBM muscle-fiber degeneration and promoting repair seems worthy of conceptualizing and testing.

Infused stem cells. Infused stem-cells, a current cachet, can be considered. They could be normal stem-cells, but as foreign cells would be subject to potential immune rejection, and they might also become victimized by the same s-IBM pathogenic mechanisms if a protective drug does not umbrella them or if they are not pre-loaded with a protective genetic mechanism (whatever those might be). Conceivably, and ultra-complexly, the individual s-IBM patient’s own stem-cells could be: harvested, proliferated; ex vivo fortified (by a yet-to-be-discovered method) against the s-IBM pathogenic process; programmed to home into muscle fibers, to also stimulate their receiving an adequate blood-supply and collateral innervation (assuming the motor nerves indeed have retained that potency); and administered.

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Inclusion-body myositis: Clinical, diagnostic, and pathologic aspects
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