The Syrian hamster polymyopathy is a hereditary disease, transmitted by an autosomal recessive gene, involving the heart and the entire musculature. The chronology of the pathologic events in the myocardium and skeletal muscle has been investigated in UM-X7.1 myopathic hamsters aged 0–250 days. A phasic pattern in the progression of the disease process was evident. Microscopic necrotic changes in the heart were visible prior to or at 50 days of age with increasing severity until 100 days of age and subsidence thereafter. More than 50% of the animals died before 250 days of age with signs of cardiac failure. The intensity and extent of myocardial calcific changes together with scar formation were determinant factors in curtailing the survival of animals. Changes in serum creatine kinase (CK) activity followed a phasic pattern similar to the progression of the myopathic disease. Because of the disparity of disease manifestations between the different myopathic hamster lines, it is essential to consider the time course of the heart and skeletal muscle microscopic changes when evaluating the severity of the hamster polymyopathy.

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HEREDITARY POLYMYOPATHY AND CARDIOMYOPATHY IN THE SYRIAN HAMSTER. I. PROGRESSION OF HEART AND SKELETAL MUSCLE LESIONS IN THE UM-X7.1 LINE

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The hereditary polymyopathy discovered in an inbred strain of Syrian hamsters has generated considerable interest in the field of genetically determined myopathies. This hamster model provides unique possibilities of studying the frequent involvement of the myocardium in human primary muscle disorders.[5,9,12,33–35,48,52]

The polymyopathy is transmitted by an autosomal recessive gene.[16] This simple mode of inheritance permits the establishment of new myopathic lines by cross-breeding homozygous diseased animals with unrelated healthy hamsters and by recovering the mutant gene in the F2 generation. The resulting lines will have a disease incidence of 100% with no significant difference in the histologic features of muscle lesions, indicating that the genotype of this hereditary disorder is constant and reliable. However, the time course and severity of the disease appear to vary somewhat between different lines and even between siblings of the same line.[15] Thus, after 28 generations of inbreeding, the BIO 14.6 animals showed a gradual decline in the severity of symptoms with modulation of signs of cardiac failure and a concomitant increase in longevity.[14,19] This shift is most likely due to a natural selection of the healthiest breeders at weaning.

Survey of the literature shows a great deal of inconsistency in appraisals of the hamster polymyopathy through biochemical or morphologic findings.[7,10,22,29–32,42,43,45–47,49,50] The objective of the present paper is to describe the essential pathologic features of the heart and skeletal muscles for use as guidelines in assessing the intensity and chronology of the myopathic process. The data have been cumulated over a period of 8 years, ever since the UM-X7.1 hamster line (a subline of BIO 14.6)[17] was established in this laboratory. Emphasis is placed on elucidating the progression of the disease process, which we consider fundamental to the investigation of such subcellular pathologic changes as mitochondrial respiration and calcium load, which is the subject of a separate report.[36]

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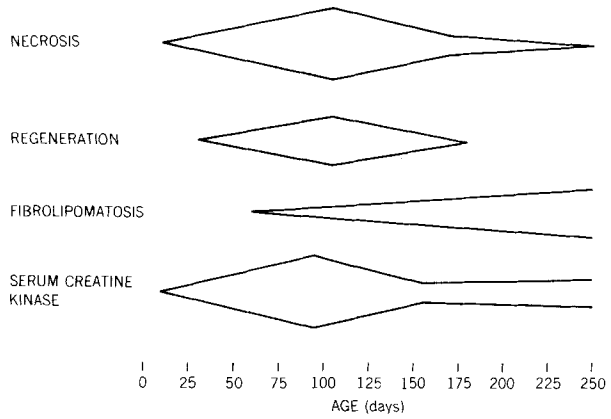

Figure 1. Diagram of skeletal muscle changes and of the relative values of serum creatine kinase activity during the course of the hamster hereditary polymyopathy in the UM-X7.1 line.

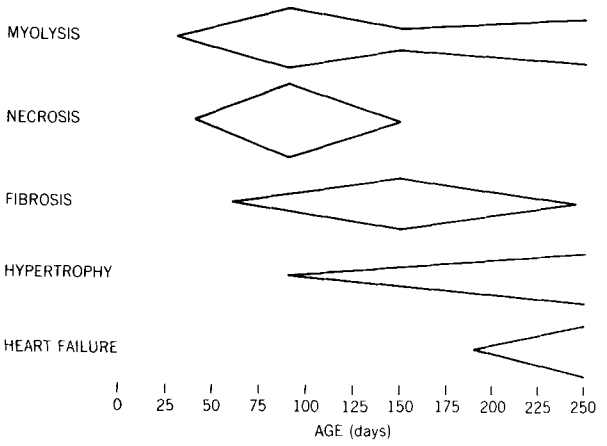

Figure 2. Diagram of heart muscle changes during the course of the hamster hereditary polymyopathy in the UM-X7.1 line.

MATERIALS AND METHODS

Male and female hamsters of the UM-X7.1 myopathic line were used in this study. Unrelated healthy hamsters (originally from Lakeview Farm, Newfield, NJ) served as controls. They were maintained under controlled housing conditions with free access to Purina laboratory chow and tap water. Groups of 10–20 animals of the same age were sacrificed by exsanguination at intervals of 25 days between 0 and 250 days of age. At autopsy, all animals were skinned for an overall estimation of necrotic foci readily visible by the naked eye. Heart lesions were also recorded. The myocardium and several pieces of skeletal muscle (tongue, diaphragm, obliquus externus abdominis, quadriceps, and tibialis anterior muscles) were fixed either in Lillie's buffered sublimate or in neutral formol for routine histology, using the hematoxylin-phloxin-saffron (HPS), alizarin, and von Kossa calcium stains.[13] The degree of cardiac hypertrophy was assessed by the overall dimension of heart cavities and the thickness of myocardial wall in tissue sections. Development of heart failure was estimated by the amount of pleural and peritoneal fluids, the liver mass, and subcutaneous edema. The severity of cardiac and skeletal muscle lesions (myolysis, necrosis, and fibrosis) was assessed on an arbitrary scale of 0–3: 0, designating no lesions; 1, occasional isolated fiber degeneration; 2, moderate lesions consisting of small scattered foci of necrosis; and 3, severe involvement with large areas of fiber destruction. The means of these microscopic findings together with the time of occurrence are shown in Figures 1 and 2.

The total creatine kinase (CK) activity in serum was determined spectrophotometrically by a kinetic procedure; samples in appropriate dilutions were analyzed at 25°C, using the CK-combination test of Boehringer Mannheim Diagnostica (BMC Diagnostics/Biochemicals Ltd., Montreal, Canada).

RESULTS

Clinical Course of the Disease. The physical appearance and behavior of the myopathic hamster remain normal for a long period despite the presence of degenerative lesions in the skeletal and cardiac muscles. Characteristic gross symptomatology develops progressively with cardiac insufficiency and becomes prominent during heart failure. However, for some undetermined reason, muscular weakness with locomotor impairment is sometimes evident in 150-day-old animals by the end of the necrotic stage. The efficiency of muscle performance is significantly diminished during forced exercise. The development of subcutaneous edema indicates the terminal stage of progressive heart failure; hyperpnea and cyanosis are prominent and the prostrated animals die within 2 weeks.

Skeletal Muscle Changes. In newborn animals until 20 days of age, the initial necrotic changes are confined to the most active respiratory muscles. At autopsy there are scattered white streaks in the muscle. With the progression of the disease, the lesions become more confluent involving bundles of fibers. Light microscopic changes at an early stage consist of hyalinization and fragmentation of isolated myofibers with little or no cellular infiltrate. The necrotizing process extends progressively to

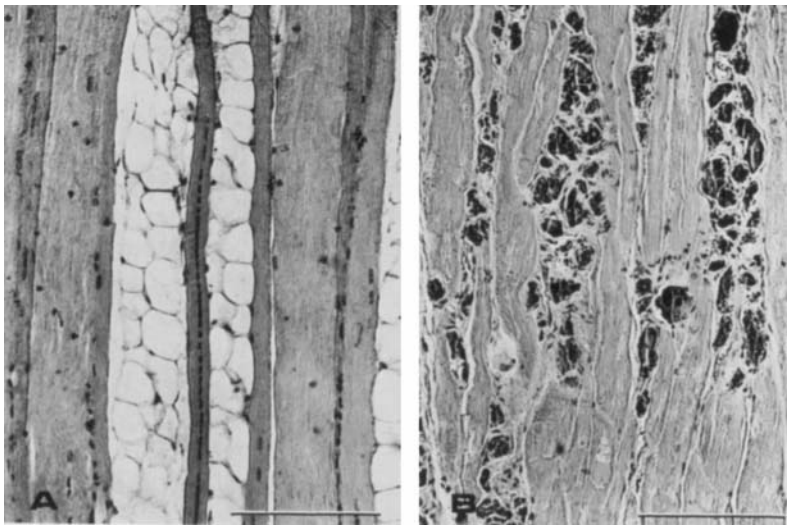

Figure 3. Microscopic degenerative changes in the diaphragm muscle of UM-X7.1 hamsters at late stages of the hamster myopathic disease (hematoxylin-phloxin-saffron stain). (A) Interfibrillar lipomatosis prominent between 200 and 250 days of age. Note in this longitudinal section a thin basophilic fiber with a row of nuclei. Bar = 0.5 mm. (B) Aggregates of calcium apatites sequestered by fibrotic tissue, irregularly found between 125 and 250 days of age. Bar = 0.5 mm.

the whole musculature, reaching its maximum severity in 100-day-old hamsters and receding thereafter (Fig. 1).

The more consistently affected muscles, in order of frequency, are the diaphragm, the intercostal muscles, the tongue, and the limb-girdle groups. Isolated groups of myofibers undergo myolysis in the absence of cellular reaction, but more often the degenerative changes consist of coagulation necrosis with phagocytosis. The phagocytic foci include small regenerative myofibers showing increased basophilia and internal proliferation of nuclei. After 160 days, necrosis and regeneration usually subside; the fibers are dysvolumenic and 80% have central nuclei. Interstitial fibrolipomatosis is prominent in the abdominal and diaphragm muscles (Fig. 3A) but is less prominent in the rest of the musculature. Calcific foci are seen (Fig. 3B) in groups of constantly contracting muscles (diaphragm, tongue) and are otherwise more discreet in the upper or lower limb muscles.

Heart Muscle Changes. Myocardial changes are rarely visible prior to 40 days of age (Fig. 2). Scattered lesions (Fig. 4A) are randomly distributed throughout the wall of both ventricles but invariably gain in severity and extent with progression of the disease. The earliest necrotic changes under the microscope consist of focal myolysis in the absence of cellular infiltration. The cardiocytes disintegrate either by myofibrillar dissolution, leaving sarcolemmal remnants and occasional few nuclei, or by coagulation of the sarcoplasm, which becomes highly granular and calcified. The degenerative changes subside by 150 days of age, and calcified fragments are sequestered within scar tissue. Interestingly, the myolytic process reappears during later stages of cardiac hypertrophy. In contrast to the skeletal muscle, the pathologic changes in the heart give rise to substantial scarring. The gross signs of circulatory failure consist of liver enlargement and fluid accumulation together with an appreciable increase of heart volume. During the terminal stage, mural thrombi are frequently seen in either cavity of the dilated flabby heart (Fig. 4B). The intensity of subcutaneous edema, ascites, hydrothorax, and hydropericardium does not strictly relate to cardiac enlargement. The best indicators of the severity and duration of heart failure are the size, color, and firmness of the liver.

Serum CK Activity. As shown in Figure 1, the dynamic profile of the relative values of serum CK conform to the intensity of the necrotic process and the phasic pattern of the polymyopathy. A significant rise in enzyme activity, for undetermined reasons, has been noted with occurrence of heart failure.

DISCUSSION

Cumulative data arising from the literature on Syrian hamster polymyopathy have contributed to a better characterization of several pathologic components of this primary, genetically transmitted muscle disease. In the present report, the chronology of pathologic events has been emphasized since the disparity between the disease manifestations of different myopathic hamster strains has been virtually ignored thus far. In our opinion, this may be important when studying the occurrence

Figure 4. (A) Myocardial lesions in a 75-day-old cardiomyopathic hamster (UM-X7.1 line). Several necrotic and myolytic foci are visible in the septum and the left ventricular wall (arrowheads). Bar = 2.5 mm. (B) Typical failing heart in a 250-day-old cardiomyopathic hamster. Note the distension of the heart cavities and a well-organized mural thrombus on the left side. Bar = 2.5 mm.

and progression of the cardiomyopathy and when attempting to interpret microscopic and biochemical findings which are necessarily related to the phasic pattern of the disease. By using the UM-X7.1 myopathic hamster line, which retains all the essential characteristics of the BIO 14.6 line originally described by Bajusz et al.,[4] we found, for instance, that oxidative phosphorylation of heart mitochondria[23,36] and the changes in adrenergic nerve activity[24] lead to consistent results if related to the chronology of the pathologic events. This similarly applies to our investigation of the plasma membrane defect[10,44] or the influence of calcium antagonists and β-adrenergic blockers on the course of the cardiomyopathy.[20,23,26,28]

In spite of the differences between several myopathic lines, all deriving from BIO 1.05,[16] we believe that the genetic defect underlying this polymyopathy is invariable, since all traits subsist under controlled mating conditions, and that variations between different lineages merely represent divergent genetic expressions of the same disease. This phenomenon in turn would suggest that several conditioning factors play an important role in the development and progression of hereditary polymyopathy[1-3] and that therapeutic trials to alleviate the symptomatology and to prolong the lifespan of animals would most likely lead to interesting and valuable results. We have already succeeded in interfering with the development and progression of necrotic myocardial changes by administering calcium antagonists.[19,21,23,28] Thus, it may be postulated that the abnormal calcium influx results from some structural or functional membrane defect. We also investigated different drugs, such as Dibenamine and propranolol, which act on adrenergic receptors, and certain prostaglandins, which influence adenyl cyclase activity.[28] All these agents proved to be effective in reducing the severity of the cardiomyopathy, thus supporting the concept that the disease is related to a basic defect in the plasma membrane.

In our attempts to elucidate the mechanism of heart muscle degeneration in this nonobstructive hereditary cardiomyopathy, we have always been puzzled by the coexistence of myolytic and coagulative necrotic lesions,[19,27,43] the latter often accompanied by deposits of insoluble calcium apatites. Such a degenerative process is not usually encountered in patients with Duchenne muscular dystrophy whose pathologic myocardial changes essentially comprise variations in fiber size with more or less extensive epimyocardial fibrosis.[12] The present cardiomyolysis is more reminiscent of anoxic lesions in autopsy cases after brain or cardiac surgery[38,39] or in cases of sudden traumatic death ascribed to "stress cardiomyopathies," presumably due to an excessive liberation of endogenous catecholamines.

We believe that the coagulative muscle changes in hamster cardiomyopathy result from mitochondrial calcium loading which interferes with ATP production and causes calcium precipitation within the mitochondrial matrix. While in light microscopy the pathologic fiber changes are essentially granular, in electron miscroscopy the collapsed fibers as well as the surrounding histiocytes are filled with calcified mitochondria.[22] Myocytolysis, on the other hand, is a more insidious process characterized by myofibrillar dissolution with a concomitant increase of calcium-dependent proteases.[8,11] The process is possibly due to increased

adrenergic tone, as suggested by Sole et al.[45] or related to abnormal catecholamine metabolism and turnover.[24] Similar myolytic lesions are readily reproduced in experimental animals by administration of isoproterenol,[6,40] methoxamine, or metaraminol.[18,25] Whatever the primary causative mechanism, the question is still debated as to whether catecholamines play a primary or a secondary role. It seems, however, that the plasma membrane defect, as evidenced by an increase in cholesterol content, largely accounts for the calcium influx in the cardiocytes and that the modality of cell necrosis probably depends upon the rate of calcium influx.[37,41,51] In this respect, we found that while calcium antagonists successfully prevent dystrophic necrotic changes, these same drugs, when administered over a long period, are less effective in interfering with the myolytic process which parallels the plasma membrane deterioration;[23] the accelerated norepinephrine turnover during the progression of the cardiomyopathy[24] as well as the generalized anoxemia due to circulatory failure can only promote the myocytolytic process in the dystrophic heart. These data give insight into the pathologic mechanism of this genetically determined myocardial disease, and we suggest that combined treatment with calcium antagonists and adrenergic blockers may prolong the viability of cardiocytes in which the plasma membrane is primarily defective.

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