ANIMAL MODEL OF HUMAN DISEASE

Myocardial Failure, Muscular Dystrophy

Animal Model: Cardiomyopathic Syrian Hamster

Contributed by: Edward W. Gertz, MD, Harvard Medical School, Peter Bent Brigham Hospital and Bio-Research Institute, Boston, Mass.

Biologic Features

In 1962 members of the staff of Bio-Research Institute (Cambridge, Mass.) described the first strain (BIO 1.5) of cardiomyopathic Syrian hamster.[1] When the disease was discovered, the line was in its twenty-second generation of brother-sister inbreeding. The cardiomyopathy was found to be hereditary and transmitted by an autosomal recessive gene.[2] The disease involves both skeletal and cardiac muscle, but in the present report only cardiac disease will be discussed.

With succeeding generations, the BIO 1.5 strain was lost. Before this occurred, diseased homozygous animals were crossed with nonrelated hamsters. After muscle biopsy, affected animals in the F_2 generation were selected and the BIO 14.6 line began.

The BIO 14.6 line is now the oldest cardiomyopathic hamster line in existence. Two additional lines (BIO 40.54 and 82.62) have been obtained from this line by outbreeding experiments similar to that described above. The major differences between the strains are the variable severity and different rate of progression of the disease. The BIO 14.6 animals live approximately 1 year, 40.54 animals approximately 190 days and 82.62 animals have an intermediate life-span. BIO 14.6 animals have been the most extensively studied and will be described in the greatest detail.

Myocardial lesions occur in all animals in both sexes. They appear between 25 to 30 days of life in females and 10 days later in males.[3] Acute lesions are widespread and occur with equal frequency in both

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Dr. Gertz's present address is Lee Hospital, Johnstown, Pa. 15905.

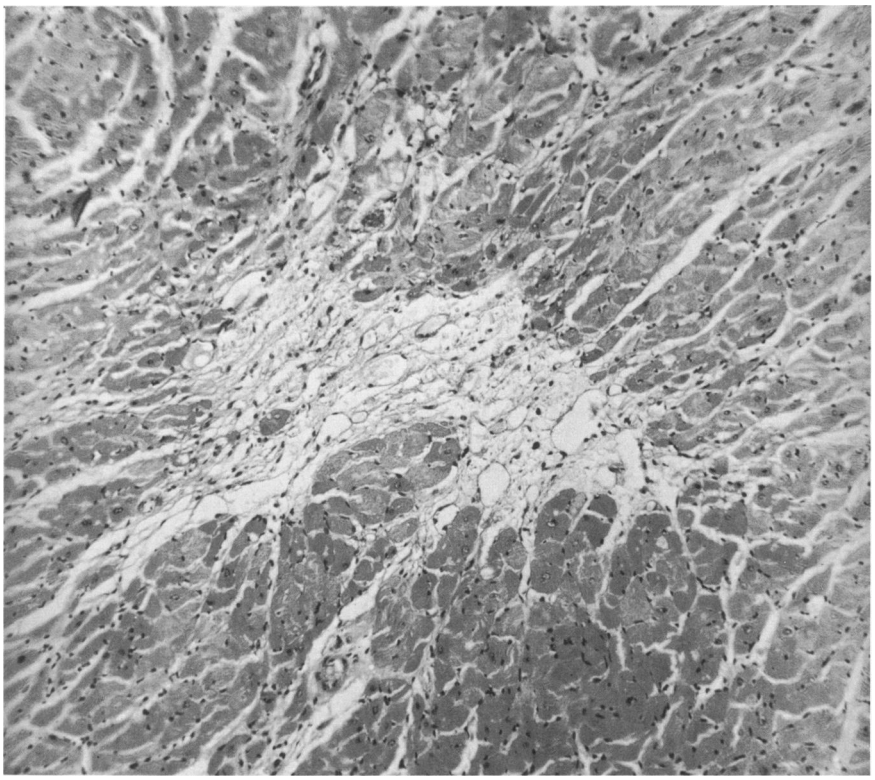

Fig 1—Section of heart of affected hamster. Myolytic lesion in the center of field. Necrotic lesions with cellular infiltration also occur.

sexes by 60 days. Two types of lesions are found (Figure 1)—acute myolysis with primary dissolution of myofilaments in the absence of significant cellular infiltration, and necrosis with significant round and inflammatory cell infiltrates. The latter is more common in strains with the shortest life-span (unpublished data). These lesions occur without vascular or valvular lesions.[4]

Healing of most of the acute lesions is complete by 100 days and new lesions are rarely observed in older animals, except in the BIO 40.54 line.

After healing, progression of the disease varies in the three lines, as stated above. Autopsy findings depend largely on the duration and extent of the congestive failure, with 90% of the animals succumbing with failure. Pathologic alterations are not usually found in early stages of cardiac involvement. In late stages, subcutaneous edema, ascites, hydrothorax and hydropericardium (Figure 2) are present. Liver, spleen, lungs, kidney and other visceral organs show congestive changes (Figure 3).

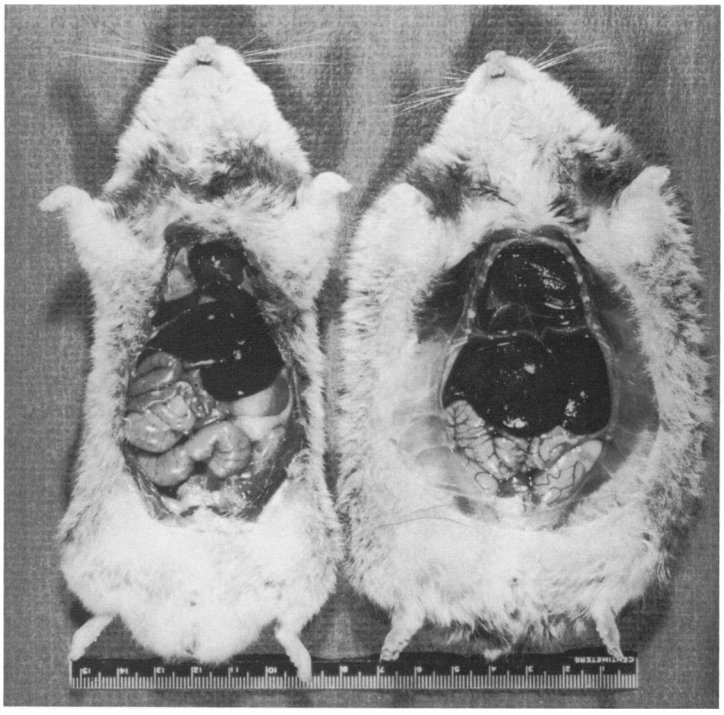

Fig 2—Gross lesions in Bio 14.6 hamster *(right)* with congestive cardiac failure. Note the enlarged heart and liver and subcutaneous edema. Normal hamster on the *left*.

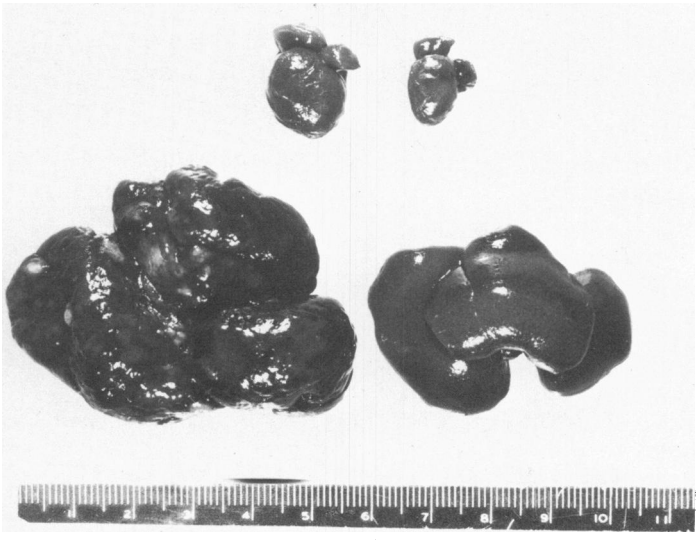

Fig 3—Grossly enlarged heart and liver *(left)*. Normal control heart and liver on the *right*.

Weight and dimensions of the heart depend upon the severity and course of the disease. Hearts from BIO 14.6 animals show marked hypertrophy (weights 2.5 to 3 times normal) without significant dilatation. Heart weights of BIO 40.54 animals increase 50 to 75% above controls, and the hearts are extremely dilated.

Comparison with Human Disease

Animals models that may have relevance to human cardiac disease have been difficult to produce. The cardiomyopathic Syrian hamster not only offers a model for the study of muscle disease but also for myocardial failure.

The muscle disease in the hamster differs from the majority of cases of muscular dystrophy in humans where skeletal muscle disease is the cause of death with failure of the muscles of respiration. However, Norris *et al*[5] reported a new form of human muscular dystrophy where the usual course of human dystrophy is reversed and the cardiac muscle disease becomes evident first. The published photomicrographs are practically indistinguishable from histologic sections of BIO 14.6 hamster hearts.

Congestive failure in these animals is clinically identical to the failure that occurs in the general category of human congestive heart failures.

As yet, the metabolic basis for human hereditary muscle degeneration has not been uncovered. The biochemical defects of muscle failure and the structure-function relationships of failing cardiac muscle have not been identified. While this model may not follow exactly the muscle disease found in humans, it offers a reproducible, spontaneous model of muscle disease and failure to which the tools of the physiologist and biochemist can be applied in an effort to answer these questions.

Availability

All dystrophic animals are available from TELACO, Bar Harbor, Me 04609.

References

1. Nixon CW, Whitney R, Baker JR, Homburger F: Primary myopathy in an inbred line (BIO 1.5 [Whitney]) of Syrian golden hamsters. Fed Proc 21: 313, 1962
2. Homburger F, Nixon CW, Harrop J, Wilgram G, Baker JR: Further morphologic and genetic studies on dystrophy-like primary myopathy of Syrian hamsters. Fed Proc 22: 195, 1963
3. Bajusz E, Homburger F, Baker JR, Opie LH: The heart muscle in muscular dystrophy with special reference to involvement of the cardiovascular system in the hereditary myopathy in the hamster. Ann NY Acad Sci 138: 213, 1966.
4. Nakao K, Oka M, Chen C, et al: Studies of the spontaneous myocardiopathy in the BIO 14.6 strain of hamster. Pathol Microbiol 35: 118-124 1970
5. Norris FR Jr, Moss AJ, Yu PN: On the possibility that a type of human muscular dystrophy commences in myocardium. Ann NY Acad Sci 138: 342, 1966