Pathology of the Syrian Hamster
Progress in Experimental Tumor Research, vol. 16
Editor: F. Homburger, Cambridge, Mass.
Publishers: S. KARGER, Basel
SEPARATUM (Printed in Switzerland)

Progr. exp. Tumor Res., vol. 16, pp. 242–260 (Karger, Basel 1972)

Cardiomyopathic Syrian Hamster: A Possible Model of Human Disease[1]

E. W. GERTZ

Harvard Medical School, Peter Bent Brigham Hospital, and Bio-Research Institute, Boston, Mass.

Contents

I. Introduction

Animal models in which to study mechanisms of myocardial failure have been difficult to create. A further problem is the need for a time-related model which may have pertinence to the prolonged onset of heart failure, as seen in man. The cardiomyopathy that occurs as an inherited defect in the BIO 14.6 strain of Syrian hamsters of the Bio-Research Institute and TELACO, Bar Harbor, Maine offers an unusual opportunity to study not only the pathology of the disease but also the biochemistry and physiology of a cardiomyopathy [1–4]. This model has the advantages of a predictable pathological course [5], adequate numbers of affected animals for study, and the development of the major characteris-

1 This work was supported in part by USPHS Grants I-FO2-HE-44215, HE-11306 (program grant), 1-TI-05890 (training grant) and HE-09791 (National Heart and Lung Institute) and General Research Support grant SO1-FR-05525 (Division of Research Facilities and Resources), and in part by grants from the American Heart Association (70-900) and the John A. Hartford Foundation.

tics of a progressive cardiomyopathy with dilatation, hypertrophy and failure.

This cardiomyopathic strain of Syrian golden hamster, first designated BIO 1.5, was derived from inbred lines of *Mesocricetus auratus* developed by Whitney in 1956 [6]. The BIO 14.6 strain, now available in greater numbers and more widely used, was derived by crossing the BIO 1.5 line with a nonrelated normal line, selecting breeders with the myopathy in the F_2 generation by means of early muscle biopsy, thus deriving a new dystrophic line (fig. 1). The cardiac disease develops from an as-yet undetermined genetic metabolic defect. In addition, this defect induces degenerative lesions in all striated muscles [7]. The genetic abnormality has been established to be inherited in a recessive autosomal mode [6, 7]. Viral and other infectious agents as well as vitamin E, potassium and magnesium deficiencies have been ruled out as etiologic factors [8].

Chronic, progressive cardiac failure amenable to cardiac glycoside therapy [9] is the ultimate cause of death in over 90% of these hamsters. The disease appears to separate into 4 histological and clinical phases during the life of the animal: prenecrotic, necrotic or myolytic, hypertrophic and terminal. During the first or 'prenecrotic' phase the animals show no clinical or histologic evidence of disease. At approximately 30 days of age in the females, and 45 days in males, the first lesions appear histologically, thus beginning the second phase. By 60 days the incidence of cardiac lesions is 100% in both males and females [5]. This phase continues until the animals are 80–90 days old. At this time healing has occurred and only mild, scattered new lesions remain (end of second phase). During the second phase, there are no clinical signs and this rapidly progressing acute phase of the disease results in negligible mortality [5].

When the disease in this strain (14.6) was first described, hypertrophy of the heart began at approximately 85 days (third phase) and the animals succumbed to congestive failure (fourth phase) at approximately 150 days of age [5]. After 28 generations of inbreeding, the number of acute *necrotic* lesions in the second phase has decreased, the third or hypertrophic phase does not begin until approximately 120 days, and the fourth or terminal phase has been prolonged so that the majority of the animals now survive over 280 days, with some living more than one and one-half years. The reason for the slower progression of the myocardial failure, with consequently increased life-span, is as yet unknown. How-

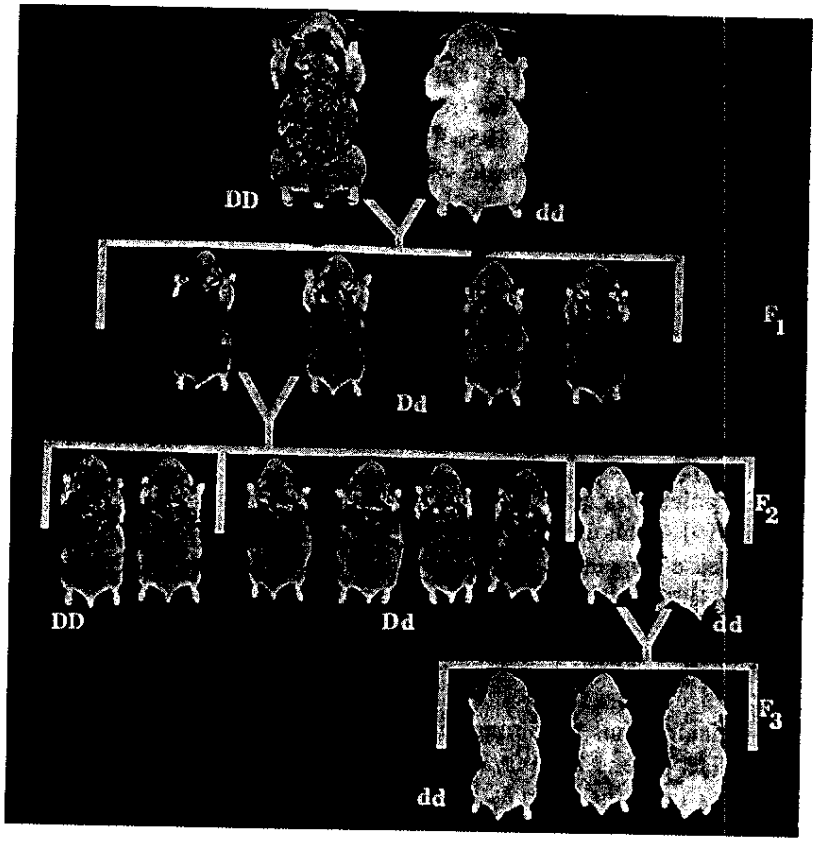

Fig. 1. Genetics of the cardiomyopathic hamster. DD represents the normal line, and dd the cardiomyopathic animals. The defect is inherited as an autosomal recessive. The Dd animals carry the gene but do not have any signs or symptoms of the disease. The gene is not linked to coat color. The dystrophic animals may have brown or white coats. The white coats were used only for demonstration. (Published with permission of the *American Heart Journal.*)

ever, one can speculate that with constant inbreeding only the less severely affected animals will produce litters or will have large litters and perpetuate the line with offspring with decreasing severity of disease.

A new line, BIO 40.54, has been developed recently by crossing a 14.6 animal with an animal of a nonrelated strain, as described above for the original BIO 1.5 strain. The new line, which is in the eleventh

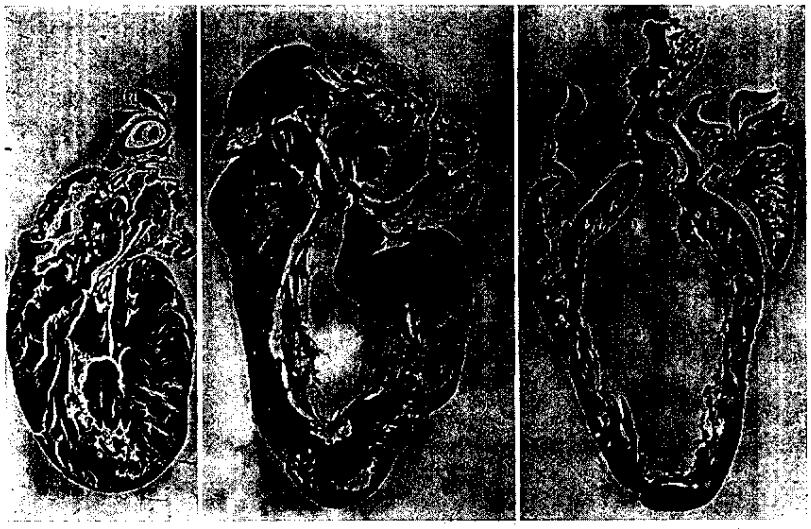

Fig. 2. Three histologic phases of the disease. *a* Necrotic phase: small hearts with focal lesions. *b* Hypertrophic phase: heart enlarged with obvious hypertrophy (note thrombi in right ventricle and atrum). *c* Terminal phase: heart enlarged with dilatation (hypertrophy not obvious). × 10. (Published with permission of the *American Heart Journal* and *Annals of the New York Academy of Sciences.*)

generation, has histological and clinical characteristics identical to those of the BIO 14.6 strain when it was first described. Ninety percent of the animals succumb with congestive heart failure before the 184th day of life. Biochemical and physiological studies are now under way to determine whether or not any differences exist between this new strain and the original BIO 14.6 strain.

II. Clinical Course and Gross Pathology

Since the disease in the BIO 14.6 strain has become less severe, it is difficult to correlate the age of the animal with the clinical and gross pathological course of the disease. Therefore, we will refer only to phases of the disease, as outlined above. During the first and second phases of the disease, no clinical or gross pathologic changes have been noted.

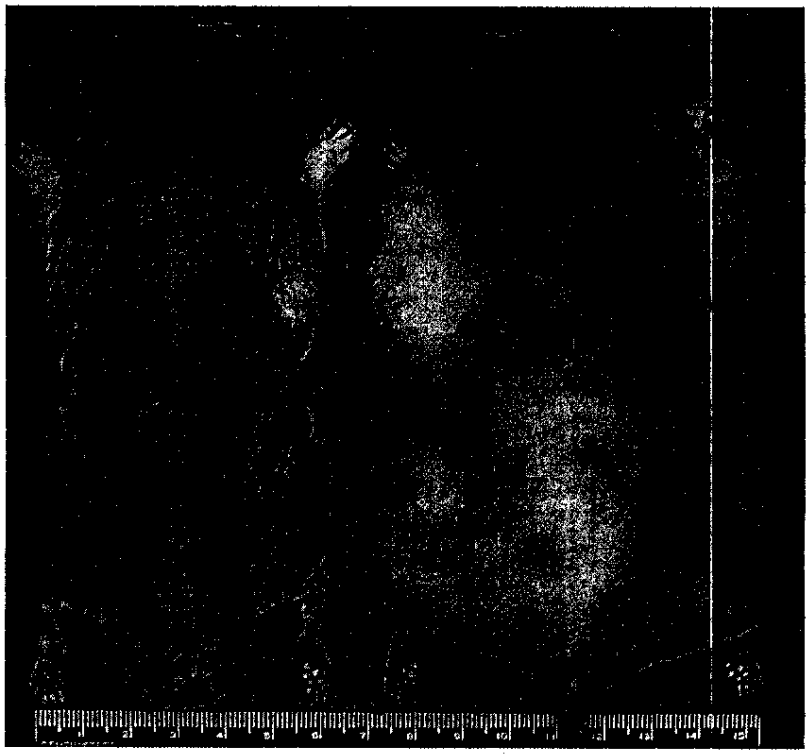

Fig. 3. Gross appearance of the hamsters. Both animals are of the same age and sex. The one on the left is the control. The one on the right is a cardiomyopathic animal in the terminal phase. The increased size is due to the subcutaneous edema. Fluid accumulation can almost double the weight of the animal.

QRS complex and spatial vector occurring coincidentally with the development of the histologic lesions [8]. In the third or hypertrophic phase, clinical signs of cardiac disease are absent but animals dying spontaneously often have hearts with clearly visible white streaks that follow the direction of the myocardial fibers. These streaks have been shown to be secondary calcification of the degenerating muscle [5]. Acute pulmonary edema (obvious pulmonary congestion without significant increase in liver weight or peripheral edema) is also observed at this time. Sometime during the third phase the animal's heart begins to dilate (fig. 2) and the animal enters the terminal or fourth stage of the disease.

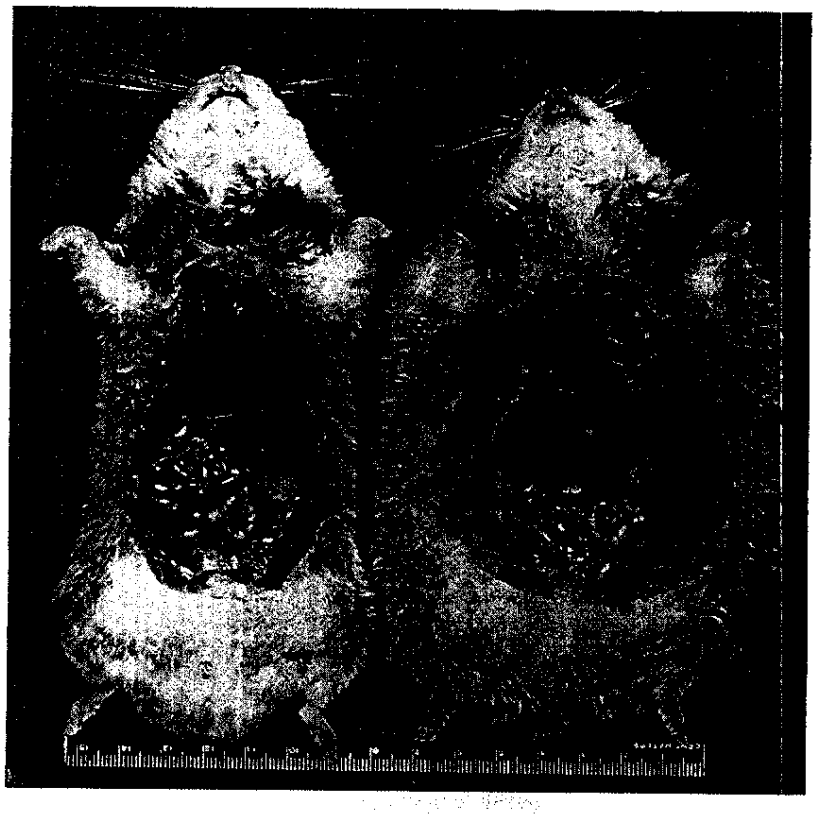

Fig. 4. Comparison of normal and cardiomyopathic body cavities. Both animals are of the same age and sex. The animal on the left is normal, the one on the right is myopathic. Note the increased size of the myopathic animal due to subcutaneous edema. (Published with permission of the *American Heart Journal.*)

In this stage all of the commonly accepted signs of progressive heart failure appear. The animal begins to gain weight through generalized fluid accumulation, with dependent subcutaneous edema following (fig. 3). Soon thereafter, hyperpnea and cyanosis appear and death occurs several days later. At autopsy the findings depend largely on the extent and duration of the congestive heart failure. There is general loss of skeletal muscle mass and adipose tissue. When the body cavity is opened (fig. 4), subcutaneous edema, ascites, hepatomegaly, hydrothorax and, in a small percentage of cases, hydropericardium are noted. The

Fig. 5. Detailed view of organs *in situ* of cardiomyopathic hamster in terminal stage. Note the ascites and pleural effusion, also the large heart and liver. Livers from these animals can weigh as much as 8 g. Normal liver weight averages $2^1/_2$ g.

liver is firm, the capsule tense (fig. 5), the lungs congested, and the heart enlarged. There is moderate congestion of the kidneys as well as other visceral organs. When the heart is opened, dilatation of the ventricles and atria are apparent. Well organized ventricular and artial mural thrombi as well as fresh thrombi are frequently seen (atrial > ventricular) [10]. Compared to controls, the heart weight (fig. 6) (exclusive of blood and

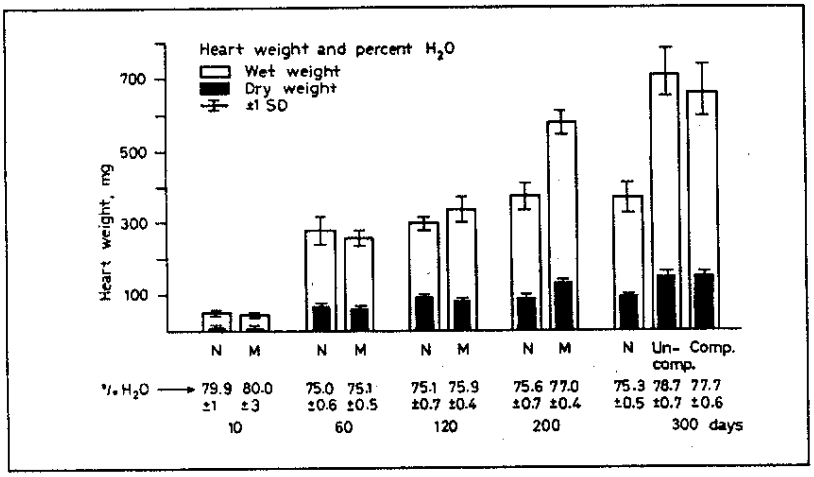

Fig. 6. Heart weight and percent water of normal and cardiomyopathic hamsters. Each bar represents the mean of at least 20 hearts. The open bars represent the wet weights, the solid bars, dry weights. The numbers below each bar indicate the mean percent water.

thrombi) increases more than two-fold with the ventricular mass increasing 30–50%. The control strains are those with heart weights similar to those of the BIO 14.6 strain before hypertrophy occurs.

In order to determine the degree of hypertrophy, one would ideally choose heart weight: body weight for comparison. However, since these animals accumulate fluid in the terminal phase of the disease, this ratio is not realistic, and heart weight: brain weight might be used as a more accurate index of hypertrophy. The brain weight varies with the size of the animal, but because of space limitations imposed by the skull, it cannot accumulate large amounts of fluid during the terminal phase. This could serve as an internal control for a study of interventions that might change the extent to which the heart hypertrophies. Part of the increased weight of the heart is due to edema. Although the accumulation is statistically significant ($P<0.05$) in the terminal phase, it is not responsible for the total increased weight of the ventricles, which actually is due primarily to the increased dry mass of the heart. There is biventricular hypertrophy in the majority of cases. After dilatation occurs, it is difficult to determine which of the three muscle layers is involved in the hypertrophy and no data are yet available in this regard.

III. Histology

Histologic lesions have never been seen in these myopathic hearts before the 25th day of life [5, 11]. Although there is a 100% incidence of the disease in these animals, the females develop the lesions first at approximately 30 days, with the males beginning at 45 days. By 60 days the incidence is 100% in both sexes. The lesions that appear initially consist of focal myolysis (fig. 7) with primary disappearance of sarcoplasm. Fiber disintegration is marked by a dissolution of myofibrils so that the sarcolemma is filled with an amorphous material [1]. The sarcolemmal remnants apparently collapse, for they become indistinguishable from the surrounding connective tissue skeleton of the heart. When the disease is at its peak histologically, another type of lesion which becomes apparent is characterized by cardiac cells undergoing necrosis (fig. 8) [5]. These lesions are usually larger than those showing only myolysis and are accompanied by massive cellular infiltration. The type of cellular infiltrate has not been well defined. Both of these lesions remain focal during the entire course of the disease; their distribution, however, shows wide variation in the muscle layers from heart to heart. In some animals a majority of the lesions appear in the myocardial and epicardial areas, while in others only the endocardium is involved. However, right and left ventricles appear to be equally involved.

Healing begins sometime after 60 days and is complete by approximately 90 days, although fresh lesions of mild severity continue to occur throughout the life of the animal. Healing progresses in various ways; some lesions show vascularization, histocytic proliferation and/or fibroplasia, and others exhibit calcification and/or sclerosis. The manner in which the lesions heal is apparently unpredictable. Recently BAJUSZ *et al.* [5] suggested that 'healing' of the myolytic lesions may occur by collapse of the surrounding fibers upon the interstitium and without collagenous scar formation. This hypothesis was based on finding fewer 'scars' in older animals than one would predict on the basis of the number of lesions seen in younger animals. One group of investigators [12] has postulated that the amount of collagen in the older myopathic hearts is greater than in normals, and this should be taken into account in studying certain biochemical and physiological parameters. This group found that at 90 days noncollagen protein nitrogen (NCPN)/g wet weight of heart was 21% lower in myopathic animals compared with age-matched controls ($P<0.001$). At 140–150 days (animals in terminal

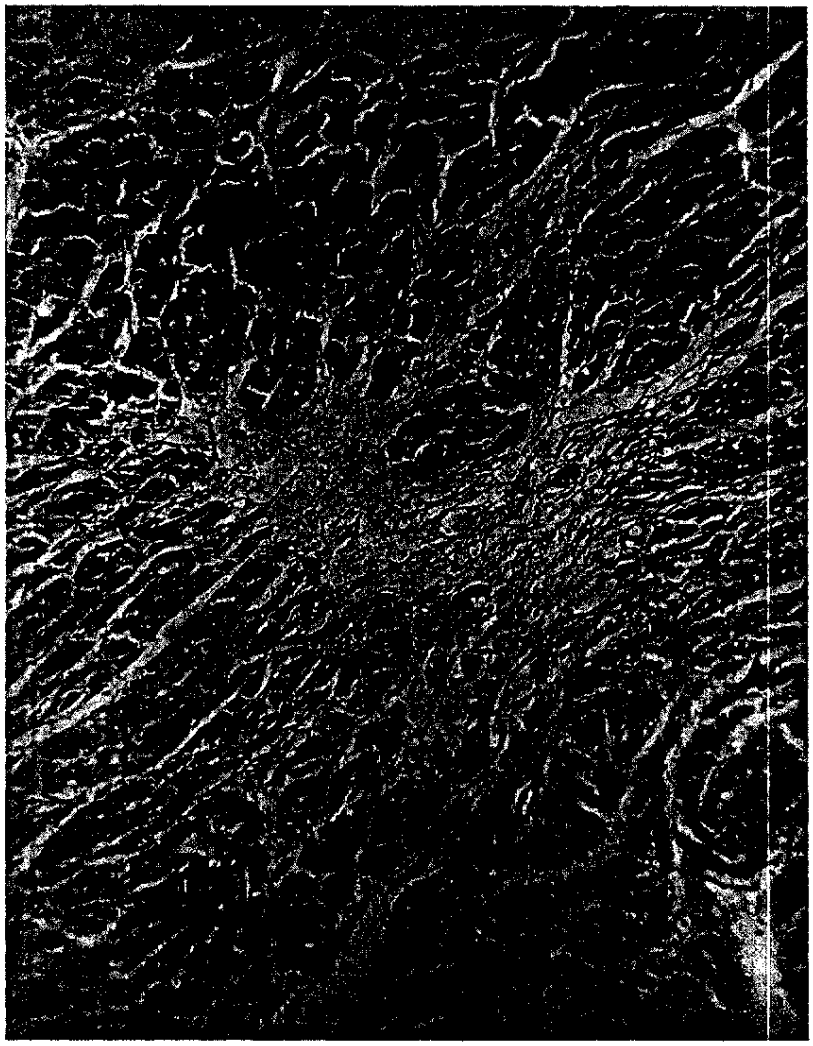

Fig. 7. Morphology of a myolytic lesion. Lysis occurs in the absence of cellular infiltration. Muscle fibers disintegrate, leaving only cell membranes. × 450.

stages of heart failure) the NCPN was approximately 15%/g wet wt.

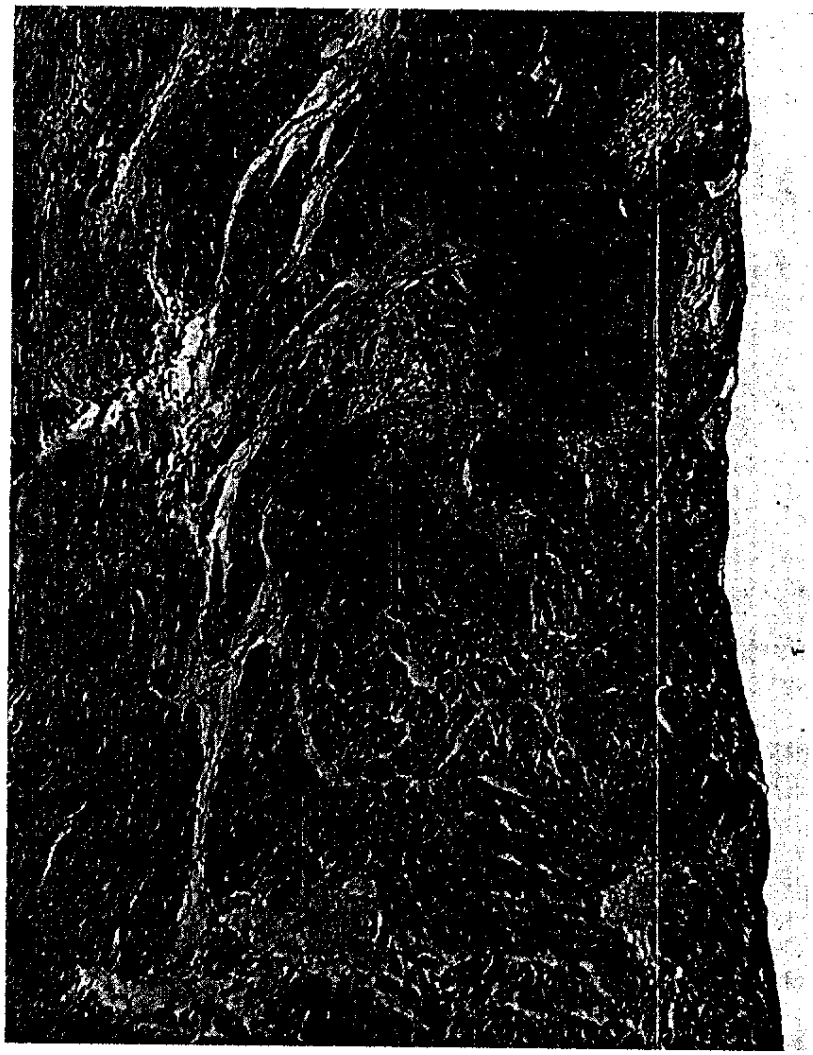

Fig. 8. Morphology of cellular necrotic lesion. Single arrows indicate the necrotic lesions with cellular infiltrate. Double arrows show a mycolytic lesion in the same field. × 40.

Table I. Hydroxyproline and collagen concentration in normal and myopathic hearts

	Age (days)	Hydroxyproline, μg/mg dry weight	Collagen[3] % wet weight	Percent change in collagen
Control	300	1.5±0.130	0.294	
Myopathic[1]	300	2.17±0.173[2] P<0.02	0.350	19.0

1 BIO 14.6 animals in terminal stage of congestive heart failure.
2 ±1 SD.
3 Mammalian collagen consisted of 13.4% hydroxyproline.

Examination of tissue sections stained for collagen by the Masson Trichrome method suggests that there is more connective tissue in the myopathic hearts. These are, however, indirect measurements of collagen and are subject to some doubt [13, 14].

Since hydroxyproline is found only in collagen and its concentration in collagen is constant, one could use this amino acid to determine the connective tissue component of the myocardium. Accordingly, myocardial hydroxyproline was determined in these hearts by the method of PROCKOP and UNDENFRIEND [15] (table I). These studies were done in conjunction with E. H. SONNENBLICK and A. C. STAM, jr.

The data would indicate that while there is a statistically significant increase in the concentration of collagen in these myopathic hearts, the increase that this represents in the total mass of the myopathic heart is, for all practical purposes, insignificant.

Other histologic abnormalities, such as valvular change, are rare. As noted above, atrial and ventricular mural thrombi do occur in the late stages of the disease but there is no correlation of their appearance with the severity of the congestive heart failure. The histologic changes seen in the lungs, liver, spleen and kidneys are all attributable to passive venous congestion. The severity of these changes depends on the duration and severity of heart failure before death. The liver appears to be most severely affected by venous congestion, over three-quarters of the cells being destroyed with moderately severe failure. Hemosiderin-laden macrophages are seen in large numbers in the lungs. The inner zones of the adrenal cortex show marked atrophy [16]. In severe heart failure the

width of the zona reticularis and inner fasciculata can be decreased by as much as 49 percent [16], compared to aged-matched controls. However, the zona glomerulosa becomes markedly hypertrophied in moderate to severe failure [16]. Skeletal muscle changes that occur in these animals are described elsewhere in this book [17].

IV. Biochemical and Physiological Studies

Studies of the hemodynamics of the *in situ* heart [18, 21], mechanics of the isolated perfused heart [11, 19, 20], and mechanics of the isolated papillary muscle have been performed [4], using the BIO 14.6 hamster. All of these studies have shown that the contractility of these hearts is depressed, i. e., they are hypodynamic hearts. The hemodynamic studies are described elsewhere in this book in great detail [21]. Isolated perfused hearts obtained from myopathic hamsters[2] more than 200 days of age have shown decreases in peak height of tension development, tension time index, tension time/min and maximum rate of rise of developed tension. In addition, time to peak tension of the hearts has been found to be prolonged in all ages from five weeks until death [11].

Myocardial mechanics performed on isolated papillary muscles have yielded some conflicting data. Developed force and maximum rate of developed force, both corrected for cross-sectional area of muscle, were depressed in all myopathic animals studied from 60 days of age until death, with the greatest depression in muscles from animals in severe failure. Time to peak force of the myopathic muscles was not found to be different from the controls at any age [4]. In addition, $V_{ce}max$ in myopathic animals 220 to 320 days of age was found to be similar to that of controls. The disparity in the results obtained by these 2 groups of investigators is most likely explained by the vast differences in their preparations. In any case, this point must be resolved for the following reasons: maximum velocity of contraction and time to peak force (TPF) theoretically represent the rate at which cross bridge formation is occurring [22]. Maximal force developed represents the number of active cross bridges [22]. If Vmax and TPF are not depressed in the myopathic hearts, and maximal force development is, one can conclude that the

2 The myopathic hamsters for this study came from an inbred line maintained in South Africa. The line was originally started by the offspring of a single BIO

number of cross bridges is less, but those remaining are normal. Two types of decrease in the number of cross bridges might be observed: (1) a defect in the excitation-contraction coupling system, leading to a decrease in the amount of calcium available for cross bridge formation, and (2) a primary defect in contractile protein synthesis, leading to decreased amounts of protein or partially inactive protein.

On the other hand, if TPF is depressed, one might be dealing with contractile proteins that not only have quantitatively fewer cross bridges but whose functioning cross bridges are qualitatively abnormal. In addition, a defect in the excitation-contraction coupling system may be present.

As yet, no genetically determined molecular defect has been found to be responsible for the muscle degeneration. Except for alterations in the calcium and magnesium levels in the cardiac tissues [23], no biochemical defect has been found before onset of the histologic lesions.

Perhaps the most widely studied biochemical reaction in these animals has been oxidative phosphorylation [2, 11, 24, 25, 26, 27, 28]. Impairment in oxidative phosphorylation of mitochondria isolated from cardiomyopathic hamster myocardium in the terminal stage of the disease has been well documented [2, 11, 24, 25, 26, 27]. Whether oxidative phosphorylation is depressed in younger animals (animals not in congestive heart failure) is still questionable. In fact, LINDENMAYER *et al.* [24] report that in hamsters with cardiomegaly but without gross signs of cardiac failure, oxidative phosphorylation may be enhanced over that of normal controls as evidenced by a higher respiratory control index.

The extent to which a defect in excitation-contraction coupling is involved in the production of the disease or the presumably secondary myocardial failure has been investigated using isolated sarcoplasmic reticulum [3].

Under physiologic conditions, the sarcoplasmic reticulum assumes a major role in supplying calcium for contraction [22]. Its ATP-dependent calcium pump brings about relaxation by sequestering the calcium from the myofilaments [22]. It has been postulated that if this pump were depressed, it would pump less calcium/unit time, leading to less calcium in the sarcoplasmic reticulum and eventually to less calcium for contraction [29]. Although no direct cause and effect relationship has been demonstrated, acute heart failure in dogs [30] and chronic heart failure in cattle [31] and in humans [32] has been associated with a depression of the sarcoplasmic reticular ATP-dependent calcium pump. Accordingly, sarcoplasmic reticulum was isolated from BIO 14.6 hamsters and appropri-

Table II. Calcium pumping rate of isolated sarcoplasmic reticulum

Age, days	Normal	Myopathic
10	1.16±0.032[1]	1.09 ±0.044
200[2]	1.07±0.061 (P<0.05)	0.837±0.023
300[3]	1.12±0.066 (P<0.05)	0.750±0.023
320[4]	1.04±0.041 (P<0.05)	0.243±0.018

Each value represents the mean of at least 3 experiments with 10–35 animals in each experiment. Rate is expressed in μmoles/mg protein/min.
1 ±1 SE of the mean.
2 Animals not in gross failure but with hepatomegaly.
3 Animals with hepatomegaly and pleural and/or peritoneal effusions.
4 Animals in terminal failure (life expectancy <1 day).

ate normal controls. It was studied with particular attention to the *quantity* of sarcoplasmic reticulum in the hearts, and the *quality* or performance of the sarcoplasmic reticulum, as characterized by the calcium oxalate capacity and calcium oxalate rates at different stages of the disease [3]. The specifics of the experimental protocol have been published elsewhere [3, 9]. The rate of ATP-dependent calcium pumping of the fragmented sarcoplasmic reticulum averaged 1.08±0.06 μmoles/mg protein/min in normals of all ages studies (table II). The rate of uptake fell as failure progressed. When the animals were not in failure, i. e., at 10, 60 and 120 days, the rates were not different from those of the normals.[3] In contrast to the rates, the calcium oxalate capacities of the sarcoplasmic reticulum were not different from those of the controls at any age (table III). Similar data have been obtained by A. SCHWARTZ *et al.* [33, 34]. The *quantity* of sarcoplasmic reticulum in the tissues as judged by the calcium oxalate capacity of the homogenate was unchanged at ten days from that of the controls, but there was a reduced 50%/unit wet wt. of heart at 200 days and older. The ventricles of the latter animals weighed 1.5–1.75 times that of appropriate controls. Most importantly then, the calcium oxalate capacity per whole heart was not reduced, while that per unit heart was.

This study provides further support for the view that there is a depression of the rate of calcium pumping by the sarcoplasmic reticulum

3 E. W. GERTZ: Unpublished observation.

Table III. Calcium oxalate capacity of isolated sarcoplasmic reticulum

Age, days	Normal	Myopathic
10	5.30±0.153	5.73±0.291
200	5.80±0.203	5.77±0.240
300	5.80±0.379	5.73±0.376
320	5.80±0.239	5.50±0.260

Values are expressed in μmoles/mg protein (see table II for additional details).

Table IV. Calcium oxalate capacity of whole heart homogenate

Age, days	Normal	Myopathic
10	43.4±0.404	42.1±0.403
200	42.4±0.393 ($P<0.05$)	22.2±0.755
300	42.9±0.825 ($P<0.05$)	21.2±0.775
320	42.4±0.731 ($P<0.05$)	21.5±0.517

Values expressed in μmoles/g wet weight of heart. Studies were done in the presence of Azide and low free calcium concentration to prevent membranes other than the sarcoplasmic reticulum from accumulating calcium (see table II for additional details).

associated with myocardial failure, and this pumping rate decreases as myocardial contractility decreases. The study also suggests that the hypertrophy occurring in these animals is associated with a 'dilution' of the sarcoplasmic reticulum (the calcium oxalate capacity of the sarcoplasmic reticulum is unchanged but the calcium oxalate capacity/unit heart is depressed; therefore, less sarcoplasmic reticulum is present). If this were the case, there would be an inadequate amount of sarcoplasmic reticulum to store the calcium needed to activate the myofilaments and failure would ensue.

V. Summary

The clinical, pathologic and histologic characteristics of the BIO [illegible] are well known. Extensive physiological and

biochemical studies have been undertaken but none has shed light on the genetically determined molecular defect in these animals. As in other genetically determined diseases, the defect probably is in an enzyme system, specifically, a protein [35]. To date no study has uncovered a specific defect in an enzyme system or individual protein before histologic evidence of the disease occurs. If these animals indeed have a genetically determined disease, the molecular abnormality should be present *in utero*. Until a defect is found in very young animals, one must assume that all of the other interesting abnormalities observed are secondary to the genetic defect or to its devastating consequences.

Acknowledgment

I wish to acknowledge Miss MARY ANN LEVKO's helpful suggestions in the preparation and review of the manuscript.

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Author's address: EDWARD W. GERTZ, M.D., Bio-Research Institute, Inc., 48 Cummington Street, *Boston, MA 02215* (USA)