MYOPATHY OF HAMSTER DYSTROPHY: HISTORY AND MORPHOLOGIC ASPECTS

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PART I. MUSCULAR DYSTROPHY IN THE HAMSTER

MYOPATHY OF HAMSTER DYSTROPHY: HISTORY AND MORPHOLOGIC ASPECTS

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On April 9, 1962, F. Homburger, J. R. Baker, C. W. Nixon, and R. Whitney submitted a manuscript to *Medicina Experimentalis*, published by S. Karger, Basel, Switzerland, then edited by R. Domenjoz of Bonn, entitled, "Primary Generalized Polymyopathy and Cardiac Necrosis in an Inbred Line of Syrian Hamsters."[1] This paper described in approximately 100 hamsters of a new inbred line identified as BIO 1.50 (Whitney) "a polymyopathy which does not interfere with reproduction, occurs at a high rate, relatively late in life (at about 20 days of age), and allows the afflicted animal to live some 220 days." It was suggested that "this myopathy may constitute a better biologic tool for study of the disease mechanism than any now available and the involvement of the heart muscle renders these hamsters interesting subjects for studies on myocardiopathies." On July 21, 1962, *The Lancet* commented editorially on our observation of the new hamster polymyopathy,[2] calling it to the attention of "all who are engaged in experimental work on muscle disease in man and animals." We proceeded to publish the results of our genetic studies[3] (crossing affected BIO 1.50 animals with healthy animals of unaffected lines, demonstrating the absence of the disease in the F_1 generation and crossing brothers and sisters within the F_1 generation with the result that 25% of their F_2 offspring exhibited the polymyopathy, concluding that the disease was transmitted by an autosomal recessive gene and proving this contention by obtaining a 100% myopathic F_3 generation when crossing affected siblings of F_2). *The Lancet* commented with a second editorial on April 20, 1963,[4] recognizing that "the myopathic trait should easily be maintained in vigorous, rapidly breeding heterozygous animals" and that "biochemical, histochemical and histological research on these animals may well throw light on the pathogenesis of the genetically determined myopathies in man." From then on, based on our initial observations and on the work of Bajusz, who joined us from Selye's group in Montreal, in addition to the studies of Sonnenblick and his group, then at the Peter Bent Brigham Hospital and Harvard University School of Medicine, the inbred cardiomyopathic hamster gained wide acceptance as a tool for the study of mechanisms of myopathy in general and cardiomyopathy in particular.[5-19] Two conferences held by The New York Academy of Sciences centered around the cardiomyopathic hamster (November 1965 and January 1967).[20, 21] Three symposia were held at the Bio-Research Institute on cardiomyopathic hamsters and on other inbred hamsters (The Pathology of the Syrian Hamster, 1970; Comparative Pathology of the Heart, 1973; The Syrian Hamster in Toxicology and Carcinogenesis Research, 1977), and the proceedings were published as Volume 13 of the series *Advances in Cardiology* (S. Karger, Basel and New York, 1974) and Volumes 16 and 24 of *Progress in Experimental Tumor Research*, S. Karger AG, Basel and New York, 1972 and 1978, respectively). Meeting reports on some of these conferences have appeared in the literature.[22-24] The literature on the subject

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is now rather extensive and international in origin. A general review is overdue but is not the subject of this report.

History of Myopathic Hamster Lines

Since the beginning of its work on Syrian hamsters, the Bio-Research Institute adopted the technique originated by Little,[25] and others for murine studies, of establishing many inbred lines by brother × sister matings and searching for new mutations among the resultant populations. The use of this technique led to the discovery of many mutant traits, described below.

The first dystrophic muscle in one of our inbred lines was noted purely accidentally by Dr. Hulda Magalhaes when she was studying hibernating glands on some of our slides and found that muscle fibers surrounding some of these glands appeared damaged, perhaps artifactually. A search was made for additional tissue of such animals, and it was noted that all sections that contained "damaged" muscle came from animals of the BIO 1.50 line. Further study of other muscles of these animals yielded the discovery of polymyopathy in these hamsters. Through an accident of inbreeding, this line had become homozygous for the gene for cardiomyopathy.

This original BIO 1.50 (Whitney) line had been derived from a white LaCasse sire and a brown Schwentker dam and had been maintained by brother × sister matings between white and brown animals. It was well past 25 generations of such inbreeding and had been in use for studies on myopathy for about 3–4 years when it was noted that the course of the disease became less rapid and the survival time more prolonged, from 220 days to more than 1 year. In August 1964, therefore, male 14 of line BIO 1.50 was crossed with female 6 of line BIO 89.9, a healthy new line then only in its ninth generation of inbreeding and derived from animals that originated from LaCasse and received by Whitney through Gulf Hamstery and Toolan. From this mating, we derived, by crossing affected, myopathic siblings, the new myopathic, homozygous line BIO 14.6. This new cardiomyopathic line, which today is the most widely used, was again employed to study the genetics and to redetermine the mode of inheritance.[26] Again, the incidence figures obtained in outcrosses and backcrosses match the figures expected for an autosomal recessive gene. Today, several cardiomyopathic lines are maintained in our foundation stocks (Table 1). They are the BIO 14.6 line, with a life expectancy of 12 months, the BIO 40.54 line, living 8–10 months, the BIO 82.62 line, living 6–8 months, and BIO 53.58, which, at a life-span of 6 months, is the shortest lived.

For the sake of historical accuracy, it must be noted that our inbred strains were nearly lost at an early stage of their development because of our inability to obtain grant-in-aid support for this type of study, namely, the definition by experimental pathology and population genetics of a neglected rodent species. A further obstacle was the delay of our first publication by nearly one year due to the obstinate refusal of a reviewer trusted by the journal *Science* who failed to accept the concept of a new disease in the hamster.

The insight and generosity of the Fannie E. Rippel Foundation, of New Jersey, eventually saved this project, and it was followed by the John A. Hartford Foundation and the Camille Dreyfus Foundation, of New York, who gave us support.

TABLE 1

CARDIOMYOPATHIC LINES OF INBRED SYRIAN HAMSTERS MAINTAINED BY BIO-RESEARCH CONSULTANTS AND ITS SUBSIDIARY TELACO, BAR HARBOR, MAINE

Designation of Line by TELACO	Number of Generations Inbred		Average Litter Size at Weaning		Survival Time † (months)	Coat Color	Genotype	Original Source
	TELACO *	Cambridge	TELACO	Cambridge				
BIO 14.6	50	51	4	4.1	12	acromelanic white	c^d/c^d, *cm/cm*	Schwentker LaCasse
BIO 40.54	33	32	4.5	4.0	8–10	agouti ‡	+/+, *cm/cm*	Schwentker LaCasse
BIO 82.62	29	38	5	3.6	6–8	acromelanic white	c^d/c^d, *cm/cm*	Schwentker LaCasse
BIO 53.58	23	22	5	5.2	6	acromelanic white	c^d/c^d, *cm/cm*	Schwentker
F_1B hybrid §				7.6	?	agouti	cross of BIO 87.20♀ with BIO 1.5♂	Ingham, Toolan National Institutes of Health, Gulf

* Continuous brother × sister matings.
† Before spontaneous death, usually from cardiac failure.
‡ Stock of TELACO 40.54 is acromelanic white, genotype c^d/c^d.
§ A nonmyopathic control animal.

Early Diagnosis of Cardiomyopathy

For the development of new cardiomyopathic lines and for other types of studies, the diagnosis of the early stages of the disease is crucial. At first, this goal was possible only by biopsy of a muscle (usually the cheek pouch retractor muscle, taken at its dorsal origin). Serum enzyme studies revealed that serum phosphocreatine kinase activity is significantly elevated in myopathic animals about 30 days of age,[26] and a new micromethod rendered this approach more practical.[27] However, it remains invasive, requiring the drawing of blood.

Forced swimming, which, after 1–4 hr, reveals adductor weakness in myopathic animals but never in normal animals, is another practical way to make an early diagnosis;[26] however, it causes by itself some aggravation of the disease. Most recently, it has been found possible to diagnose cardiomyopathy by inspection of the lower surface of the tongue.[28] After 55 days of age, there appear in all cardiomyopathic animals whitish dots of 1–5 mm diameter, located at the lower and lateral surfaces of the tongue. Histologically, these lesions are calcified focal areas of myolysis. They were seen in only four of 220 healthy control animals and only occurred after 100 days of age.

Histopathology of Hamster Polymyopathy (skeletal muscle)

The description of hamster polymyopathy is mostly our own, because the work of others has predominantly dealt with physiologic or biochemical observations. Our first descriptions were based on only 100 animals of the cardiomyopathic BIO 1.50 line.[1] Perhaps erroneously, we emphasized at first the reactive aspects of the muscle change, likening the histopathology to that of human necrotizing myopathy.[29] In a later systematic study,[30] which included 1000 animals, the following features emerged as the important ones: There is disappearance of muscle fibers through atrophy and fragmentation. The remaining muscle fibers vary greatly in size, and sarcolemmal nuclei are increased in numbers, enlarged, and of greatly variable shapes (Figure 1). There are hyaline and granular degeneration and appearance of myoblasts. Bands of young connective tissue and fat cells may separate the atrophic muscle fibers. Occasionally, there exists in hamster dystrophy the element of necrosis and interstitial connective tissue reaction referred to above.

The earliest lesion of hamster dystrophy is a perinuclear halo (Figure 2), clearly distinctive of the type of artifactual change occasionally noted in the perinuclear area of normal muscle fibers. The perinuclear halo of muscular dystrophy has irregular borders and contains finely granular material. These perinuclear halos gradually become larger and more eosinophilic as the disease advances, and, in the course of the formation of nuclear rows, they fuse to form the pale sleeves that surround nuclei arranged in rows. In contrast to an apparently similar phenomenon described by West and Murphy,[31] the perinuclear halos of hamster myopathy do not contain ribonucleic acid. The perinuclear zone appears to be the area wherein the first visible changes (by light microscopy) of muscular dystrophy in hamsters are occurring.

The most severely affected muscle in autopsied animals was the supraspinatus (shoulder muscle). In animals under 30 days of age, central nuclei and internally rowing nuclei are normally present, since at that age the muscles are still growing. Up to 30 days, fiber necrosis is the only sign of dystrophy.

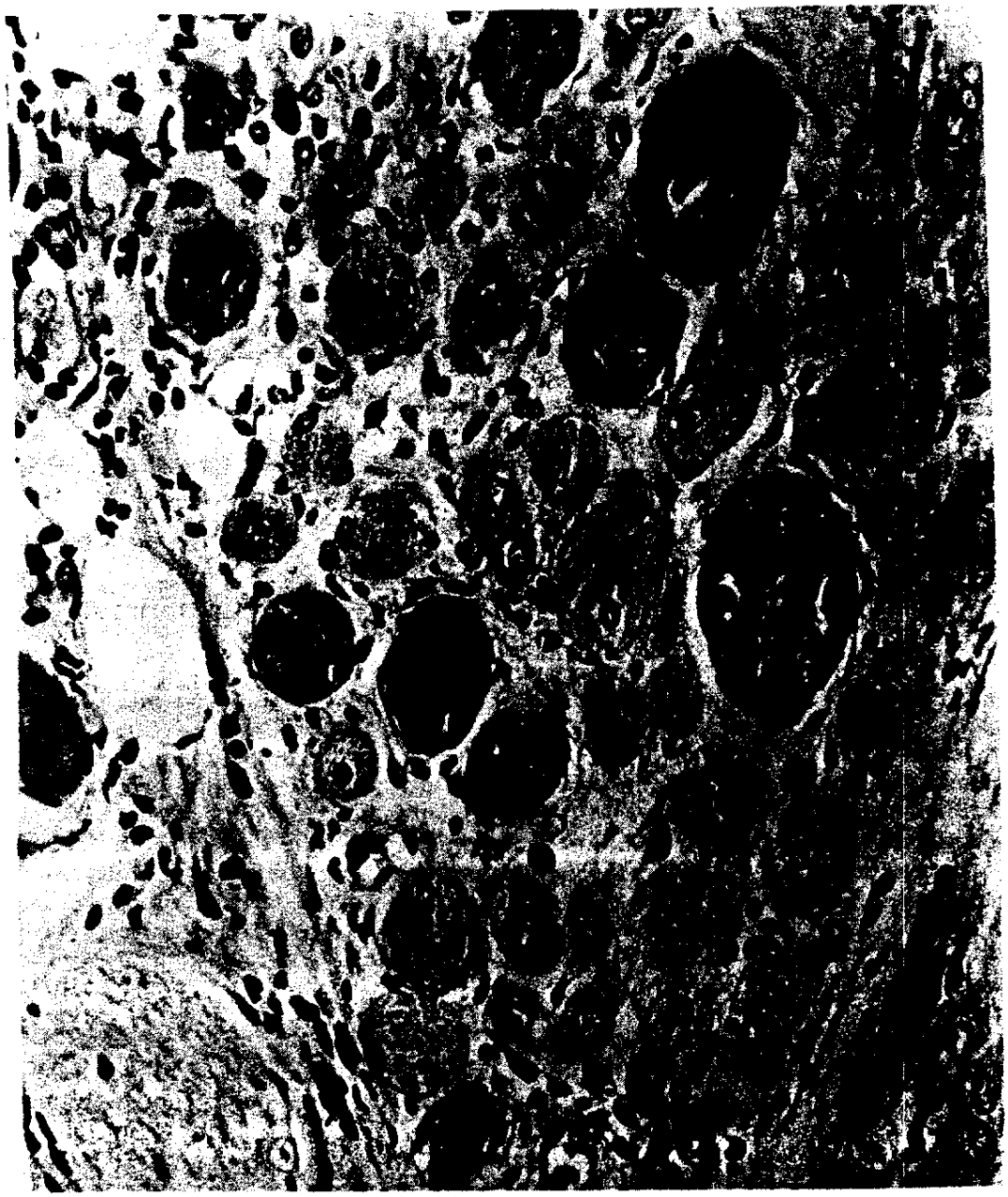

FIGURE 1. BIO 14.6 male, 70 days old. Back biopsy reveals multinucleated, necrosed, and regenerating fibers. Hematoxylin and eosin. ×260.

After 200 days of age, the finding of even a mild degree of dystrophy in any muscle (more than four centrally placed nuclei per 100 fibers cut transversally, more than four rowing nuclei per 100 fibers cut longitudinally, occasional sarcoplasmic basophilia, nuclear atypicalities) is pathognomonic of dystrophy, which will become more severe if the animal lives on.

In very old animals, muscular necrosis, myositis, and scarring may be found entirely without any relation to dystrophy. There may even be some rowing of nuclei in such lesions. However, such focal lesions in aging hamsters may represent senescent changes or may be the consequences of microtraumata, such as bites.

This description has been limited to skeletal muscle. Mohr and Lossnitzer [32] recently described light microscopic changes and their timing in BIO 82.62 inbred hamsters. Since these hamsters were bred at the facilities of the University of Ulm, Germany, these 82.62 animals are actually a subline and should be so designated (BIO 82.62/U). The skeletal lesions appear to be essentially the same as those described above.

Histopathology of Hamster Cardiomyopathy

Bajusz *et al.*[5] noted that cardiac muscle lesions develop in 100% of Syrian golden hamsters of the BIO 14.6 line. They compared 150 animals of the myopathic line with a similar number of hamsters of a dystrophy-free line (LSH, now identified as BIO 2.4). At the time of their studies, hamsters of the BIO 14.6 line had a life-span of about 146 days (about one third of the expected normal life-span). The first myocardial lesions appeared at approximately the 30th day of age, at a time when all animals were already affected by skeletal

FIGURE 2. BIO 14.6 male, 70 days old. Perinuclear halos in biopsy of back muscle. Hematoxylin and eosin. ×520.

muscle lesions. Gross inspection of the heart revealed lesions only in the most advanced stages. The earliest histologically detectable lesions in the heart muscle occurred at the age of 30–70 days. There was focal myolysis with disappearance of sarcoplasm in the absence of any significant cellular infiltration. There were small vacuoles within muscle fibers that resembled hydropic vacuolar degeneration. There was a dissolution of myofibrils, so that the sarcoplasm became filled with a more or less amorphous material. Eventually, the myofibrils disappeared, resulting in "spotty myolysis." Often, myofibrils were edematous, and nuclei in such fibers were enlarged and globe-shaped, with pyknosis and karyolysis. While the process was progressive and became locally diffuse, it nevertheless remained focal. Eventually, disintegrated fibers were replaced by connective tissue and occasionally became calcified (FIGURE 3).

While in the BIO 14.6 line hypertrophy and eventual dilatation invariably occurred, Mohr and Lossnitzer[32] noted that in their BIO 82.62/U animals, despite a similarity of the cardiopathology in its early stages to the lesions observed in other cardiomyopathic strains, no significant hypertrophy or terminal cardiac failure was noted.

FINE STRUCTURE OF HAMSTER CARDIOMYOPATHY

The first electron microscopic study of cardiomyopathy in hamsters was performed by Caulfield[33] in 1966. He examined skeletal muscle of cardiomyopathic hamsters at rest and after forced swimming, which accentuated the observed lesions. He noted interstitial edema, lipid deposition, degeneration of Z and I bands, and mineral deposition in mitochondria. Early electron microscopic studies on heart muscle in cardiomyopathy were those of Bajusz *et al.*[34]

Schwartz *et al.*,[35] in 1973, observed in mitochondrial preparations of the human failing heart decreased calcium transport capability and impaired respiratory activity. These biochemical lesions at the subcellular level appeared to be related to the severity of the heart failure in cardiomyopathic hamsters. Earlier, Nakao *et al.*[9] and Onishi *et al.*[36] also reported derangement of mitochondria in electron microscopic studies on cardiomyopathic hamster hearts, which the latter authors described as suggesting "transient insufficiency in mitochondrial function."

Onishi *et al.*[36] studied fine structural changes throughout life in the hearts of cardiomyopathic hamsters and noted delayed maturation of cardiomyocytes in early phases. Cardiomyoblasts with poorly developed myofilaments were present. Signs of increased protein synthesis, ribosomes, particularly polysomes, were often found. Juxtanuclear ergastoplasm was markedly increased, reaching a peak at about 20 days and again terminally. There were frequent mitoses. Dissolution of nuclear membranes with release of ribosome-sized granules into the cytoplasm occurred at about 20 days of age. Quite similar observations in embryonal stages of cardiomyopathy have recently been published by Wada *et al.*[37] These phenomena are compatible with the perinuclear halos seen by light microscopy (in skeletal muscle) at early stages of cardiomyopathy. A more recent (1976) study on the subject, with comparable results, is that of Lazarus *et al.*[38] Patterson *et al.*[39] have shown an increased number of pinocytotic vesicles in endothelial cells, suggesting an alteration of the microvasculature.

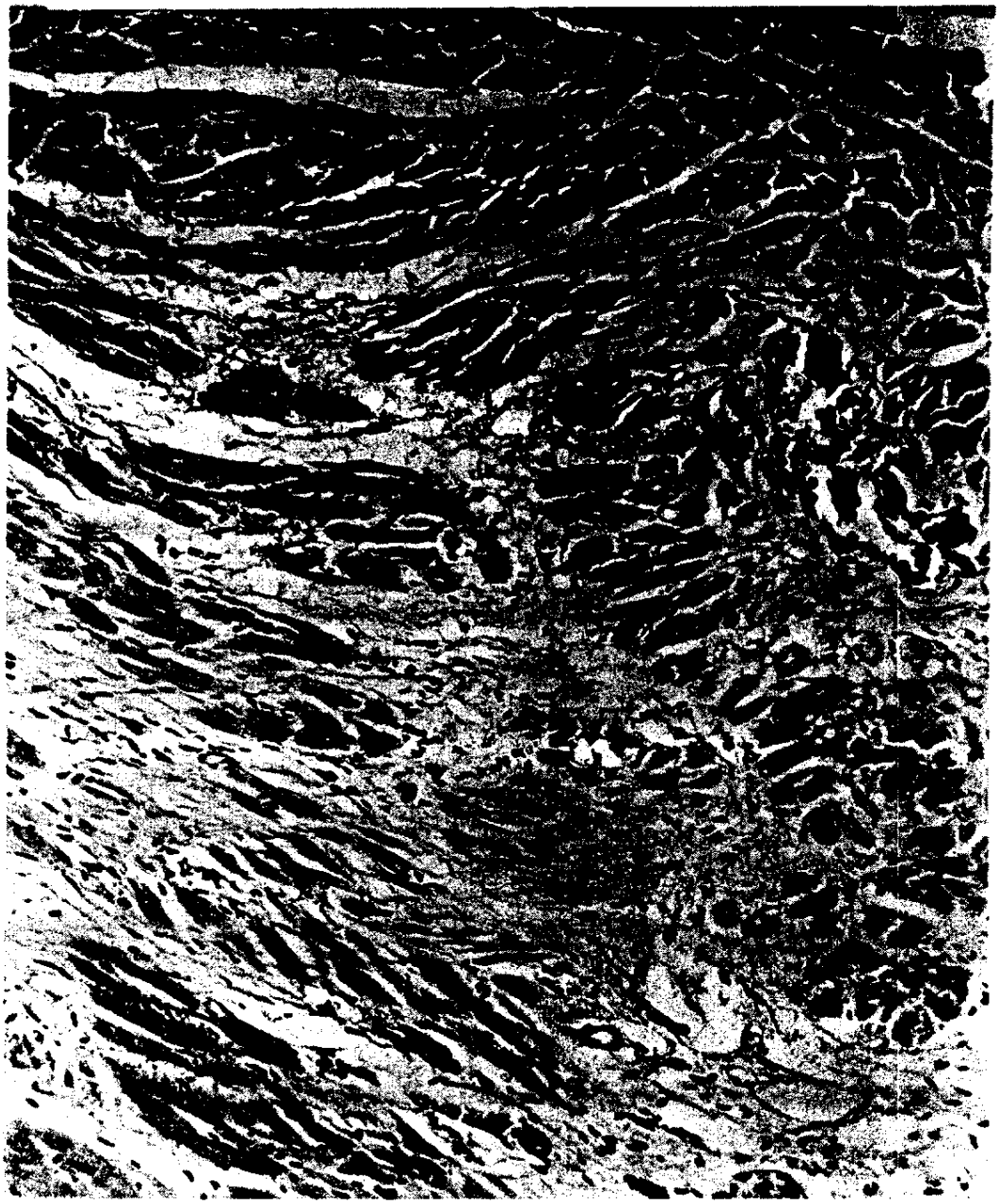

FIGURE 3. BIO 14.6 female, 144 days old, with myolysis and calcifications in myocardium. Hematoxylin and eosin. ×80.

Clinical Course of Hamster Polymyopathy and Cardiomyopathy

The clinical picture of hamster myopathy differs somewhat from muscular dystrophy in mice and humans. These differences are responsible for those features that make the disease in hamsters most useful for the study of cardiomyopathy.[40]

The onset of clinical signs of muscle disease in hamsters occurs late in life, and involvement of heart muscle happens relatively early.[1] Thus, most animals will die from cardiac failure rather than from atrophy of respiratory muscles or paralysis of deglutition, as so frequently happens in human dystrophic patients. While this sequence of events appears to be the same in all dystrophic hamster lines (except for the BIO 82.62 subline[32]), the time frame for these events varies among the different lines, as shown in Table 1.

Discussion

Those who use cardiomyopathic hamsters in their work are mostly interested in these animals as models of human disease. To be properly understood, however, the disorder must be placed in its own frame of reference, among the other known mutations encountered in Syrian hamsters. Table 2 lists the mutations so far described in Syrian hamsters.[41] The list includes 18 mutations that affect coat color and eye color, six mutations that affect the characteristics of fur, five mutations that affect the nervous system [epilepsy, microphthalmia, anophthalmia (retinal degeneration), hydrocephalus, amyotropic lateral sclerosis (hind-leg paralysis)], and one mutation that affects the skeletal and cardiac muscle (dystrophy). About half of these mutations were first described by Bio-Research Institute staff.[41]

Thus, the methods of population genetics and experimental pathology have been most fruitful in gaining new information on the Syrian hamster and in producing models of several human diseases.[75, 76]

The history of the cardiomyopathic hamster indicates that its discovery and the application of the discovery to biomedical research problems were hampered and delayed by the low priorities assigned by peer reviewers to such types of research and by the poor judgment of journal reviewers. These unique animals with cardiomyopathy would surely have been lost if our support had depended on governmental sources.

The cardiomyopathic hamster was saved for use by the biomedical research community through our own persistence and the foresight and generosity of private foundations. By their support, they allowed us to demonstrate that classic experimental pathology and population genetics can contribute significantly to the progress of biomedical science. In the present case, it was through provision of a new, well-defined cardiomyopathic organism that has now been widely used by many disciplines that a contribution has been made toward an understanding of diseased muscle and of the failing heart.

It is to be hoped that this lesson of recent history will not be lost on those who shape governmental research support policy.

TABLE 2

KNOWN HAMSTER MUTATIONS

Name	Gene Symbol	Mode of Inheritance	Description	Reference
Genes That Affect Coat Color and Eye Color				
Acromelanic white	c^{al} *	autosomal recessive	white pelage with pink eye and dark pinnae	42
Brown	*b* *	autosomal recessive	eumelanin changed to brown	43
Cream	*e* *	autosomal recessive	rich creamy yellow	44
Dark gray	*dg*	autosomal recessive	dark gray with less brown or yellow	45
Dermal pigmentation	—	genetics not completely analyzed	dermal melanism suppressed	46
Dominant spotting	*Ds* *	autosomal dominant	small irregular patches of white fur over the back and sides; homozygotes lethal	47
Frost	*f* *	autosomal recessive	fur becoming lighter with age; occasional eye anomalies	49
Jute	*J* *	autosomal dominant	creamy yellow; homozygotes lethal	50
Lethal gray	*Lg* *	autosomal dominant	coat gray; homozygotes lethal	45, 51
Light undercolor	—	genetics not completely analyzed	very light or whitish undercolor	52
Heterochromia iridis	— *	genetics not completely analyzed	one eye darker than the other	53
Mottled white	*Mo*	sex-linked dominant	heterozygous females have white patches	54, 55
Piebald	*s* *	autosomal recessive	white patches; small-sized urogenital abnormalities	56, 57

TABLE 2—(*Continued*)

me	Gene Symbol	Mode of Inheritance	Description	Reference
	ru	autosomal recessive	pupils with ruby mien, dilutes coat color	44
	r *	autosomal recessive	similar to brown but darker	58
ll	*To*	sex-linked semidominant	yellow in males, yellow in homozygous females, and yellow patches in heterozygous females	59
	T *	sex-linked incompletely dominant	similar to agouti but lighter and paler	60, 61
	Ba *	autosomal dominant	white band in trunk region	62
		Genes That Affect Hair		
	Fs	autosomal recessive	animals lose hair incompletely	77
	hr *	autosomal recessive	sparse hair that eventually falls out	63
	l *	autosomal recessive	longhair	64
	N	autosomal semidominant	heterozygotes have sparse hair; homozygotes are devoid of hair, except for a short down	65
	rx	autosomal recessive	wavy hair	66
	Sa	autosomal semidominant	hair has satiny sheen in heterozygotes and is satiny, thin, and straggly in homozygotes	67
ncy	*fd* *	autosomal recessive	sparse fur	77

Neurologic Mutants				
Anophthalmia	*Wh* *	autosomal semidominant	homozygotes show acromia and anophthalmia and anomalous optic nerve and hearing; heterozygotes have diminished (in color) ventral hair	68–70
Hind-leg paralysis	*pa* *	sex-linked recessive	hind legs become paralyzed between 6 and 10 months; penetrance in females not complete	71, 75
Hydrocephalus	*hy* *	autosomal recessive	distended ventricles and displacement of various brain structures	72
Spontaneous seizure	*sz* *	autosomal recessive	frequent seizures between the third and fourth weeks	73
Extreme microphthalmia	—	autosomal recessive	homozygotes have extremely small eyes or no eyes; coat color white; no allelic test with anophthalmia (*Wh*) has been made	74
Mutation That Affects Muscle				
Cardiomyopathy	*dd* *	autosomal recessive	see text	26

* Maintained at Bio-Research Institute.

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DISCUSSION

UNIDENTIFIED SPEAKER: You have described the pathologic changes in the young dystrophic hamster that occur after forced swimming. Do you have any information regarding whether exercise of this type influences the rate of progression of the disease clinically and regarding long-term prognosis?

HOMBURGER: Unfortunately, we do not.

B. W. WILSON: Do you have any information on the ultrastructure of that perinuclear change, which was the first change you noted?

HOMBURGER: No, we do not have any information regarding your question.