*Review Article*

# MYOCARDIAL DISEASES OF ANIMALS

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# *Myocardial Diseases of Animals*

JOHN F. VAN VLEET, DVM, PhD, and
VICTOR J. FERRANS, MD, PhD

*From the Pathology Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland*

INTEREST in the cardiomyopathies first developed in the 1960s, at which time the terms "primary myocardial disease," "cardiomyopathy," and "myocardiopathy" were proposed to identify a series of disorders that affected primarily the myocardium. More recently it was suggested that the use of the term "cardiomyopathy" be restricted to myocardial diseases of unknown etiology, and that cardiomyopathies of known etiology be referred to as "myocardial diseases" associated with a given specific entity or causative factor. In this review, we use the term "myocardial diseases" in its original connotation to refer to all disorders that affect primarily the heart muscle by producing degeneration, necrosis, or inflammation. A wide spectrum of such disorders has been demonstrated in human patients. However, a much larger number of myocardial diseases occur, either spontaneously or experimentally induced, in animals. The myocardial diseases of animals provide many unique opportunities to explore diverse aspects of cardiovascular medicine. Some of these diseases correspond closely to conditions known to affect humans; others constitute model systems for specific aspects of certain human disorders; and still others represent situations of intrinsic genetic, morphologic, toxicologic, or pharmacologic interest. We have attempted to emphasize many disorders that have received only limited attention in the literature; and, whenever possible, we have referred the reader to extensive reviews that have been published recently on some types of myocardial diseases of animals. In keeping with the definitions given above, we have excluded from consideration in this review the following groups of disorders: ischemic heart disease; valvular, pericardial, and endocardial diseases; diseases of the conduction system; congenital malformations; and diseases caused by metazoan parasites.

## Myocardial Diseases With Known or Suspected Heritability

This group of diseases continues to expand, with recent descriptions of examples in the rat, cow, and mouse. The cardiomyopathies in hamsters, mice, rats, turkeys, cattle, and animals with glycogenosis may have progressive clinical courses and some morphologic alterations similar to those in certain cardiomyopathies in human patients and may provide useful models for the human diseases. The hamster model, especially, has been used extensively for studies on the morphologic and biochemical alterations of cardiomyopathies and the development of potential therapeutic agents. For the most part, these diseases may be eliminated from animal populations by selective breeding or may be maintained as models by breeding of affected or carrier animals.

Address reprint requests to Dr. John F. Van Vleet, Department of Pathology, School of Veterinary Medicine, Purdue University, West Lafayette, IN 47907.

### Hereditary Cardiomyopathy (Muscular Dystrophy) in Hamsters

In 1962, Homburger reported the coexistence of cardiomyopathy and skeletal myopathy in Syrian golden hamsters of the BIO 1.50 line. Numerous reports have followed on this hereditary polymyopathy in other lines such as BIO 14.6, 40.54, 82.62, 53.58, CHF146, CHF 147, and UM-X7.1[1-12] The cardiac disease is more severe than the skeletal muscle involvement in dystrophic hamsters. The condition is inherited as an autosomal recessive trait and affects both sexes. Some of the affected lines of hamsters, such as 40.54, survive for approximately one-third of the usual 600-day life span of nondystrophic hamsters. However, considerable variability exists in the rate of progression of the disease in various affected lines. Clinical signs of the disease include subcutaneous edema, muscle weakness, exercise intolerance, poor growth, ascites, hyperpnea, cyanosis, and death.

Numerous studies have characterized the myocardial pathology in affected hamsters.[2-4,9,13,14] In general, these studies have divided the disease into four phases: 1) prenecrotic, 2) necrotic, 3) hypertrophic, and 4) terminal. Most hamsters survive until they die in the terminal phase with congestive heart failure, cardiac dilatation, atrial thrombi, and multifocal pale areas of myocardial fibrosis. The initial histopathologic alterations were prominent by 30–50 days of age as focal myolysis and focal necrosis with myocyte calcification, macrophagic invasion, and postnecrotic fibrosis. By 100 days of age, myocardial hypertrophy had developed.

Ultrastructural study of the hearts of fetal hamsters from affected lines and young hamsters in the prenecrotic phase of the disease revealed increased numbers of cardiomyoblasts in fetal hearts, prolonged postnatal myocyte mitotic activity, increase in number and size of myocyte mitochondria, abnormal myofibril formation, focal myofibrillar lysis, increased numbers of polysomes, and edema of myocytes and the interstitium.[9,12,13,15]

The biochemical pathogenesis and the pathophysiologic alterations in the myocardium of the cardiomyopathic hamster have been studied extensively, and many hypotheses have been proposed to account for the observed changes. Most recently, the myocardial damage has been attributed to: 1) microvascular spasm produced by catecholamine release; 2) an inherited hypersensitivity of cardiac and smooth muscle to catecholamine stimulation; 3) repeated episodes of ischemia, reperfusion, and eventual necrosis of hypersusceptible myocytes; 4) secondary hypertrophy of surviving myocytes; and 5) a final stage of cardiac decompensation with congestive heart failure.[6,11] Myocardial protection was provided by verapamil administration.[6,16,17] Other studies have shown protection against the development of this cardiomyopathy by administration of α-adrenergic blockers, β-adrenergic blockers, verapamil, or taurine.[14,18-20] Potentiation of the cardiomyopathy is seen in affected hamsters fed diets low in potassium or magnesium. Affected hamsters are strikingly susceptible to catecholamine-induced myocardial necrosis. Myocardial calcium accumulation, defective carnitine transport, abnormalities in contractile proteins, altered distribution of myosin isoenzymes, and decreased sarcolemmal $Na^+$, $K^+$-adenosine-triphosphatase activity and adenosine triphosphate-independent $Ca^{2+}$ binding capacity have been reported in cardiomyopathic hamsters.[20-25]

Muscular dystrophy occurs in the hamster, mouse, chicken, dog, turkey, mink, and sheep; however, among these species only in the hamster and mouse has concurrent cardiomyopathy been shown to develop.[26]

### Hereditary Cardiomyopathies of Mice

Mice with hereditary muscular dystrophy may have accompanying myocardial alterations. Dystrophy was originally described as an autosomal recessive trait in mice of the inbred strain 129/ReJ in 1955 at the Bar Harbor laboratory and later was also reported in C57BL/6J mice.[26-30] Affected mice show poor growth, muscular atrophy, and gradual onset of ataxia and posterior paresis. Most animals die by 1–6 months of age. Some mice have microscopic and ultrastructural alterations in the myocardium.[31-33] In Strain 129 mice, myocytes have fatty change, SR dilatation, and mitochondrial swelling with accompanying edema and fibrosis.[31,32] Delayed myofibrillogenesis was observed in the hearts of C57BL/6J-dydy mice.[33]

An inherited cardiomyopathy has also been described[33] in KK mice, a strain in which diabetes mellitus and spontaneous soft tissue calcification also occur.[34-38] However, morphologic study of the myocardial alterations indicated that the cardiac lesions develop prior to the onset of diabetes mellitus.[33] The myocardial lesions were extensive at 8 and 11 weeks of age and were characterized by myofibrillar lysis, focal necrosis, and calcification and postnecrotic fibrosis (Figures 1 and 2).[33,39] Some affected myocytes had cytoplasmic inclusions with the appearance of nemaline rods. No thickening of capillary basement membranes was observed, suggesting that the myocardial lesions of the KK mouse are not secondary to diabetes mellitus.[39] However, Tomita[40] described focal thickening and dispersion of the glycocalyx of cardiac myocytes in 40-week-old KK mice (Figure 3). The severity of the cardiomyopathy in

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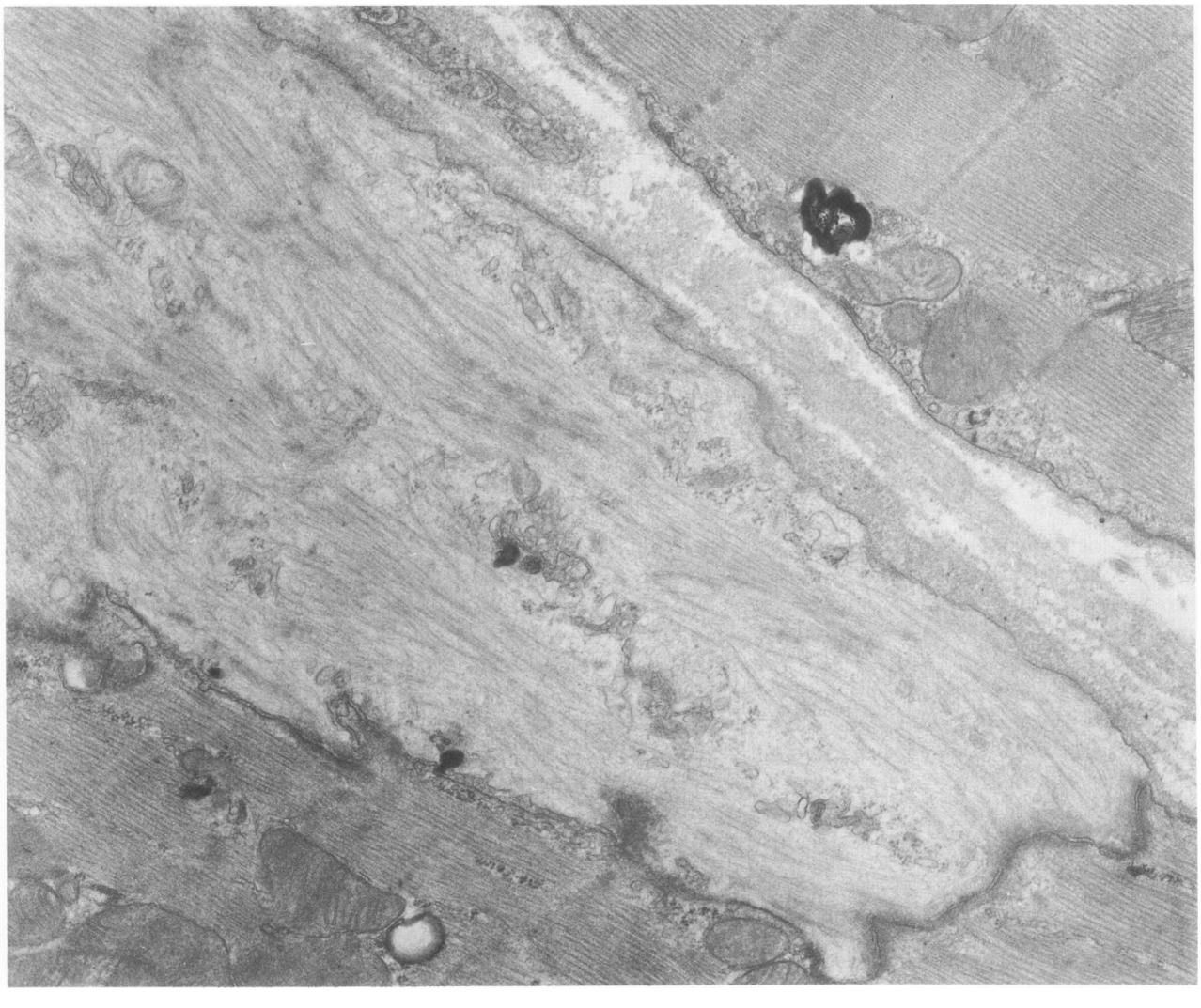

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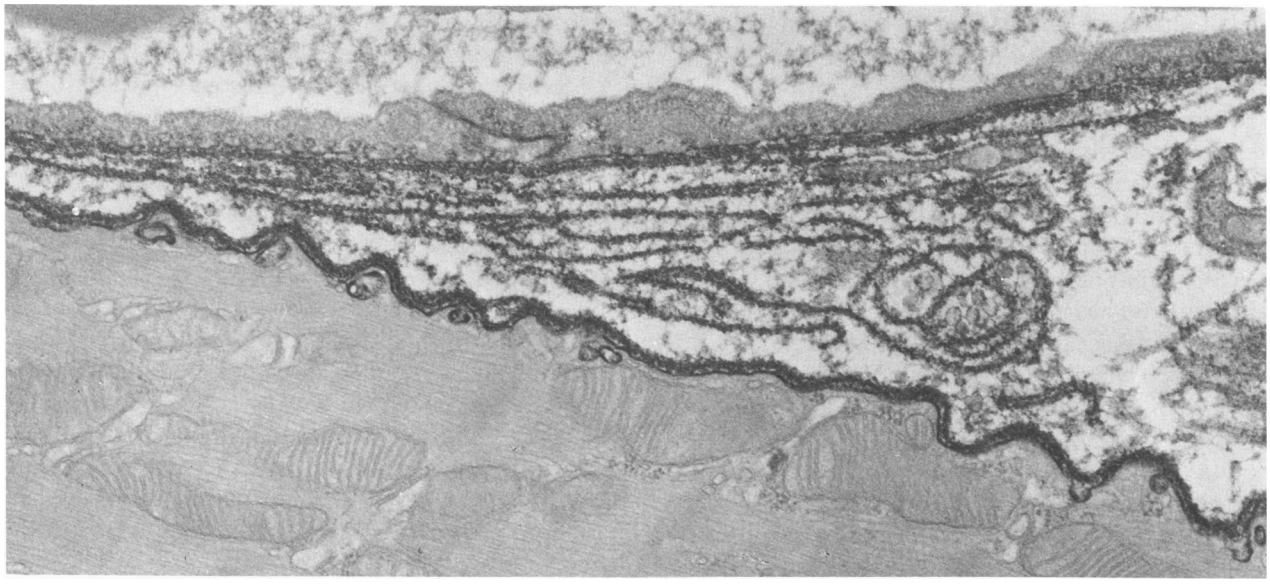

**Figure 3**—Hereditary cardiomyopathy. KK mouse (40-week-old male). Reduplicated external lamina is present adjacent to a capillary. (Ruthenium red, ×28,000)

KK mice was found to be considerably reduced by treatment with diltiazem, a calcium channel blocker.[40]

### Hereditary Cardiomyopathy of Rats

Rubin et al[41] recently described cardiomyopathy with congestive failure in SHR/N-cp rats. Affected rats had subcutaneous and facial edema, dyspnea, cyanosis, and malaise and survived from 5 to 14 days after the onset of clinical signs. Hypertension was present in 100% of the animals, and 25% were obese. Congestive heart failure developed in 75% of males 11 months of age or older and in 25% of females 24 months of age or older. At necropsy, lesions included hydrothorax, ascites, cardiomegaly, thickened ventricular walls, left atrial dilatation, and thrombosis, and hepatomegaly. Microscopic findings were myocardial hypertrophy and interstitial fibrosis. Ultrastructural study revealed altered Z bands.

### Hereditary Cardiomyopathy ("Round Heart Disease") of Turkeys

Sporadic death losses from "round heart disease" occur in turkey poults. The literature on this disease was recently reviewed.[42] The frequency of the cardiac disease in several commercial turkey flocks in Canada varied from 3% to 28%.[43] However, an inbred flock of turkeys maintained at the University of Minnesota as a source of research animals had a 70% incidence of the cardiac disease at 1 month of age, with 30% mortality in the affected birds by 10 days of age. Thus, it appears that the cardiac disease is heritable, although superimposed stresses have been suggested to play a role in precipitating deaths in some affected flocks.[44] It is important to differentiate inherited cardiomyopathy of turkeys from toxic cardiomyopathies produced in this species by either furazolidone or sodium chloride, because all three diseases may result in terminal cardiac dilatation ("round heart") and congestive heart failure.[45-47] The findings in furazolidone- and sodium chloride-induced cardiotoxicity are described in a later section of this review.

Clinically, turkeys with inherited cardiomyopathy have stunted growth and often have sudden, unexpected deaths. Mortality is highest in the first few weeks of life. Males are more frequently affected than females. Some affected birds will survive into adulthood but will be stunted. At necropsy, ascites and hydropericardium are often present. In poults, the hearts are dilated, especially the right ventricle, and assume a rounded shape ("round heart"). In older birds, left ventricular dilatation and hypertrophy and white, firm thickening of the left ventricular endocardium by fibroelastosis are seen.[43,44,48-51] Epicardial vessels are congested. In contrast, venticular dilatation, but without hypertrophy

**Figure 1**—Hereditary cardiomyopathy. KK mouse (40-week-old male). Degenerate myocytes have numerous myelin figures. (×7400) **Figure 2**—Hereditary cardiomyopathy. KK mouse (40-week-old male). Degenerated myocyte (center) has extensive myofibrillar lysis. (×22,000)

and endocardial fibroelastosis, occurs in furazolidone- and sodium chloride-induced cardiomyopathy in turkeys.[45,46]

Microscopic alterations described in poults have varied from interstitial myocarditis with focal myocardial necrosis[51] to myocardial congestion and hemorrhage and epicardial fibrosis.[44] Ultrastructural study demonstrated type C viral particles in myocytes from affected hearts,[51,52] but no further evidence for a viral etiology of the disease has been reported. Other ultrastructural alterations described include accumulation of sarcoplasmic glycogen deposits and myofibrillar lysis.[53]

Biochemical studies also demonstrated increased myocardial glycogen concentration in affected turkey poults.[54] However, there is no convincing evidence to suggest that the biochemical pathogenesis of inherited cardiomyopathy in turkeys is related to a known form of glycogen storage disease. Other biochemical studies demonstrated altered composition and function of nuclear nonhistone proteins in the hearts of affected turkeys[55,56] and altered plasma and tissue carnitine concentrations.[57] Decreased myocardial activities of lactic dehydrogenase, isocitric dehydrogenase, and creatine phosphokinase were also described.[58] Studies of regional myocardial blood flow in affected turkeys indicated decreased subendocardial perfusion and led to the suggestion that this alteration may play a role in the development of endocardial fibroelastosis.[59] Daily administration of propranolol to newly hatched turkey poults from an inbred flock with a high incidence of hereditary cardiomyopathy delayed, but did not prevent, mortality from the disease.[60] The delayed mortality may have resulted from amelioration of cardiac arrhythmias and abnormal calcium transport demonstrated in young affected turkeys.[61,62] The inducibility of ventricular tachyarrhythmias in cardiomyopathic turkeys was directly related to the extent of ventricular dilatation.[63]

## Hereditary Cardiomyopathies of Cattle

A single report has characterized a cardiomyopathy in Japanese black calves in western Japan.[64] Affected animals, usually less than 1 month old, died suddenly after the onset of dyspnea that lasted for several minutes to a few hours. At necropsy, evidence of congestive cardiac failure was present as ascites, hydropericardium, hydrothorax, pulmonary edema, and hepatic congestion. The heart showed cardiomegaly and left ventricular dilatation. Microscopically, multifocal myocardial degeneration and necrosis were present and were most frequent in the left ventricular papillary muscles. Older lesions appeared as areas of myocardial fibrosis without infiltrating inflammatory cells. The disease was inherited as an autosomal recessive trait. In 1975 bulls suspected of being carriers for the trait were destroyed, and no further cases have been seen.

More recently, another cardiomyopathy which seems to be hereditary has been described in Holstein–Friesian cattle in Japan.[65–67] The disease affects animals from 1 to 7 years of age (average, 3.3) and is manifested clinically by edema, venous distension, and hepatic congestion. The hearts of the affected animals are dilated and increased in weight, but the ventricular walls are not thickened. Histologically, hypertrophic and nonspecific degenerative changes are found, together with diffuse interstitial fibrosis involving both ventricles. Ultrastructural studies have shown splitting of myofibrils, mitochondrial swelling, intracellular edema, increase in Z-band material, and increased numbers of mitochondria that are smaller than normal. Cellular reaction (lymphocytic infiltration) was infrequently seen.

A suspected hereditary cardiomyopathy in young adult cattle, mainly Simmental/Red and White Holstein crossbreds, was reported from Switzerland.[68,69] Affected cattle had subcutaneous edema, hydrothorax, and ascites. It was suggested that an unknown environmental factor may precipitate the clinical onset of the disease. Grossly, cardiac enlargement and dilatation were observed. Myocardial degeneration and fibrosis were present microscopically, accompanied by hepatic congestion, pulmonary edema, sclerosis of pulmonary arteries, and chronic interstitial nephritis.

A cardiomyopathy has been reported from Australia in polled Hereford calves with dense curly coats.[70] Affected calves die before 6 months of age and have severe myocardial necrosis and fibrosis.

## Myocardial Alterations in Glycogenosis

The glycogenoses (glycogen storage diseases) reported in animals were recently analyzed in a comprehensive review.[71] Animal models have been documented for four of the eight types identified in man: Type I, or Von Gierke's disease (glucose-6-phosphatase deficiency), in mice; Type II, or Pompe's disease (acid maltase or α-1, 4-glucosidase deficiency), in Shorthorn and Brahman cattle, Corriedale sheep, Lapland dogs, and Japanese quail[72–84]; Type III, or Cori's disease (amylo-1, 6-glucosidase deficiency), in German shepherd and Akita dogs[85–87]; and Type VIII (phosphorylase kinase deficiency) in rats and mice. Significant myocardial involvement occurs only in animal models of Types II and III, in which myocardial glycogen accumulation has been demonstrated by light and electron microscopy and by biochemical analysis. In cattle with Type II glycogenosis, glycogen accumulated free within the sarcoplasm and within lysosomes[73]; in dogs with Type

III glycogenosis, generalized cytoplasmic glycogen deposition was present[87]; and intralysosomal glycogen deposits were described in Japanese quail with Type II glycogenosis.[78] In calves affected with Type II glycogenosis progressive muscular weakness developed, and they died at 9–16 months of age. Some animals had cardiomegaly and lesions of congestive cardiac failure at necropsy.[82] Autosomal recessive inheritance has been described in Type II glycogenosis of cattle[74]; but the mode of inheritance in Type II glycogenosis of sheep, dogs, and quail, and in Type III glycogenosis of dogs has not been established. Morphologic and biochemical study of muscle biopsy specimens from newborn calves homozygous for Type II glycogenosis revealed accumulation of free and membrane-bound glycogen.[73] Adult heterozygotes were detected by assay of acid α-glucosidase activity in blood lymphocytes.

### Myocardial Calcification in Mice and Other Laboratory Animals

Myocardial calcification is a frequent finding (90–100% incidence) in certain inbred mouse strains and has also been described in guinea pigs and rats.[1,88–96] Generally these cardiac lesions are clinically insignificant, but mice with severe calcification may die with congestive failure.[91] Inbred mouse strains with a high incidence of cardiac calcification include DBA/2, C, C3H, BALB/c, A, CBA, and CHI. Genetic studies in DBA/2 mice indicate that cardiac mineralization is inherited as an autosomal recessive trait and that three or four alleles are involved.[89] The frequency and severity of the cardiac lesions may be modified by age, sex, parity, and diet in the affected inbred mouse strains.[91] The lesions are more frequent and severe with advancing age, are generally seen at a younger age and are more severe in females than in males, are more severe in mice following multiple pregnancies than in virginal females, and are increased in frequency and severity in mice fed increasing amounts of dietary fat.

Many terms have been applied to this cardiac lesion, including "dystrophic cardiac calcinosis" (calcification), "dystrophic epicardial mineralization," "calcareous pericarditis," and "metastatic calcification." Affected mice and guinea pigs often have accompanying extracardiac calcification involving the kidney, lung, testis, ovary, skeletal muscle, stomach, intestine, and aorta. The distribution of the cardiac lesions varies between the various affected mouse strains, with epicardial localization in BALB/c, myocardial involvement in C3H and C3Hf, and both epicardial and myocardial lesions in DBA/2. Grossly, multiple small white to yellow flecks of calcification are seen in the epicardium and myocardium with mild lesions; a diffuse plaque of firm, white, gritty material is seen in the right venticular epicardium in severe cases. Histologically and ultrastructurally, the initial alteration is focal myocyte necrosis with subsequent calcification (Figures 4 and 5); older lesions may have a mild macrophagic response and accompanying fibrosis.

### Myocardial Lipofuscinosis (Xanthosis)

Myocardial lipofuscinosis, or brown atrophy, occurs in association with advanced age or cachexia in animals.[1,97] Affected myocytes have perinuclear accumulations of residual bodies that appear as yellowish-brown granules by light microscopy of hematoxylin and eosin-stained sections. The pigment granules have orange-yellow autofluorescence. Several recent reports have described lipofuscinosis of cardiac and skeletal muscles of healthy adult Ayrshire and Friesian cattle in England.[98–100] Presumably, these animals have adequate vitamin E and selenium status. The affected myocardium and skeletal muscles appeared dark brown grossly and contained abundant lipofuscin granules by light and electron microscopy. The affected cattle had observable coat color alterations with yellowing of white areas, deep brown appearance of brown areas (Ayrshires), and brown discoloration of black areas (Holsteins). Frequent occurrence (9%) in Ayrshires suggests an inherited tendency in this breed.

## Myocardial Diseases Produced by Nutritional Deficiencies

Most of these diseases are produced in animals only under laboratory conditions by feeding purified diets. The exception is selenium–vitamin E (Se-E) deficiency, which has been of vast economic importance in animal production in many areas of the world. Widespread supplementation of selenium and vitamin E to animals in affected areas has largely controlled the occurrence of this disease in animals and has also proven effective in prevention of Se-E deficiency-related cardiac diseases in man (Keshan disease in China and the cardiomyopathy associated with parenteral hyperalimentation therapy).

### Selenium–Vitamin E Deficiency

Necrosis of myocardium and skeletal muscles is a consistent finding in the numerous animal species in which spontaneous or experimental Se-E deficiency have been described. A number of excellent reviews[26,97,101–112] and many specific reports on the disease in chickens,[113–118] foals,[119] dogs,[120] nonhuman primates,[121] cats,[122,123] rats,[124–126] and mink[127,128] have

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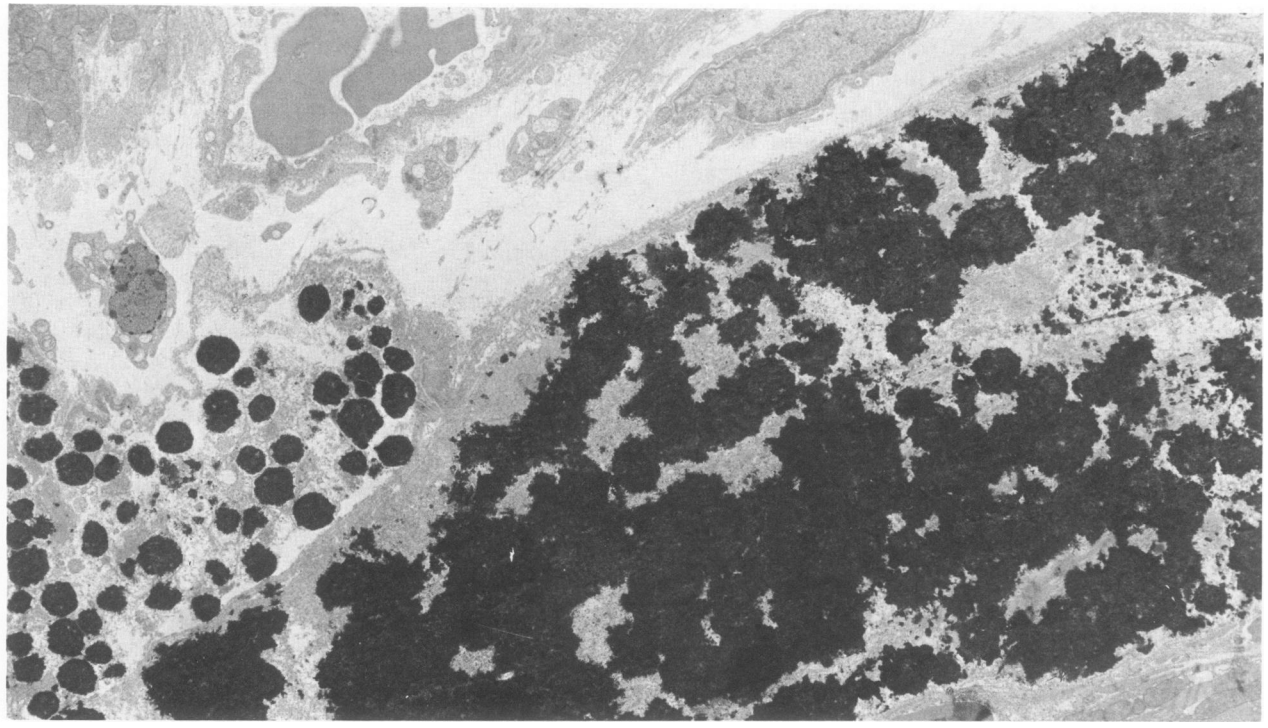

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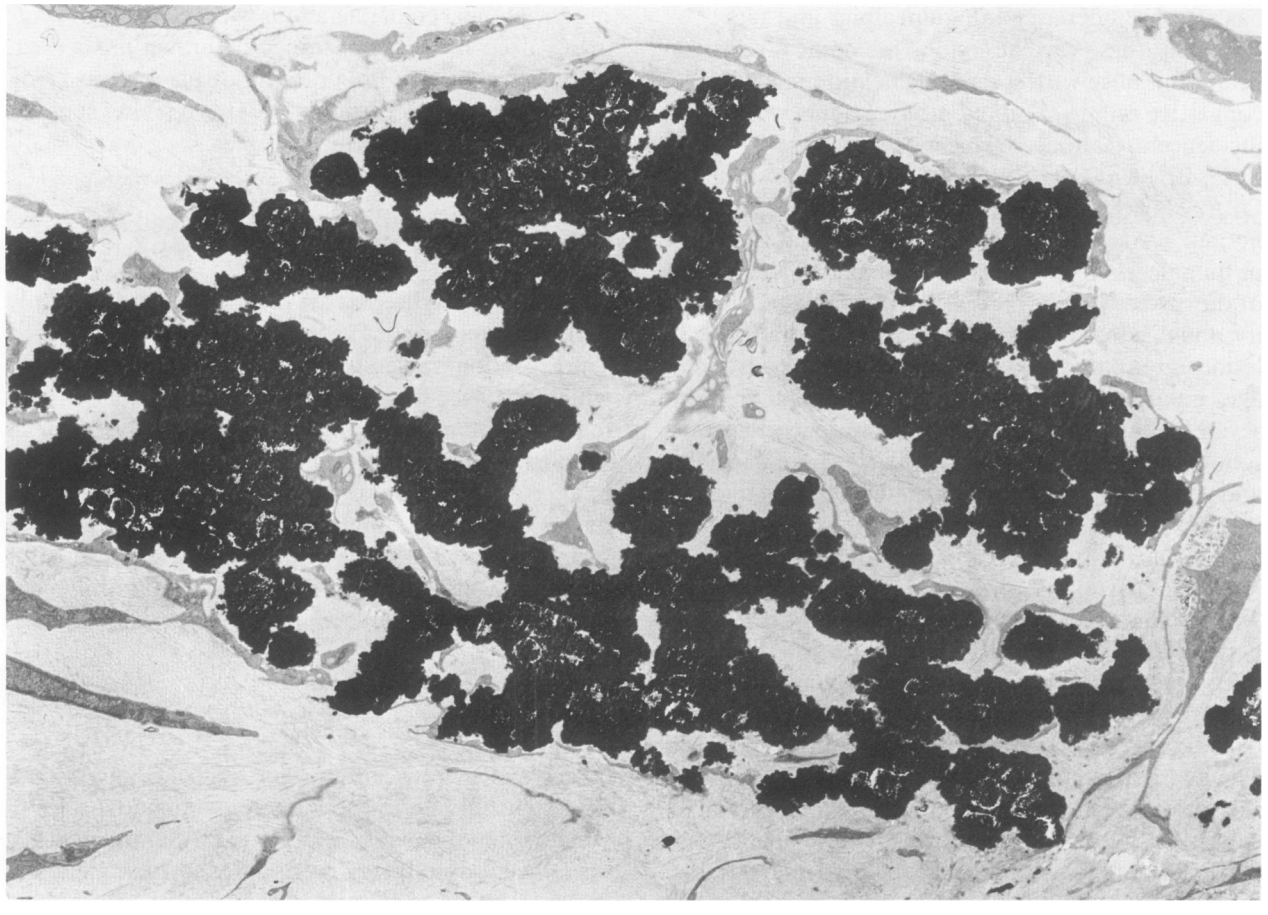
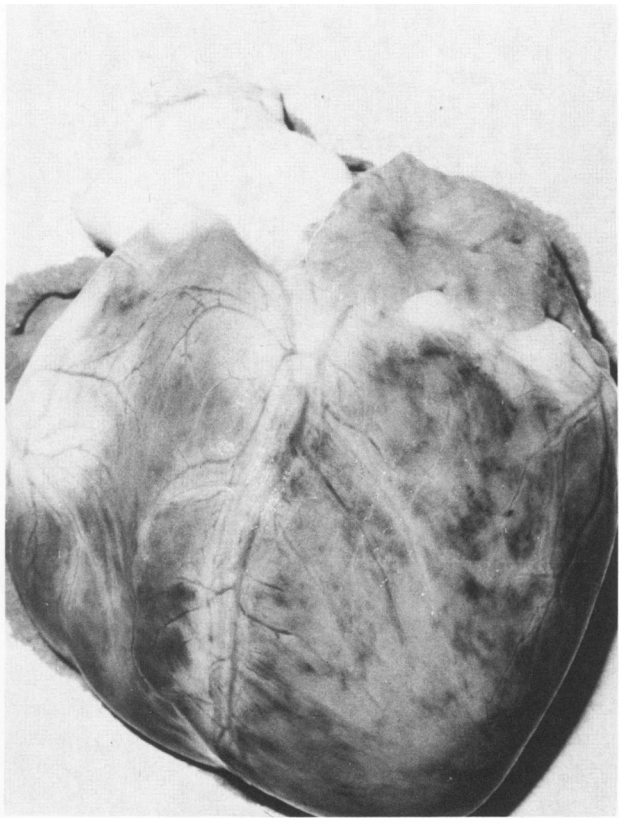


**Figure 4**—Hereditary calcinosis. DBA mouse. One necrotic myocyte shows mitochondrial mineralization (*left*); another myocyte has more severe confluent sarcoplasmic mineralization (*center* and *right*). (×6200) **Figure 5**—Hereditary calcinosis. DBA mouse. Mineralized sarcoplasmic debris of a necrotic myocyte is surrounded by cytoplasmic processes of mesenchymal cells. (×6200)



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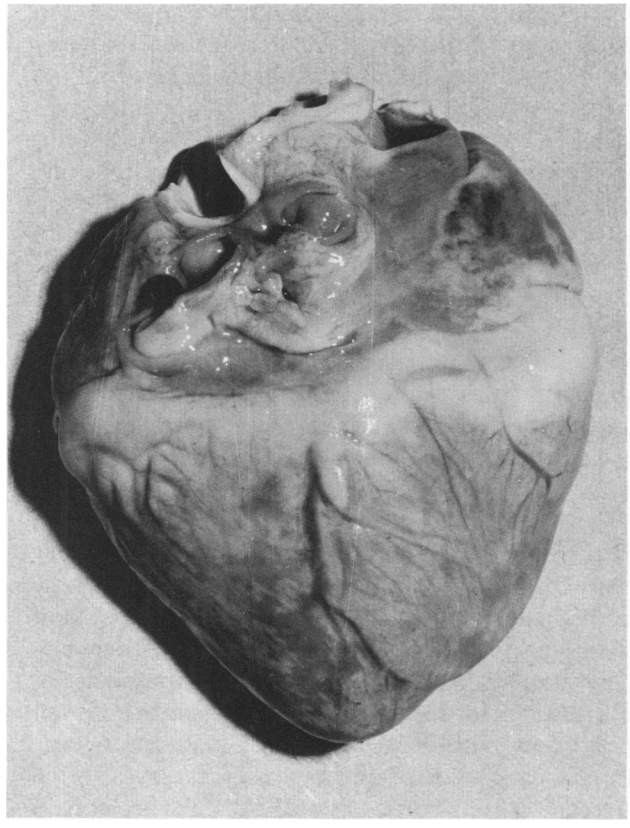

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**Figure 6**—Selenium-vitamin E deficiency. Pig. Disseminated dark areas of epicardial and myocardial hemorrhage produce lesions termed "mulberry heart." **Figure 7**—Selenium-vitamin deficiency. Pig. Disseminated pale areas of myocardial necrosis are present in the ventricular myocardium of a pig with nonhemorrhagic cardiac lesions following experimentally induced deficiency.

described the cardiac and skeletal muscle alterations and also the variety of other lesions seen in animals with Se-E deficiency. These lesions include necrosis of gizzard and intestinal musculature in turkey poults and ducklings; hepatic necrosis in pigs, rats, and mice; gastric ulceration in pigs and rats; encephalomalacia in chicks; embryonic death and resorption in rats, mice, pigs, guinea pigs, and hamsters; testicular degeneration in rats, hamsters, guinea pigs, rabbits, dogs, monkeys, and chickens; steatitis in cats, mink, and foals; anemia in monkeys, rats, and pigs; exudative diathesis in chicks; pancreatic necrosis in chicks; incisor depigmentation in rats and hamsters; lipofuscinosis in rats and dogs; nephrosis in rats and mice; alopecia in rats, monkeys, and quail; cataract formation and pulmonary hemorrhage in rats, and localized axonal dystrophy in rats.

Etiologic factors involved in the development of these lesions include 1) low dietary levels of selenium, vitamin E, and sulfur-containing amino acids; 2) high dietary concentrations of polyunsaturated fats; 3) exposure to prooxidant compounds; and 4) intake of selenium antagonists such as silver salts and various other metals.[129-133] Some of the above deficiency diseases (eg, encephalomalacia in chicks; embryonic death and resorption in rats, mice, pigs, guinea pigs, and hamsters; steatitis in cats, mink, and foals; and lipofuscinosis in rats and dogs) are the result of pure vitamin E deficiency. Liu et al[134] have observed lesions of cardiomyopathy in various zoo animals, including Nyala antelopes, elephants, deer, baboons, and exotic birds, in which blood selenium levels were normal while plasma α-tocopherol levels were very low. Pure selenium deficiency only rarely produces deficiency disease (eg, alopecia in rats and monkeys and feather loss in quail). The dietary requirement for selenium and vitamin E will be increased if the animal is exposed to prooxidant conditions (eg, toxicity by ozone, oxygen, iron, various drugs such as doxorubicin, and radiation injury) or ingests excessive amounts of certain metals that act as selenium antagonists (eg, silver, mercury, copper, cobalt, cadmium, tellurium, tin, and zinc).[129]

Myocardial lesions in Se-E-deficient animals are seen most frequently in calves, lambs, pigs, turkey poults and ducklings.[135-143] In calves and lambs with cardiac lesions the clinical finding is generally sudden, unexpected death following vigorous exercise. At necropsy,

affected calves have extensive pale areas of necrosis and calcification in the left ventricular free wall and ventricular septum, whereas in lambs the pale lesions are present in the subendocardial myocardium of the right ventricle.[102,108] Histologically, areas of myocardial damage have hyaline necrosis with or without accompanying calcification, subsequent macrophagic invasion, and eventual formation of areas of stromal collapse and fibrosis.

Growing pigs, usually 2 to 4 months old, with the cardiac form of Se-E deficiency are generally found dead with no premonitory signs of disease.[142] At necropsy, abundant serous transudates are generally present in the body cavities, and the lungs have severe congestion and edema. The heart may have scattered pale streaks in the ventricular myocardium, but the most striking alterations are widespread epicardial and myocardial hemorrhages. These have resulted in the term "mulberry heart disease" for this lesion (Figures 6 and 7). The cardiac lesions may or may not be accompanied by multifocal massive hemorrhagic necrosis of the liver, a lesion termed "hepatosis dietetica." Skeletal muscle necrosis is also usually seen histologically but is not apparent grossly in Se-E-deficient pigs. Ulceration of the esophageal portion of the gastric mucosa is also often present in affected pigs. Histologically, the hearts have both vascular and myocyte lesions (Figure 8). Vascular changes include fibrinoid necrosis in intramyocardial arteries and arterioles and numerous fibrin microthrombi in myocardial capillaries. Myocardial hemorrhage and edema accompany the vascular lesions. Multifocal hyaline necrosis and calcification is followed by macrophagic invasion and myocardial fibrosis in some pigs with prolonged survival, but most animals have only the acute vascular and myocyte lesions. The myocardial lesions are present in the walls of all four chambers but tend to be most severe in the atria. Ultrastructural study of these hearts has demonstrated myocyte alterations that have included mitochondrial swelling and mineralization, myofibrillar lysis, and necrosis with contraction bands (Figures 9–12). Endothelial cell damage and necrosis with fibrin accumulation in the walls and lumina were observed in affected vessels (Figures 13 and 14).[144,145]

In turkey poults and ducklings with Se-E deficiency, polymyopathy is produced.[140] Necrosis and calcification develop in the smooth muscle of the gizzard and intestine, in myocardium, and in skeletal muscles. Ultrastructurally, gizzard smooth muscle showed initial mitochondrial damage and subsequent myofibrillar lysis and mineralization with macrophagic invasion.[146] Birds with heart lesions have serous transudates in body cavities and scattered pale areas of myocardial necrosis and calcification in the ventricles (Figures 15 and 16). Histologically and ultrastructurally, the myocardium shows hyaline necrosis and calcification and prominent interstitial edema (Figures 17–19).[147]

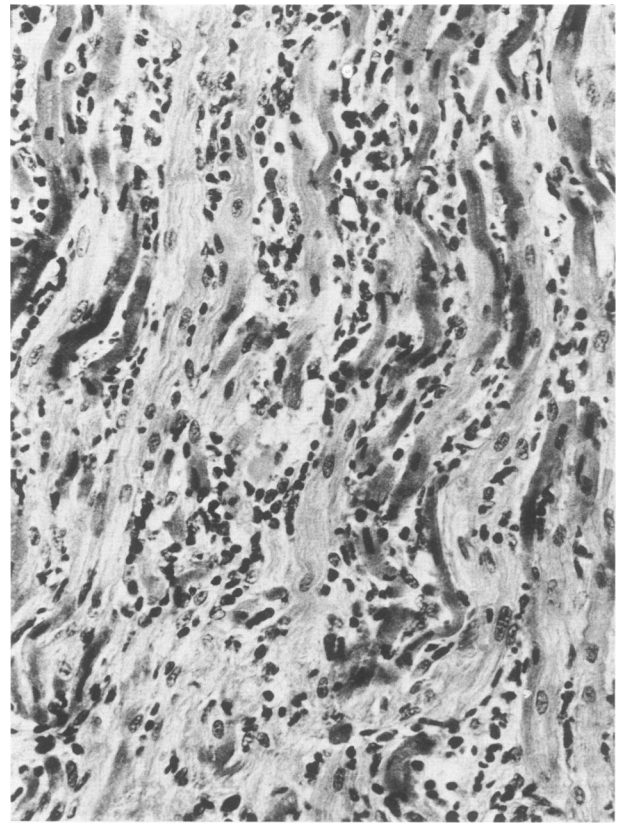
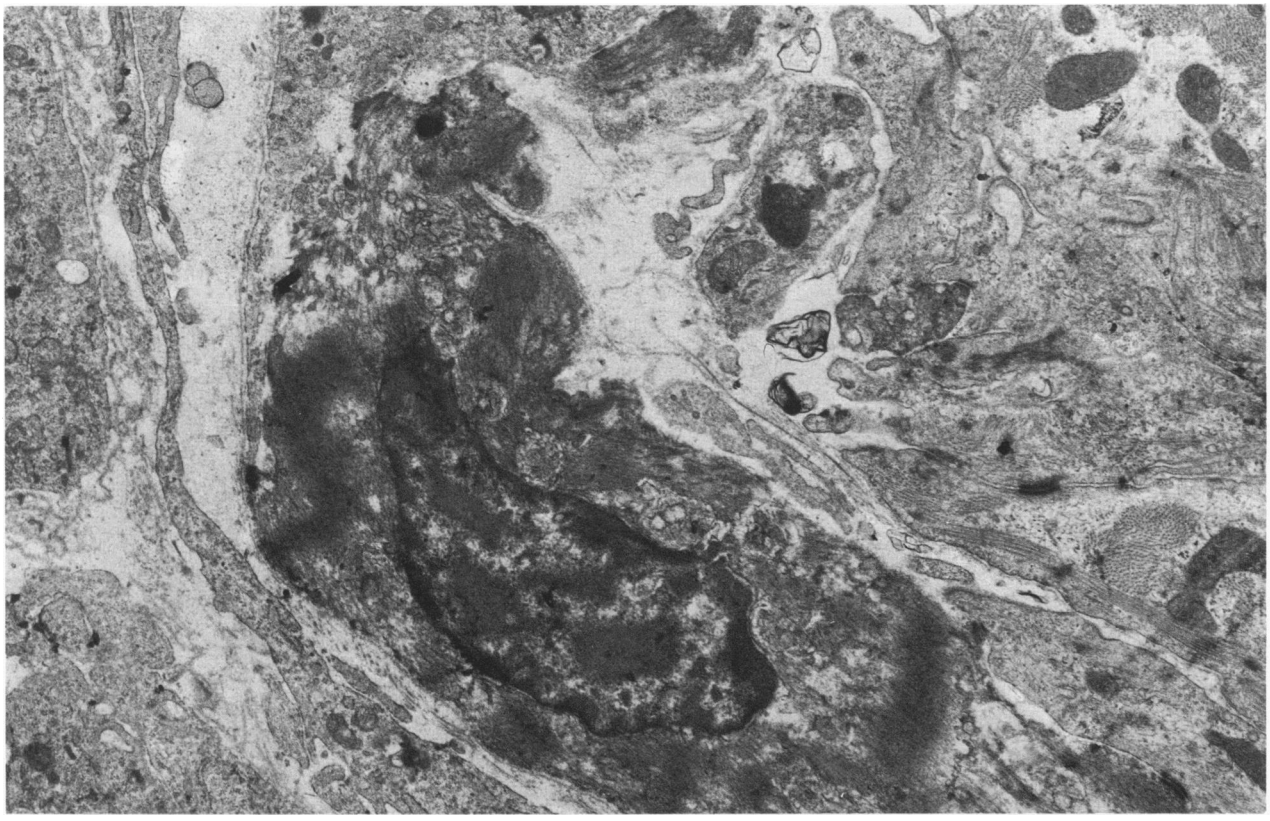


**Figure 8**—Selenium–vitamin E deficiency. Pig. The atrial myocardium shows numerous dark necrotic myocytes with surrounding macrophagic infiltration. (H&E, ×250)

In many other species, myocardial necrosis is inconsistently observed with Se-E deficiency. In most cases the lesions are detected microscopically but are not apparent grossly. Affected species include dogs, foals, mink, rats, goats, mice, guinea pigs, rabbits, Rottnest quokka, and monkeys. Recently we produced myocardial lesions in mice fed Se-E deficient diets (Van Vleet and Ferrans, unpublished data).

It is necessary to emphasize that Se-E deficiency is an important cause of cardiomyopathy in human patients in China. Recent reports[148–154] have established that selenium deficiency is associated with the development of congestive cardiomyopathy in Chinese patients with the naturally occurring form of the deficiency (Keshan disease) and in American patients maintained on long-term parenteral hyperalimentation. Keshan disease is an endemic cardiomyopathy that occurs in a belt running from the northeast to the southwest of China and results from consumption of products with low selenium concentration from the soil–plant–ani-



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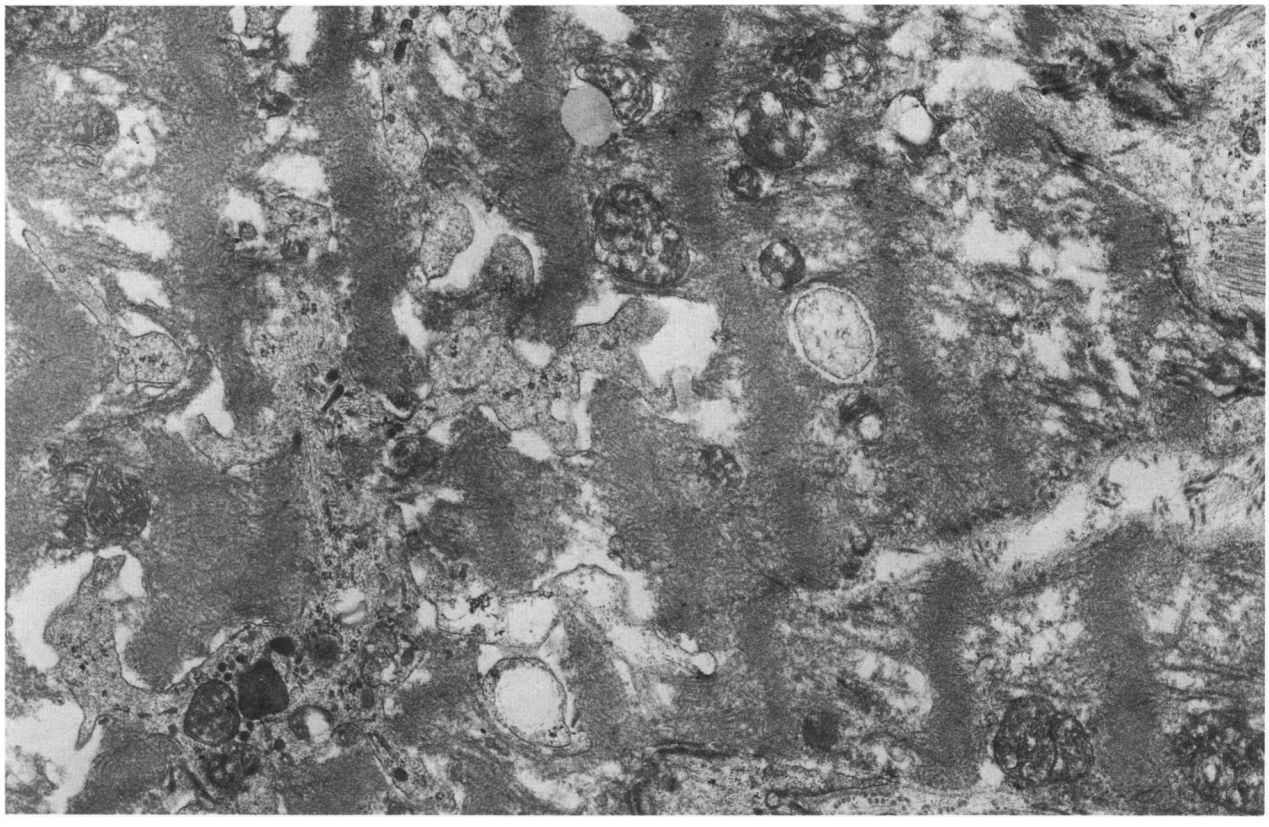

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**Figure 9**—Selenium–vitamin E deficiency. Pig. Necrotic atrial myocyte has a dense pyknotic nucleus and dense transverse hypercontraction bands. (×12,000) **Figure 10**—Selenium–vitamin E deficiency. Pig. Necrotic myocyte with numerous lysing hypercontraction bands is invaded by a macrophage. (×18,000)

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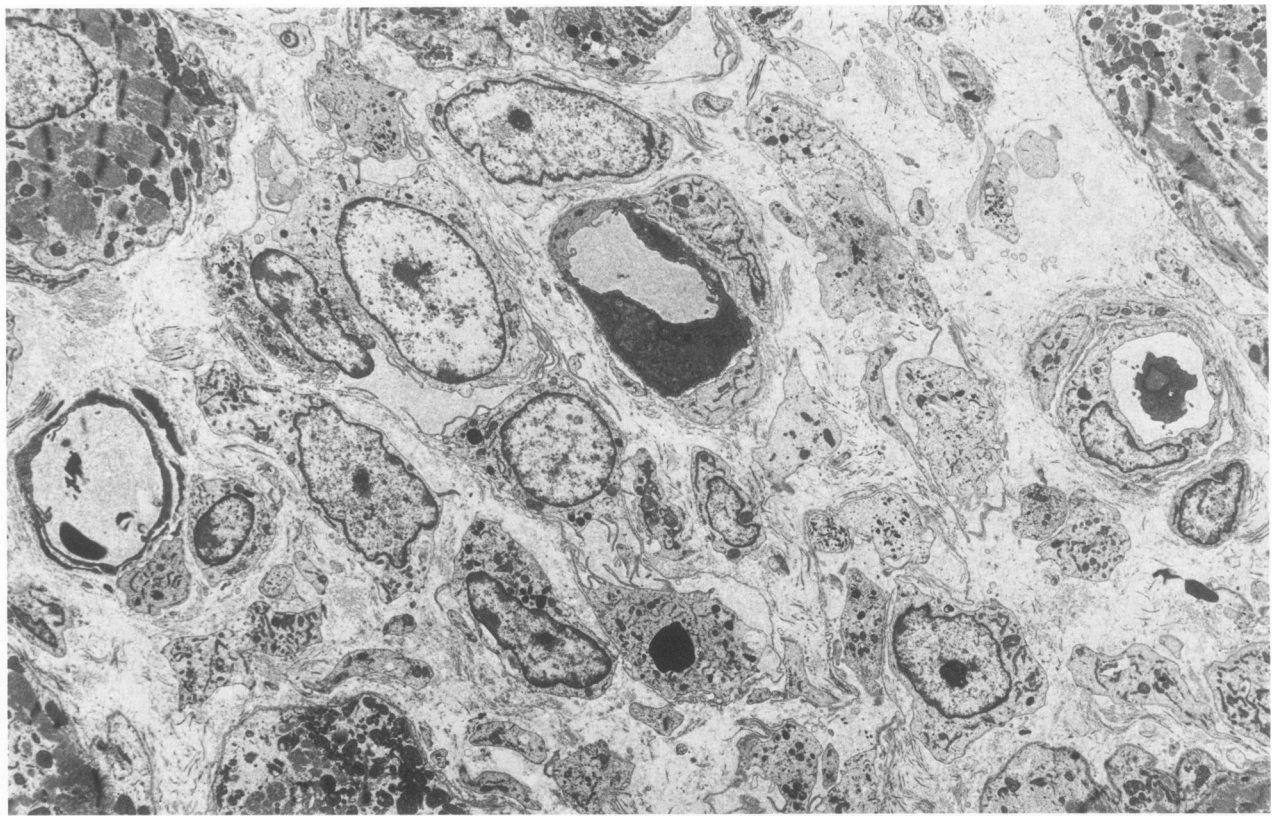

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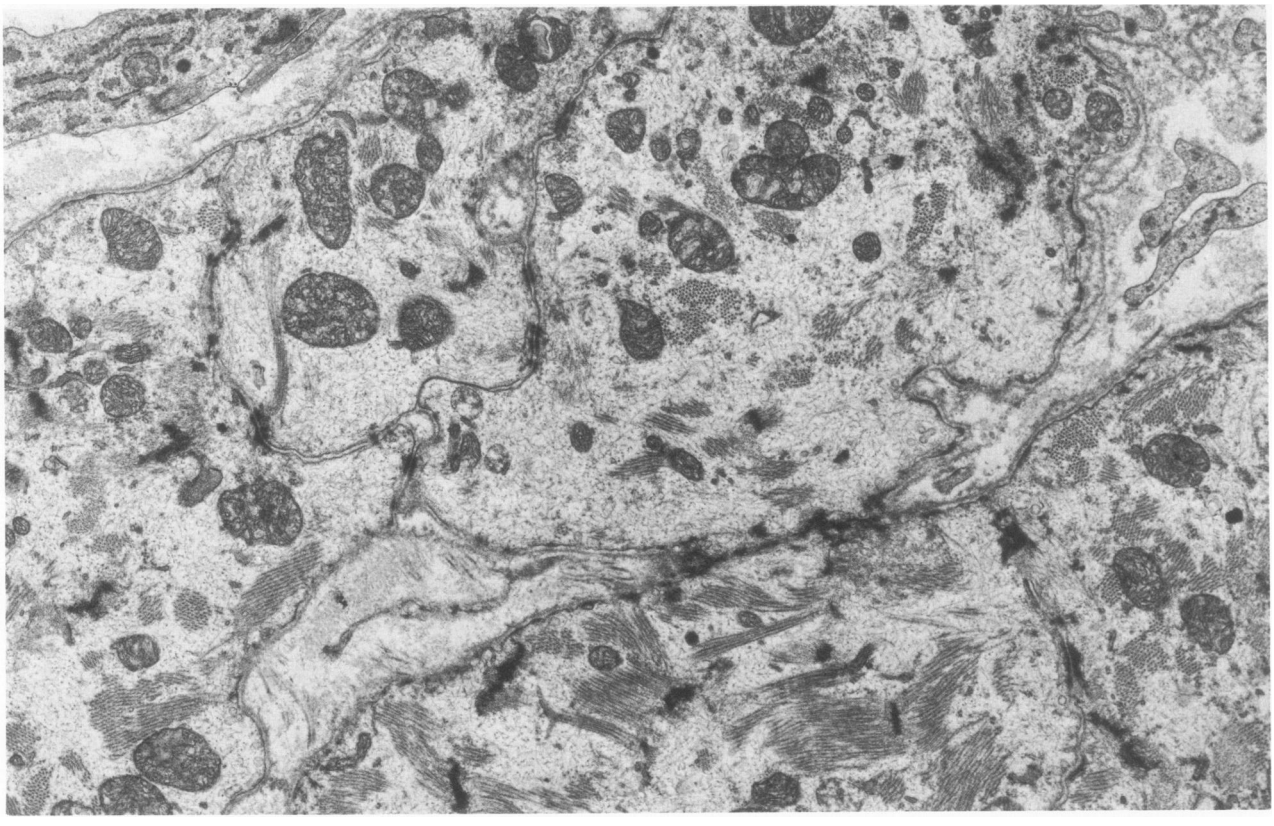
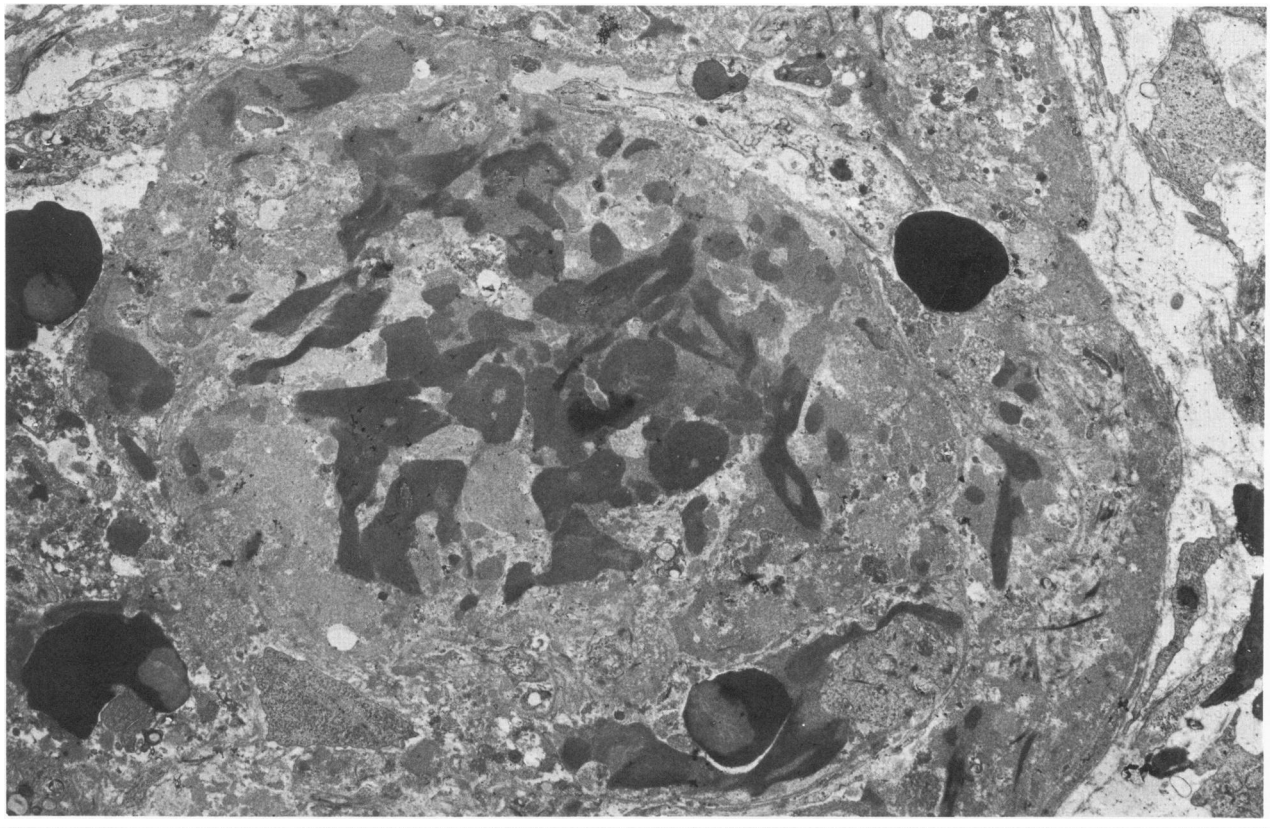


**Figure 11**—Selenium–vitamin E deficiency. Pig. Low magnification electron micrograph of an area of postnecrotic resolution in the atrial myocardium. Several "tubes," lined by the external lamina of missing myocytes, contain numerous macrophages. The interstitium shows edema and macrophagic invasion. (×4000) **Figure 12**—Selenium–vitamin E deficiency. Pig. Atrial myocytes show myocytolysis with numerous free myofilaments scattered throughout the sarcoplasm. (×13,000)



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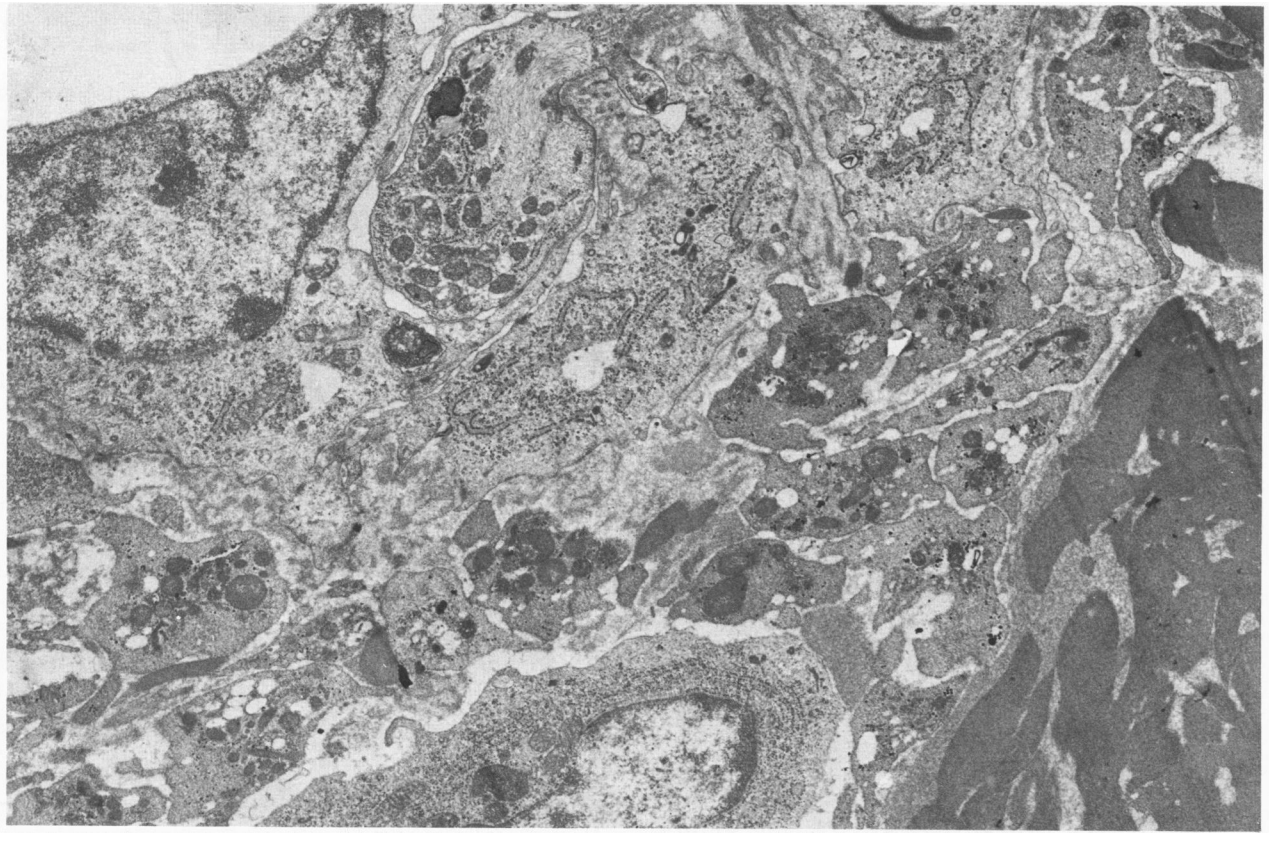

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**Figure 13**—Selenium–vitamin E deficiency. Pig. Low magnification micrograph of a thrombosed intramyocardial arteriole shows dense masses of fibrin and serum protein deposits in the lumen and throughout the wall. Several erythrocytes lie in the outer wall and adventitia of the affected arteriole. (×5000) **Figure 14**—Selenium–vitamin E deficiency. Pig. Inner wall of an intramyocardial arteriole with fibrinoid necrosis has large loosely-attached endothelial cells (*top*) with numerous underlying platelets and a dense mass of accumulated fibrin fibrils (*right*). (×11,000)

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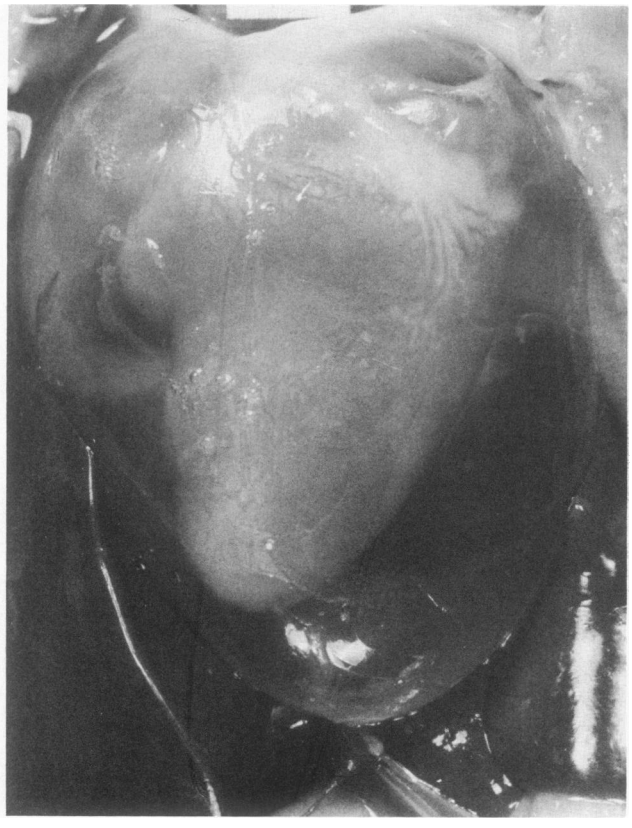

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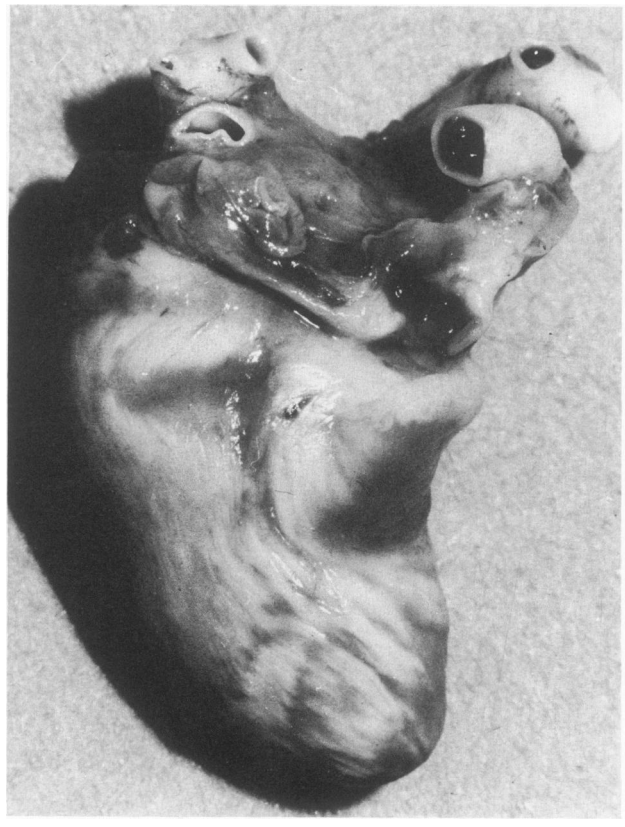
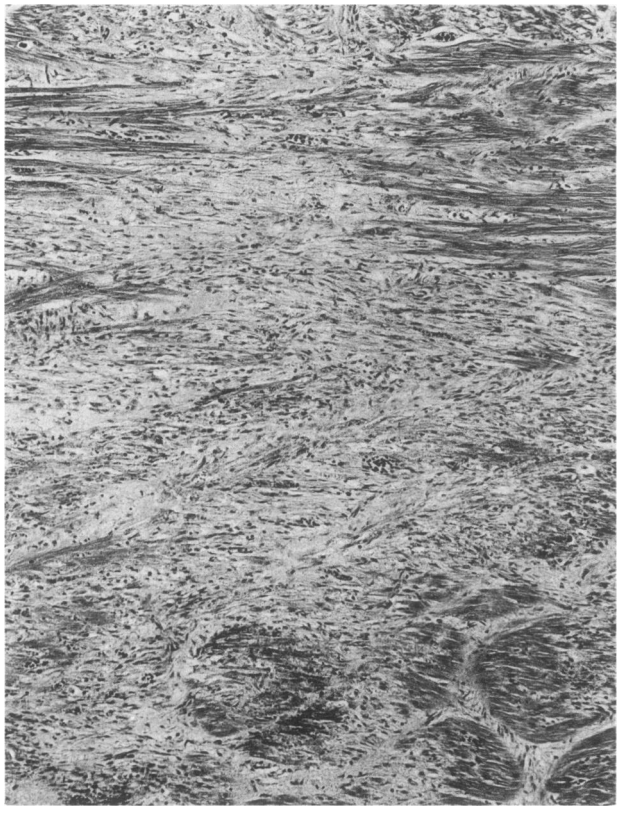


**Figure 15**—Selenium–vitamin E deficiency. Duckling. Marked hydropericardium in a bird fed tellurium (a selenium antagonist) at 500 ppm for 21 days. **Figure 16**—Selenium–vitamin E deficiency. Duckling. Extensive pale areas of myocardial necrosis in the ventricular myocardium.



mal–man food chain in affected areas. Patients have low blood and hair selenium content. Cases are generally found in peasants, mostly in children and women of childbearing age. Clinically, Keshan disease has been classified into acute, subacute, chronic, and latent types. In fatal cases, the hearts show biventricular dilatation; mural thrombi may be present. Histologically, myocardial necrosis with contraction bands and mitochondrial calcification is seen in early, acute lesions; postnecrotic fibrosis is present in chronic cases. Necrosis of skeletal muscles has been reported in some patients with Keshan disease.[151] Administration of selenium supplements, such as sodium selenite tablets or soybean supplements, has provided protection in endemic areas of China.

Congestive cardiomyopathy has also been reported in a few human patients with low selenium status following long-term parenteral hyperalimentation.[155–157] Also, cardiomyopathy may develop in human patients in whom vitamin E deficiency is presumed to be induced by chronic intestinal lipid malabsorption syndromes

**Figure 17**—Selenium–vitamin E deficiency. Duckling. Extensive areas of postnecrotic fibrosis and a focus of mineralized necrotic fibers (*bottom*) are present in the left ventricular myocardium. (H&E, ×100)

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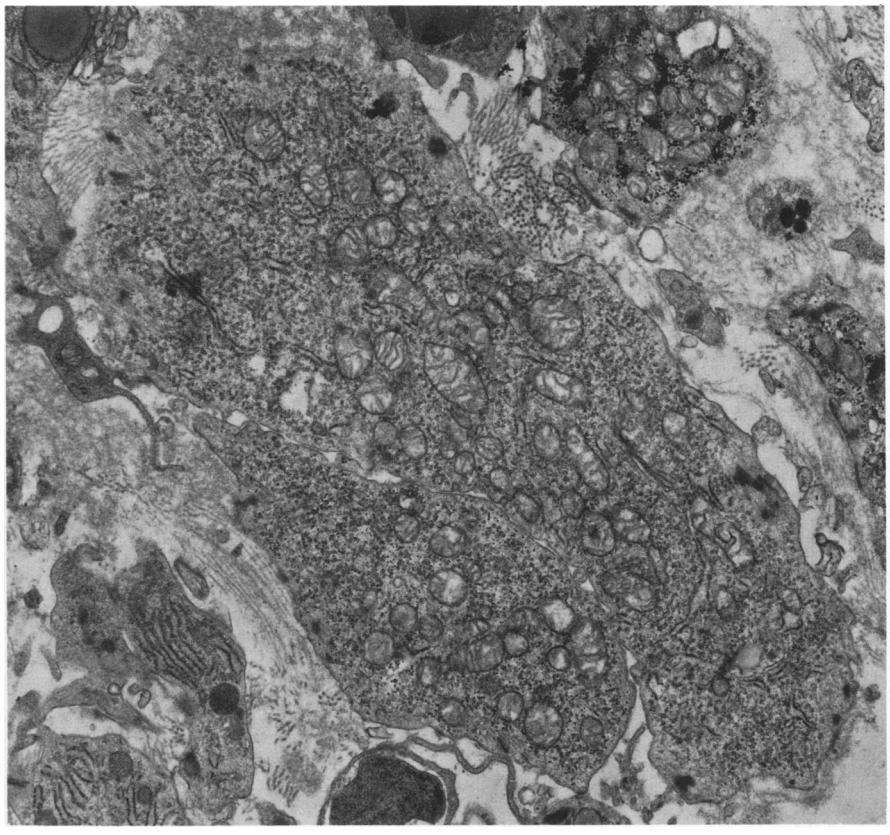

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**Figure 18**—Selenium–vitamin E deficiency. Duckling. High magnification of a necrotic myocyte has multiple calcified mitochondria with dense granular matrical deposits, linear profiles of cristae, and scattered lucent foci in the matrix. (×20,000) **Figure 19**—Selenium–vitamin E deficiency. Duckling. Area of resolving necrosis in the left ventricular myocardium has a dedifferentiated myocyte with numerous mitochondria and polysomes and a few scattered masses of Z-band material at the periphery. (×12,000)

such as cystic fibrosis, Byler's disease, and Bassen–Kornzweig syndrome.[158–161]

### Potassium Deficiency

Multifocal myocardial necrosis has been produced in rats, pigs, and dogs by potassium deficiency caused either by feeding potassium deficient diets, by inducing hypokalemia by administering glucocorticoids, or by hemodialysis.[162–174] In potassium-deficient calves, degenerative alterations were described in Purkinje fibers.[175] In dogs, the cardiac lesions were accompanied by renal and skeletal muscle lesions.[172] Myocardial lesions were present mainly in the left ventricular free wall and ventricular septum. In rats, histologic study showed foci of myocytolysis and scattered mononuclear cells in the interstitium; ultrastructural study showed myofibrillar lysis in damaged myocytes, with restoration of the myocardium, but without accompanying fibrosis, upon repletion with potassium.[169] These findings were interpreted to indicate that damaged myocytes underwent dedifferentation during potassium depletion and were restored to their mature form upon repletion.

### Copper and/or Iron Deficiency

Naturally occurring copper (Cu) deficiency is seen in adult cattle maintained on copper-deficient pastures. The disease has been described in Australia, Europe, and the southeastern United States.[176–179] Affected cattle suffer weight loss and anemia and die unexpectedly. Because animals may literally "drop dead," the disease has been termed "falling disease." At necropsy, the hearts are atrophic, pale, and flabby. Extensive myocardial fibrosis is present microscopically.

Experimentally induced Cu deficiency was produced in newborn pigs fed deficient diets for 61–127 days.[180–182] Anemia developed, and 20 of 33 pigs died with hemopericardium from rupture of the myocardium, pulmonary, or coronary arteries. Rupture of papillary muscles, with or without atrial rupture, was seen in 6 pigs. Myocardial hypertrophy was present.

In rabbits with experimental Cu deficiency, myocar-

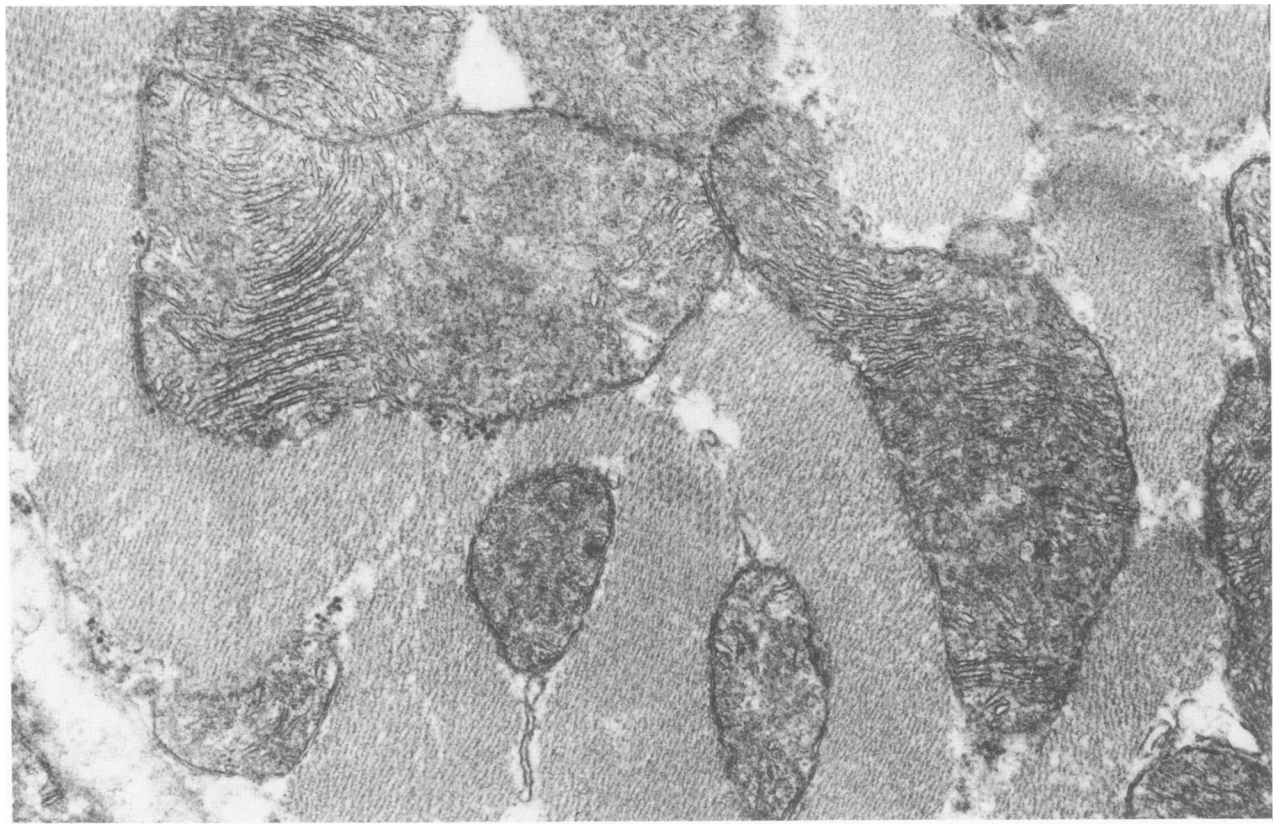


**Figure 20**—Copper deficiency. Rat. Ventricular myocyte has several enlarged mitochondria. (×22,500)

dial necrosis and calcification were present together with degenerative changes in elastic fibers of large blood vessels.[183]

Rats fed diets deficient in copper, iron (Fe), or both, developed myocardial hypertrophy.[184-187] In rats with combined Cu and Fe deficiency, severe anemia and congestive heart failure developed after 8–10 weeks. At necropsy, transudation was seen as hydrothorax, hydropericardium, ascites, and subcutaneous edema; and biventricular hypertrophy was present. Microscopically, multiple foci of myocardial degeneration, necrosis with calcification, infiltration with mononuclear leukocytes, and fibrosis were present. These lesions were concentrated in the inner third of the left ventricular wall and were attributed to anoxic injury from severe anemia. Development of myocardial hypertrophy appeared to precede the onset of severe anemia and was characterized ultrastructurally by an increase in the number and in the cell volume fraction of mitochondria (Figure 20).[184,187] An increased ratio of Type III to Type I collagen was demonstrated in the hearts of Cu-deficient rats.[186] Young rats born of Cu-deficient dams had heart failure.[188] The hearts were hypertrophied and pale. Ventricular aneurysms and hemopericardium were occasionally seen. Microscopically, diffuse myocardial lipidosis and hypertrophy with focal necrosis was present. Extensive myocardial necrosis and hemorrhage occurred in the walls of the ventricular aneurysms.

Neonatal pigs with chronic Fe deficiency-induced anemia developed cardiac dilatation and hypertrophy.[189] Weanling mice with Cu deficiency developed anemia, atrial thrombosis and rupture, hemopericardium, hemothorax, and pleural effusion.[190]

### Thiamine Deficiency

Cardiac lesions may accompany the neural lesions in animals with severe thiamine deficiency and have been reported in the rat, mouse, pigeon, pig, fox, sea lion, dog, and monkey.[191,192] Clinical signs of deficiency in the rat included weight loss, anorexia, and death.[193] The gross lesions in the hearts of thiamine deficient pigs were dilatation and scattered pale streaks of necrosis in the myocardium.[194] Histologically, multifocal myocardial necrosis was present in the atria and ventricles. Pigeons with chronic thiamine deficiency developed congestive heart failure and myocardial necrosis.[195] Affected dogs and foxes had multifocal myocardial necrosis and fibrosis.[196,197] Several ultrastructural studies of the hearts of

thiamine deficient rats have shown early mitochondrial alterations of swelling or condensation and later formation of vesicles and myelin figures from damaged mitochondria. Scattered, severely damaged myocytes had contraction band necrosis in rats fed the deficient diet for 28 days.[193,198,199] Rats with moderate thiamine deficiency were resistant to the cardiotoxic effect of isoproterenol.[191]

### Magnesium Deficiency

Experimentally induced magnesium deficiency has been produced in rats, dogs, calves, and hamsters.[200-207] The clinical signs of deficiency in rats and dogs were slow growth, alopecia, cutaneous edema and erythema, hyperirritability, convulsions, and death.[201,206] At necropsy, myocardial lesions were usually present as scattered foci of necrosis with calcification; the lesions occasionally involved the full thickness of the ventricular wall. Selective involvement of the inner myocardium was seen. The extent of myocardial damage was increased in rats subjected to concurrent cold stress but was decreased in hamsters with concurrent thiamine deficiency.[203-205]

Microscopic and ultrastructural study of the myocardial lesions revealed initial alterations in mitochondria with swelling and vacuolation.[200-202] Affected necrotic myocytes had extensive mineralization of mitochondria. Areas of necrosis were infiltrated by mononuclear leukocytes, and healing of the lesions resulted in residual areas of fibrosis.

### Protein Deficiency and Protein-Calorie Malnutrition (Kwashiorkor, Marasmus)

Monkeys fed a protein-deficient diet for 12 weeks lost approximately 20% of their body weight.[208] At necropsy, the hearts were atrophic, pale, and flabby. Microscopically, myocytes were atrophic; and multiple foci of myocardial degeneration, necrosis, and fibrosis were present. Fibrosis was most extensive in the atria.

Experimental protein-calorie malnutrition for 7 weeks in dogs resulted in approximately 40% weight loss, lethargy, and the death of 4 of 19 animals from superimposed sepsis.[209,210] The dogs that died had bronchopneumonia, hemorrhagic enterocolitis, hepatic lipidosis, ascites, edema of skeletal muscles, and depletion of fat depots. All of the starved dogs had cardiac atrophy with decreased heart weight and decreased myocardial glycogen content. Histologic and ultrastructural study of the hearts revealed atrophy of myocytes and prominent interstitial edema. Physiologic studies showed decreased left ventricular function, which was attributed to decreased cardiac compliance from myocardial edema and to decreased myocardial contractility from atrophy.

### Tryptophan Deficiency

In rats fed maize and bean diets containing nutritionally inadequate amounts of tryptophan for 15–30 months congestive heart failure developed with cardiomegaly.[211,212] At necropsy, the hearts had dilatation and hypertrophy and thick, opaque, left ventricular endocardium. Microscopically, endocardial and myocardial fibrosis was present. Feeding low tryptophan and low protein diets containing large amounts of plantain produced endocardial fibrosis, but not myocardial lesions, in rats and guinea pigs; however, these diets did not produce cardiac lesions in monkeys.[211,213,214] It was suggested that the high content of 5-hydroxytryptamine in plantains offers protection from the myocardial damage associated with feeding tryptophan-deficient diets. Adding supplements of tryptophan to the ration of rats after they had been fed the deficient diet for 1 year did not cause regression of the cardiac lesions.

### Choline Deficiency

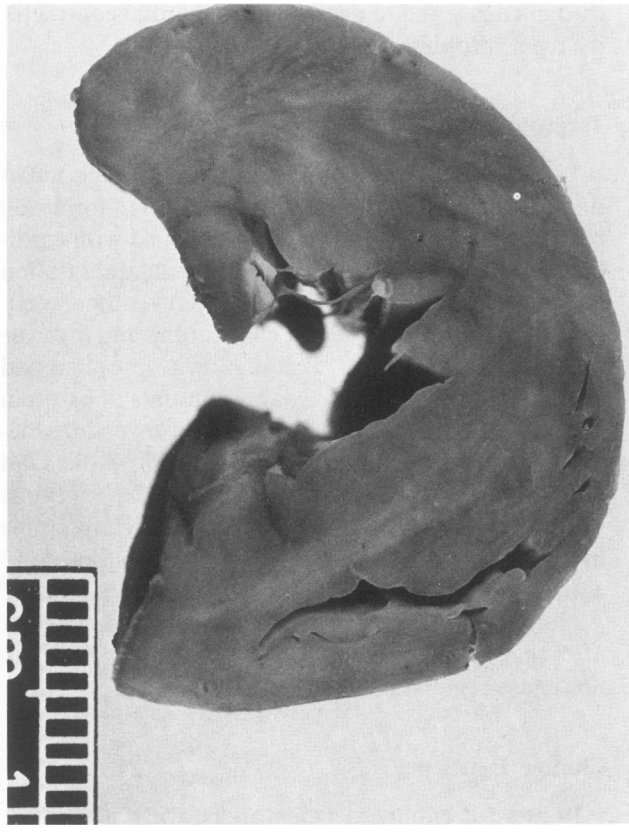
In rats fed choline-deficient diets, with or without added ethyl laurate, myocardial lipidosis initially developed, followed by multifocal myocardial necrosis.[215-220] Affected rats died suddenly and had hydropericardium and fatty livers at necropsy. The cardiac lesions were accentuated by feeding large amounts of fats and were more severe in males than in females. Administration of choline supplements protected against the cardiac lesions.

## Myocardial Diseases of Unknown Etiology

This group of diseases is heterogeneous in clinical course and morphologic alterations. The idiopathic or primary cardiomyopathies in animals offer progressive diseases with many clinical and pathologic similarities to the human diseases. However, the value of these animal models of cardiomyopathy is limited by our present inability to reproduce the diseases for laboratory studies. Other diseases in this group include age-related lesions that are seen in various animal species and a syndrome of sudden cardiac failure observed in birds.

### Hypertrophic Cardiomyopathy in Cats, Dogs, and Pigs

Although this disease is known to occur in several species of animals, hypertrophic cardiomyopathy has been studied most extensively in humans, in which it occurs mostly as a genetically transmitted disorder



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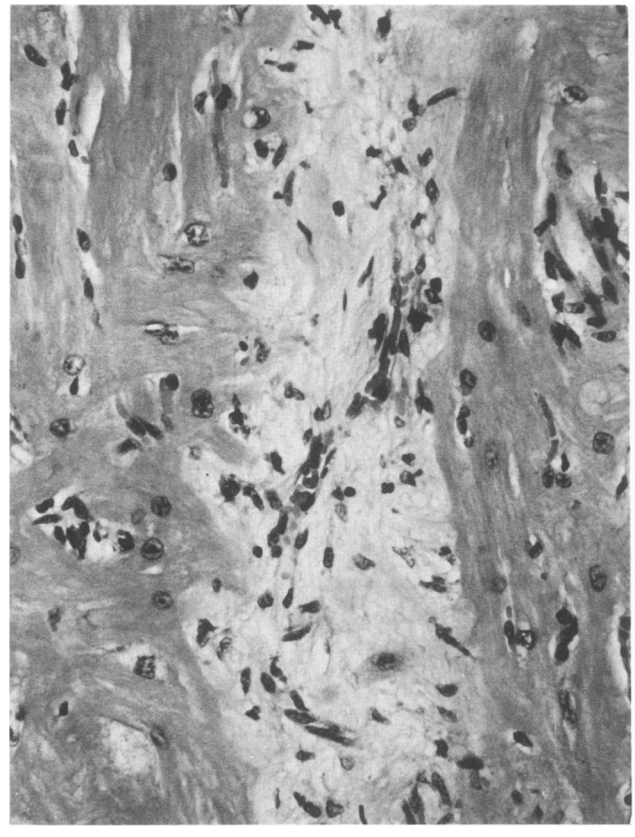

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**Figure 21**—Hypertrophic cardiomyopathy. Cat. Cross-section of ventricles reveals prominent myocardial hypertrophy in the left and right free walls and septum. **Figure 22**—Hypertrophic cardiomyopathy. Cat. Section of left ventricle has interweaving hypertrophied myocytes with extensive perivascular fibrosis. (H&E, ×300)

characterized by 1) severe hypertrophy that affects all chambers, but particularly the left ventricle; 2) asymmetric hypertrophy of the ventricular septum, the maximal thickness of which exceeds that of the left ventricular free wall (measured in the posterolateral region, at the level of the free margin of the posterior mitral leaflet) by a ratio of 1.3 (normal, 1.0); 3) a small, abnormally shaped left ventricular cavity; 4) relatively frequent occurrence (about 25%) of obstruction to left venticular outflow (caused by narrowing of the left ventricular outflow tract by hypertrophic septal muscle and by abnormal anterior systolic motion of the anterior mitral leaflet); 5) widespread disarray of ventricular myocytes (which in the majority of patients involves >5% of the myocytes in the ventricular septum and in the left ventricular free wall); and 6) a high incidence of fibromuscular intimal and medial thickening and adventitial fibrosis involving small, intramural coronary arteries.[221] The presence of fibrous plaquelike lesions in the septal endocardium of the left ventricular outflow tract is regarded as evidence of contact between the anterior mitral leaflet and the ventricular septum (thus indicating the occurrence of obstruction). A small minority of cases of hypertrophic cardiomyopathy in humans have diffuse, symmetric hypertrophy, rather than the asymmetric hypertrophy described above. However, it is believed that these are two variants of the same disease, rather than two different, unrelated entities, because they coexist in some families.[222] Other uncommon anatomic variants of hypertrophic cardiomyopathy, including the midventricular obstruction[223,224] and the apical hypertrophy syndromes,[225,226] form part of the anatomic spectrum of this disorder in humans.[227-229]

Hypertrophic cardiomyopathy occurs frequently in cats and occasionally in dogs,[230] but only a single report[231] has described the disease in pigs. Numerous reports of series of cases in cats and dogs at the Animal Medical Center in New York over the past 13 years have characterized the clinical and pathologic aspects of the disease.[230,232-242] Early reports called all cases of primary myocardial disease in cats and dogs idiopathic cardiomyopathy; however, in publications since 1977, Liu has classified these cardiac diseases into hyper-

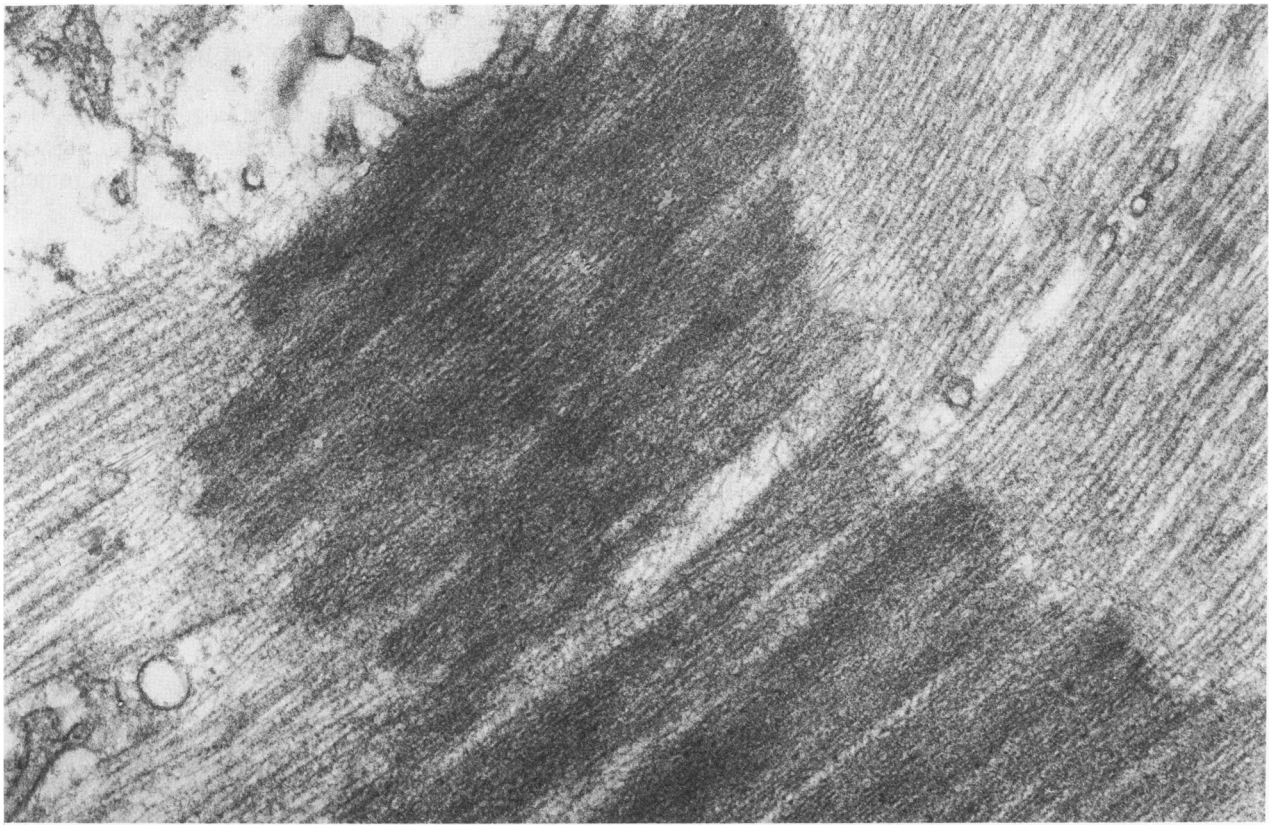

**Figure 23**—Hypertrophic cardiomyopathy. Cat. Thick block of Z-band material in right ventricular myocyte. (×60,000)

trophic, congestive, and restrictive cardiomyopathies in the cat and hypertrophic and congestive cardiomyopathies in the dog.

Hypertrophic cardiomyopathy in cats tends to affect middle-aged males most frequently. The disease is three times more frequent in males than females. However, the age range of affected cats may be wide, as seen in a large series (n = 128) of affected cats that ranged from 8 months to 16 years of age.[232] The etiology is unknown, but the occurrence of cases in related cats suggests an hereditary role.[230] Clinically, affected cats generally present with sudden onset of congestive heart failure with dyspnea, anorexia, and lethargy. Approximately half of affected cats will have aortic thromboembolism and posterior paresis. Some cats may have sudden, unexpected death without previous clinical signs. At necropsy, extracardiac findings include aortic thromboembolism, renal infarction, and pulmonary congestion and edema. Affected hearts are enlarged and have diffuse hypertrophy of the left ventricular free wall, ventricular septum, and left ventricular papillary muscles, marked dilatation and hypertrophy of the left atrium, and a narrow left ventricular cavity (Figure 21). In a few cats, asymmetric septal hypertrophy is observed, as manifested by a septal/free wall thickness ratio of 1.1 or greater (rather than by the 1.3 or greater ratio used to classify the human cases). Histologically, diffuse hypertrophy, myocyte disarray (disarray occurs mostly in association with asymmetric septal hypertrophy), interstitial fibrosis, and fibromuscular hyperplasia of small intramural coronary arteries are seen (Figure 22). Of 129 cat hearts with hypertrophic cardiomyopathy, 44% had foci of myocyte disarray in the ventricular septum; in 31% the disarray involved at least 5% of the myocytes in the section.[232] Ultrastructural study confirmed the presence of myocyte hypertrophy, disarray, interstitial fibrosis, lipofuscin accumulation, focal myofibrillar lysis, accumulation of masses of Z-band material, and distension of elements of sarcoplasmic reticulum (Figure 23).[243,244]

Hypertrophic cardiomyopathy in dogs predominates in males. German shepherds are most frequently affected, but cases in dogs of small breeds have also been reported.[230,232,236,237,239,241] Approximately 50% of the dogs had sudden unexpected death (which occurred in some dogs during routine surgical procedures); the remaining dogs had evidence of congestive cardiac failure with dyspnea and cough. At necropsy, the hearts

were enlarged and showed ventricular hypertrophy, decreased left ventricular cavity size, and left atrial dilatation. Asymmetric septal hypertrophy (septal/free wall thickness ratio, >1.1) was often present. Microscopically, myocyte disarray was seen in the ventricular septum of 20% of the dogs.

In a series of 1906 necropsy cases of pigs at the Pig Research Institute of Taiwan, 32 cases of hypertrophic cardiomyopathy were reported.[231] Twenty-three of these had the symmetric form, and 9 the asymmetric form (which was defined by a septal/free wall thickness ratio of 1.1, rather than by the 1.3 ratio used in classifying the human disorder). Relative heart weights were increased by 50%. The ventricular walls were severely thickened, and the left ventricular cavity was small in size and abnormal in shape. Microscopic study revealed consistent myocyte hypertrophy; however, only some cases had disarray of myocytes. Thus, it seems that hypertrophic cardiomyopathy in pigs (and also in dogs and cats) is more frequently of the symmetric type and is less frequently associated with myocyte disarray than is the case in humans. A pattern of inheritance for hypertrophic cardiomyopathy has not been established in animals and is only incompletely understood in humans.[245]

The pathogenesis of hypertrophic cardiomyopathy in humans and animals in unclear. The nature of the basic defect in this disease is unknown. It has been suggested that the disease may result from a disturbance of the delicate interaction between immature, myocardial adrenergic receptor sites and extracardiac catecholamines, leading to myocyte hypertrophy and disarray.[246] Ferrans and Rodriguez[247] have postulated an abnormal sensitivity to hypertrophic stimili. In dogs infused with subhypertensive doses of nonepinephrine for 12–63 weeks left ventricular hypertrophy develops, and these dogs may offer a model for hypertrophic cardiomyopathy.[248,249]

### Dilated (Congestive) Cardiomyopathy in Cats, Dogs, and Pigs

Congestive (or ventricular-dilated) cardiomyopathy is a group of conditions in which systolic pump failure and ventricular cavity dilatation are common denominators. In many cases the cause of the disorder cannot be established, and it is termed "idiopathic." In others, congestive cardiomyopathy occurs in association with pregnancy or the postpartum period, toxic agents, and nutritional deficiency states.[221,247]

The heart is flabby and dilated and may show some degree of endocardial fibroelastotic thickening. Mural thrombi are common. Inflammatory reaction is absent or very scanty; variable degrees of fibrosis and small foci of myocytolysis may be present.[221,247]

Idiopathic congestive cardiomyopathy occurs frequently in cats and somewhat less frequently in dogs[230]; a single report[231] has described the disease in pigs. In cats, the disease predominates in males (approximately 3 male/1 female), affects middle-aged cats (range, 3–16 years of age), and has no specific breed predilection.[230,239,242,244,250–252] Hydrothorax was present in 74% of 133 cats. Presenting features were dyspnea (60%), anorexia (30%), and posterior paresis from aortic thromboembolism (25%). At necropsy, the hearts showed cardiomegaly, with increase in heart weight and marked dilatation of all chambers (Figure 24). The papillary muscles and ventricular trabeculas were atrophic. Mild interstitial edema and fibrosis and occasional foci of myocytolysis were seen in the ventricular myocardium by light- and electron-microscopic study.[232,239,244] Extensive microscopic and ultrastructural alterations were described in severely dilated atria, including myocyte degeneration and hypertrophy and interstitial fibrosis.[242] Atrial tachyarrhythmias were associated with the left atrial lesions.

Numerous reports of congestive cardiomyopathy in dogs have been published since 1970.[230,232,239,240,253–262] The disease predominates in males (approximately 3 males/1 female) of middle age (range, 2–9 years of age). Generally, dogs of large breeds are affected, especially Doberman pinschers.[253,257] However, English cocker spaniels in western Australia also are affected.[256,261] In New England, cardiomyopathy occurs frequently in Boxers.[263] Frequent involvement of specific breeds suggests an inherited basis for the disease in the dog. Detweiler et al[264] have suggested that some cases of canine cardiomyopathy are the result of an autoimmune reaction that follows canine parvoviral myocarditis. Clinical signs include ascites, weight loss, weakness, dyspnea, and cough. Atrial fibrillation was detected in 90% of 57 affected dogs.[232] At necropsy, ascites and hydrothorax were present. The hearts had markedly dilated ventricles with opaque endocardium and dilated atria with a rough granular epicardial surface (Figure 25). Pulmonary and hepatic congestion were present. Microscopically, multifocal myocardial fibrosis and medial hyperplasia of intramyocardial arteries were observed. Ultrastructurally, nonspecific alterations in myocytes were present as myocytolysis, lipofuscin accumulation, myelin figures, proliferation of sarcoplasmic reticulum, and altered mitochondria (Figures 26 and 27).[254,260,262]

In pigs, 17 cases of congestive cardiomyopathy were reported from Taiwan.[231] However, all 17 pigs had accompanying aortic stenosis, pericarditis, or vegetative

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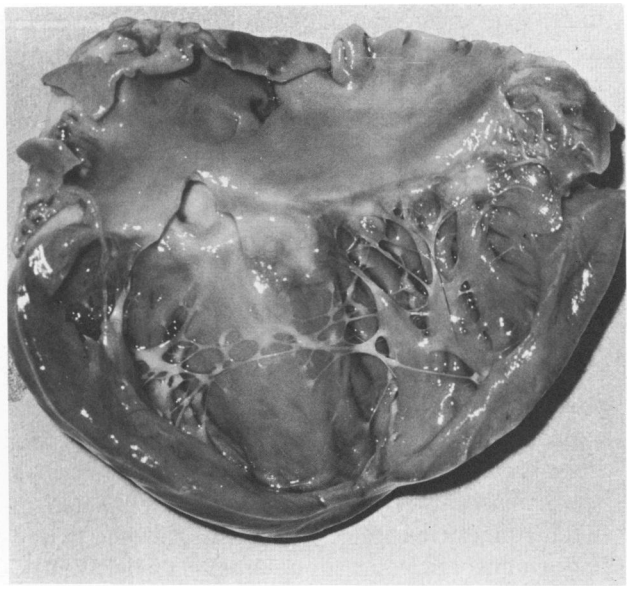

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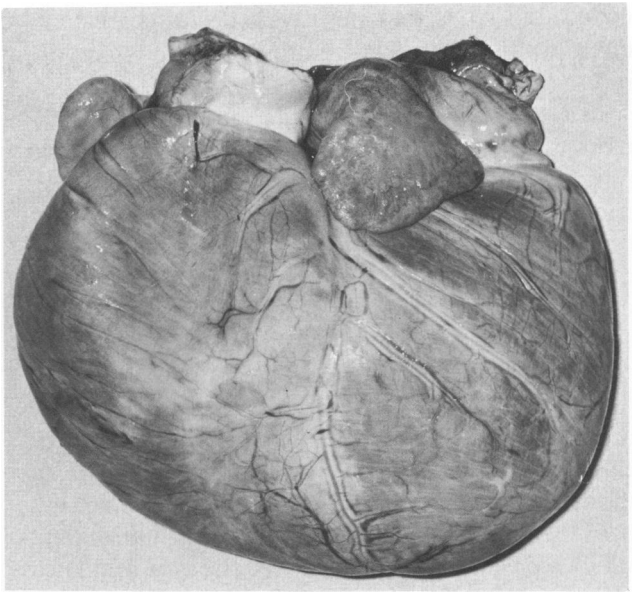

**Figure 24**—Congestive cardiomyopathy. Cat. The left ventricle is dilated and the wall is thin. **Figure 25**—Congestive cardiomyopathy. The heart from a 1-year-old Great Dane with congestive heart failure has cardiomegaly and a rounded shape from biventricular dilatation.

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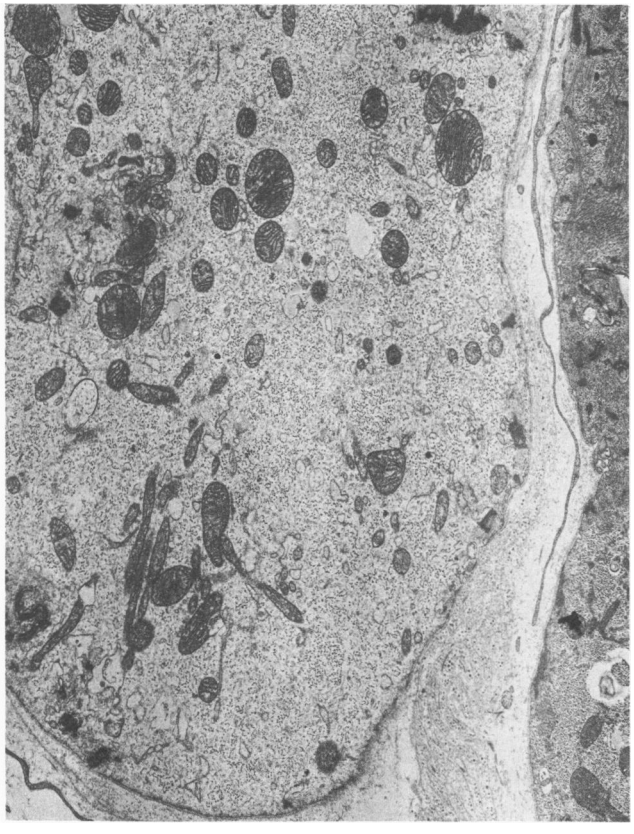

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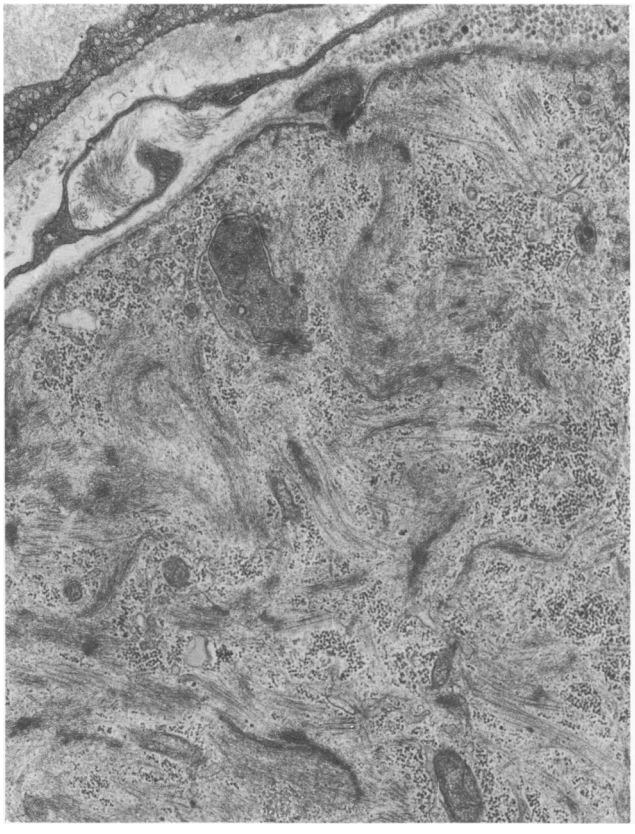

**Figure 26**—Congestive cardiomyopathy. Dog. Myocyte of left atrium has extensive myofibrillar lysis. The sarcoplasm contains numerous free filaments, scattered mitochondria, and a few lipofuscin granules. (×9000) **Figure 27**—Congestive cardiomyopathy. Dog. Sarcoplasm of a left atrial myocyte contains lysed myofibrils and numerous glycogen granules. (×18,000)

endocarditis; thus, they may have had end-stage cardiac disease with nonspecific, terminal cardiac dilatation, rather than congestive cardiomyopathy.

In a recent case report,[265] acute congestive heart failure was described in a 6-week postpartum Doberman pinscher dog. The animal had been normal at two physical examinations during the pregnancy. The onset of cardiac failure was rapid, and the dog collapsed and died upon admission to a veterinary hospital. At necropsy, the dog had ascites, pulmonary and hepatic congestion, and biventricular dilatation. Microscopically, the myocardium showed multifocal degeneration, necrosis, and fibrosis. The lesions were most extensive in the left ventricle. The authors concluded that the clinicopathologic picture in this dog was compatible with the diagnosis of postpartum cardiomyopathy, which has been the subject of a number of reports in humans and which represents a clinically distinctive type of dilated cardiomyopathy.[247,266]

### Restrictive Cardiomyopathy and Endomyocardial Diseases in Cats and Rats

The term "restrictive cardiomyopathy" designates a group of disorders characterized by impairment of ventricular filling by unyielding endocardial, subendocardial, or myocardial tissue.[247] Restrictive cardiomyopathy may be primary or may be due to infiltrative disorders (such as amyloidosis), endocardial fibroelastosis (in which both collagen and elastic fibers are abundant in the thickened endocardium), or endomyocardial fibrosis (in which the endocardial thickening is due to deposition of collagen). In humans, endomyocardial fibrosis often occurs in association with blood and tissue hypereosinophilia[267]; however, we are not aware of such an association in animals.

In cats, restrictive cardiomyopathy occurs less frequently than hypertrophic and congestive cardiomyopathy. In 47 cases, middle-aged male cats were generally affected, and no breed predilection was observed.[232] Clinically, dyspnea, anorexia, and posterior paresis from aortic thromboembolism were observed. At necropsy, two types of cardiac lesions have been characterized in feline restrictive cardiomyopathy.[230,232-234,238,239,268] In the first type, the left ventricle shows diffuse, marked endocardial fibrosis, which appears as a thick, white, firm covering, especially over the inflow and outflow tracts, papillary muscles, and chordae tendineae. Massive left atrial enlargement is present. Histologically, the affected endocardium shows marked fibrosis with focal chondroid metaplasia. Myocardial hypertrophy and fibrosis also may be present. Intimal and medial hyperplasia of intramural coronary arteries are seen. Focal myocyte disarray has been found in the ventricular septum of some affected cats. In the second type of restrictive cardiomyopathy, increased numbers of left ventricular moderator bands were found to be the cause of the disease.[268] Left atrial dilatation and hypertrophy were present, with left ventricular hypertrophy in younger affected cats and left ventricular dilatation in older cats. Pulmonary edema was prominent. The anomalous development of these moderator bands is presumed to represent a congenital defect with delayed onset of clinical cardiac disease.

A disease termed "endocardial disease" or "subendocardial fibrosis" has been described in five strains of rats and may represent an example of restrictive cardiomyopathy.[269-273] The incidence of the lesion varied from 1% to 7% in the various strains examined and was increased in older rats. Some affected rats had terminal congestive cardiac failure with chronic pulmonary and hepatic congestion. Grossly, the left ventricular endocardium was white and thick. Histologic and ultrastructural study revealed uniform diffuse or focal tumorlike masses of fibroblastic proliferation and collagen deposition in the subendocardium.

Endomyocardial fibrosis developed in Sprague-Dawley rats that were treated for 1-14 weeks with the carcinogen N-nitrosomorpholine.[274] The incidence of the lesion was 5% and 20% in rats examined at 29-78 and 79-108 weeks after exposure, respectively. The lesion was usually limited to the left ventricle, the endocardium of which was diffusely involved; but a few rats had focal involvement with polypoid endocardial masses. Some rats had accompanying myocardial hypertrophy.

Endocardial fibroelastosis is characterized by diffuse thickening of mural endocardium by fibrous and elastic tissue. Mitral valvular endocardium also may be involved. The condition can be either primary (when it is congenital and not associated with other cardiovascular anomalies or myocardial lesions) or secondary (when it is associated with other disorders, including storage diseases, myocardial necrosis, radiation injury, and turbulent flow in the ventricular cavity after cardiac valvular replacement).[275] Several reports have documented the occurrence of primary endocardial fibroelastosis as an inherited congenital anomaly in Burmese cats,[276-278] and other reports have described sporadic cases of this disorder in dogs and cats.[279,280] The disease is manifested by tachycardia, gallop rhythm, systolic murmur, cardiomegaly, and signs of congestive heart failure, especially dyspnea and often terminal cyanosis. The onset is commonly precipitated by a respiratory infection at between 3 weeks and 4 months of age. Sudden death is common. The mode of inheritance is complex. The left atrium and left ventricle are severely dilated; in Burmese cats with endocardial fibro-

elastosis the endocardium is opaque and thickened (up to 200 μ) by a subendothelial layer of collagenous and elastic fibers, which are thicker and more organized in the areas adjacent to the myocardium. The diameters of both the elastic and collagenous fibers are larger than normal. Endocardial edema and dilated lymph vessels are seen in the endocardium in early stages, suggesting that lymphatic obstruction is involved in the pathogenesis of the disorder. This also has been suggested by the results of studies of experimental obstruction of cardiac lymphatics in dogs[281] and monkeys.[213] Other studies have suggested that viral infection of the heart can be a cause of endocardial fibroelastosis in humans[282,283] as well as in dogs.[284]

### Cardiomyopathy of Chickens and Geese

A syndrome of sudden collapse and death, usually at the time of excitement or exertion, occurs in chickens and geese. Many names have been applied to this disease, including "round heart disease," "enzootic syncope," "toxic heart degeneration," "Eierherz" ("egg-heart"), "Kugelherz" ("bullet-heart"), "yellow heart degeneration," "idiopathic cardiac dilatation of hens," "toxic heart disease," and "enzootic Herztod."[285-295] The etiology of this cardiac syndrome is unknown. A wide spectrum of cardiac lesions has been described, including cardiomegaly with rounded apex, left ventricular hypertrophy, and myocardial pallor. Mild ascites and hydropericardium may be present, with pulmonary and hepatic congestion. Microscopically, the hearts have acute alterations of myocardial degeneration and necrosis.

Recently a similar clinical syndrome was described in 24–30-week-old broiler-breeder hens in Australia.[296-298] The birds collapsed and died unexpectedly. Necropsy showed edema of the head, mild ascites, hydropericardium, visceral congestion, cardiomegaly, and ventricular hypertrophy with and without dilatation. Microscopically, the lesions were concentrated in the left atrium and consisted of myocardial degeneration, inflammatory cell infiltration, and prominent endocardial fibroelastosis. Intramyocardial arteries in the left atrium showed medial hypertrophy, adventitial fibrosis, and focal fibrinoid deposits in the walls. The syndrome was reproduced experimentally in broiler-breeders fed a diet low in potassium, phosphorus, protein, and caloric content.[297]

Recent reports have demonstrated the economic importance of a cardiac failure syndrome in growing broiler chickens.[299-301] The disease has been termed "sudden death syndrome," "acute death syndrome," and "flip-over" by poultry diagnosticians. The etiology is unknown, but mortality is greater in males than in females, tends to be increased in heavier birds of the same age, is increased by continuous lighting, and tends to peak at 3–4 weeks of age. Affected hearts tended to be enlarged. Generalized visceral congestion was present. Microscopic studies have revealed inconsistent myocardial alterations varying from absence of lesions to hearts with extensive edema and interstitial leukocytic infiltration.[299,301]

Broiler chickens are also affected by heart failure due to a condition termed "hydropericardium-ascites syndrome," "edema disease," "toxic fat syndrome," or "water belly."[302,303] Severe ascites and cardiac dilatation are consistent findings. Suggested etiologies include toxic factors in dietary fats and polychlorinated biphenyl toxicosis.

Chickens raised at high altitudes may suffer high death losses from "high altitude disease." Necropsy findings include edema, hydropericardium, cardiac dilatation and hypertrophy, and visceral congestion.[304,305]

### Atrial Thrombosis in Hamsters and Mice

Atrial thrombosis is the most common cardiovascular lesion seen in aged Syrian hamsters and also occurs frequently in certain strains of mice.[1,306,307] Affected hamsters may have hyperpnea, tachycardia, and cyanosis for up to a week prior to death. At necropsy, the thrombosed atria in both hamsters and mice are swollen, firm, and mottled. The atrial wall may have pale areas of scarring. The exposed thrombus is gray to tan, often laminated, and may be large enough to extend into the orifice of the mitral valve. Rarely atrial rupture occurs in mice. The left atrium is usually affected in hamsters and mice, but occasionally both atria are thrombosed and ventricular thrombi may be seen in some animals with atrial lesions. In mice with atrial thrombosis induced by feeding a high fat, low protein, and hypolipotropic diet the thrombi are found with equal frequency in both atria.[308,309] Hamsters may also have pulmonary edema and pleural effusion at necropsy.

Microscopically, the atrial thrombi vary from recently formed layered masses of fibrin to mature organized thrombi with fibrous connective tissue and occasionally metaplastic foci of cartilage and bone.[1] Atrial myocarditis may be present, but opinions vary as to whether this lesion is the cause or the effect of thrombosis.[308,310] Hamsters with atrial thrombosis frequently have accompanying myocardial hypertrophy, degeneration, and fibrosis.[310] Thus, it has been suggested that cardiac failure develops initially, with subsequent stasis of blood and initiation of thrombosis.[310]

The sequential cardiac ultrastructural alterations were studied in mice fed a high fat, low protein, and hypolipotropic diet.[311] The atrial endocardium had ini-

tial alterations after 4 weeks, with subendothelial edema and thickening and duplication of the endothelial basement membrane. At 5 and 7 weeks, degeneration was present in the atrial endothelium. By 8–9 weeks, early thrombosis was seen over the severely damaged endothelium. Endothelial damage and disruption were observed by scanning electron microscopy prior to thrombus formation.[312]

Multiple factors are thought to be involved in the development of atrial thrombosis, including heredity, sex, age, diet, and number of pregnancies. In hamsters, females are affected at a younger age than males, but eventually both sexes may have 70–75% involvement.[310] Endocrine studies showed that thrombosis was inhibited by testosterone injections in both sexes and was enhanced by castration of males.[313] In mice, the BALB/c strain has a high frequency of left atrial thrombosis; 65% of inactive female breeder animals are affected.[306] In three mouse strains fed high fat, low protein, and hypolipotropic diets for 40 weeks, the incidence of atrial thrombosis was 64% in the TS strain, 48% in the RF strain, and 10% in the C strain.[308] DBA mice fed the same diet for 12 weeks had a 50% frequency of atrial thrombosis, but betaine-supplemented mice had increased involvement, with an 80% incidence.[88] However, C strain mice fed the thrombogenic diet with and without choline supplementation had no difference in frequency of atrial thrombosis.[314] The frequency of atrial thrombosis was also increased in BALB/c mice after multiple pregnancies[306] and in pregnant versus nonpregnant RF mice.[315] Male and female TS mice had a similarly high frequency of atrial thrombosis, but gonadectomized mice of both sexes given estrone had a low incidence of thrombosis.[316] Feeding the thrombogenic diet with lard as 6%, 28%, and 40% of the diet resulted in 30%, 36%, and 65% frequency of atrial thrombosis, respectively.[317] In comparing the effect of various types of fats, mice fed butter had the highest frequency of atrial thrombi (92%), and those fed cod liver oil had the lowest (20%).[318]

Further studies in mice fed the thrombogenic diet have demonstrated that the affected animals develop severe anemia concurrently with atrial thrombi, that administration of erythropoietin or packed erythrocytes prevents anemia and thrombosis,[319–321] and that feeding a normal diet to affected mice leads to remission of the lesions.[322] A recent report has shown that the thrombogenic diet is deficient in copper and that adding supplements of copper prevents the formation of atrial thrombi.[323] Mice with experimental copper deficiency have a high incidence of atrial thrombosis and rupture, with hemopericardium and hemothorax.[190]

### Spontaneous Rupture of the Left Atrium in Dogs

Two autopsy series have reported a total of 41 cases of left atrial rupture in dogs.[324,325] In one series, 11 cases were found in 4033 canine necropsies.[325] In the other report, 30 cases were detected over a 5-year period.[324] The lesion was consistently found in old dogs, with males predominating. Dachshunds and cocker spaniels were the most frequently affected breeds. All affected dogs had extensive endocardiosis (noninflammatory valvular thickening by fibrous and myxomatous tissue) of the mitral valve, and most cases also involved ruptured chordae tendineae. At necropsy, three types of lesions were observed. In the first type, seen in 17 of 30 affected dogs, nonperforating left atrial endocardial or endomyocardial splits were present and were often apparent by an elongated zone of subepicardial hemorrhage before the atrium was opened. In 2 of these dogs, atrial thrombi were attached to splits. In the second type of lesion (9 of 30 dogs), perforations of the lateral wall were associated with hemopericardium. In the third type (4 of 30 dogs), the atrial septum had perforated, which resulted in acquired atrial septal defects.

The pathogenesis of atrial rupture in these dogs is not certain. Consistent concurrent lesions were 1) valvular endocardiosis, often with mitral regurgitation and "jet lesions" of the atrial endocardium, 2) ruptured chordae tendineae and 3) intimal thickening of intramural coronary arteries. The event initiating atrial rupture may be rupture of a chorda tendinea. Buchanan[324] has suggested that genetically influenced degeneration of collagen may be involved in the development of the atrial lesion.

### Myocardial Fibrosis in Aged Rats

Myocardial fibrosis is the most common cardiac disease of rats.[1,271,326–329] The lesion is age-related; it is seen initially at approximately 13 months of age. Males are somewhat more susceptible than females. The lesion develops earlier in males, and they have more severe involvement than do females at a given age. In several large necropsy series on aged rats, the frequency of myocardial fibrosis varied from 60% in Wistar (mean age 31 months) and inbred albino rats (mean age 24 months) to 90% in Wistar and BN/Bi rats (mean age greater than 37 months).[271,326,329]

Clinical evidence of cardiac disease has not been reported in rats with myocardial fibrosis. At necropsy, the lesions usually are not detected grossly, but in cases with severe lesions, areas of pallor may be scattered in the left ventricular myocardium.[1] Microscopically, the

lesions are concentrated in the left ventricular papillary muscles, the left ventricular free wall, and the ventricular septum. The fibrotic areas often are detected initially at either the base or the apex of the left ventricle.[329] The inner third of the left ventricular free wall is selectively affected. The lesions may be focal or disseminated and appear as prominent interstitial fibrosis with atrophy and degeneration of adjacent myocytes. Scattered lesions of myocardial necrosis and mineralization may be seen and probably represent early alterations that would be expected to progress to myocardial fibrosis.[328]

The pathogenesis of myocardial fibrosis in aged rats is unclear. It has been proposed that the lesion is secondary to chronic renal disease or coronary arteriosclerosis, lesions that are also found frequently in aged rats.[328,329] However, myocardial fibrosis may be present in the absence of these two lesions.

### Myocardial Degeneration and Fibrosis in Aged Horses

In several studies of hearts from horses, which either had been normal clinically or had had arrhythmias, myocardial fibrosis was observed at a frequency varying from 15% to 80%.[330–335] In a clinical study of 2477 horses, 63 (2.5%) were found to have atrial fibrillation.[334] Necropsy of 45 of the animals with atrial fibrillation revealed gross atrial lesions of patchy or diffuse fibrosis and dilatation in 80% of the hearts. In a large study of 2076 healthy horses, ponies, and donkeys, 14.3% had focal myocardial fibrosis.[330] Most reports of myocardial fibrosis in equine hearts have described the affected hearts to have concurrent lesions of arteriosclerosis in the intramyocardial arteries.[330,333,335,336] In general, the vascular lesions and myocardial scarring were present more frequently in horses with advancing age. Rarely, atrial rupture has occurred in horses with severe atrial damage.[337,338]

Grossly, the areas of myocardial fibrosis are usually apparent as pale, depressed streaks or foci on the epicardial surface. The lesions tend to be most frequent toward the base of the ventricle. Microscopically, the affected areas have central myocyte loss with replacement fibrosis, and adjacent myocytes have degenerative alterations such as sarcoplasmic vacuolation and myocytolysis.[330,333–339] The pathogenesis of the myocardial lesions remains unclear but may be due to focal ischemic injury associated with intramyocardial vascular lesions like those that occur in dogs.[340] Another proposed mechanism attributes the myocardial lesions to microembolization from *Strongylus vulgaris*-induced lesions of endarteritis of the proximal aorta.[330]

### Basophilic Degeneration of Myocardium

Basophilic degeneration of cardiac muscle cells was described as a frequent finding in the atria and ventricles of horses with atrial fibrillation or with chronic myocardial disease.[5,335] This lesion is occasionally present in the myocardium of dogs with chronic mitral endocardiosis and myocardial hypertrophy.[5] Affected cells have a mass of perinuclear basophilic material that gives a positive reaction with the periodic acid–Schiff (PAS) stain.

No ultrastructural studies of this material have been reported in animals; however, it appears histologically similar to the basophilic, finely fibrillar carbohydrate material that has been described as a nonspecific finding in the hearts of elderly humans.[341,342] Similar fibrils of basophilic, PAS-positive material also have been found in human myocardium in the Lafora type of myoclonic epilepsy (Lafora's disease, in which the metabolic defect is unknown), in Type IV glycogen storage disease (branching enzyme deficiency), and in phosphofructokinase deficiency.[342–344] Lafora's disease has been described in dogs,[345] but myocardial alterations were not reported in these animals. Type IV glycogen storage disease and phosphofructokinase deficiency have not been described in animals.

## Myocardial Diseases of Toxic Etiology

In this large group of diseases various biochemical mechanisms elicit morphologic evidence of cardiotoxicity as degeneration (myofibrillar lysis, vacuolar degeneration, fatty degeneration, lipofuscin deposition) and contraction band necrosis with or without mineralization. Many of these diseases have been utilized as models for studies of myocardial injury. Similar human diseases of toxic origin exist for many of these examples, including toxicity by cobalt, catecholamines, antihypertensives, antineoplastic agents, vitamin D, ethanol, uremia, and various infrequently used drugs. The cardiotoxic properties of many of these compounds were recognized in animals during drug safety studies. It is necessary to emphasize that a number of these cardiotoxicities have emerged as important naturally occurring diseases in animals including toxicities by ionophores, antineoplastic agents, furazolidone, poisonous plants, and vitamin D.

### Toxicity of Metallic Salts

Numerous metallic compounds, including salts of lithium, cadmium, nickel, barium, lanthanum, man-

ganese, vanadium, lead, and cobalt, are known to have cardiotoxic properties.[346] However, detailed structural studies of the changes induced by these compounds have been made only with respect to lead and cobalt.

*Lead Cardiotoxicity*

The cardiotoxicity induced by intake of excessive amounts of lead has received relatively little attention, although it is of biochemical interest because this metal interferes with certain actions of calcium.[347] Moore et al[348] observed various minor mitochondrial changes in rats given 1 mg lead per liter of drinking water for 1 year. In rats given 1% lead acetate in the drinking water for 6 weeks, Asokan[349] observed myofibrillar fragmentation, intracellular edema, dilatation of sarcoplasmic reticulum, and twofold to threefold swelling of mitochondria with deformed, loosely packed cristae. The animals showing these changes had plasma lead levels of 112 ± 5 μg/100 ml, which were considered comparable to those in mild, clinical lead poisoning. In mice, Khan et al[350] found a correlation between blood lead levels and cardiac ultrastructural changes. No changes were detected in animals with blood levels <20 μg/100 ml. Animals having levels >20 μg/100 ml showed clumping of nuclear chromatin and nucleolar disorganization. Those having levels >40 μg/100 ml also had sarcotubular dilatation and mitochondrial changes consisting of mitochondrial enlargement, disarray of the crista, and an increase in intramitochondrial matrix. Animals with lead levels >60 μg/100 ml also had focal myofibrillar degeneration, focal areas of separation of the apposed membranes of the intercalated disks, and appearance of increased numbers of lysosomelike cytoplasmic dense bodies.

*Cobalt Cardiotoxicity*

"Beer-drinkers' cardiomyopathy," characterized by acute cardiac failure with myopericarditis and lactic acidosis, occurred in human patients in Canada, the United States, and Belgium in the 1960s, when cobalt salts were added to some beers to improve the quality of the foam.[351-353] Cobalt cardiotoxicity has been induced experimentally in rats, rabbits, dogs, and guinea pigs,[354-362] but with the use of much larger doses of cobalt than those ingested by patients in whom beer-drinkers' cardiomyopathy developed. Animal experiments led to the conclusion that coexisting protein deficiency played an important role in the pathogenesis of the cardiomyopathy observed in humans, by increasing absorption of cobalt from the gastrointestinal tract.[360] In an effort to develop a large animal model for cobalt cardiotoxicity, we administered cobalt sulfate, in doses of 125 mg/kg of body weight daily for 3 days, to weanling conventional pigs.[363] Surviving pigs were euthanatized 2 days later. The pigs showed anorexia, lethargy, vomiting, and diarrhea; and 6 of 20 treated pigs died. Serum activities of creatine phosphokinase and aspartate aminotransferase were markedly increased after administration of cobalt.

At necropsy, the affected pigs had mild to moderate hydropericardium and pale atria (Figure 28). Microscopically, the atria showed diffuse myocardial necrosis and calcification. The affected fibers showed necrosis with contraction bands and basophilic granular sarcoplasm from mitochondrial calcification. Within 2–3 days after necrosis, numerous macrophages had invaded the necrotic cells and the adjacent interstitium. The interstitium also showed edema and fibroblastic proliferation.

Ultrastructurally, cardiac muscle cells with mild injury had loss of glycogen granules, dilated elements of sarcoplasmic reticulum, and focal myofibrillar lysis. Myocytes with severe damage had necrosis, with contraction bands, pyknotic nuclei, damaged mitochondria, and ruptured plasma membranes (Figure 29). The damaged mitochondria showed swelling, striking accumulations of dense granular deposits containing large amounts of calcium and phosphorus, and disrupted membranes (Figure 30). The interstitium showed edema,

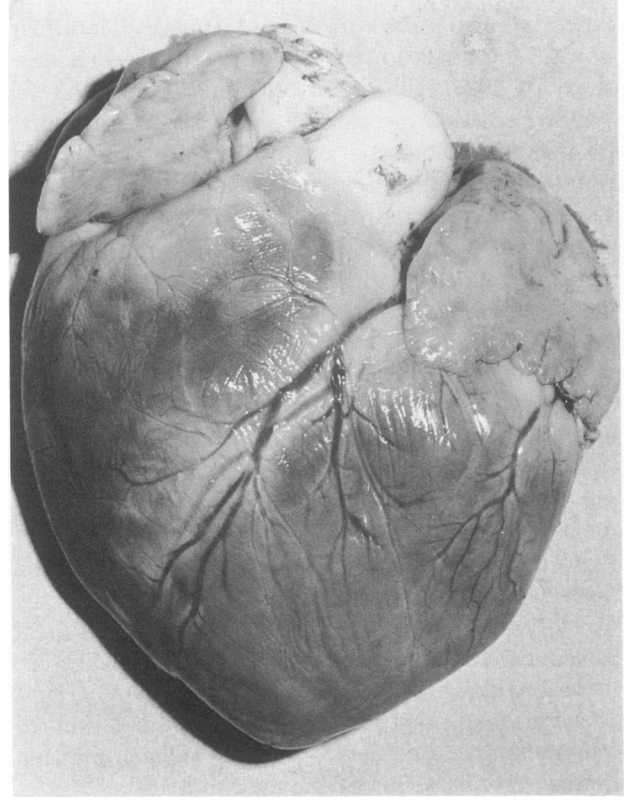

**Figure 28**—Cobalt cardiotoxicity. Pig. Extensive necrosis of the atrial myocardium is evident by pallor of both atria.

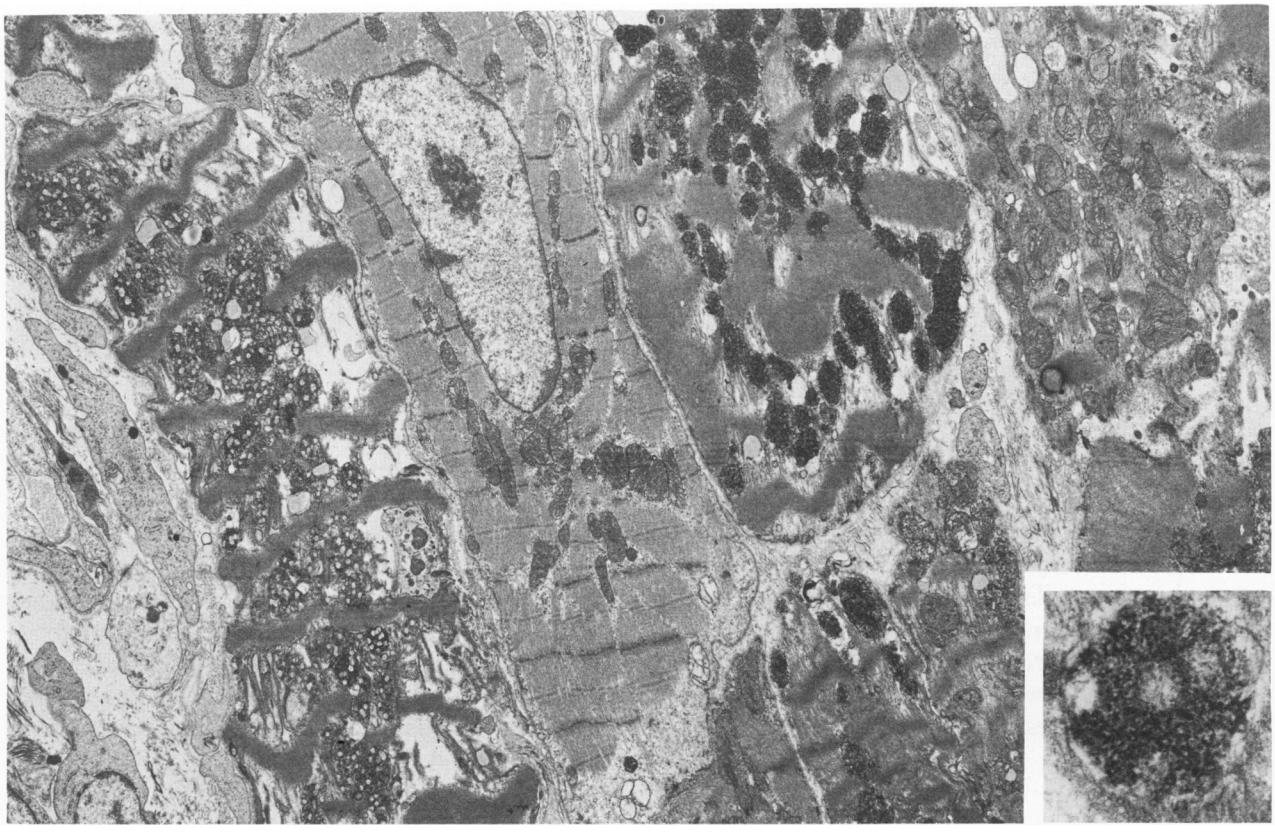

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**Figure 29**—Cobalt cardiotoxicity. Pig. Necrotic myocytes in atria have dense transverse hypercontraction bands and either dense granular calcified mitochondria or swollen mitochondria. (×6000) **Figure 30**—Cobalt cardiotoxicity. Pig. Calcified mitochondrion has dense granular matrical deposits and scattered lucent foci. (×50,000)

deposits of serum protein, occasional strands of fibrin, invading macrophages, and activated fibroblasts.

In this pig model of cobalt cardiotoxicity, the severity of the cardiac disease was markedly decreased in animals given selenium–vitamin E by injection 24 hours before cobalt administration. Pigs with inherited stress susceptibility had more severe cobalt-induced cardiac damage than did animals without this trait.

In the dog model, lesions of a dilated cardiomyopathy were produced by intravenous infusions of cobalt with or without feeding of a protein- and thiamine-deficient diet.[361,364,365] The myocardium was pale grossly, and myocyte degeneration and necrosis were scattered in both the ventricles and the atria.

The biochemical lesion in cobalt cardiotoxicity was demonstrated to involve blocking of the oxidation of α-ketoglutarate and pyruvate by complexes formed between cobalt and the sulfhydryl groups of α-lipoic acid.[366] Thus, myocardial energy metabolism is compromised as in thiamine deficiency. Cobalt cardiotoxicity was potentiated in rats by increasing age, thiamine deficiency, protein deficiency, thyroidectomy, and preexisting cardiac disease (see Ferrans et al for review).[352]

## Catecholamine Cardiotoxicity

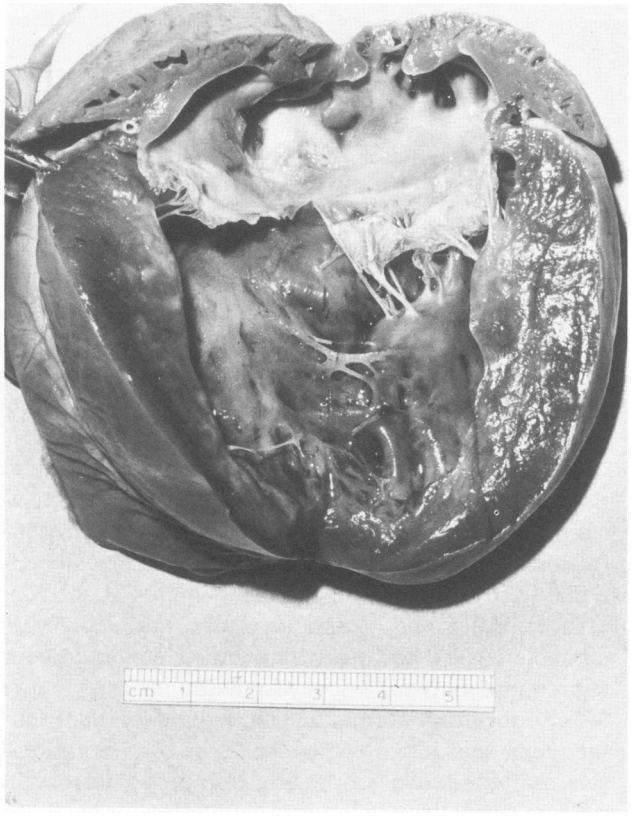
Several recent reviews have summarized the voluminous literature on the cardiotoxicity of catecholamines.[367–371] The myocardial lesions produced by endogenous and synthetic catecholamines have generally similar features. Most animal studies have utilized isoproterenol, but reports on epinephrine, norepinephrine, salbutamol, terbutaline and ephedrine are also numerous. Most pathologic studies have been done in rats, rabbits, and dogs.[371–381] In these species, the typical lesions are multifocal myocardial necroses with concentration of the damage in the left ventricular subendocardium and papillary muscles (Figures 31 and 32). Histologically and ultrastructurally, the damage is characterized by necrosis with contraction bands, with subsequent macrophagic invasion and fibrosis (Figure 32). Endocardial fibrous thickening and left ventricular aneurysms develop when the lesions are very extensive, as in the case of isoproterenol-induced necrosis in rats.[371] Catecholamine-induced cardiac lesions have also been described in poikilotherms.[382]

Catecholamine cardiotoxicity was induced in swine

by administration of large doses of isoproterenol (125 mg/kg) intraperitoneally to weanling pigs.[363] Dyspnea, vomiting, ataxia, anorexia, and lethargy developed; and the pigs were reluctant to rise for 6–8 hours after treatment. Cutaneous alterations were evident as piloerection and patchy erythema. Moderate increases in serum creatine phosphokinase and aspartate aminotransferase activity were present. Twelve of 20 pigs died within 5 days of treatment.

At necropsy, the cardiac lesions included hydropericardium; scattered pale areas of myocardial necrosis, especially in the left ventricular papillary muscles; and focal left ventricular endocardial hemorrhages (Figure 31). Microscopically, hyaline necrosis was frequent in left ventricular subendocardial myocardium and was only occasionally present in atrial myocardium. Some necrotic myocytes had mineralized deposits. At 4–5 days after isoproterenol injection, the necrotic areas were evident as empty sarcolemmal tubes invaded by numerous macrophages and surrounded by proliferating fibroblasts. The severity of this cardiotoxicity was not affected by pretreatment with selenium–vitamin E but was increased in stress-susceptible pigs.[363]

Numerous studies have been done for evaluation of procedures used to modify isoproterenol cardiotoxicity.[367-388] Cardiac damage is potentiated by cold exposure, long-term isolation, administration of corticosteriods or thyroxine, diets high in fat and carbohydrates, and using obese animals. Protection against isoproterenol cardiotoxicity has been demonstrated with induction of hypocalcemia[384] and administration of propranolol and other β-adrenergic receptor blockers, verapamil, ribose, and adenosine.[389] Also, resistance to induction of myocardial necrosis with further doses of isoproterenol occurs in animals after production of an initial focus of myocardial damage.[367,390,391] Decreased severity of isoproterenol cardiotoxicity was seen in rats in which body weight was reduced by limiting food intake,[383] in rats fed normal diets after malnutrition for the first 7 weeks of life, and in exercised rats.[386,392] Recent studies have shown that the cardiotoxicity of isoproterenol is considerably reduced, compared with that in normal animals, in rats made diabetic by administration of streptozotocin[393] and in mice with alloxan-induced or with genetically transmitted diabetes mellitus.[394] In mice, treatment with insulin was shown

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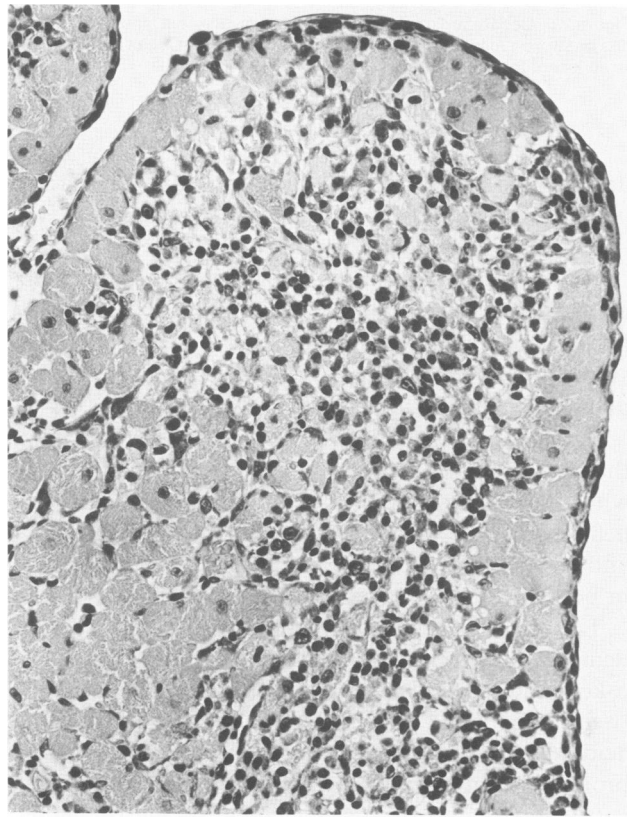

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**Figure 31**—Isoproterenol cardiotoxicity. Pig. Incised left side of the heart shows multiple pale areas of myocardial necrosis in the inner half of the left ventricular wall. **Figure 32**—Isoproterenol cardiotoxicity. Rat. Area of necrosis in the left ventricular subendocardial myocardium is invaded by mononuclear leukocytes. (H&E, ×250)

to correct the diabetes and to restore the sensitivity to the cardiotoxic effects of isoproterenol.

Other recent studies have suggested that free radical injury may be one of the factors mediating isoproterenol cardiotoxicity.[395,396] Vitamin E-deficient rats had increased susceptibility to isoproterenol-induced myocardial damage; and animals pretreated with vitamin E, an antioxidant, or Zn, a membrane-stabilizing agent, also showed evidence of protection.[396]

### Histamine Cardiotoxicity

In rabbits given histamine multifocal myocardial necrosis developed, with concentration of the lesions in the right ventricle, ventricular septum, and papillary muscles.[397,398] Microscopically, the lesions showed edema and hemorrhage and necrosis with contraction bands. During resolution, a mixed population of inflammatory cells was present, and late lesions showed stromal collapse and fibrosis. The myocardial lesions were not prevented by adrenergic blockade, which suggests that the damage was caused directly by histamine and was not mediated by catecholamines.

### Cardiotoxicity of Minoxidil and Other Vasodilating Antihypertensives

Minoxidil is a vasodilating antihypertensive drug that is useful in human patients with refractory hypertension. In animal safety testing it was demonstrated that minoxidil produced hemorrhagic right atrial lesions in dogs given doses as low as 1 mg/kg.[399-402] Minoxidil can also produce left ventricular papillary muscle necroses and superficial endocardial and epicardial hemorrhages in various regions of the heart. The hemorrhagic atrial lesions were associated with fibrinoid necrosis of arterioles, focal myocyte damage, and epicardial inflammation; they progressed to eventual fibrosis. Protection against minoxidil-induced lesions in dogs was provided by pretreatment for several days with furosemide, but not with propranolol or hydrochlorothiazide.[400] The mechanism of this protection is unknown.

In miniature swine, administration of minoxidil, 10 mg/kg/day for 2 days, produced tachycardia and hypotension.[403] At necropsy, 24 hours after minoxidil treatment, the cardiac lesions were diffuse left atrial epicardial hemorrhage and focal pale areas of myocar-

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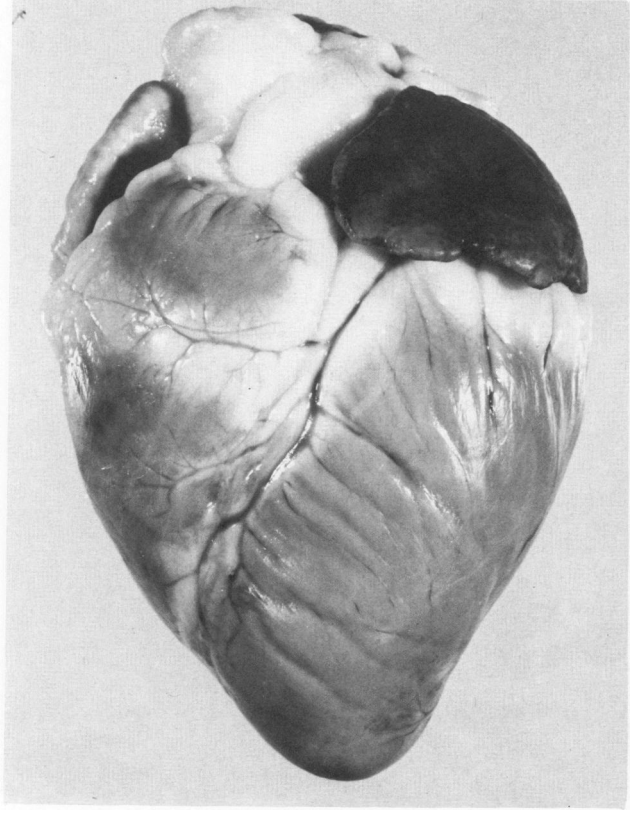

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**Figure 33**—Minoxidil cardiotoxicity. Pig. The left atrium has diffuse hemorrhage. **Figure 34**—Minoxidil cardiotoxicity. Pig. Scattered dark necrotic myocytes are present in the left atrium. Endothelial thickening is present in an arteriole (*center*). (Plastic-embedded section 1 μ thick, alkaline toluidine blue, ×700)

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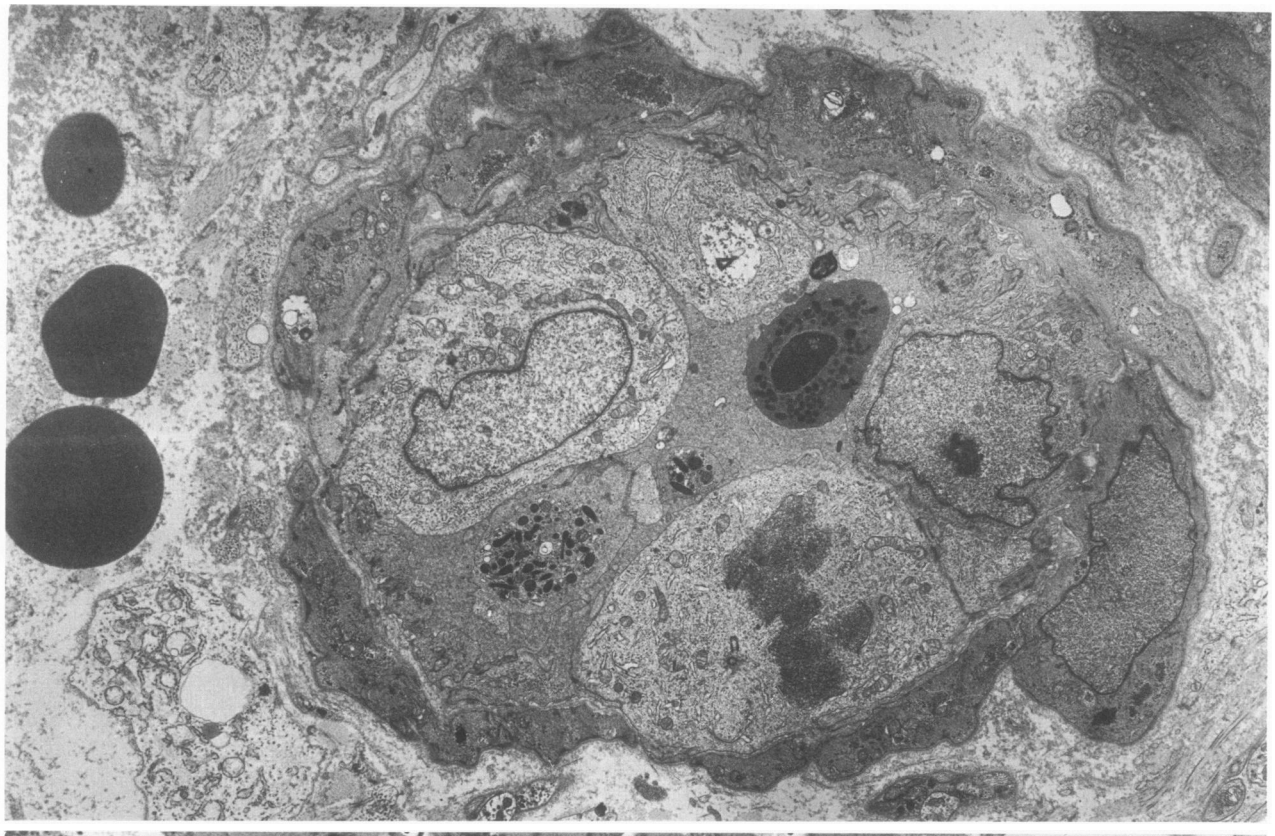

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**Figure 35**—Minoxidil cardiotoxicity. Pig. Damaged arteriole in the left atrial epicardium has endothelial swelling, an endothelial cell in mitosis, and several leukocytes in the lumen. The surrounding interstitium has hemorrhage and edema. (×4000) **Figure 36**—Minoxidil cardiotoxicity. Pig. Myocytes with coagulation necrosis surround a capillary occluded by leukocytes and erythrocytes in the left ventricular papillary muscle. Lysis of I bands is extensive, and mitochondria contain flocculent densities. (×5000)

dial necrosis in the left ventricular papillary muscles (Figure 33).

Microscopic and ultrastructural study of the porcine cardiac lesions revealed vascular damage in the hemorrhagic left atria. Arterioles were selectively injured and showed endothelial swelling with prominent transmural and perivascular accumulations of leukocytes, fibrin deposits, and edema fluid (Figures 34 and 35). Thrombosis and endothelial necrosis were not present in damaged arterioles. The interstitium was edematous and had activated fibroblasts. In necrotic areas of left ventricular papillary muscles, myocytes had necrosis with contraction bands. The necrotic cells had pyknotic nuclei, mitochondrial matrical densities, and accumulations of sarcoplasmic lipid droplets (Figures 36 and 37). These studies demonstrate that the pig offers a suitable model for producing minoxidil cardiotoxicity and that the regional distributions of the cardiac lesions caused by this agent in the dog and in the pig are different.[404]

Other vasodilating antihypertensive drugs, such as hydralazine, diazoxide, and SK&F 24260, produce left ventricular lesions similar to those produced by minoxidil.[367,368,405,406] However, these agents are not known to produce atrial hemorrhagic lesions such as those induced by minoxidil and theobromine.[407] The left ventricular papillary muscle lesions are thought to result from a decrease in vascular perfusion.

### Methylxanthine Cardiotoxicity

Cardiotoxicity has been demonstrated for the methylxanthine compounds theobromine, theophylline, and caffeine. Long-term theobromine administration produced a distinctive lesion in the right atrium of dogs.[407] The affected atria developed hemorrhage, myocardial necrosis, and residual fibrosis. Grossly, the atria were red. Arteries and arterioles in the right atrium had medial hyperplasia and perivascular fibrosis and inflammatory cell infiltration. Similar hemorrhagic lesions were present in both atria in pigs with acute theobromine toxicity (Figure 38) (Herman et al, unpublished data).

Acute theophylline and caffeine toxicity in rats caused extensive myocardial necrosis.[408,409] Lesions were concentrated in the left ventricular subendocardium and were similar to those produced by isoproterenol cardiotoxicity. In pigs, theophylline toxicity induced prominent endocardial hemorrhage (Figure 39).

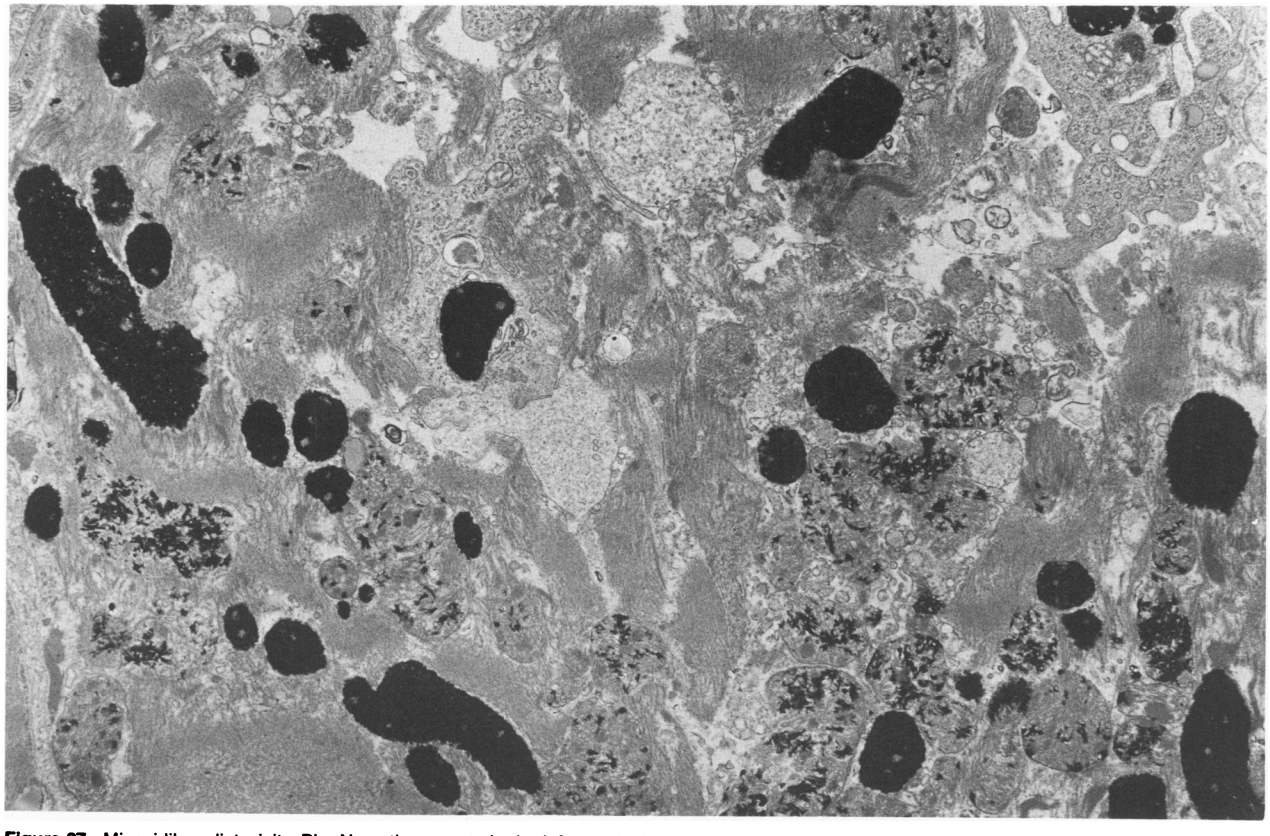

**Figure 37**—Minoxidil cardiotoxicity. Pig. Necrotic myocyte in the left ventricular papillary muscle has dense calcified mitochondria, clumps of disrupted contractile material, and multiple cytoplasmic processes of an invaded macrophage. (×12,000)

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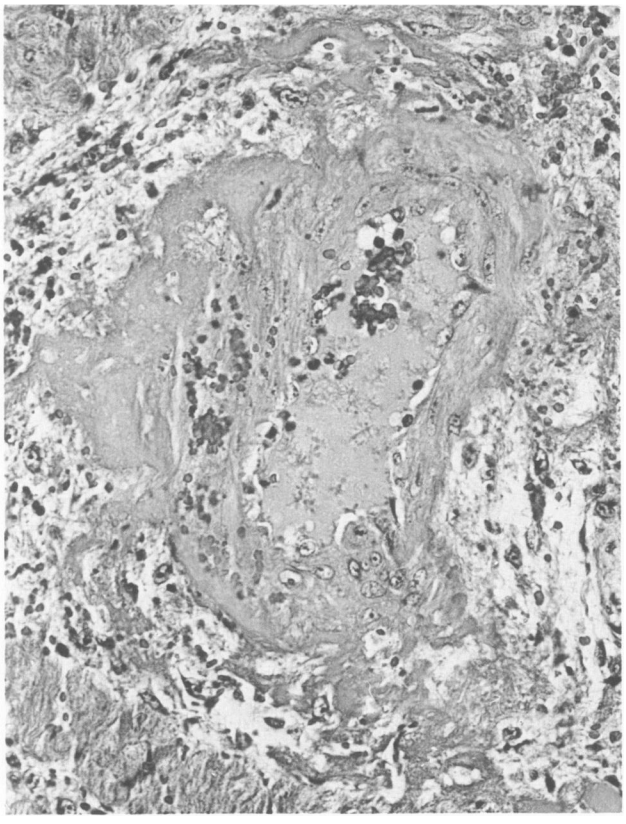

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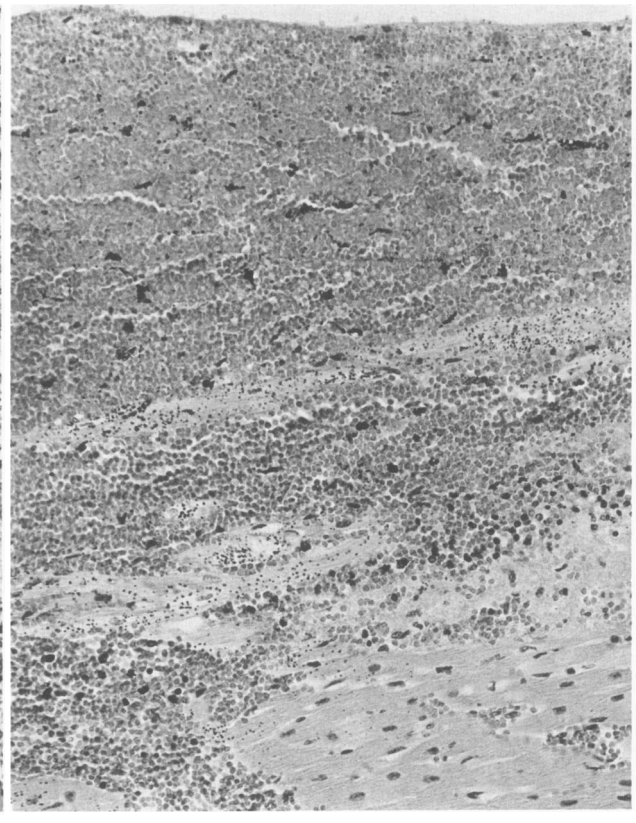
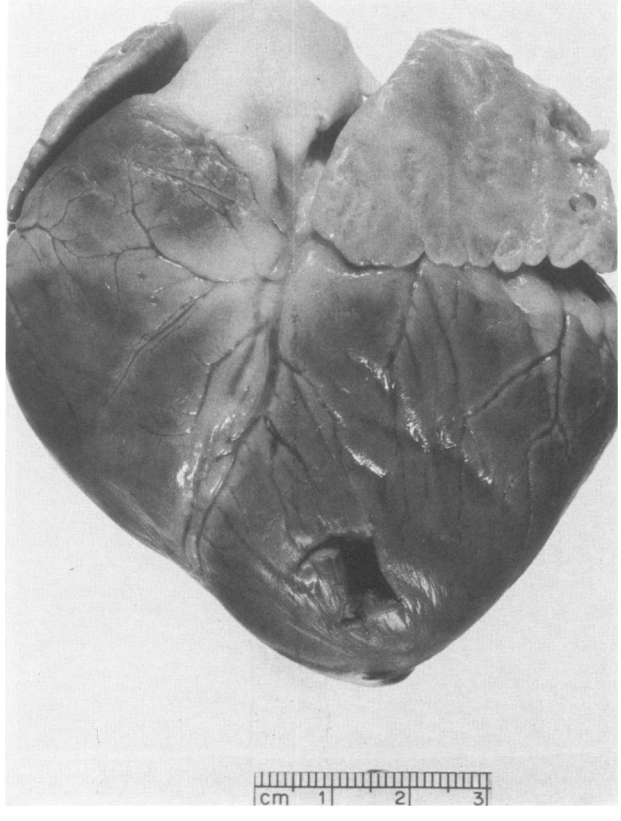


**Figure 38**—Theobromine cardiotoxicity. Pig. Fibrinoid necrosis and hemorrhage in the wall of an artery in the left atrial epicardium. (H& E, ×160) **Figure 39**—Theophylline cardiotoxicity. Pig. Extensive endocardial hemorrhage is present in the left ventricle. (H&E, ×100)




## Cardiotoxicity of Monensin and Other Ionophores

Monensin, a $Na^+$-selective carboxylic ionophore, is used extensively in veterinary medicine as a coccidiostat for poultry and as a growth-promoting agent for cattle. Reports of toxicosis in horses, cattle, sheep, pigs, dogs, and poultry have emphasized the occurrence of necrosis of skeletal and cardiac muscle.[410–447] Because few studies have been made of monensin toxicosis in pigs, we experimentally induced this toxicosis in weanling swine and characterized its clinical and pathologic features.[440–442] The severity of clinical signs of toxicosis was dose-related. These signs occurred in pigs given 20, 30, 40, or 50 mg/kg of monensin orally and included dyspnea, lethargy, anorexia, ataxia, muscular weakness, myoglobinuria, and death. Serum activities of creatine phosphokinase and aspartate aminotransferase were increased.

At necropsy, the skeletal muscles had consistent lesions of pallor from myonecrosis. Less frequently, cardiac damage was apparent as pallor of the left atrium (Figure 40). Some pigs died within 24 hours and had generalized myocardial mottling. Histologic and ultra-

**Figure 40**—Monensin cardiotoxicity. Pig. Left atrium appears pale, indicating myocardial necrosis.

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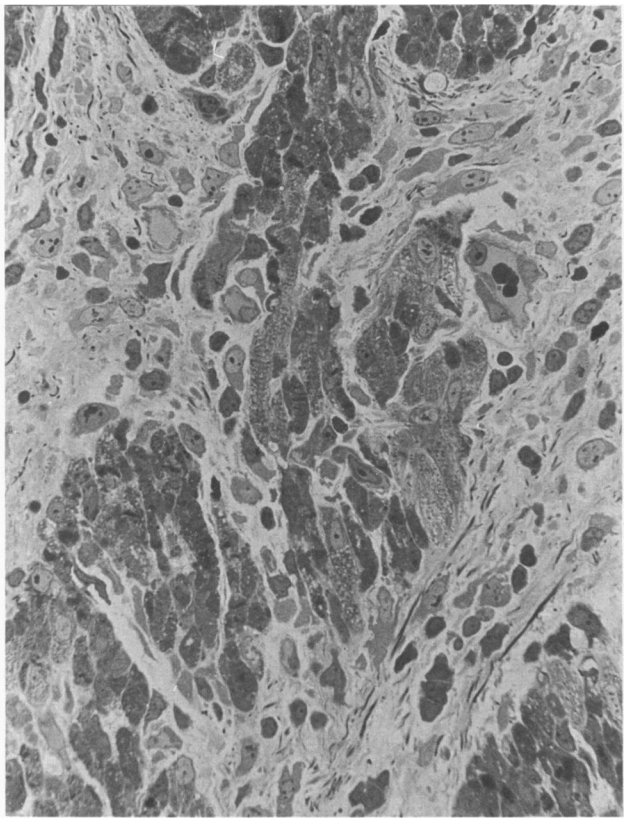

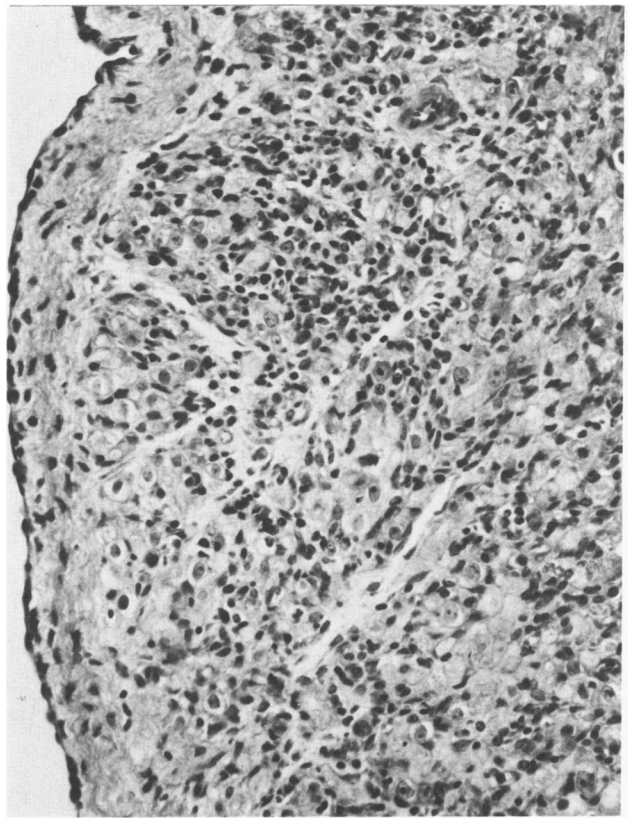

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**Figure 41**—Monensin cardiotoxicity. Pig. Left atrium contains numerous dense necrotic myocytes with contraction bands at 1 day after monensin administration. (Plastic-embedded section 1 μ thick, alkaline toluidine blue, ×400) **Figure 42**—Monensin cardiotoxicity. Pig. Atrium has extensive infiltration of mononuclear leukocytes into an area of myocardial necrosis. (H&E, ×250)

structural study of the left atrial lesions demonstrated myocytes with contraction band necrosis (Figures 41–44). By Day 2 after monensin administration, numerous macrophages had invaded the necrotic myocytes and had engulfed sarcoplasmic debris. On Day 16 after treatment, the areas of necrosis of left atrial myocardium showed lysis of myocytes and persistent tubes of myocyte external lamina within supporting stromal tissue. Myocytes with sublethal injury had mitochondrial alterations, focal myofibrillar lysis, and sarcoplasmic vacuolation. Administration of selenium–vitamin E, 24 hours prior to monensin, provided protection against the development of necrosis of skeletal and cardiac muscle.

Our studies of monensin toxicosis in cattle[439,443] have shown that initial signs of intoxication were anorexia, diarrhea, and lethargy. Cardiac and skeletal muscle damage was reflected by marked elevations of serum aspartate aminotransferase and creatine phosphokinase activities. One of 12 calves given monensin at 40 mg/kg died 7 days later from acute congestive heart failure. At necropsy, the myocardial lesions were disseminated pale yellowish brown areas of necrosis in the ventricles (Figure 45). Microscopic and ultrastructural study showed early sarcoplasmic vacuolation from lipid droplet accumulation and mitochondrial swelling (Figure 46). Numerous myelin figures were present by Day 4. Myocyte necrosis was present at 4 days after monensin administration. Necrotic fibers had disrupted contractile material and contraction bands (Figures 47–49). Macrophages invaded areas of necrosis and engulfed fragments of sarcoplasmic debris.

Cardiotoxicity has also been demonstrated for other ionophores including lasalocid in horses and cattle,[448,449] A204 in rats,[450] and salinomycin and narasin in turkeys.[451,452]

## Doxorubicin and Daunorubicin Cardiotoxicity

Doxorubicin (Adriamycin; Adria Laboratories, Inc., Columbus, Ohio) is an antineoplastic compound that is used widely in human patients. However, a significant complication of long-term therapy with this agent, and with daunorubicin, a closely related compound, is the development of a dose-related chronic cardiotoxicity characterized by congestive heart failure. Suitable ani-

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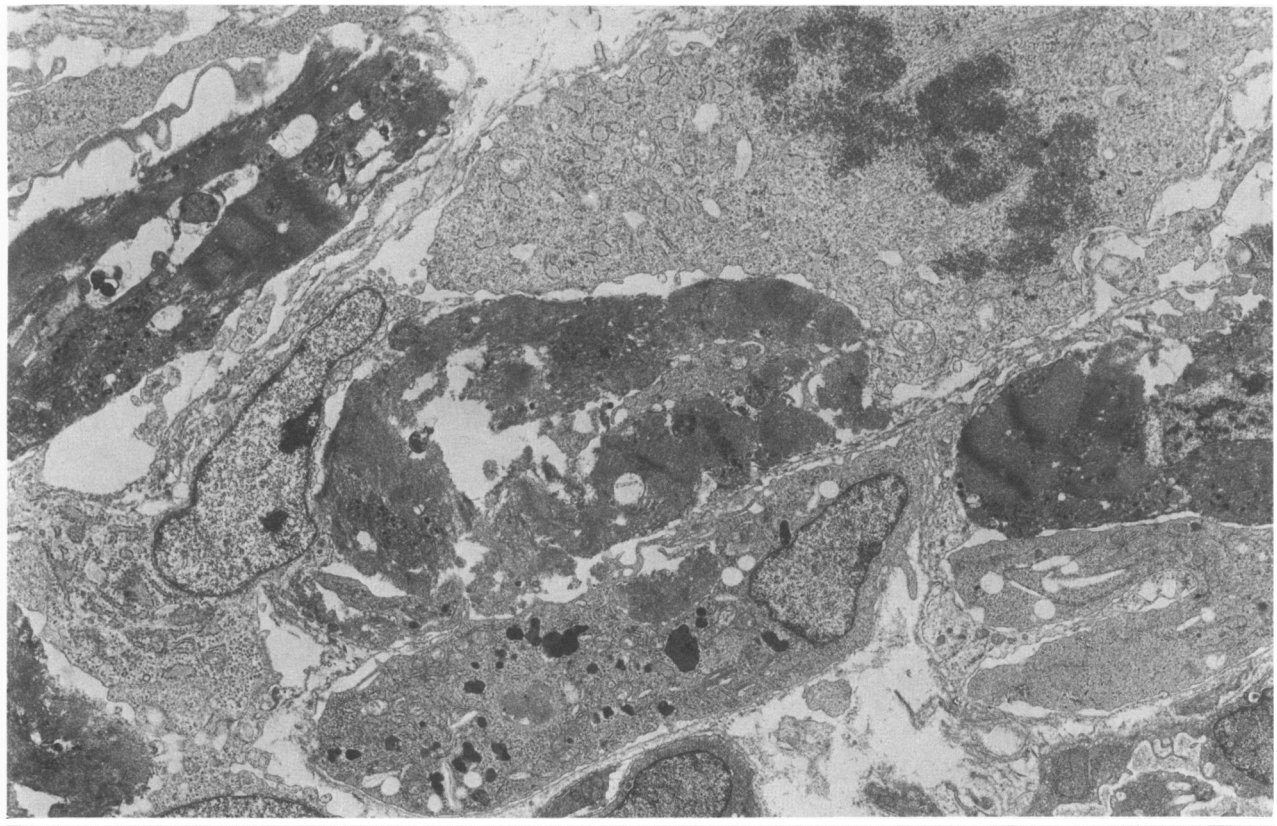

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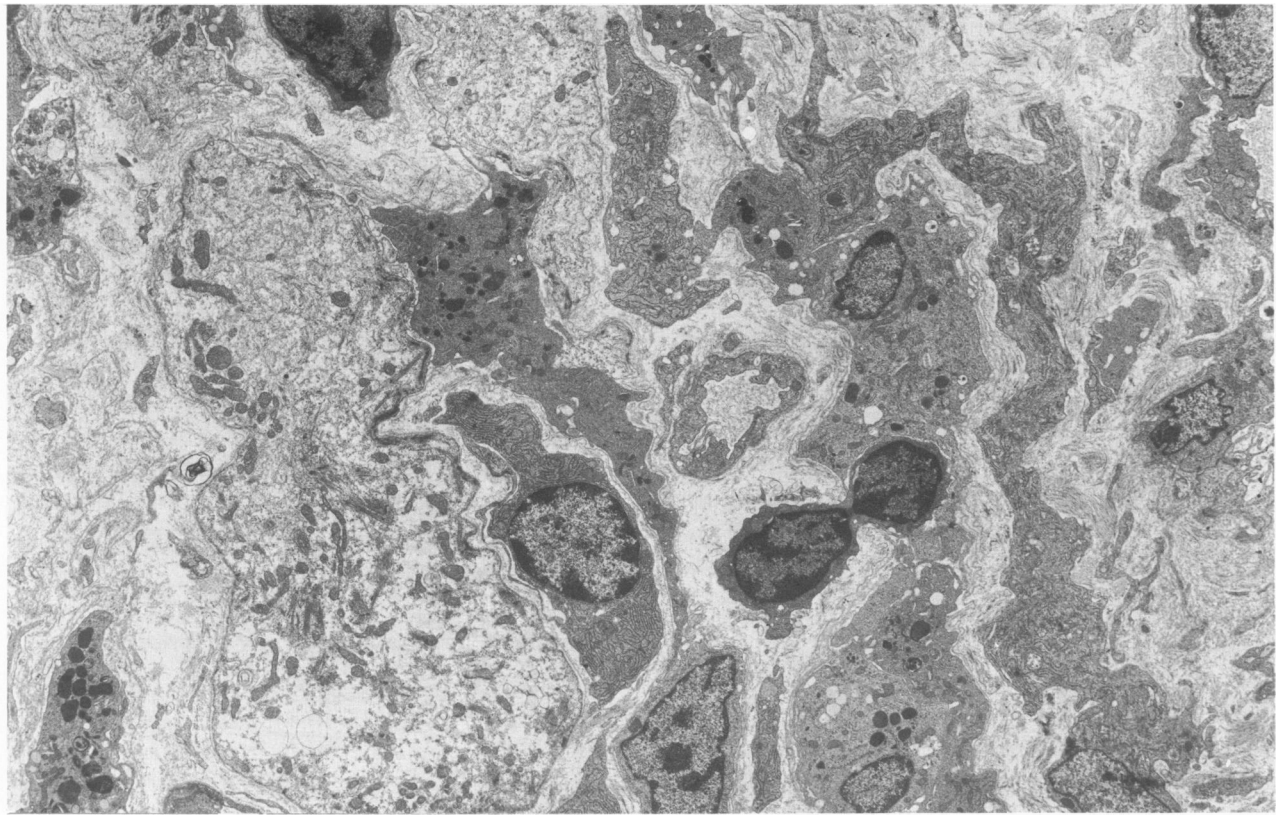

**Figure 43**—Monensin cardiotoxicity. Pig. Dense necrotic left atrial myocytes are invaded by macrophages at 2 days after monensin administration. (×6000) **Figure 44**—Monensin cardiotoxicity. Pig. Left atrial myocardium at 4 days after monensin administration has several myocytes at the *right* with extensive myofibrillar lysis. Macrophages lie within the external lamina of necrotic myocytes. (×4500)

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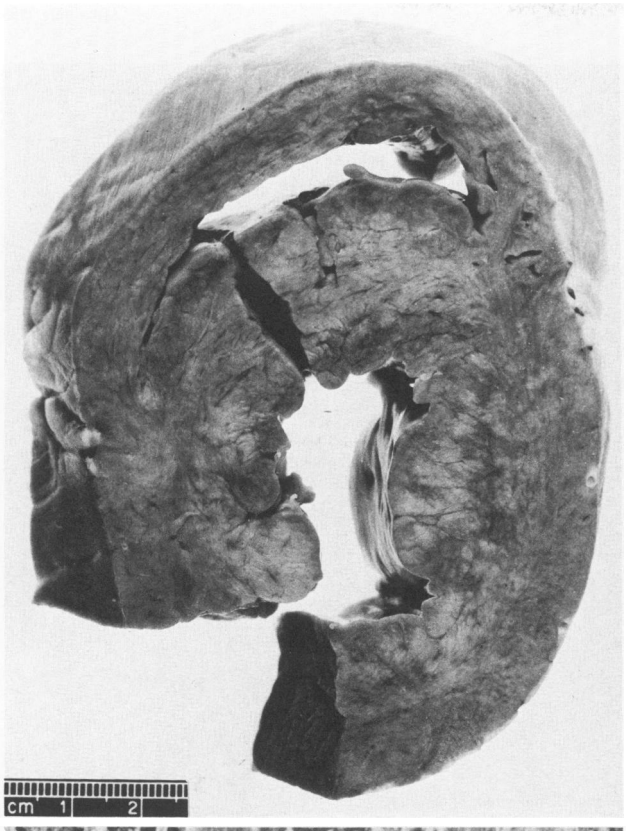


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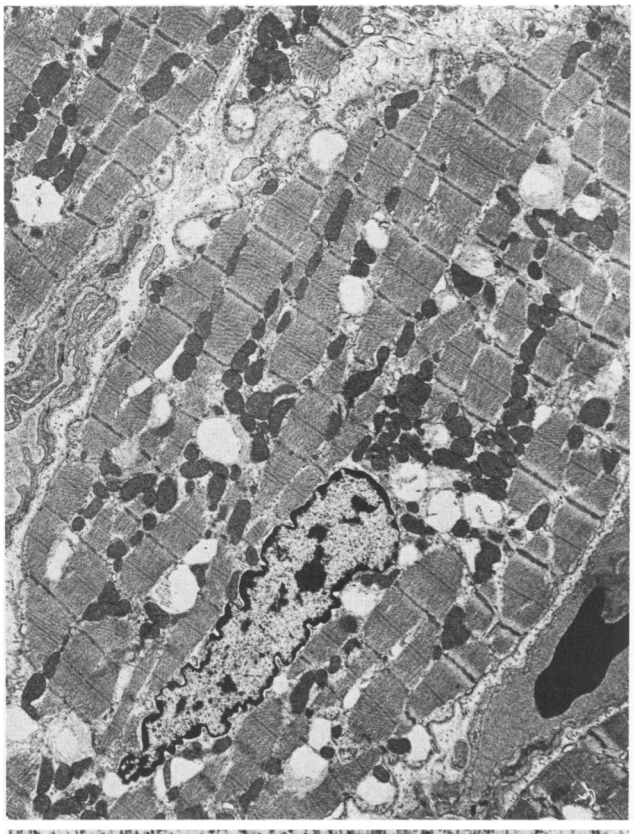

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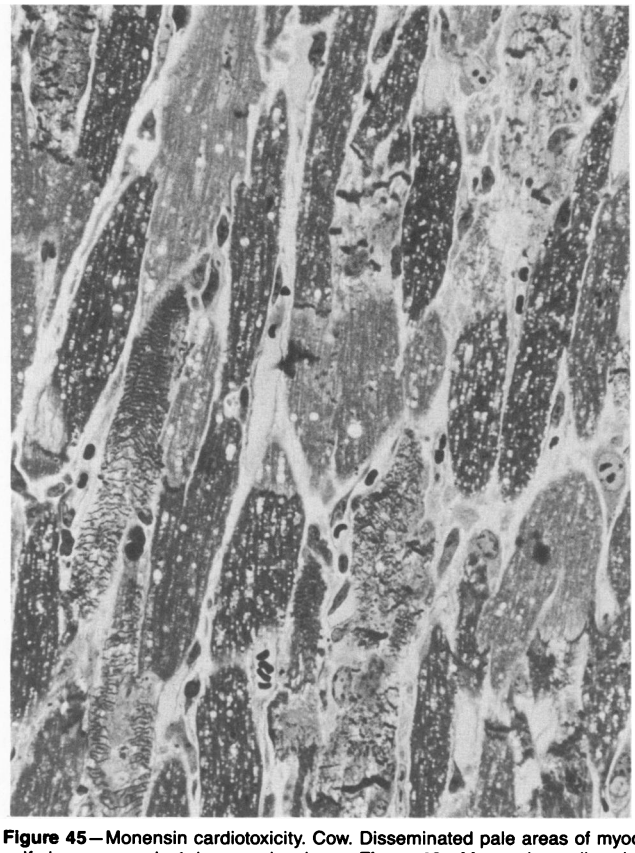

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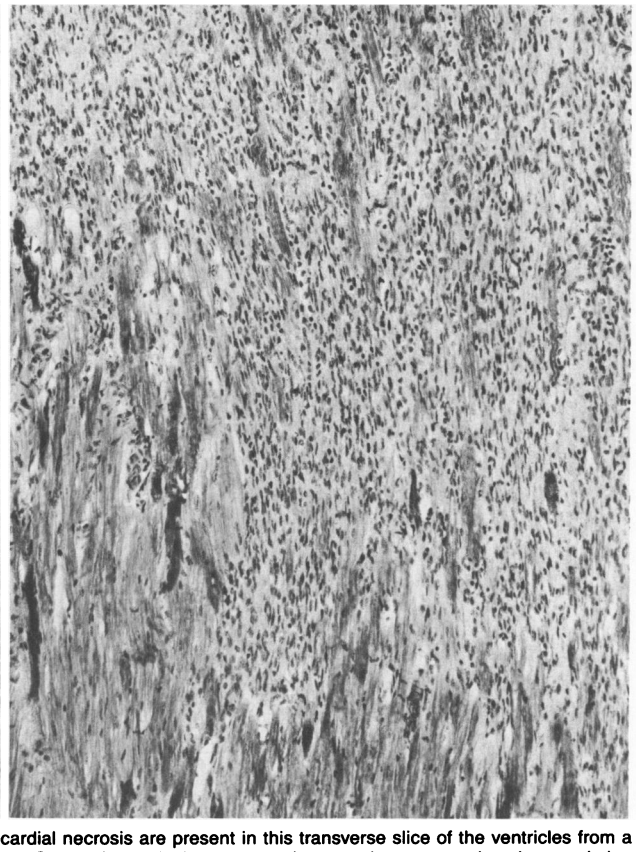


**Figure 45**—Monensin cardiotoxicity. Cow. Disseminated pale areas of myocardial necrosis are present in this transverse slice of the ventricles from a calf given monensin 4 days previously. **Figure 46**—Monensin cardiotoxicity. Cow. Left ventricular myocytes have moderate sarcoplasmic vacuolation at 2 days after monensin administration. (×6000) **Figure 47**—Monensin cardiotoxicity. Cow. Numerous dark necrotic myocytes are present in the left ventricle. Affected fibers have sarcoplasmic vacuolation and transverse hypercontraction bands. (Plastic-embedded section 1 μ thick, alkaline toluidine blue, ×500) **Figure 48**—Monensin cardiotoxicity. Cow. Area of resolving myocardial necrosis in ventricular septum has prominent fibroblastic stroma with a few scattered dark necrotic myocytes in an adjacent area of myocardium. (Phosphotungstic acid hematoxylin, ×150)

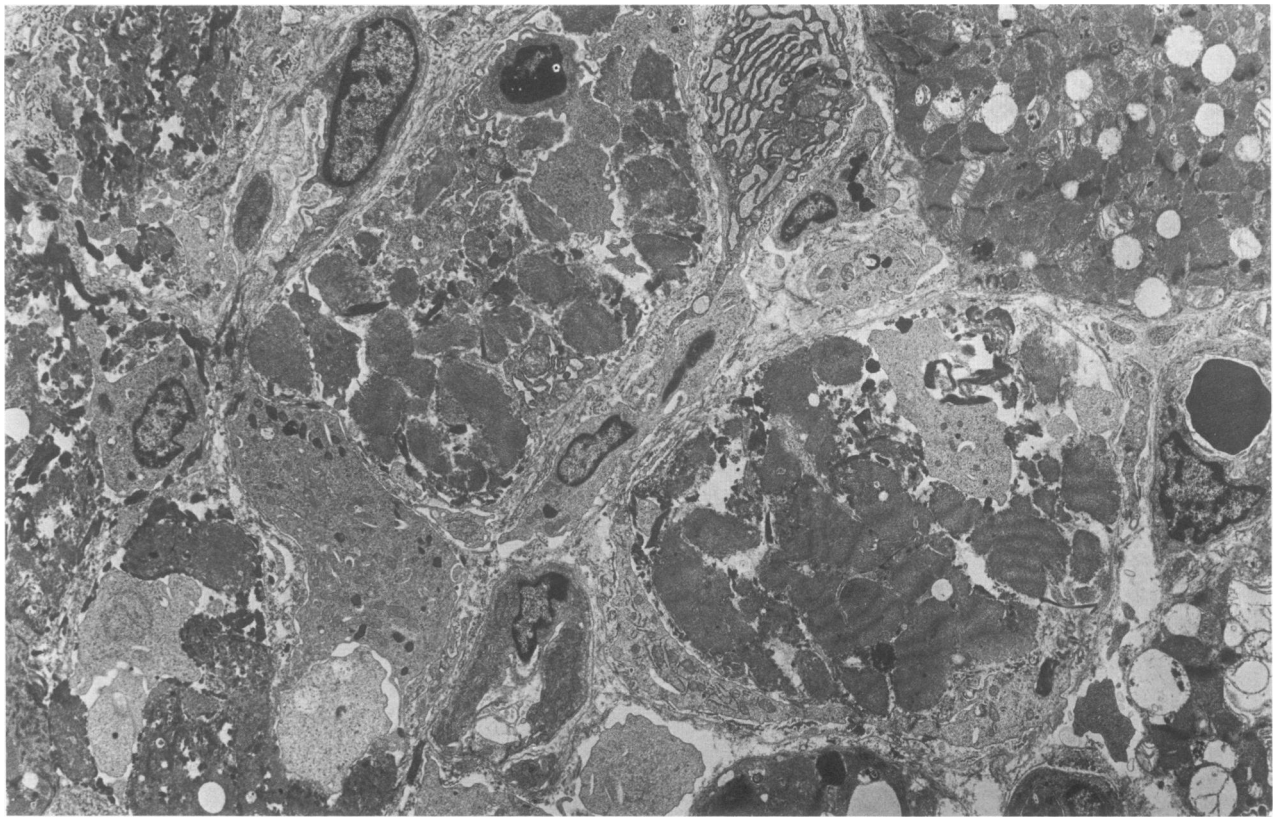


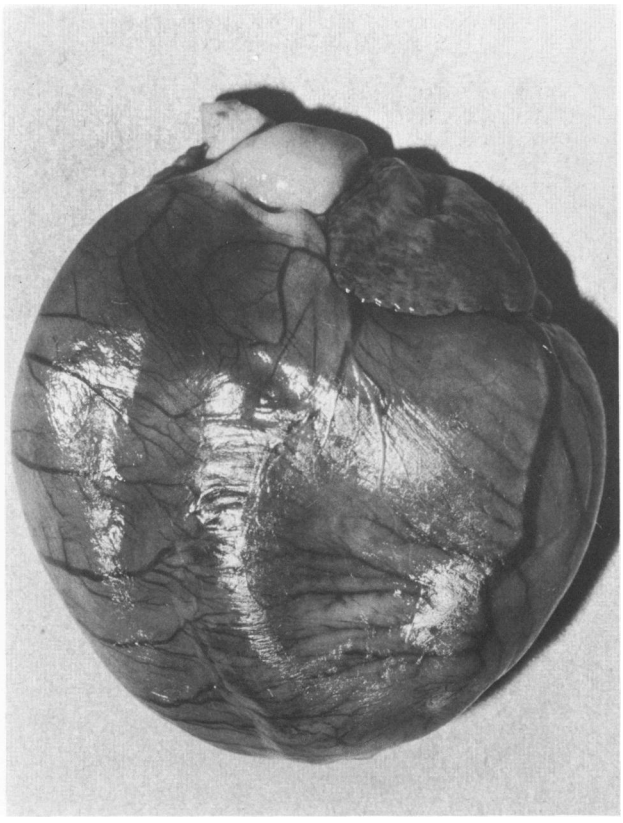
**Figure 49**—Monensin cardiotoxicity. Cow. Several necrotic myocytes have dense clumps of disrupted contractile material. Numerous macrophages lie in the interstitium and invade necrotic myocytes. Myocytes at left have prominent sarcoplasmic vacuolation. (×4500)

mal models of chronic doxorubicin-induced cardiotoxicity are used for studying the prevention and management of this complication. Studies in the mouse, rat, rabbit, dog, and monkey have revealed development of chronic cardiotoxicity similar to that seen in human patients with prolonged administration of doxorubicin.[453-473] The dog has been shown in a number of studies[454-457] to provide an excellent model for studies of chronic doxorubicin cardiotoxicity. Characteristic myocardial lesions have been consistently produced in dogs by weekly doses of 1 mg/kg for 15 or 20 weeks or with administration of 1.75 mg/kg every 3 weeks for 7 doses. In rodents, chronic administration of doxorubicin produces not only cardiotoxicity but also renal toxicity and a nephrotic syndrome.[470,471] Spontaneously hypertensive rats (SHRs) are much more sensitive than Kyoto-Wistar rats to the cardiotoxic effects of doxorubicin.[458]

In our initial studies in pigs, we observed that conventional pigs were susceptible to damage to the alimentary tract and myeloid and lymphoid tissue if large doses of doxorubicin were given.[459] However, pigs given 0.64, 1.0, or 1.6 mg/kg once a week or 1.6 or 2.4 mg/kg every 3 weeks (mean cumulative dose, 520 mg/sqm) had prolonged survival and frequently developed subacute or chronic doxorubicin cardiotoxicity. Miniature pigs given doxorubicin, 2.4 mg/kg every 3 weeks for six doses (cumulative dose, 475 mg/sqm), developed consistent lesions of cardiomyopathy with good survival.[455,460]

Gross lesions of cardiotoxicity in pigs, rabbits, and dogs were hydropericardium, hydrothorax, and ascites. In occasional pigs, fibrinous pericarditis was present. The myocardium was pale, and the hearts were dilated when compared with control hearts (Figures 50 and 51); however, many animals had no gross evidence of cardiotoxicity at necropsy. The microscopic and ultrastructural alterations in the myocardium of pigs, rabbits, and dogs with chronic doxorubicin cardiotoxicity were similar to those in humans and in other species of animals.[453,457,461-473]

The three major lesions observed in myocytes were 1) sarcoplasmic vacuolization, 2) myocytolysis, and 3) hyaline necrosis (Figures 52–56). The distinctive vacuolar lesions resulted from distention of elements of the sarcoplasmic reticulum and the T-tubules. In mildly affected myocytes, the vacuoles varied from 0.1 to 1 μ in diameter, but in severely affected cells the vacuoles were 1–5 μ in diameter. Myocytolysis was present in



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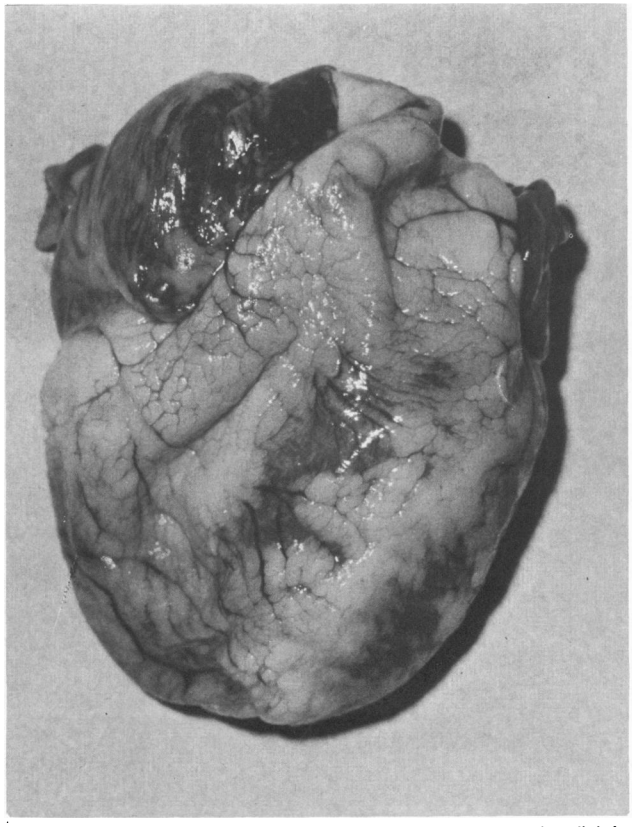

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**Figure 50**—Chronic doxorubicin cardiotoxicity. Rabbit. The heart has marked biventricular dilatation, diffuse pallor, and depleted epicardial fat deposits. **Figure 51**—Heart of a control rabbit has abundant epicardial fat deposits and normal shape.

damaged myocytes either with or without sarcoplasmic vacuolization. Thick myofilaments were preferentially lysed, and irregular clumps of Z-band material were present. Accumulation of glycogen granules and elements of sarcoplasmic reticulum occurred in some fibers undergoing myofibrillar lysis. Affected myocytes also had mitochondrial alterations, consisting of swelling and disruption of membranes, and scattered accumulations of residual bodies. Occasional myocytes showed hyaline necrosis with dense masses of disrupted contractile elements, pyknotic nuclei, and macrophagic invasion. The interstitium showed edema, activated fibroblasts, and a few invading macrophages. Vacuolar degeneration and myocytolysis also were present in Purkinje fibers.

Rabbits, dogs, and pigs have been utilized to evaluate the ability of various compounds such as ICRF-187, vitamin E, selenium, N-acetyl cysteine, and thyroxine and lysosomal encapsulation to ameliorate the chronic cardiac lesions.[454-457,460,474-479] These studies have further established these species as suitable animal models for studies of the cardiotoxicity produced

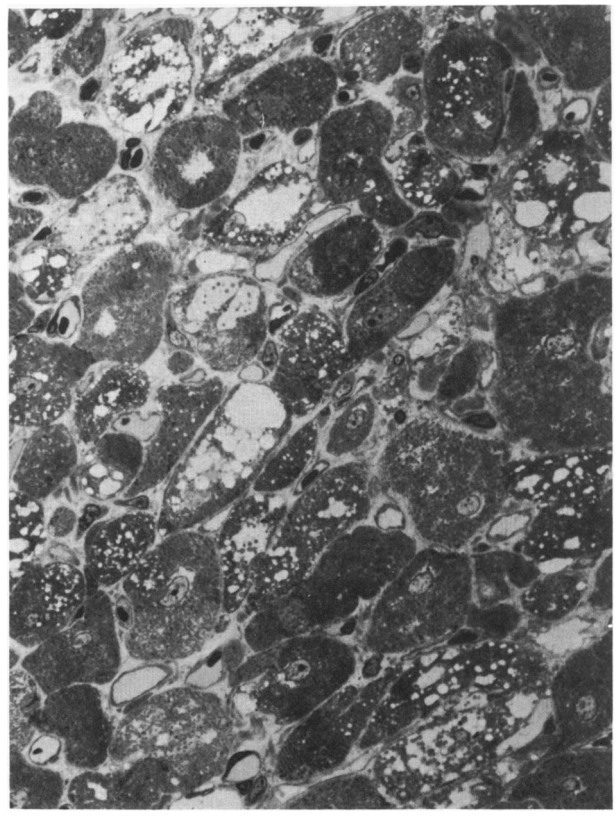

**Figure 52**—Chronic doxorubicin cardiotoxicity. Rabbit. Prominent sarcoplasmic vacuolation is present in the left ventricular myocardium. (Plastic-embedded section 1 μ thick, alkaline toluidine blue, ×350)

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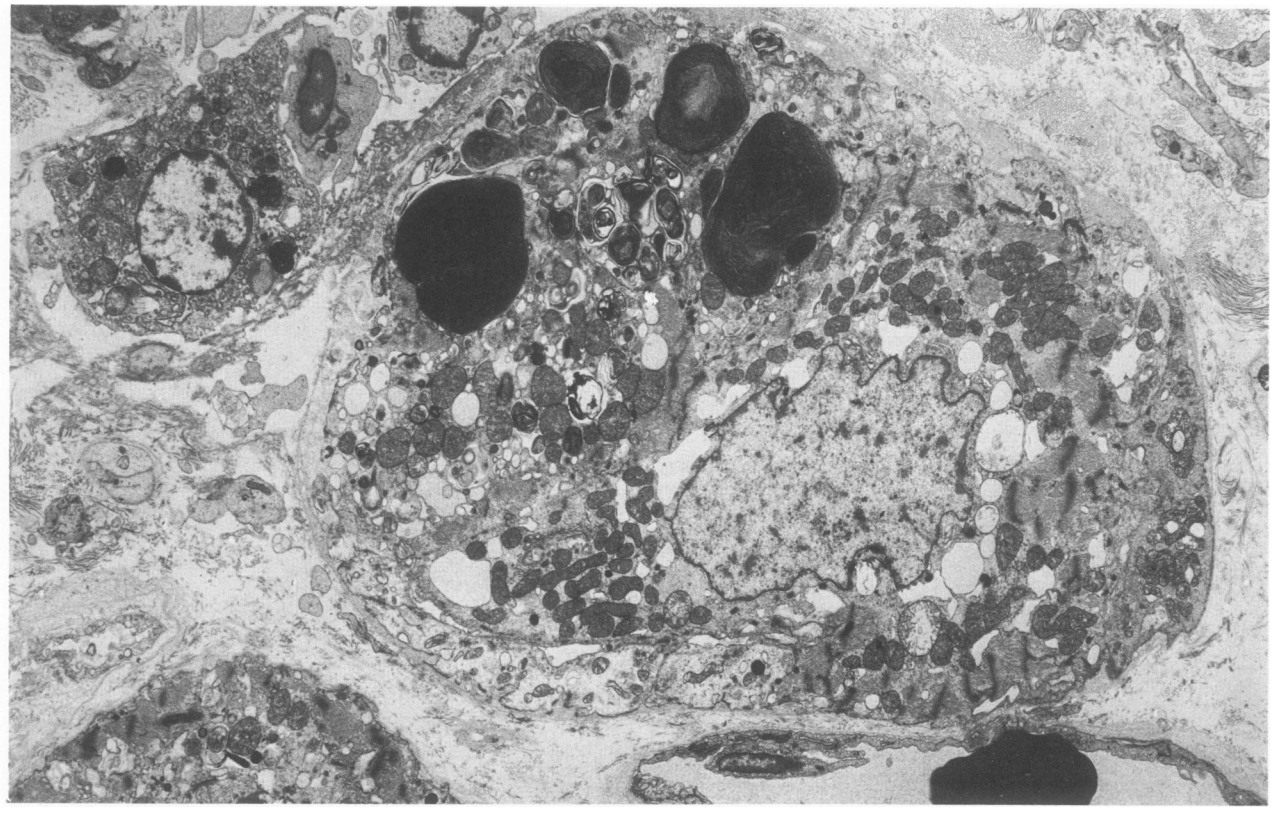

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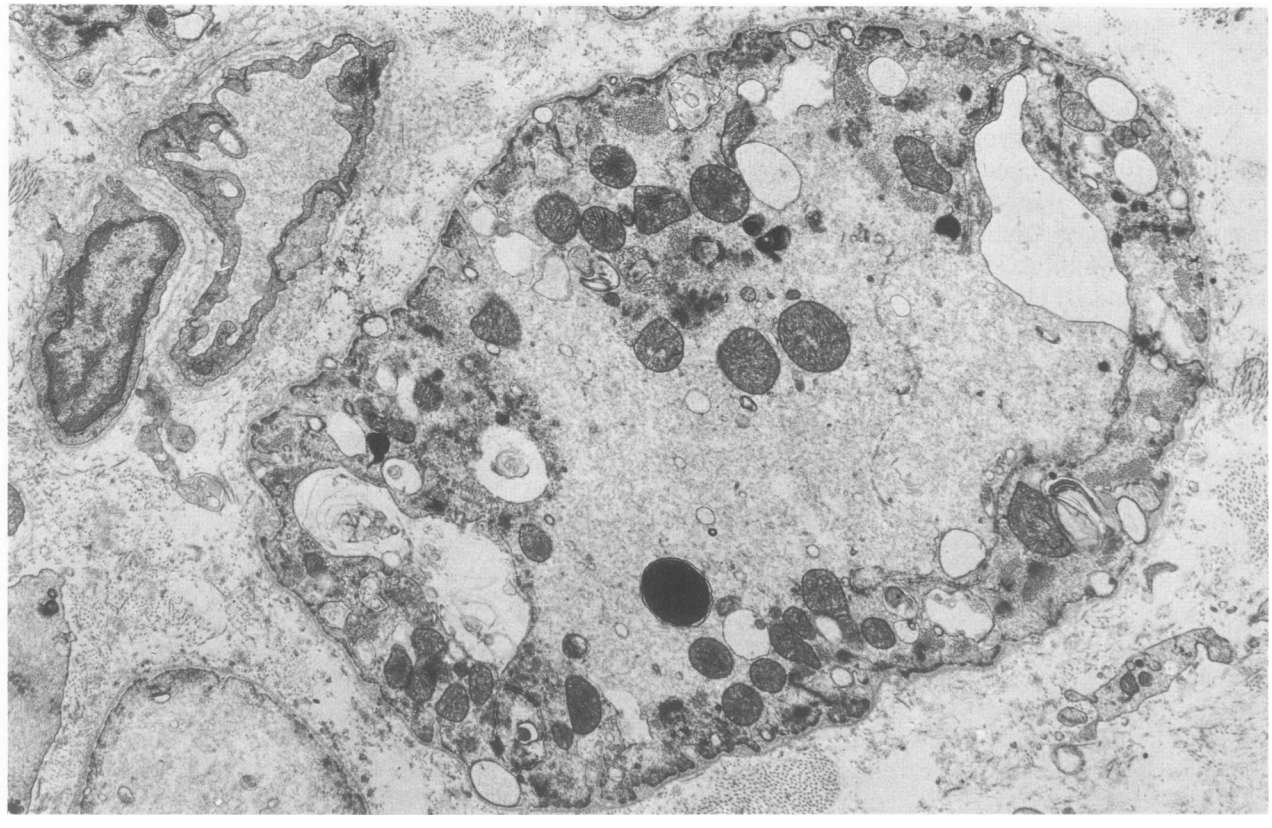
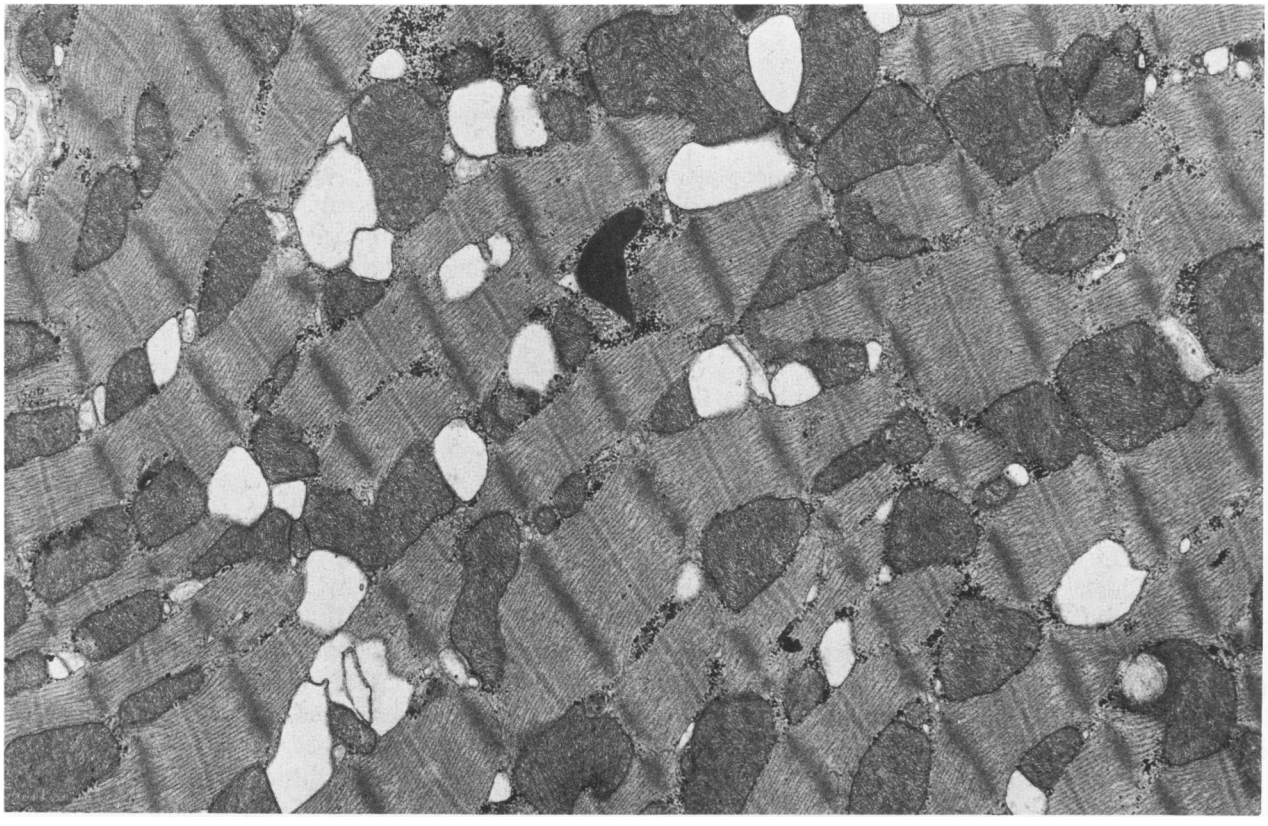


**Figure 53**—Chronic doxorubicin cardiotoxicity. Rabbit. Affected myocytes have myofibrillar lysis, sarcoplasmic vacuolation from distention of elements of sarcoplasmic reticulum, and several dense myelin figures. The interstitium is edematous. (×4500) **Figure 54**—Chronic doxorubicin cardiotoxicity. Rabbit. Myofibrillar lysis is severe, and the interstitium is edematous. (×10,000)



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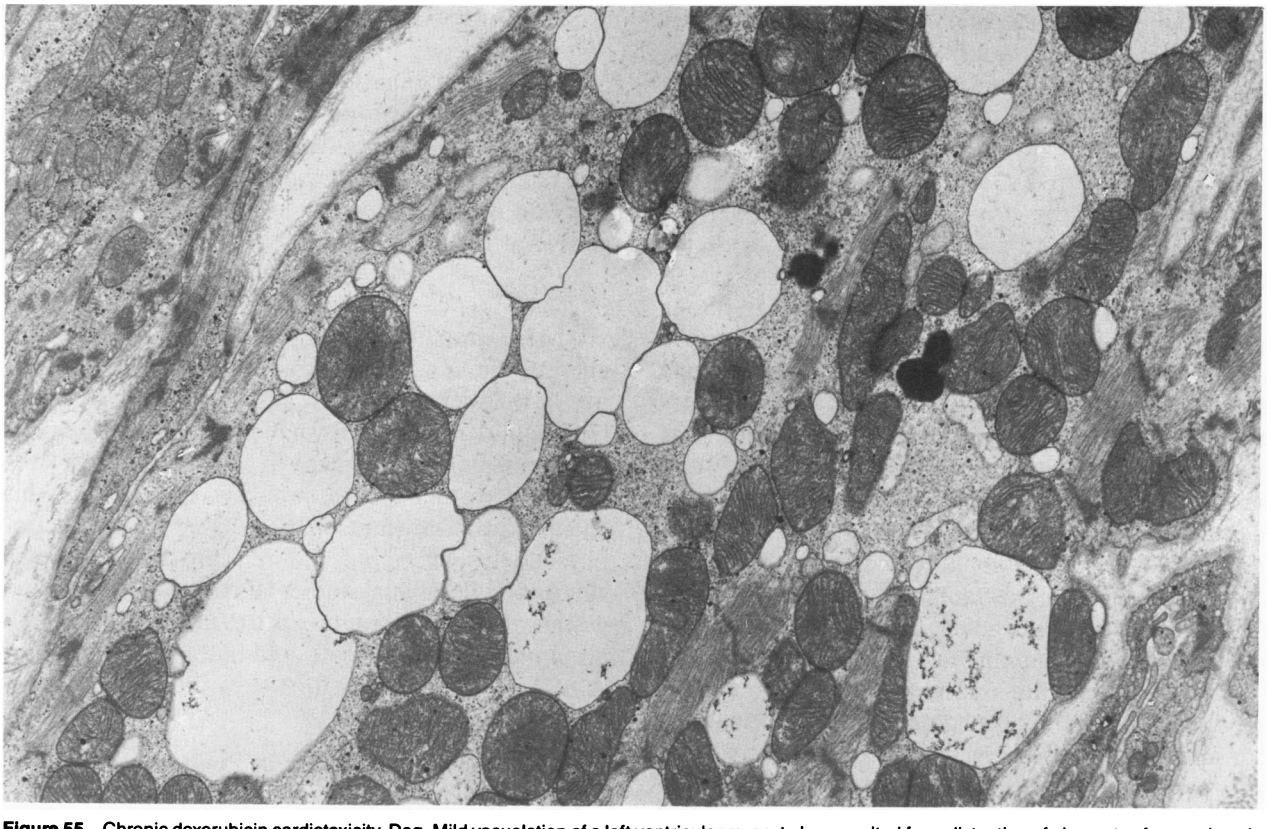

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**Figure 55**—Chronic doxorubicin cardiotoxicity. Dog. Mild vacuolation of a left ventricular myocyte has resulted from distention of elements of sarcoplasmic reticulum. (×18,000) **Figure 56**—Chronic doxorubicin cardiotoxicity. Dog. Marked myofibrillar lysis and sarcoplasmic vacuolation is present in left ventricular myocytes. (×15,000)

by doxorubicin and by other compounds of the anthracycline family.

## Cardiotoxicity of Other Antineoplastic Agents

In addition to anthracyclines, other antineoplastic agents are capable of producing myocardial dysfunction and/or anatomic lesions. Among these drugs are mitoxanthrone, cyclophosphamide, 5-fluorouracil, vincristine, and amsacrine (m-AMSA).

### *Mitoxanthrone*

Mitoxanthrone is a synthetic anthraquinone that shares some of the biochemical effects of doxorubicin on nucleic acids. Chronic administration of mitoxanthrone to mice[480] and monkeys[481] produced myocardial alterations similar in type and severity to those induced by doxorubicin. Affected myocytes showed degeneration and sarcoplasmic vacuolization due to dilatation of sarcoplasmic reticulum. Similar changes were found in myocardial biopsies from human patients receiving mitoxanthrone.[482,483] However, previous safety studies in dogs had failed to demonstrate significant myocardial morphologic alterations from mitoxanthrone.[484]

Anthracenedione diacetate (NSC-287513), an analog of mitoxanthrone, was found to exert significant acute depression of cardiovascular function in dogs. When administered over 12 weeks, this agent was judged to be less toxic than doxorubicin, but it produced cardiomyopathy in 5 of 6 rabbits and renal toxicosis in 3 of 6.[485]

### *Cyclophosphamide*

Cyclophosphamide, a widely used alkylating agent, produces a syndrome of acute cardiac failure associated with myocardial edema and hemorrhage and fibrinous pericarditis when given to human patients in large doses (45 mg/kg/day for 4–6 days) in order to ablate bone marrow in preparation for bone marrow transplantation.[486–490] Similar myocardial hemorrhagic necrosis has been produced by cyclophosphamide in dogs[491] and monkeys.[492] This toxicity is thought to be mediated by damage to endothelial cells, with transudation of the drug and its toxic metabolites into the extravascular compartment. In rhesus monkeys, cyclophosphamide and ifosfamide cause hypotension, bradycardia, cardiac depression, and histamine release.[493] Recent evidence suggests that formation of acrolein, a by-product of the metabolism of cyclophosphamide, is an important factor in the pathogenesis of these toxic effects and that they can be ameliorated by disulfiram.[494] In inbred female ACI rats, cyclophosphamide (three intraperitoneal doses of 150 mg/kg) produced a less acute syndrome of cardiotoxicity characterized by myocyte vacuolization and hypertrophy, vascular damage, marked lymphocytic infiltration, focal calcification, interstitial fibrosis, and cartilaginous metaplasia.[495]

### *5-Fluorouracil*

Focal myocardial necroses and associated inflammatory reaction were produced in 3–6-month-old Wistar rats by administration of large doses of 5-fluorouracil (125 mg/kg daily for 3 days).[496] This compound accumulates in myocardium, but to a lesser extent than in other organs,[497] and is an infrequent cause of cardiac complications (which consist mainly of anginal pain) in humans.[498–502]

### *Vincristine*

In 3-month-old male CBA/Kw mice, weighing 20–30 g, given 0.4 or 0.8 mg/kg/day of vincristine sulfate for 1–12 days, cardiac ultrastructural changes developed, consisting of focal mitochondrial lysis, increased amounts of autophagic vacuoles, accumulation of myelin figures, dilatation of sarcoplasmic reticulum, and widening of the intercalated disks, with separation of the apposed membranes.[503] Another electron-microscopic study showed that administration of single large doses (3 mg/kg) of vincristine or vinblastine to male 250–280-g Wistar rats produced degeneration of noradrenergic nerves (cholinergic nerves were unaffected) and a marked decrease in norepinephrine content in the atria within 24–48 hours.[504] However, the administration of vincristine to human patients only very rarely has been associated with cardiovascular dysfunction, which has consisted of manifestations suggestive of ischemic heart disease.[505]

### *AMSA*

AMSA (m-amsacrine, 4′-(9-acridinylamino) methanesulfon-m-anisidide), an acridine compound effective in the therapy of some refractory leukemias and lymphomas, has been shown to produce severe ventricular arrhythmias, particularly in patients with hypokalemia.[506–513] In mice, dogs, monkeys, and rabbits, this agent had significant hemodynamic and electrophysiologic effects but did not produce histologic changes.[514–518] Animal studies failed to support the suggestion that the solvent mixture (containing dimethylacetamide and lactic acid) used in the formulation of AMSA was responsible for the cardiotoxic effects.

## Furazolidone Cardiotoxicity in Poultry

Congestive cardiomyopathy is produced in turkeys, ducklings, and chickens by excessive intake of furazoli-

done (FZ).[42,45,47,53,57,519-542] This disease was first reported by Jankus et al[45] in 1972 in turkey poults accidentally exposed to excessive amounts of this antibacterial drug. Since then, numerous studies have been reported on the clinical, pathologic, and biochemical alterations of FZ-induced cardiomyopathy.[42,519,532] The disease is produced readily by oral administration or feed supplementation of FZ.[47,528] In turkeys, the gross appearance of the heart is similar in the inherited cardiomyopathy ("round heart disease") described above and in FZ-induced cardiomyopathy.

In ducklings, FZ induced dose-related frequency and severity of clinical disease.[47,540-542] Signs were growth retardation, ascites, and death. Ducklings fed 750 mg FZ/kg of feed for 28 days developed a high incidence of cardiomyopathy and a low mortality. Cessation of FZ feeding resulted in regression of ascites and reversal of the cardiomyopathy. At necropsy, congestive heart failure was manifested as severe ascites and hydropericardium. The lungs and liver were congested. The hearts were large, with marked biventricular dilatation and thin ventricular walls ("round heart") (Figures 57–60). However, light-microscopic study of the myocardium failed to demonstrate necrosis, inflammation, or fibrosis and instead revealed myocytolysis with pale sarcoplasm (Figure 61). Ultrastructurally, the outstanding alteration was myofibrillar lysis (Figures 62–64). Affected myocytes showed a loss of intact myofibrils, with scattered masses of free thick and thin filaments, clumps of Z-band material, and accumulations of cytoskeletal filaments. Numerous polyribosomes were present in the areas of myofibrillar lysis. It is not known whether the myofibrillar lysis results from FZ-induced decreased synthesis, increased degradation, or disaggregation of contractile proteins. FZ-induced cardiotoxicity in ducklings offers an attractive model for studies of congestive cardiomyopathy.

The clinical and pathologic features of FZ cardiotoxicity appear to be similar in turkey poults and ducklings. Turkeys are slightly more sensitive to the cardiotoxicity; the disease was produced in this species by feeding 300 mg of FZ/kg of feed. Cardiac dilatation in turkeys developed initially in the right ventricle, with subsequent left ventricular distention.[519] Numerous biochemical studies in FZ-fed turkeys have suggested that FZ may induce 1) inhibition of monoamine oxidase activity, 2) altered carbohydrate metabolism, 3) altered protein metabolism, 4) decreased myocardial content of taurine, and 5) altered lipid metabolism.[57,525-528,535-537,539] In ducklings, feeding supplements of taurine, selenium, and vitamin E have not ameliorated the cardiotoxicity.[540] However, administration of propranolol to FZ-fed turkey poults provided protection against the development of cardiomyopathy.[531] Further studies are needed to establish the primary biochemical alterations induced by FZ in the myocardium of birds.

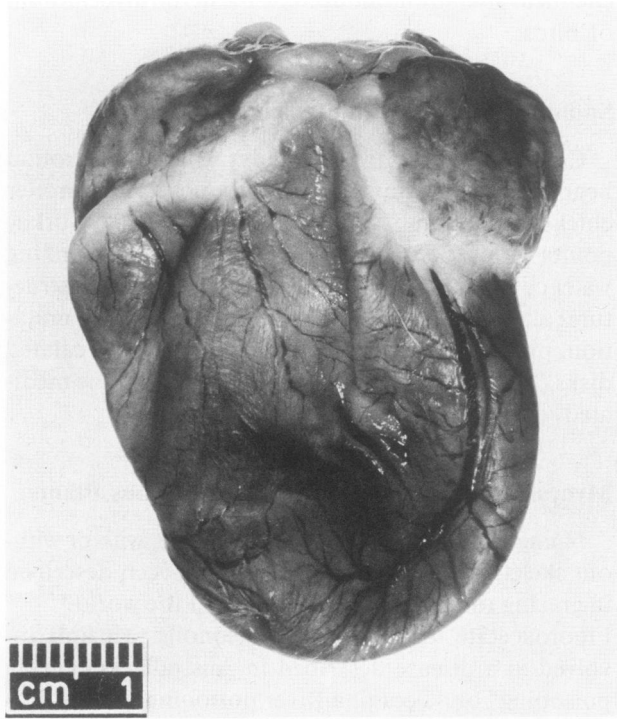
### Sodium Chloride Cardiotoxicity in Poultry

Cardiotoxicity with ventricular dilatation ("round heart") and ascites occurs in turkey poults and broiler chicks with sodium chloride toxicity.[46,543-546] Turkey poults with experimental disease, induced by drinking water containing 0.75% NaCl for 3 days, had ultrastructural alterations of myocytes with glycogen accumulation, myofibrillar lysis, and disruption of intercalated disks.[46] The cardiac lesions were suggested to be mediated via hypertension.

### Myocardial Diseases Induced by Poisonous Plants

Numerous syndromes of cardiac failure, with or without skeletal muscle involvement, have been described in grazing ruminants in many areas of the world.[547-560] Fluoroacetate toxicity is the poisonous principle involved in a disease described in Australia as "gidyea poisoning" or "Georgina River poisoning" and is produced by *Acacia georginae*, *Gastrolobium* spp. and *Oxylobium* spp. In South Africa the same syndrome is produced by *Dichapetalum cymosum* and is called "gifblaar." Also in South Africa, ruminants may develop a toxic congestive cardiomyopathy called "gousiekte" ("quick disease") from ingestion of *Pachystigma pygmaeum*, *Pachystigma thamnus*, *Pavetta harborii*, *Pavetta schumaniana* and *Fadogia monticola*. In the United States, toxic cardiomyopathy has occurred in ruminants following consumption of *Cassia occidentalis* (coffee senna), *Cassia obtusifolia*, *Karwinskia humboldtiana* (coyotillo), and *Vicia villosa* (hairy vetch). Other plants implicated as cardiotoxic were *Trigonella foenum-graecum* in Israel and *Palicourea marcgravii* in South America. The toxic compound(s) involved with poisoning by the above plants and their mechanisms of cardiotoxicity are generally not known except for those plants containing fluoroacetate, a compound that interferes with cellular aerobic metabolism by blockade of the tricarboxylic acid cycle.

Clinically, most of these plant poisonings are characterized by the sudden onset of congestive cardiac failure. At necropsy, hydropericardium, hydrothorax, and ascites are generally observed. The heart may appear mottled, with dilatation and subserosal hemorrhage. Microscopically, the findings vary, depending on the time of cardiotoxic exposure prior to death. Acute damage will produce multifocal necrosis, and older lesions

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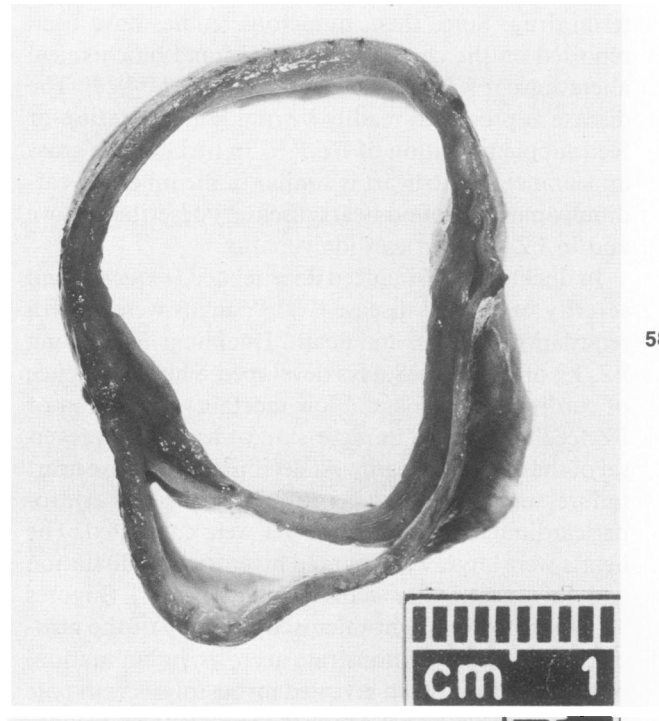


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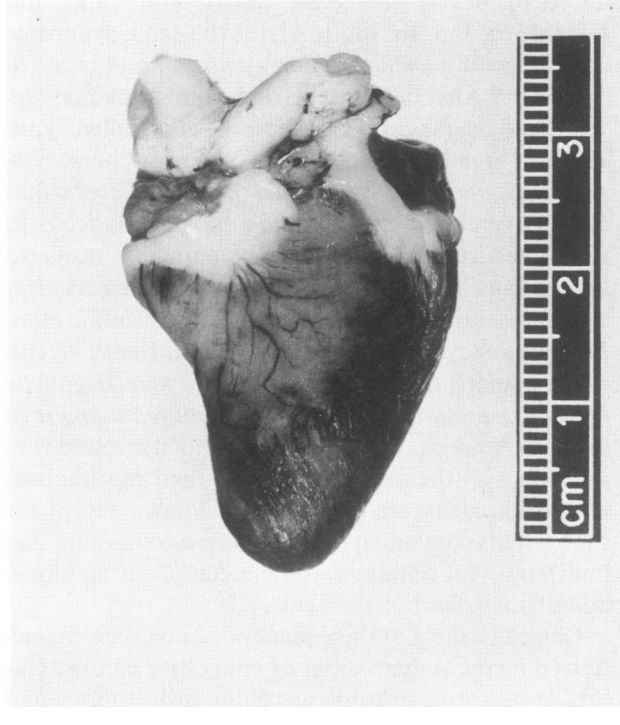


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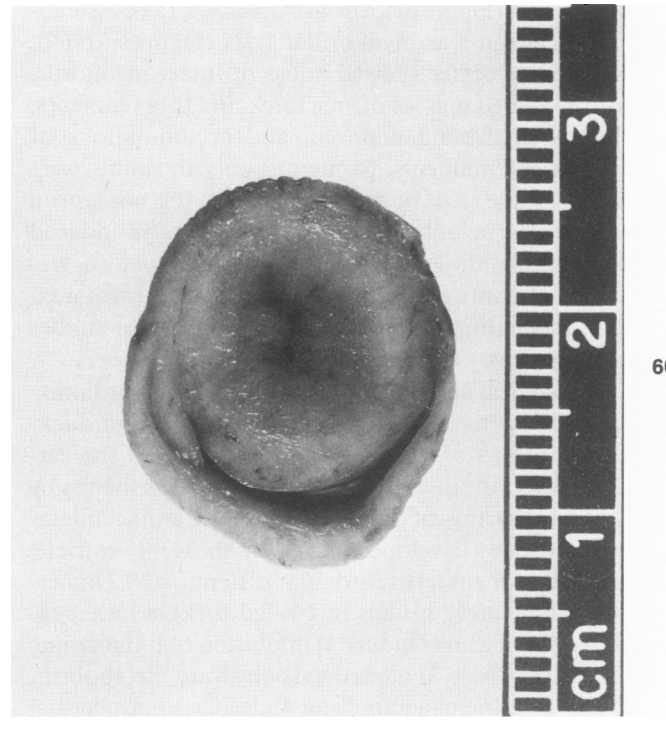


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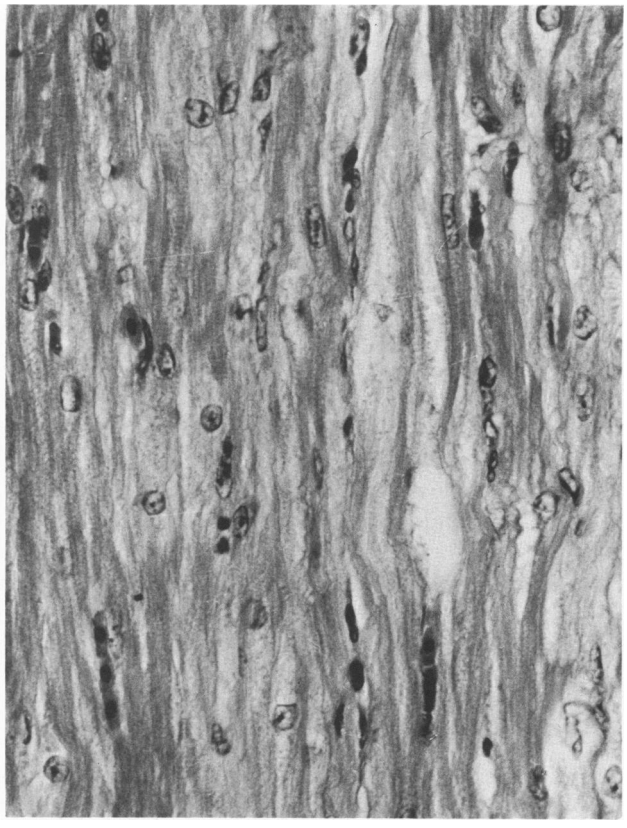
**Figure 57**—Furazolidone cardiotoxicity. Duckling. Marked cardiomegaly and biventricular dilatation are present. **Figure 58**—Furazolidone cardiotoxicity. Duckling. Transverse section of the ventricular walls of the heart in Figure 57 shows marked dilatation of the ventricular chambers and thinned walls. **Figure 59**—Heart from a control duckling has normal size and shape. **Figure 60**—Transverse section of the ventricles of the heart in Figure 59 shows normal chamber size and wall thickness.



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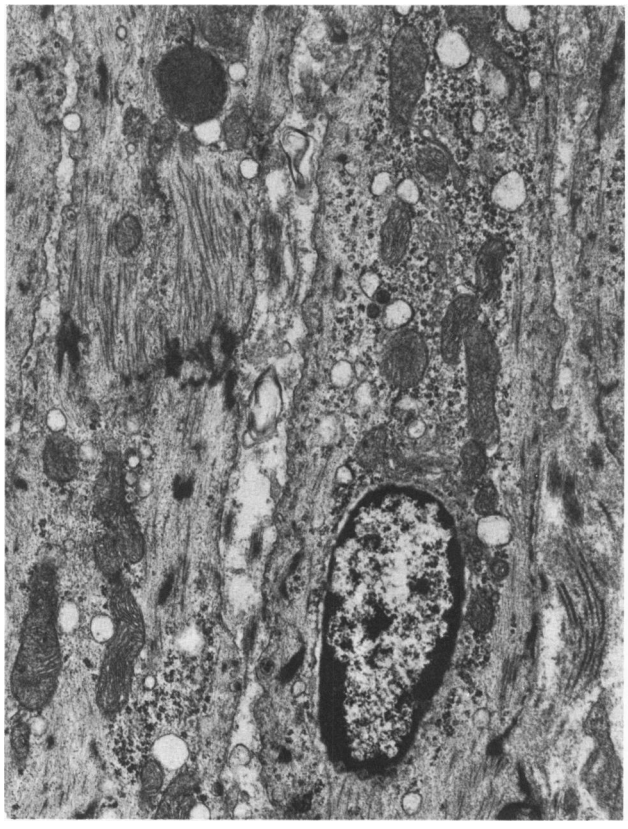

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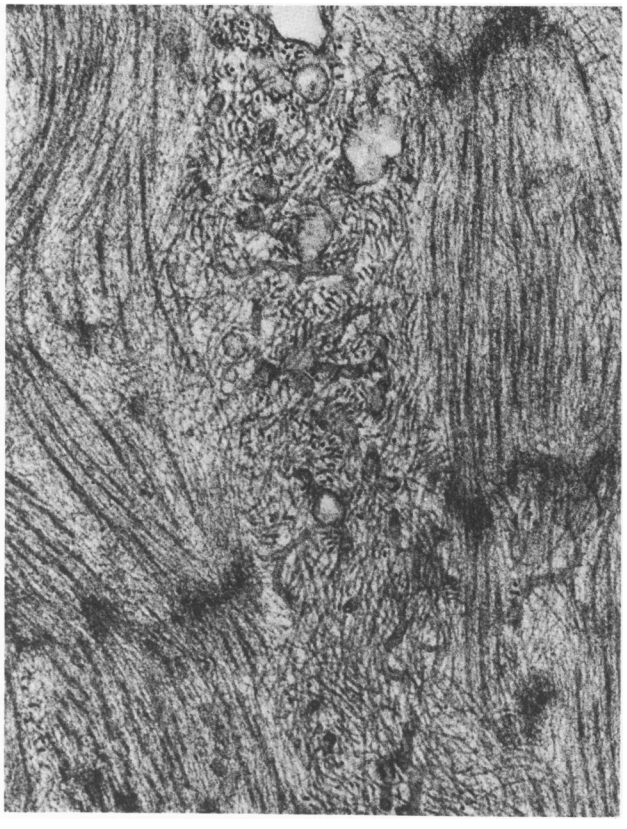

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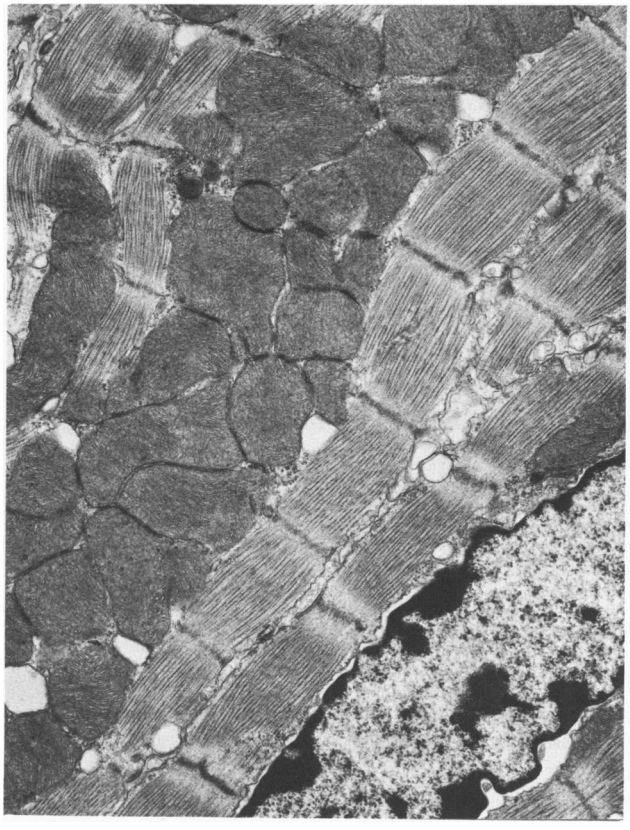

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**Figure 61**—Furazolidone cardiotoxicity. Duckling. Left ventricular myocardium shows extensive myofibrillar lysis. (H&E, ×500) **Figure 62**—Furazolidone cardiotoxicity. Duckling. Diffuse myofibrillar lysis is present in left ventricular myocytes. The sarcoplasm contains scattered free myofilaments and dense clumps of Z-band material and numerous polysomes and mitochondria. (×14,000) **Figure 63**—Furazolidone cardiotoxicity. Duckling. Myocyte with early myofibrillar lysis shows abundant intermediate filaments and elements of sarcoplasmic reticulum lying between lysed myofibrils. (×35,000) **Figure 64**—Myocytes from the left ventricle of a control duckling have intact myofibrils and numerous mitochondria. (×14,000)

may show mild inflammatory cell infiltration and replacement fibrosis.

### Myocardial Alterations From Vitamin D Toxicosis and Calcinogenic Plants

Myocardial calcification has occurred in pigs fed a calcinogenic plant (*Cestrum diurnum*)[561] or large amounts of vitamin D.[562,563] The lesions consist of multifocal myocardial calcification and focal calcification of smooth muscle cells in the walls of intramyocardial arteries.

Extensive endocardial mineralization occurs in cattle and horses following prolonged ingestion of calcinogenic plants.[564-566] Many names have been applied to this disease in cattle throughout the world, including "Manchester wasting disease" in Jamaica, "enzootic calcinosis" in European countries, "naalehu" in Hawaii, "enteque seco" in Argentina, and "espichamento" in Brazil. The implicated plants include *Solanum malacoxylon*, *Solanum torvum*, *Trisetum flavescens* and *Cestrum diurnum*. The endocardial lesions are accompanied by extensive mineralization of the aorta, lungs, and tendons.

Vitamin D toxicosis in rats produced extensive myocardial damage.[567-574] Necrosis and calcification were seen as patchy white areas in the myocardium. Microscopically and ultrastructurally, dense spherical calcified bodies, representing calcified mitochondria, were present in intact and necrotic myocytes (Figures 65 and 66).[574] Calcification was also present within valves and the walls of intramyocardial arteries (Figures 67 and 68).

### Myocardial Damage in Blister Beetle Poisoning of Horses

Ingestion of baled hay contaminated with dead striped blister beetles (*Epicauta*) was reported to produce myocardial, gastrointestinal, and urinary lesions.[575] The affected myocardium showed pale patches grossly; and necrosis, with or without calcification, was observed microscopically.

### Cardiotoxicity of High Erucic Acid Rapeseed Oil

Myocardial lesions occur in rats, rabbits, monkeys, gerbils, turkeys, chickens, ducklings, and pigs fed diets containing long-chain monoenoic fatty acids such as erucic acid, which is found in rapeseed oil.[576-584] Male rats were more susceptible than females to the cardiac lesions.[578] Light- and electron-microscopic studies revealed early lesions of myocardial lipidosis. Later lesions were focal myocardial necrosis, macrophagic invasion, and fibrosis. Ducklings and chicks, but not turkey poults, were highly susceptible to the cardiotoxicity and developed prominent hydropericardium, ascites, and myocardial pallor.[581] New varieties of rape plants produce rapeseed oil that contains only small amounts of erucic acid.

### Cardiotoxicity of Brominated Vegetable Oils

Brominated vegetable oils have been used in North America for nearly 50 years to adjust the density of essential flavoring oils used in the manufacture of citrus-flavored beverages. Safety studies in rats have demonstrated that feeding large amounts of various brominated vegetable oils, including cottonseed oil, corn oil, sesame oil, and olive oil, will induce myocardial lesions.[585-590] The earliest myocardial alteration was lipid droplet accumulation; the liver and kidney also showed lipidosis. Later myocardial alterations were multifocal necrosis and myocytolysis.

### Cardiotoxicity of Rancid Fat in Mice

Mice inadvertently fed rancid powdered purified diets developed high mortality and cardiac lesions.[591] Affected hearts appeared mottled grossly and had necrotizing hemorrhagic myocarditis on microscopic study. Many animals had hemothorax. Elevated levels of lipoperoxides were detected in feed samples, but selenium and vitamin E concentrations were adequate.

### Gossypol Cardiotoxicity

Pigs are very susceptible to poisoning by gossypol, which is found in cottonseed meal, a protein supplement used in swine rations. In affected pigs, congestive heart failure develops, with prominent ventricular dilatation and pulmonary edema.[103,592] Hepatic necrosis and pale degenerated skeletal muscles also may be present. Microscopically, myocardial necrosis is seen. Similar lesions have been described in dogs with gossypol poisoning.[593,594]

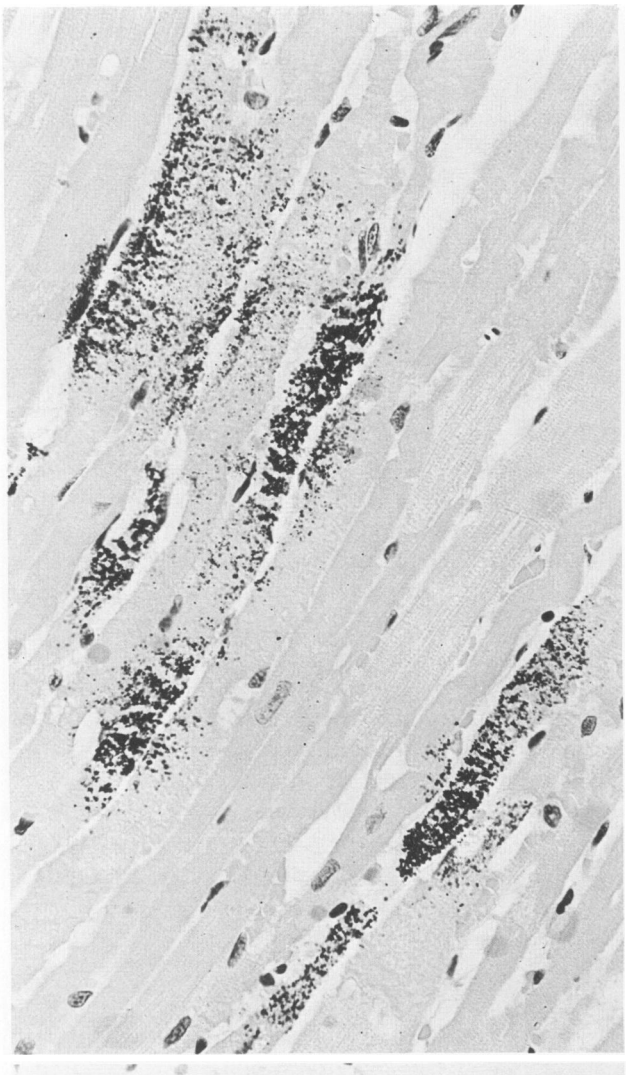
### Myocardial Alterations Induced by Chloroquine

Myocardial alterations were produced in rabbit, rat, and fetal mouse hearts by chloroquine.[595-597] In rabbits, multifocal myocardial necrosis was seen. In rat and mouse hearts, numerous myelin figures were found by light and electron microscopy. In rats, the myocardial alterations were shown to be reversible.

### Carbon Monoxide and Cigarette Smoke Cardiotoxicity

Myocardial damage has been produced by exposure

65



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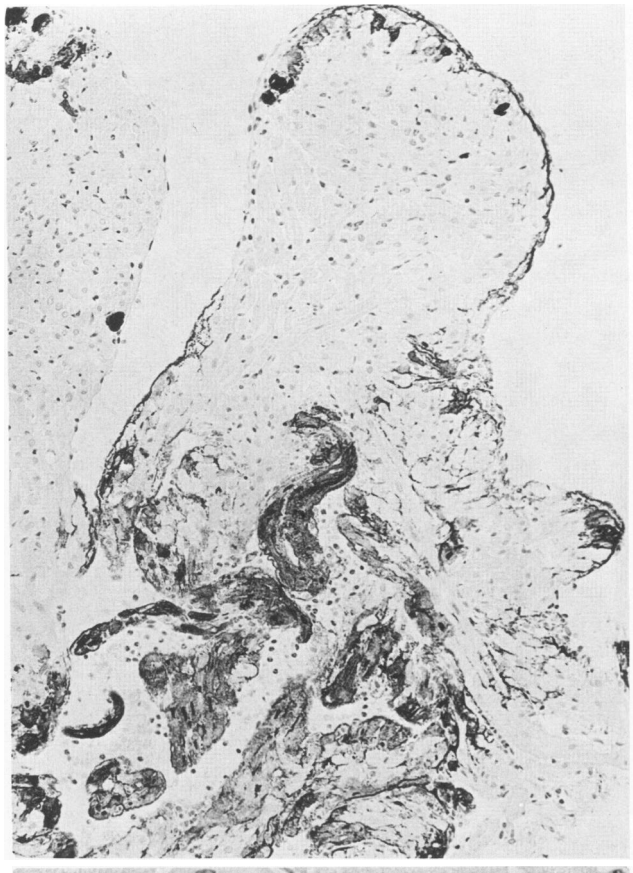

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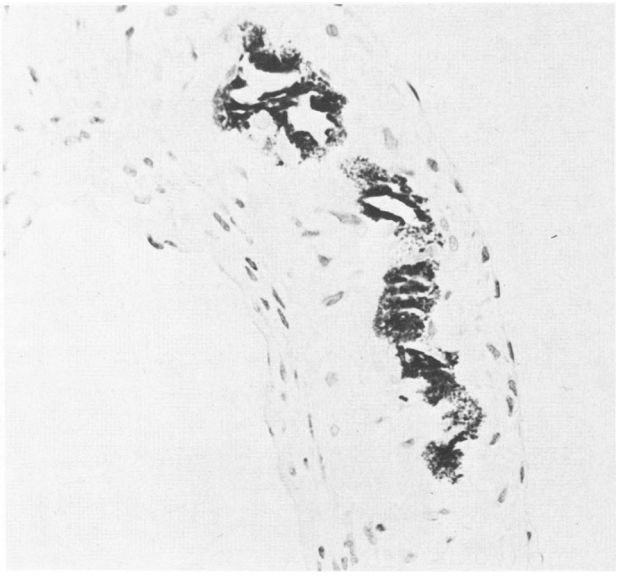

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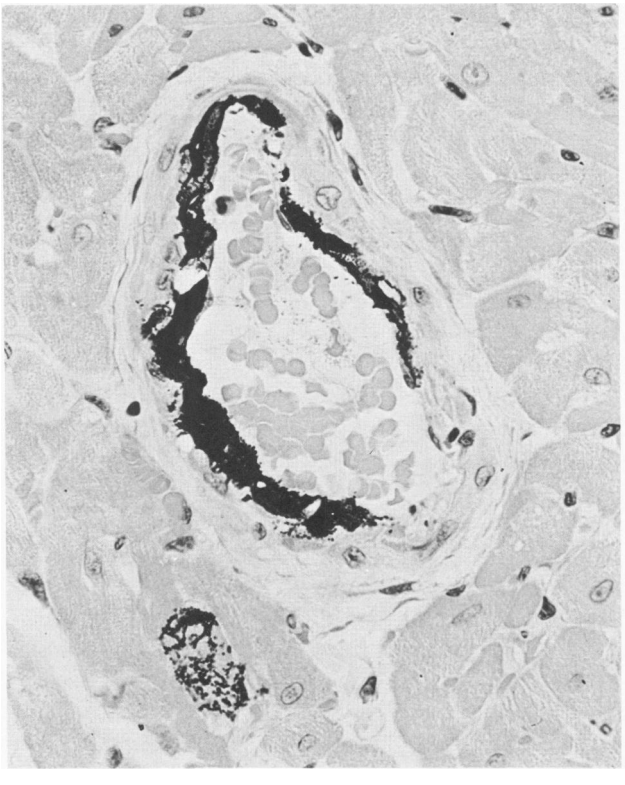

**Figure 65**—Vitamin D toxicity. Rat. Scattered left ventricular myocytes have granular deposits of mineral. (von Kossa, ×350) **Figure 66**—Vitamin D toxicity. Rat. Extension mineralization is present in left atrial myocardium and endocardium. (von Kossa, ×100) **Figure 67**—Vitamin D toxicity. Rat. Focal mineralization is present in the mitral valve leaflet. (von Kossa, ×350) **Figure 68**—Vitamin D toxicity. Rat. Prominent mineralization is seen in the inner wall of an intramyocardial artery. (von Kossa, ×400)

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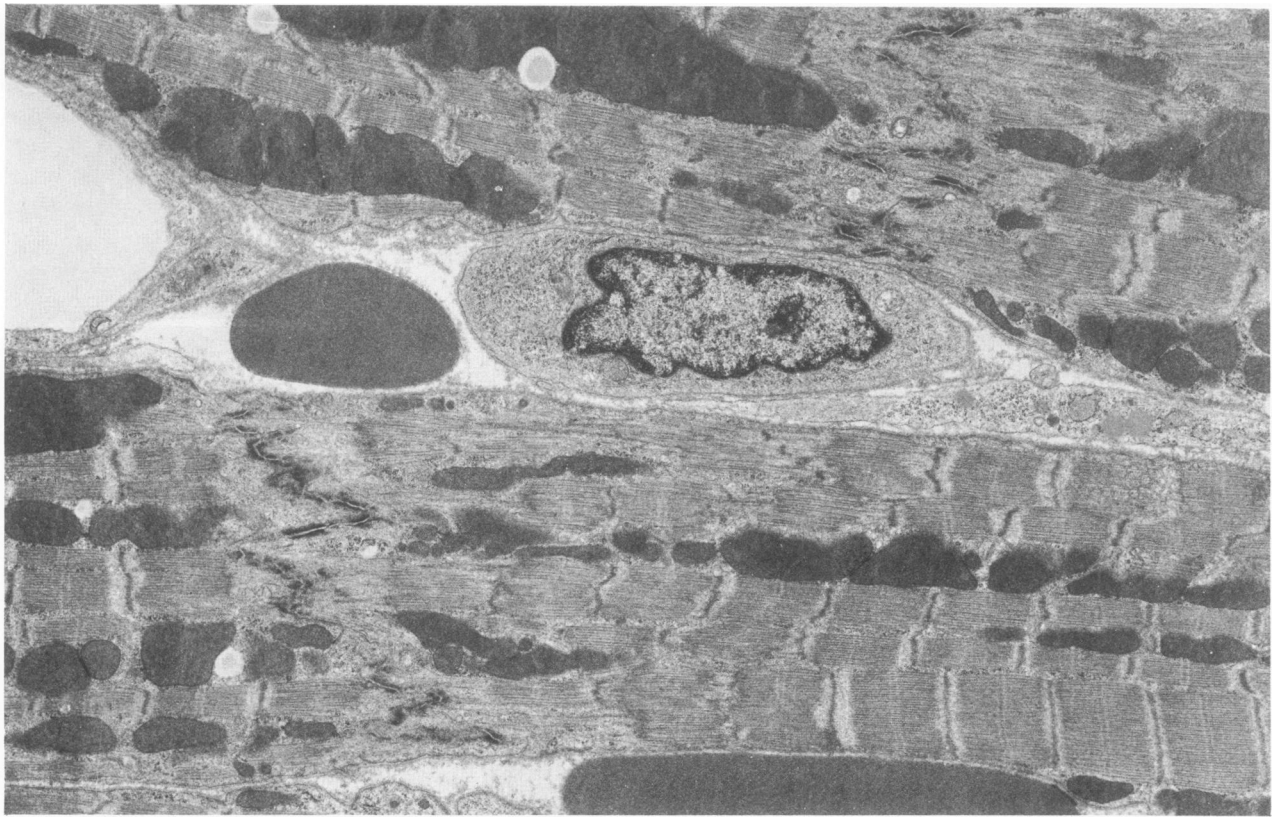

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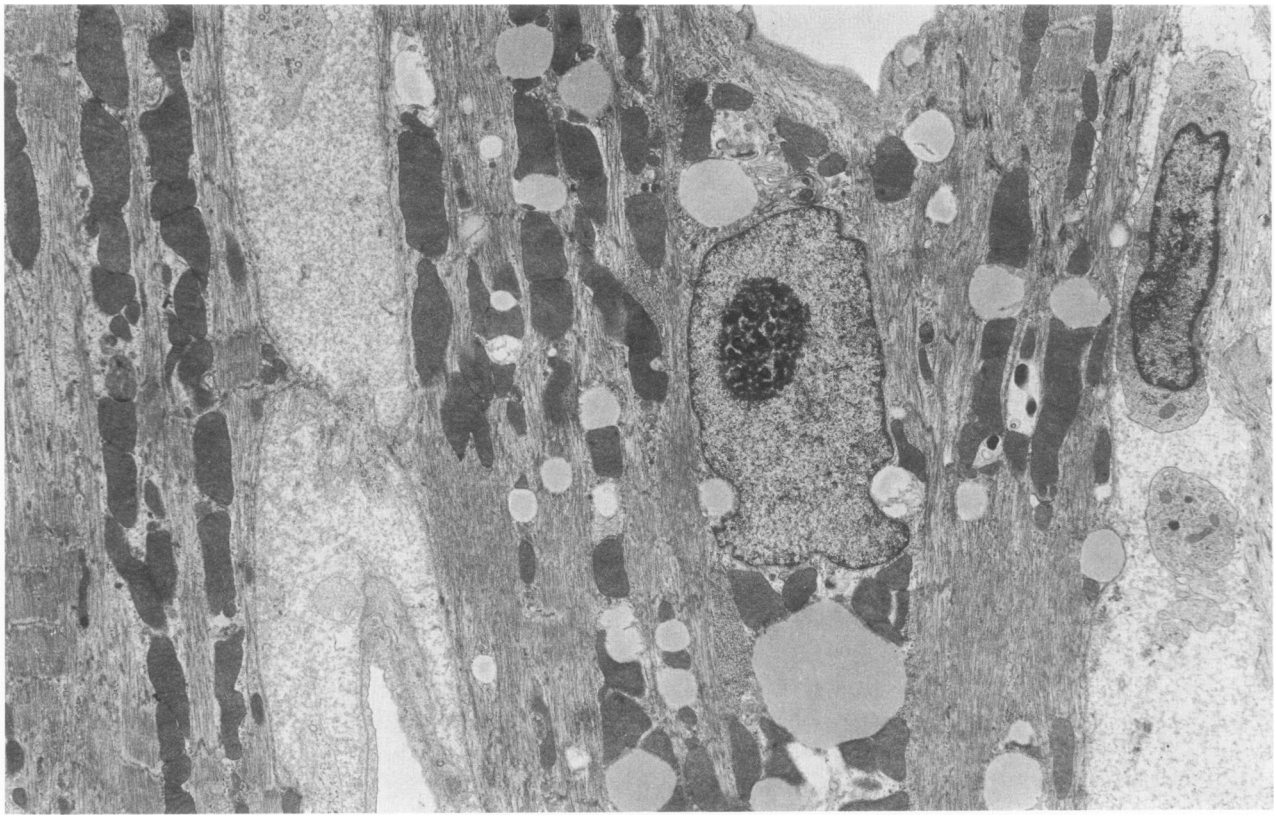

**Figure 69**—Allylamine cardiotoxicity. Rat. Early damage is seen as myofibrillar lysis in areas adjacent to intercalated disks. (×15,000) **Figure 70**—Allylamine cardiotoxicity. Rat. Myocytes with more advanced injury (compare with Figure 69) have diffuse myofibrillar lysis and lipid droplet accumulation. The interstitium shows severe edema. (×15,000)

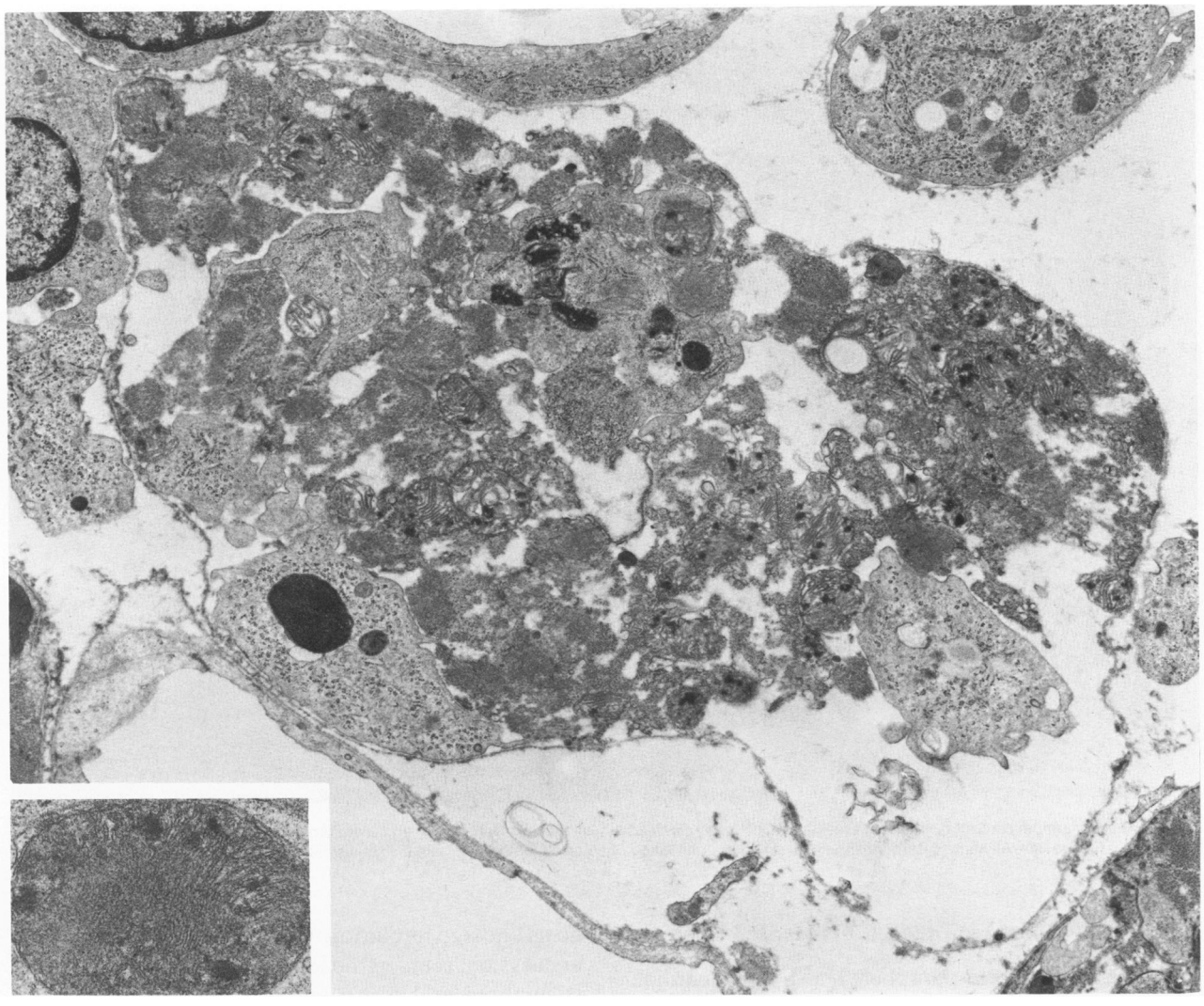

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**Figure 71**—Allylamine cardiotoxicity. Rat. Necrotic myocyte has disrupted contractile material and mitochondria with matrical densities. Macrophages are in the interstitium and within the "tube" of external lamina of the necrotic myocyte. (×11,000) **Figure 72**—Allylamine cardiotoxicity. Rat. Matrical densities are seen in a mitochondrion of a necrotic myocyte. (×20,000)

to carbon monoxide in dogs and rabbits.[598-602] In dogs, myocardial degeneration and fibrosis were described. Ultrastructural study of the hearts of exposed rabbits demonstrated myocyte alterations, including contraction bands, myofibrillar lysis, myelin figures, and dehiscence of intercalated disks.

Cigarette smoke inhalation by guinea pigs produced ultrastructural alterations in cardiac muscle cells, including mitochondrial damage, lipid droplet accumulation, and increased numbers of myelin figures and residual bodies.[600] These alterations were attributed to carbon monoxide exposure.

### Cardiotoxicity of T-2 Mycotoxin

Rats given single or multiple doses of T-2 mycotoxin developed myocardial lesions concentrated in the left ventricular subendocardium.[603] Microscopic and ultrastructural study showed myocardial edema and necrosis with subsequent fibrosis.

### Papain-Induced Myocardial Necrosis in Rats

Intravenous administration of the proteolytic enzyme papain produced myocardial necrosis in rats.[604,605] The necrotic foci were observed as yellow-grey areas scattered throughout the myocardium but most numerous in the left ventricle. Microscopic and ultrastructural study showed interstitial edema and myocyte damage with myofibrillar lysis and sarcolemmal disruption. Necrotic myocytes were invaded by inflammatory cells, and late lesions showed fibrosis.

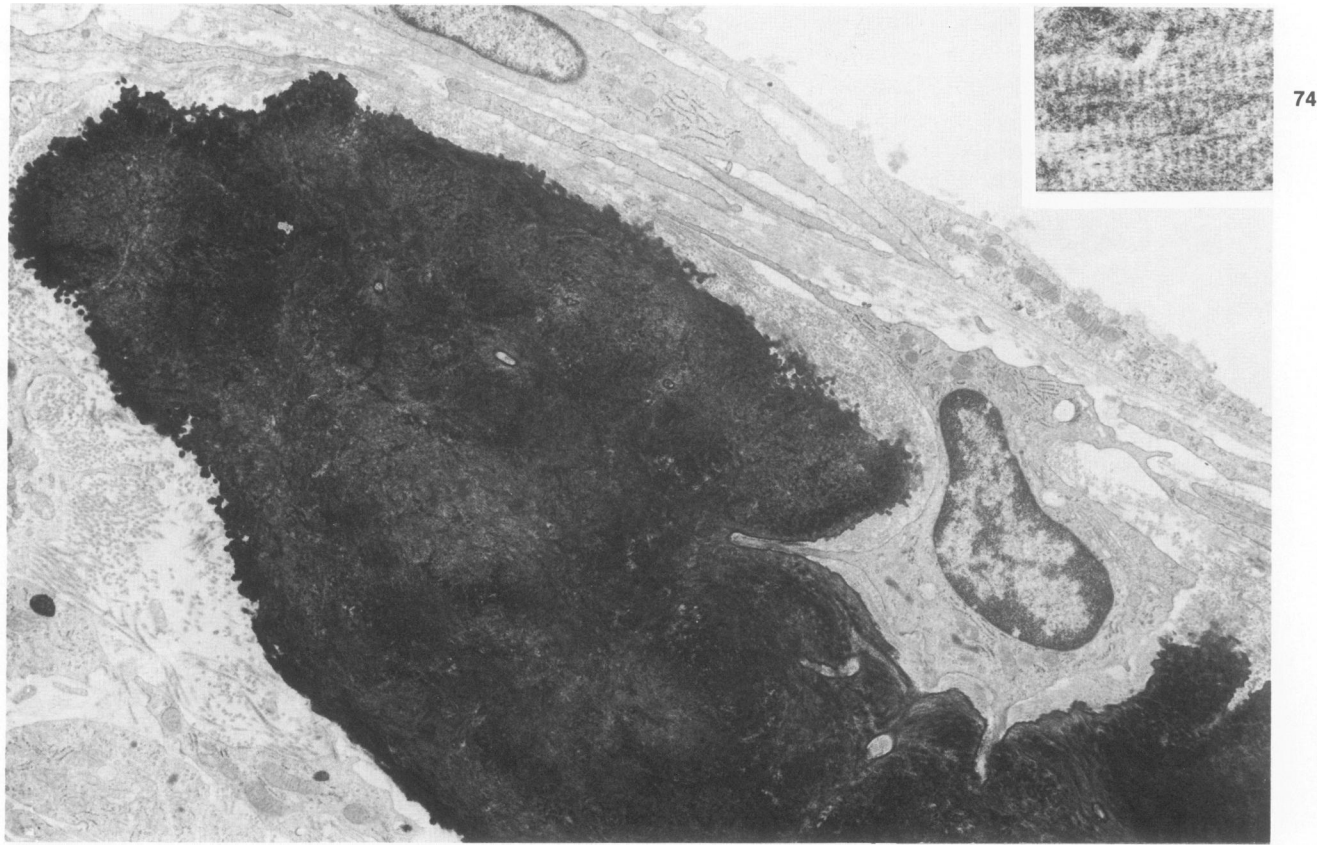



**Figure 73**—Allylamine cardiotoxicity. Rat. Late lesion of focal calcification of the left ventricular endocardium is seen as a large, dense deposit. (×9000) **Figure 74**—Allylamine cardiotoxicity. Rat. High magnification of calcified lesion in Figure 73 shows calcification of collagen fibrils. (×24,000)

### Paraphenylenediamine-Induced Myocardial Necrosis

In rats administered paraphenylenediamine cardiac and skeletal muscle lesions developed.[606,607] Necrotic foci were concentrated in the subendocardium. Microscopic study revealed necrosis, cellular infiltration, and residual fibrosis.

### Cardiotoxicity of Brown FK

Brown FK, a food-coloring agent, produces cardiac and skeletal muscle lesions in rats.[608] In rats given massive doses, myocytes showed myofibrillar lysis and necrosis. Macrophagic invasion and fibrosis subsequently occurred in the necrotic foci. With lower doses of Brown FK, myocardial lipofuscinosis was produced.

### Allylamine Cardiotoxicity

Allylamine, an aliphatic amine used in the production of pharmaceuticals and polymers, produces myocardial and vascular alterations in rats.[609–613] The myocardial alterations are multifocal necrosis concentrated in the left ventricular subendocardium. These necrotic areas undergo resolution with extensive fibrosis to form aneurysmal scars in the left ventricular and right ventricular apices. Ultrastructurally, the myocardial damage is evident as interstitial edema with prominent cellular activation and numerous mitoses in interstitial cells and capillary endothelium (Figures 69 and 70).[609] Severely damaged myocytes develop contraction band necrosis with lipid droplet accumulation (Figures 71 and 72). Erythrocytes are present in the interstitium. Extensive macrophagic invasion occurs into the areas of myocardial necrosis. Endocardial thickening, calcification, and cartilaginous metaplasia also are found in late stages of the lesions (Figures 73 and 74).[611]

Calves given allylamine developed acute vascular injury and thrombosis with multiple foci of myocardial ischemic damage.[613] In rats the vascular lesions led to severe fibromuscular intimal thickening in intramural coronary arteries.[610,612]

### Plasmocid Cardiotoxicity

Rats administered toxic amounts of plasmocid had myocardial and skeletal muscle necrosis.[614–616] The myo-

cardial damage was most severe in the subendocardium of the left ventricle; and microscopic and ultrastructural study showed early mitochondrial alterations, lipid droplet accumulation, and necrosis of myocytes. Macrophagic invasion occurred into necrotic areas. At lower doses, damaged atrial myocytes showed selective lysis of I bands and Z-band alterations; but ventricular myocytes showed intact myofibrils.[614]

### Hyperoxia Cardiotoxicity

Myocardial lesions have been produced in rats, rabbits, guinea pigs, and hamsters subjected to prolonged normobaric and hyperbaric hyperoxia.[617-619] Animals that die may have lesions of congestion cardiac failure with cardiac dilatation and visceral congestion. Multifocal myocardial necrosis is present, and the most severe lesions are concentrated in the left ventricular papillary muscles and subendocardium. Microscopic and ultrastructural studies showed prominent mitochondrial alterations, dilatation of elements of sarcoplasmic reticulum, lipid droplet accumulation, and necrosis with contraction bands.[619] Macrophagic invasion and fibrosis occur in resolving areas of necrosis.

### Ethanol Cardiotoxicity

Numerous attempts have been made to establish an animal model of alcoholic cardiomyopathy in humans. Some reports have demonstrated various myocardial alterations in animals fed large amounts of ethanol, with and without various superimposed nutritional deficiencies.[620-625] Biochemical and morphologic alterations produced in myocardium of experimental animals by ethanol appear to be numerous[626-634] and include dilatation of sarcoplasmic reticulum, separation of intercalated disks, alterations in mitochondrial structure, formation of megamitochondria, decreased volume fraction of mitochondria, presence of increased amounts of glycoprotein material in myocardial interstitium, triglyceride deposits within myocytes, depression of myocardial contractility, diminished calcium content and reduction in the uptake and binding of calcium to the sarcoplasmic reticulum, and decrease in protein synthesis (an effect mediated by acetaldehyde). However, Ferrans et al[352] reviewed the literature of alcoholic cardiomyopathy in humans and animals and concluded 1) that considerable variability existed in the morphologic data on the cardiotoxicity of ethanol in different studies of a given animal species and among different species, and 2) that none of the animal studies has produced cardiac morphologic alterations comparable to those found in humans with alcoholic cardiomyopathy.

Administration of ethanol potentiated the cardiac damage in animals with isoproterenol cardiotoxicity, Coxsackie $B_3$ myocarditis, and *T cruzi* myocarditis.[635,636] Administration of 3-amino-1,2,4-triazole, an inhibitor of catalase, caused considerable worsening of morphologic changes caused by ethanol in rat myocardium.[626]

### Emetine Cardiotoxicity

Administration of emetine to rabbits, cats, and dogs, but not rats, produced myocardial lesions.[637-641] In rabbits, affected hearts were pale grossly, and microscopic and ultrastructural study showed contraction-band necrosis. Mitochondrial damage has been observed in myocardial biopsies from human patients with emetine cardiotoxicity.[639] Myocardial necrosis and fibrosis was described in rabbits and cats with emetine cardiotoxicity.[637,640]

### Renal Failure

Cardiac lesions have been described in animals with experimentally induced and spontaneously occurring renal disease.[108,642-650] Myocardial necrosis is consistently found in rats, dogs, and rabbits with experimentally induced acute renal hypertension.[643-645,648,650] Procedures used to create renal hypertension have included unilateral renal ischemia, bilateral nephrectomy with administration of crude kidney extracts, and angiotensin administration. Focal myocardial necrosis with contraction bands was especially prominent in the left ventricular subendocardium.[645] In early lesions, hemorrhage and edema were present; mononuclear leukocytic infiltration was prominent in the necrotic foci after several days. The myocardial lesions may be the direct effect of angiotensin or may be mediated by increased release of endogenous catecholamines.[643]

Other cardiac lesions occur in uremic dogs with experimental toxic nephroses and spontaneous nephritis.[108,642,646,649] In acute renal insufficiency, distinctive necrotizing ulcerative lesions are present in the left atrial endocardium and intima of the proximal aorta and pulmonary arteries. In dogs that recover, raised, firm, rough healed lesions remain as residual alterations in the left atrium, aorta, and pulmonary artery. Dogs with chronic renal disease may have cardiac hypertrophy.[647,649] Uremic pericarditis, although frequent in human patients, occurs only rarely in dogs and cats.[108]

## Myocardial Diseases Associated With Physical Injuries

This group of diseases represents a wide variety of insults that produce myocardial necrosis. In general, similar diseases have been seen in man. In animals, these

diseases occur sporadically under natural conditions or are solely recognized as experimental diseases.

### Central Nervous System Lesions and Trauma

Myocardial necrosis and/or hemorrhage has been described in animals with spontaneous and experimentally induced central nervous system (CNS) lesions. King et al[651] reported 59 cases in dogs, sheep, cows, goats, pigs, and horses. Occasionally the cardiac lesions produced death by arrest or resulted in arrhythmias, but generally the cardiac damage was detected as an incidental finding at necropsy following euthanasia or natural death from irreversible CNS disease. The CNS lesions found in animals with heart lesions included trauma associated with vertebral and skull fractures, infections, and degenerative diseases. Cardiac lesions have been produced experimentally by intracranial injection of blood in mice,[652-654] rats,[655] and dogs,[656] and by electrical stimulation of stellate ganglia in dogs,[657,658] mesencephalic reticular formation in cats,[659] vagus nerve in baboons,[660,661] and hypothalamus in cats and monkeys.[662-665]

In a clinical study of 10 dogs with development of cardiac arrhythmias (premature ventricular contractions and ventricular tachycardia) from 1 to 48 hours after trauma, disseminated myocardial necrosis was observed in a dog that died 4 days after trauma.[666] Eight of 10 affected dogs had been hit by an automobile, and most of the dogs had multiple skeletal fractures.

The cardiac lesions associated with this group of injuries were multiple pale foci or streaks of necrosis and calcification with preferential involvement of the left ventricular subendocardium and left ventricular papillary muscles and left ventricular subendocardial hemorrhage. Light-microscopic and ultrastructural studies revealed myocardial necrosis with contraction bands, infiltration of mononuclear leukocytes, and proliferation of fibroblasts.

The cardiac lesions are presumed to result from sympathetic overactivity and local catecholamine release in the myocardium.[667] The myocardial lesions are similar to those produced by administration of excessive doses of catecholamines. Protection studies in mice with experimentally induced intracranial hemorrhage showed cardioprotection by reserpine (blocked catecholamine release) and partial protection by atropine, propranolol, and adrenalectomy.[654,655]

### Stress

Cardiac necroses, which occur in association with various forms of stress in animals, can be divided into two groups: those in which cardiac lesions develop without coexisting lesions in skeletal muscle and those in which skeletal muscle lesions are associated with cardiac lesions and constitute a predominant or important aspect of the clinicopathologic picture. This latter group includes the exertional rhabdomyolysis, or "capture myopathy" syndrome, and the porcine stress syndrome.

Stress-induced cardiac necroses without accompanying skeletal muscle lesions (the latter, however, may not have been specifically searched for) have been observed in immobilization or restraint in rats,[668] overcrowding in rats[669] and rabbits,[670,671] repeated small electric shocks in rats[672] and squirrel monkeys,[673-675] exposure to cold in kangaroo rats,[676] exposure to heat in rats,[677] restraint and water immersion in rats,[678,679] various emotional and painful stresses in rats,[680-683] conflictive situations in rats with borderline hypertension,[684] the stress associated with acceleration in pigs and a variety of other species,[685] auditory stimuli (tape recording of hissing cats and squealing rats) in wild rats and to a much lesser extent in domesticated rats,[686] gastric dilatation/volvulus in dogs,[32,687-689] and sudden death with focal myocardial necroses in calves.[690-692]

The cardiac lesions in rabbits subjected to overcrowding progressed to myocardial fibrosis, endocardial thickening, and ventricular dilatation. Of 44 rabbits subjected to crowding, only 9 survived more than 10 months; 20 died during the first month, and 15 died between the second and ninth months.[671] No necrosis was found in animals subjected to prolonged isolation[693]; however, these animals had a greatly increased sensitivity to the cardiotoxicity of isoproterenol,[694,695] epinephrine,[693] and d-amphetamine.[696]

Perret[697] made histologic investigations over a 10-year period on 164 lesser mouse lemurs (*Microcebus murinus*) that died spontaneously in captivity. The principal lesions found were chronic nephrosis with nephritis (which affected 90% of the animals), focal areas of myocardial necrosis or fibrosis in the left ventricular wall, various changes in the endocrine glands, and a variety of other abnormalities. Analysis of the data led to the conclusion that the whole captive population of lesser mouse lemurs suffered from a syndrome leading to renal insufficiency and premature death. Most of the pathologic changes observed in this syndrome were of the type considered to be associated with aging in mammals. Perret hypothesized that these changes were due to an overload of cortico- and medulloadrenal secretions, and that they could be induced by stress factors occurring in captivity.[697]

Gastric dilatation, with or without associated volvulus, is a potentially fatal disease of humans, dogs, and other animals.[688] Large-breed dogs are commonly affected. The mortality is high and is attributable to hypovolemic and neurogenic shock, endotoxemia, dis-

seminated intravascular coagulation with secondary fibrinolysis, acid-base and electrolyte imbalance, circulating myocardial depressant factors, and a surprisingly high incidence (42%) of cardiac arrhythmias. The latter were generally ventricular in origin (ventricular tachycardia in 23 of 48 dogs) and were considered to be due to reduced cardiac output (decreased venous return as a consequence of compression of the caudal vena cava and the portal vein by the dilated stomach). Nevertheless, of 13 dogs with gastric dilatation/volvulus, 8 had cardiac arrhythmias and cardiac necrosis with contraction bands.[689] One dog had cardiac lesions with arrhythmias; 2 had arrhythmias without lesions, and 2 had neither. Thus, myocardial damage (whether due to ischemia, to stimulation of the autonomic nervous system, or to a combination of these factors) also must be considered a potential contributing factor in the pathogenesis of these arrhythmias.

Five of 8 dogs in which experimental gastric distention was induced for 20 minutes had gross and microscopic lesions of myocardial necrosis, especially in the left ventricular myocardium, 3 days later. The lesions were evident as yellow to white subendocardial areas in the papillary muscles and free wall of the left ventricle.[687]

### Overexertion

Captured wild animals may die from stress-associated necrosis of skeletal and cardiac muscle. This syndrome has been termed capture myopathy, exertional rhabdomyolysis, and overstraining disease.[698–700] Cases have been described in nonhuman primates, 22 different African ungulates, deer, mountain goats, antelopes, seals, and flamingoes. In affected animals generalized muscle weakness and dyspnea develop. Some animals die within several hours after overexertion, most die after 2–4 days, and a few die 1–4 weeks after stressing. Necropsy reveals generalized pallor of necrotic skeletal muscles, myoglobinuria, myoglobinuric nephrosis, and multifocal myocardial necrosis. Cardiac lesions attributed to capture have been reported in some species in the absence of massive skeletal muscle necrosis.[701]

In Chacma baboons, Weber et al[702] found a high incidence of focal myocardial necroses in various stages of evolution. Adrenal cortical necroses were common in animals with cardiac lesions. Stress was considered to be an etiologic factor; however, this could not be clarified, because many of the animals in this study had been used for various surgical procedures.

Exertional rhabdomyolysis has long been recognized in horses, and myocardial necrosis may be present in fatal cases, along with skeletal muscle necrosis, myoglobinuria and myoglobinuric nephrosis.[97,103,703] Various terms have been applied to the disease, including azoturia, paralytic myoglobinuria, and exertional rhabdomyolysis. Similar lesions have also been described in cattle and sheep with transport myopathy, a syndrome produced by overexertion.[26,102] The clinical disease in horses is often precipitated shortly after the onset of muscular exertion that followed a period of several days of rest.

Focal myocardial necrosis was reported in 15–30% of nonhuman primates that underwent necropsy after death from various spontaneous diseases and experimental procedures.[701,702,704] Microscopic examination revealed myocardial necrosis with contraction bands, mitochondrial mineralization, invasion of a few mononuclear leukocytes, and resolving lesions with fibrosis. The etiology of these lesions has not been established, although a relationship to stress has been postulated.

A syndrome of sudden death with myocardial necrosis precipitated by intense, excitement, such as that produced at feeding time, has been described in calves.[680–692,705,706] The disease is sporadic but may occur repeatedly in affected herds. Affected calves are generally 1–8 weeks old and die within several minutes to several hours following the onset of dyspnea, bawling, and hemorrhagic nasal discharge. At necropsy, lesions of acute congestive failure may be seen, including pulmonary edema, hydrothorax, and hepatic congestion. Grossly, the hearts may be dilated and show pale areas of myocardial necrosis, especially in the subendocardium of the left ventricular free wall and the ventricular septum. Microscopic and ultrastructural study reveals damaged myocytes with hyaline necrosis or necrosis with contraction bands. In some cases, myocardial necrosis is not detected in paraffin-embedded hematoxylin and eosin (H&E)-stained sections but is observed in sections stained by hematoxylin–basic fuchsin–picric acid and in semithin sections of plastic-embedded tissue stained with toluidine blue. Skeletal muscle lesions have not been found, and the selenium status of other animals in affected herds was either deficient or adequate. Etiologic factors suggested have included enterotoxemia and inherited susceptibility, but as yet the syndrome must be considered idiopathic.

Myocardial necrosis may occur in pigs dying of porcine stress syndrome (PSS) or malignant hyperthermia and in swine subjected to restraint stress.[5,101,564,707–712] A high degree of heritability has been shown for PSS in several breeds, and the basic metabolic defect apparently involves abnormal $Ca^{2+}$ movement in cardiac and skeletal muscle cells. The clinical syndrome may be precipitated in susceptible pigs by administration of halothane or succinylcholine or by various emotional and physical stresses such as transportation, high am-

bient temperatures, high humidity, running, fighting, or mating. Affected pigs show exhaustion, collapse, dyspnea, hyperthermia, patchy cutaneous congestion, muscular rigidity, severe lactic acidosis, and death within minutes. At necropsy, the skeletal muscles may be pale and moist; and some pigs will show cardiac lesions of scattered pale areas in the left ventricular myocardium and epicardial and endocardial hemorrhages. Microscopic and ultrastructural studies of myocardium show either hyaline necrosis or necrosis with contraction bands.

Restraint stress, produced by administration of muscle relaxants and subsequent electrical stimulation, resulted in extensive myocardial necrosis with elevated blood catecholamine concentrations. Amygdalectomy and administration of propranolol prevented the development of cardiac lesions and the increase in catecholamine levels.[710,713] Affected hearts had pale areas of necrosis in the left ventricular free wall, with selective involvement of the inner third of the myocardium and the papillary muscles and multiple areas of epicardial, endocardial, and myocardial hemorrhage. Pharmacologic restraint induced by succinylcholine produced more severe myocardial and skeletal muscle necrosis in stress-susceptible than in non-stress-susceptible pigs.[714]

Cardiac failure precipitated by stress is increasing in frequency in modern swine after continual genetic selection for prominent carcass musculature because the PSS trait and prominent muscularity are transmitted by similar genes. The hearts of these pigs have limited reserve capacity, due, in part, to the relatively low cardiac weight.[715]

A syndrome of malignant hyperthermia also occurs in humans, most often on a familial basis, and has many clinical and pathologic similarities to the syndrome in pigs, including having stress and anesthesia (halothane and succinylcholine) as precipitating factors[716] and the occurrence of myocardial necrosis with contraction bands.[717,718]

## Radiation

Rabbits and rats exposed to single or fractionated doses (2000 rads) of roentgen radiation developed myocardial fibrosis with congestive cardiac failure.[719-729] The severity of myocardial damage was dose-dependent. Sequential morphologic studies revealed an initial acute pancarditis followed by a latent phase from 2 to 70 days after irradiation and a late phase of progressive cardiac disease after 70 days. Ultrastructural study showed selective damage to blood capillary endothelium in the myocardium. Fibrin and platelet microthrombi were present in damaged vessels, and ischemic injury was initiated in the myocardium. Slowly progressive myocardial fibrosis followed, and congestive heart failure developed terminally.

A synergistic effect of combined cardiac X-radiation and doxorubicin-induced cardiotoxicity produced myocardial damage in rabbits[719] at considerably lower cumulative doses of doxorubicin than in rabbits given doxorubicin alone.

Cardiac irradiation in dogs produced dose-related severity of cardiac damage.[730-732] Grossly, the pericardium was thickened by fibrosis. Accumulation of serosanguinous pericardial fluid resulted from vascular damage, and both atrial appendages showed hemorrhage and fibrosis. Microscopically, dose-related fibrosis was present in the epicardium, endocardium, and myocardium; and decreased capillary volume was seen in the myocardium. In a previous study of radiation injury in dogs, it was reported that selective damage with hemorrhage and fibrosis occurred in the right atrium.[733] However, this selective damage apparently resulted from a greater irradiation dose having been given to the right atrium than to the other portions of the heart.

## Electrical Defibrillation

In dogs, administration of strong shocks of intensity several times greater than threshold intensity by electrodes positioned on the thoracic wall, on the epicardium, or against the endocardium produces lesions of myocardial necrosis.[734-747] By 2 hours after shock, pale areas of myocardial necrosis are seen grossly in areas of high current density. Such areas are either adjacent to the electrodes on the serosal surfaces of the heart or within a path between the electrodes placed on the thoracic wall. By 2 days after shock, the necrotic myocardium is calcified and appears yellowish-white. Microscopically and ultrastructurally, the damaged fibers have necrosis with contraction bands and mitochondrial mineralization. Macrophagic invasion is prominent at 4 days after shock. At 2 and 8 weeks after shock, the residual lesions of shock-induced damage are focal loss of myocytes and stromal collapse.

Factors that increase the severity of shock-induced myocardial necrosis are 1) application of shocks of increased strength, 2) use of small electrodes, 3) delivery of multiple shocks, and 4) application of several shocks with short intervals between each shock.

## Acceleration Stress

In pigs exposed to acceleration stress cardiac lesions developed that were similar to those seen after restraint stress.[685,748-752] At necropsy, prominent subendocardial

hemorrhages were present in the left ventricle. The cardiac hemorrhages were more prominent in adult miniature swine than in adult conventional pigs. Microscopically, extravasated erythrocytes surrounded Purkinje fibers; and areas of necrosis with contraction bands were present in the left ventricular subendocardial myocardium, especially in the papillary muscles. The hemorrhagic lesions were prevented by propranolol, but not by atropine. The cardiac lesions may have been the result of emotional stress sustained by the pigs during the manipulations related to the acceleration procedure, because control pigs that were handled similarly but were not exposed to the acceleration had lesions that were similar to those in pigs exposed to high, sustained acceleration.[752]

Cardiac lesions have also been produced in rats and chickens exposed to acceleration stress.[753,754]

### Hemorrhagic Shock

Myocardial lesions consistently develop in dogs, cats, rabbits, pigs, and monkeys subjected to hemorrhagic shock and may play a major role in the evolution of irreversible shock.[755-762] Numerous studies in dogs have characterized the pathophysiologic and pathologic alterations involved in development of this cardiac damage. Two types of myocardial lesions are induced by shock, and the severity of the lesions is related to the duration of shock and subsequent survival time. Subendocardial hemorrhage and necrosis are concentrated in the ventricular subendocardium and are especially pronounced in the papillary muscles of both ventricles and in the middle of the ventricular septum. These lesions are related to hypoxia and are prevented by administration of hyperbaric oxygen.[761] The second type of myocardial alteration is reversible and has been termed "zonal lesions." Zonal lesions are the result of hypercontraction of cardiac muscle cells and are characterized microscopically and ultrastructurally by an organelle-free zone that is adjacent to intercalated disks and results from longitudinal displacement of the myofibrils and mitochondria.[760] Zonal lesions are more extensive and widespread in hearts than are subendocardial hemorrhage and necrosis. The zonal lesions are most frequent in the subendocardial myocardium and in the ventricular papillary muscles. Zonal lesions are not due to hypoxia and hyperbaric oxygen is not protective. However, zonal lesions are ameliorated either by administration of β-adrenergic blockers or by prevention of tachycardia by surgical production of complete heart block.[759] Several papers[755,759,762] have suggested that zonal lesions appear to be the result of mechanical injury to myocytes from the tachycardia and the small intraventricular volumes that are present in severe hemorrhagic shock.

The myocardial lesions of hemorrhagic shock vary somewhat among species. Subendocardial hemorrhage and necrosis develop in dogs, pigs, cats, and monkeys, but not in rabbits. Zonal lesions are prominent in dogs, cats, pigs, and are less obvious in rabbits, and are not present in monkeys with hemorrhagic shock.[755] These differences remain unexplained.

## Myocardial Diseases Associated With Endocrine Disorders

In animals, most of these diseases are induced experimentally but may serve as models of similar diseases that occur naturally in man. A recently recognized, spontaneously occurring disease of some importance in cats is hyperthyroidism.

### Glucocorticoid Excess

A few reports have demonstrated myocardial damage in rabbits, mice, and rats given large doses of glucocorticoids.[763-768] Heart weights were often increased. The major microscopic and ultrastructural alterations were accumulation of lipid droplets, increased numbers of mitochondria, degenerative changes in mitochondria, and myofibrillar lysis.[763,765-768] The severity of the myocardial alterations varied considerably among studies using different animal species and dose regimens of corticosteroids. Cardiac lesions have not been described in Cushing's disease of animals, although it represents an important disease of dogs. It would appear that rodents are more sensitive than humans to the cardiotoxic effects of corticosteroids.

Numerous studies have demonstrated the role of corticosteroids in the production of myocardial necrosis in rats with so-called electrolyte–steroid cardiopathy or necrotizing cardiomyopathies.[769-778] These studies have demonstrated the interaction of endocrine, nutritional, and toxic factors in cardiac injury. Exposure to many experimental stresses has produced myocardial necrosis in these studies. Such necroses appear to be mediated via a combination of excessive cardiac work and altered concentrations of endogenous catecholamines, adrenal cortical hormones, and electrolytes. In rats, similar cardiac lesions may be induced by a wide variety of exogenous manipulations, including administration of glucocorticoids, aldosterone, and various sodium salts and by producing deficiencies of potassium, magnesium, and chlorine. The production of a common cardiac lesion by these numerous manipulations suggests mediation of the injury via a common pathogenetic mechanism, such as exposure to excessive

amounts of endogenous catecholamines or potentiation of the toxic effects of these agents.

### Functional Pheochromocytomas

Pheochromocytomas occur in dogs, in which they may be functional neoplasms, and produce clinical and pathologic alterations suggestive of hypertension.[779] Affected dogs showed lethargy and weakness, periods of incoordination, cardiac arrhythmias, and respiratory distress. Vascular degenerative alterations of arteriolar sclerosis and medial hyperplasia were observed in the kidneys, lungs, and spleen. However, myocardial lesions of necrosis with contraction bands seen in human patients (see McAllister[780] for review) have not been described in animals with this tumor. In two case reports, myocardial lipidosis was described in dogs with pheochromocytomas.[781,782]

### Diabetes Mellitus

Cardiomyopathy has been reported in human diabetes patients in the absence of coronary atherosclerosis. However, the morphologic findings in these patients have not been completely correlated with the functional changes. These findings include thickening of the basement membranes of cardiac capillaries and myocytes, and microaneurysms.[780,783] Animal models utilized in the study of this myocardial disease include mice with genetically transmitted diabetes, rats with streptozotocin-induced diabetes, and dogs and rabbits with alloxan-induced diabetes.[7,783-795] Ultrastructural studies of the hearts from C57BL/KsJ db+/db+ genetically diabetic mice showed progressive damage to ventricular myocytes.[790] The initial alteration was lipidosis. Mitochondria had dense matrical material, numerous residual bodies were present, and myofibrillar lysis resulted in atrophied myocytes. Myocardial capillaries had reduplication of their external laminas. Similar alterations developed in the hearts of rats given a single dose of 65 mg streptozotocin/kg body weight.[794]

In rats with streptozotocin-induced diabetes, the myocardial lesions were markedly increased in animals with concurrent renovascular hypertension.[785-788] In animals with diabetes alone, the cardiac muscle cells had increased lipid droplets and mild focal myofibrillar lysis. In diabetic-hypertensive rats, loss of myocytes was produced, with fibrosis and proliferation of basal lamina.

Myocardium of dogs with alloxan diabetes had lipidosis but vascular lesions and myocardial fibrosis were not observed.[792] In alloxan-diabetic rabbits, myocytolysis with replacement fibrosis was described.[795]

### Hyperthyroidism

Hyperthyroidism has been described in various animal species, including the rat, cat, dog, rabbit, and guinea pig.[796-815] Cardiac hypertrophy was consistently produced and regressed after restoration of normal thyroid functional status.[811,812] Cats given l-thyroxine (0.75 mg/kg/day for 10 months) had biventricular hypertrophy with weight increases of 86% in the left ventricle and 60% in the right ventricle.[812] Light-microscopic and ultrastructural studies have demonstrated hypertrophy of cardiac muscle cells and increased numbers of mitochondria that showed densely packed cristal membranes.[801,802]

Hyperthyroidism in cats has recently been recognized as occurring frequently, and the clinical and pathologic features have been characterized. Affected cats usually have functional thyroidal adenomatous hyperplasia, but occasionally have functional thyroid adenocarcinomas. Clinically, the cats are middle- to old-aged; each sex is equally affected. They have weight loss, polyphagia, increased activity, polydipsia, polyuria, vomiting, tachycardia, and marked increases in serum $T_3$ and $T_4$ concentrations.[799,804] Congestive heart failure with pulmonary edema and pleural effusion occurred in 12% of 131 hyperthyroid cats.[805] Liu et al[800] has recently described the cardiac pathology of 23 hyperthyroid cats. Ventricular hypertrophy was symmetric in the left ventricular free wall and ventricular septum in 20 cats and asymmetric in 3 animals. Microscopic study showed myofiber hypertrophy, interstitial fibrosis, endocardial fibrosis, and fibrosis of the atrioventricular node. Disorganization of cardiac muscle cells was found in the 3 cases with asymmetric hypertrophy (ventricular septal/left ventricular free wall thickness >1.1). The cardiac alterations in these 3 cats may have resulted either from the effects of hyperthyroidism alone or from hyperthyroidism with concurrent idiopathic hypertrophic cardiomyopathy (which, as mentioned previously, is relatively frequent in cats).

Clinical hyperthyroidism is rarely seen in dogs and is difficult to produce experimentally. The condition was successfully produced in dogs given 1.2 mg/kg of l-thyroxine daily for several months; and in 13 of 30 treated dogs cardiac failure developed.[806,807]

The offspring of pregnant rats administered triiodothyroacetic acid (TRIAC), a thyroid hormone analog had hypertrophy and myofibrillar disarray of cardiac muscle cells, but only hypertrophy was seen in young rats treated with TRIAC.[797,803,815] Administration of propranolol to TRIAC-treated dams prevented the development of myofibrillar disarray, but not of the hypertrophy, in the hearts of the offspring.[797,803] The significance of these findings for the pathogenesis of hypertrophic cardiomyopathy is unclear.

### Hypothyroidism (Myxedema) in Dogs

Several of 19 dogs administered antithyroid medication for 4 to 7 years developed clinical signs of myxedema.[816] Ultrastructural study of myocardium and skeletal muscle showed marked thickening of capillary basement membranes. Myocytes had mitochondrial alterations, lipid droplet accumulation, and myelin figures.

Spontaneous cases of hypothyroidism occur frequently in dogs, but accompanying cardiac lesions have not been described.[817]

### Growth Hormone Excess

In rats implanted with a growth hormone-secreting tumor cardiomegaly develops with prominent ventricular hypertrophy.[818,819] Similar cardiac lesions occur in human patients with acromegaly.[780]

## Myocarditis

Many studies of myocarditis in animals have addressed the role of various host and infectous agent factors in the pathogenesis of the disease. In particular, many such studies have utilized experimental infection of laboratory animals with Coxsackie or encephalomyocarditis viruses. Another group of diseases with myocarditis represents naturally occurring infections in various animal species.

### Coxsackie Viral Myocarditis

Several excellent reviews have summarized the virologic and pathologic findings in viral myocarditis of humans and have also considered the results of numerous studies done in animal models of viral myocarditis.[820-827] The majority of animal studies have been done in the mouse and have utilized Coxsackie B viruses, the viruses most frequently isolated from affected human patients. Some studies have also been done with hamsters, monkeys, and chimpanzees. In mice, yellowish-white foci of myocarditis may be present on the ventricular surface. Microscopically, nonsuppurative myocarditis or perimyocarditis is present, with necrosis and calcification of myocytes. Ultrastructural studies have demonstrated viral crystals in some infected myocytes.[828] However, this is not a consistent finding. Damaged myocytes have myofibrillar lysis and mitochondrial alterations. Myocyte necrosis is followed by macrophagic invasion and phagocytosis of debris.[828-833] In animals that survive the early stages of the disease extensive myocardial fibrosis and calcification develop.[834-837] Ventricular aneurysms have been observed in mice and hamsters with late lesions.[838-840] Ventricular aneurysms also have been reported in humans with viral myocarditis.[841]

Numerous animal studies have been done to determine the effect of many variables on the severity of viral myocarditis. In studies of Coxsackie B infections in mice, the cardiac disease was enhanced by young age, male sex, pregnancy, poor nutrition, whole-body ionizing radiation, cold environmental temperatures, alcohol ingestion, exercise, cortisone administration, and in certain strains of mice.[822,826] Also, considerable variation in cardiotropism and virulence was seen between different viral isolates.

The model of Coxsackie $B_3$ viral myocarditis developed by Woodruff, Huber, and associates[842-848] in male BALB/c mice is of particular interest in that it has revealed a number of complexities in the immunologic response to viral infections of the heart. This model also has provided a system for investigating the possibility that Coxsackie viral infections are involved in the pathogenesis of chronic congestive (ventricular dilated) cardiomyopathy by inducing immunologic reactions which are directed against normal myocyte antigens and which persist after the viral infection has subsided. The histologic lesions produced by viral inoculation in this model system are very similar to those found in the human disease. Evidence has been presented to show that in this model most of the cardiac injury is produced by an immune, rather than by viral, mechanism: 1) cardiac cellular necrosis starts after the concentration of virus in the myocardium has begun to decrease; 2) virus is not detected in myocardium at the time when cellular and humoral immunity are maximal; and 3) studies on variant strains of Coxsackie $B_3$ and $B_4$ suggest that viral replication in the heart is not a direct cause of the necrosis. Cytolytic T lymphocytes from mice inoculated with Coxsackie $B_3$ virus have been found to lyse primary cultures of both virus-infected and noninfected myocytes. Huber and Lodge[846] demonstrated the existence of two distinct populations of cytolytic T lymphocytes in the infected animals. One population preferentially absorbed to and lysed uninfected myocytes (autoreactive cytolytic T lymphocytes), whereas the other absorbed to and lysed virus-infected myocytes (virus-specific cytolytic T lymphocytes). Neither population of cells adsorbed to monolayers of HeLa, L929, or umbilical cord endothelial cells or to myocytes infected with a related but nonmyocarditis variant of Coxsackie $B_3$. Inoculation of T-lymphocyte-deficient mice with the virus failed to induce significant myocarditis, even though equivalent concentrations of virus were isolated from the hearts of T-lymphocyte-deficient and control animals. Both autoreactive and virus-specific cytolytic T lymphocytes induced myocarditis *in vivo*,

but the lesions produced by the autoreactive cells were more extensive and necrotizing than those produced by virus-specific cells. Thus, these results support the hypothesis that Coxsackie $B_3$-induced myocarditis results in part from autoimmunity to myocyte antigens. It remains to be determined whether these mechanisms become operational in myocarditides induced by other types of viruses.

### Encephalomyocarditis Viral Myocarditis in Pigs, Primates, and Mice

Spontaneous outbreaks of encephalomyocarditis virus (EMCV) infection occur in swine and nonhuman primates.[108,849-853] Initially described in 1945 in gibbons and chimpanzees, the disease was recognized in swine in 1958 in Panama, in 1960 in Florida, and in 1970 in Australia and New Zealand. Rats serve as the reservoir host of infection. Young pigs are particularly susceptible and die unexpectedly of acute cardiac failure. At necropsy, effusions with or without small amounts of fibrin are found in the body cavities. The affected hearts are dilated, and scattered white streaks are present in the right ventricular myocardium. Microscopically, lymphocytic myocarditis is found, with myocyte necrosis and calcification. Pigs that survive beyond the acute phase of the disease have scattered areas of resolving necrosis that initially appear as red highly vascular streaks and eventually form white fibrous scars. Inclusion bodies are not present.

Experimental infection of mice by the M variant of EMCV resulted in necrotizing myocarditis on Days 5–14, deaths with lesions of congestive heart failure on Days 10–14, and myocardial fibrosis on Days 28 and 90.[854-857] Ultrastructural findings in infected mice included early nuclear alterations, occasional viral crystals, myocyte necrosis, and inflammatory cell infiltration (Figure 75).[829,857-859] These workers have proposed the experimental disease in the mouse as a suitable model for congestive cardiomyopathy. Attempts to produce myocarditis in various mouse strains showed that A/J and C57BL were resistant and BALB/c, C3H, and DBA were susceptible.[860] Right ventricular aneurysms which were considered morphologically similar to the findings in right ventricular dysplasia or Uhl's anomaly were occasionally seen in mice 8–10 months after infection.[861]

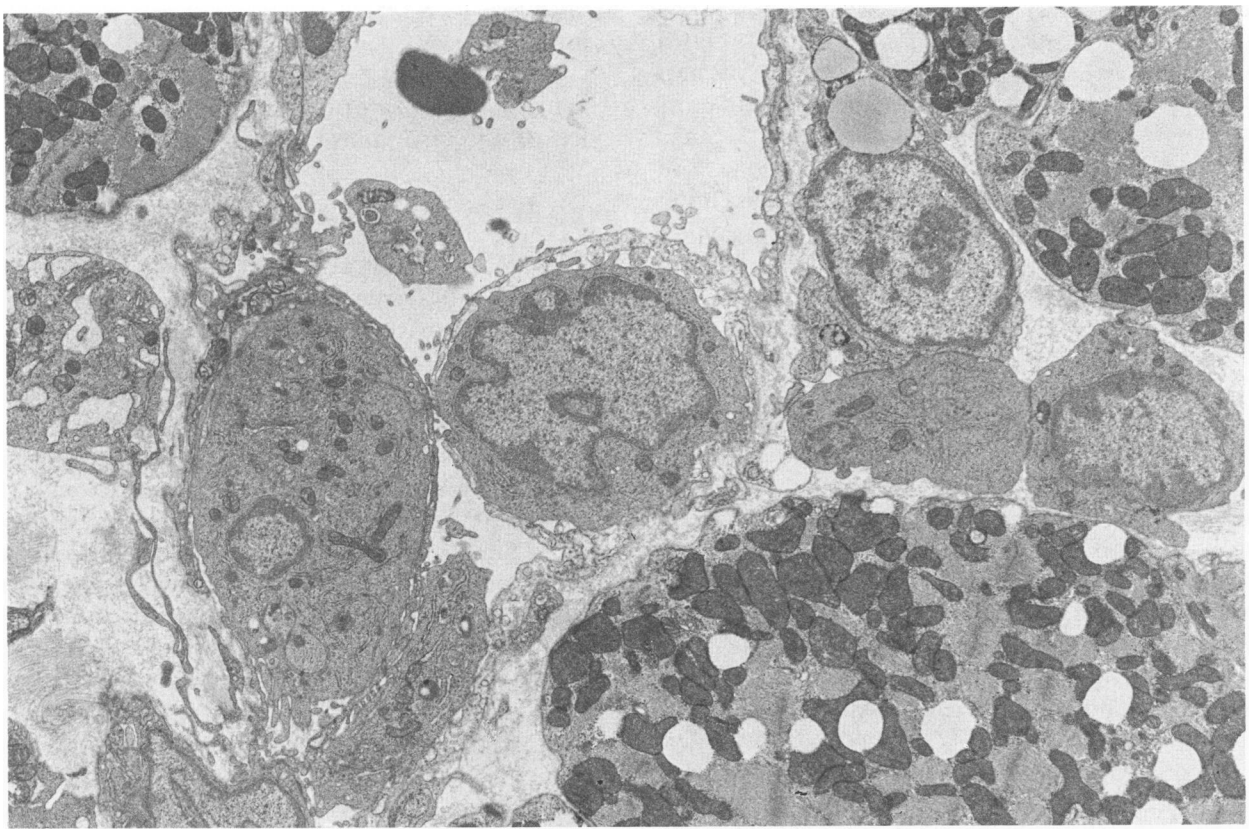
### Canine Parvoviral Myocarditis

This disease is relatively new; outbreaks were first recognized in 1978.[862] Manifestations in affected dogs usually are hemorrhagic diarrhea and vomiting associated with a viral-induced necrotizing enteritis. Similar enteric lesions are present in cats with infection by feline parvovirus, which is antigenically similar to the canine parvovirus but does not infect dogs. Myocarditis develops in approximately 5% of dogs with parvovirus infection. Dogs with the cardiac form of the disease are generally free of enteric lesions, although in some animals cardiac disease develops several weeks after recovery from the enteric disease.

It has become apparent that several syndromes may develop in dogs with parvoviral myocarditis.[863-872] In the peracute form that is seen most frequently, several puppies in a litter are affected suddenly with dyspnea and either die soon after clinical signs of disease are observed or may be found dead without any premonitory signs. Necropsy reveals lesions of acute congestive failure with pulmonary edema, hepatic congestion, ascites, and hydrothorax. The heart is dilated and diffusely pale or may have discrete white streaks in the ventricular myocardium. Histopathologic alterations in the myocardium are diagnostic and consist of diffuse lymphocytic myocarditis and scattered myocytes with large basophilic intranuclear inclusion bodies. Occasional necrotic myocytes are present. Increased numbers of fibroblasts are present in the interstitium.

In the delayed-onset clinical form congestive heart failure may develop rapidly with underlying chronic parvoviral myocarditis. Most cases have been approximately 5 months old and were littermates of puppies that suffered clinical signs of parvovirus infection, often fatal, at 3–8 weeks of age. Necropsy reveals lesions of congestive heart failure with pulmonary edema, hepatic congestion, ascites, and hydrothorax. The hearts are dilated and scattered white streaks of myocardial fibrosis are apparent beneath the ventricular epicardium. Microscopically, scattered foci of necrosis are present without accompanying leukocytic infiltration or viral inclusion bodies.

In a litter of puppies experimentally given injections *in utero* 8 days before parturition, 2 puppies died unexpectedly at 3–4 weeks of age with acute parvoviral myocarditis, and 2 puppies remained clinically normal but had multifocal chronic myocarditis without inclusion bodies when euthanized at 3 and 4½ months of age.[873] In another report, 3 clinically normal 6–8-month-old beagle dogs with high serum titers indicative of previous natural infection with parvovirus were found to have electrocardiographic alterations when screened for use in drug safety studies. The dogs were necropsied and had scattered gray streaks in the ventricular myocardium. Microscopically, multifocal chronic myocarditis was present with myocyte degeneration, fibrosis, and sparse infiltrates of lymphocytes and plasma cells.[874] Experimental infection of 5-day-old pups produced myocyte degeneration and necrosis with inclu-



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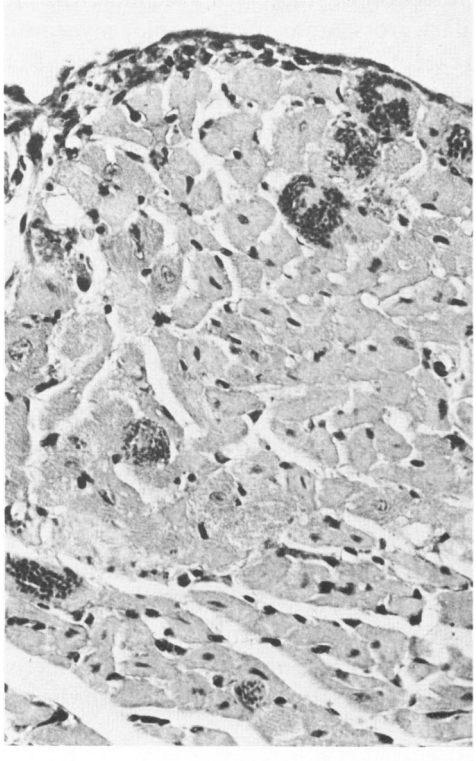

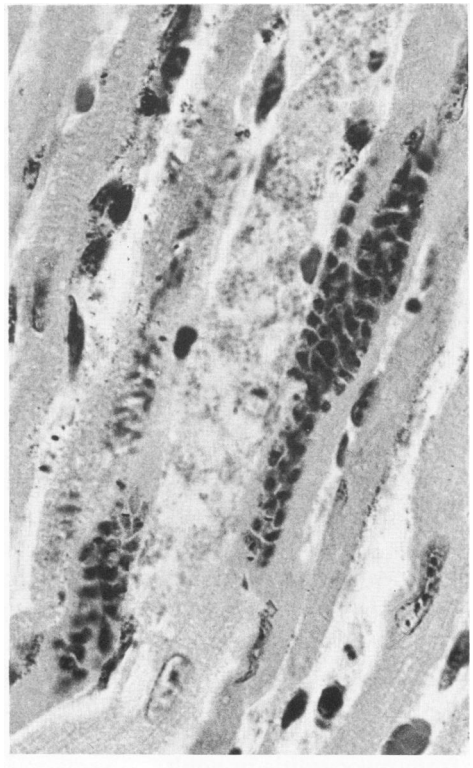

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**Figure 75**—Encephalomyocarditis viral myocarditis. Mouse. Left ventricular subendocardium 10 days after experimental infection with EMC virus, showing endothelial cell damage, interstitial edema, accumulation of lipid droplets in myocytes, and lymphocytic infiltration. (×9000) **Figure 76**—*T cruzi* myocarditis. Mouse. Clusters of darkly stained parasites are present within left ventricular myocytes. Inflammatory reaction is mild. (Giemsa, ×250) **Figure 77**—*T cruzi* myocarditis. Mouse. High-magnification view showing myocyte necrosis and amastigotes of *T cruzi* within the cytoplasm of other, adjacent myocytes. (Giemsa, ×1000) **Figure 78**—*T cruzi* myocarditis. Mouse. Intracellular parasites have differentiated from amastigotes to trypanosomes, assuming elongated shapes. (Giemsa, ×1000)

sion bodies at 4 weeks after infection, lymphocytic myocarditis at 8 weeks, and multifocal myocardial fibrosis at 16 weeks.[875] A third clinical presentation of canine parvoviral myocarditis was described recently with development of fatal acute myocarditis, with inclusion bodies, in an adult 3½-year-old dog.[876] The dog initially developed fever, lethargy, and vomiting, and died unexpectedly on the eighth day of the illness.

### Other Canine Viral Myocarditides

Young puppies that die with multisystemic lesions of canine distemper may have myocarditis. Cardiac lesions developed in puppies that were infected experimentally at 5–7 days of age but not those which were infected at 10–21 days of age.[877] Grossly, scattered pale foci were observed. Microscopically, focal necrosis, with or without calcification, and minimal inflammatory cell infiltration were present. Electron-microscopic study showed infected myocytes with occasional sarcoplasmic inclusion bodies that contained aggregates of virus particles.

Experimental intrauterine infection of puppies during the second trimester of pregnancy with canine herpesvirus (CHV) resulted in fetal and perinatal deaths with disseminated lesions of CHV infection. Focal necrotizing myocarditis with intranuclear inclusion bodies was present.[878]

Infection with the herpesvirus of pseudorabies in naturally infected swine and in experimentally infected dogs and cats may result in multifocal necrotizing myocarditis.[879]

### Foot-and-Mouth Disease Viral Myocarditis

Foot-and-mouth disease (FMD) is a disease of domesticated and wild cloven-footed animals and is of great historic and international importance.[103,880] Currently the disease does not exist in North America, Central America, Australia, or New Zealand; and rigorous regulatory procedures are followed to prevent entry of infected animals into these areas. The causative virus is a picornavirus. Generally, the disease in adults produces high morbidity with mucocutaneous vesicular lesions, but mortality is low. However, myocarditis develops frequently in affected young calves, lambs, pigs, and goats, and 50% mortality may result. In some cases, outbreaks caused by FMD virus type C also have produced a high mortality from myocarditis in adult animals.

Gross lesions in the heart are multiple pale streaks in the ventricular myocardium, resulting in the term "tiger heart." The atria are only rarely affected. Microscopically, lymphocytic myocarditis is present, with hyaline necrosis and scattered neutrophils. Similar cardiac lesions are produced by experimental infection of mice and guinea pigs.

### Other Viral Myocarditides in Laboratory Animals

Myocarditis was produced in mice by experimental infections with adenovirus, reovirus, vaccinia virus, and herpes simplex virus.[881–884] Adenoviral myocarditis was characterized by scattered pale foci in the myocardium with hydropericardium and hydrothorax. Microscopically, multifocal nonsuppurative myocarditis with myocardial necrosis and calcification and intranuclear viral inclusion bodies were present. Mice infected with herpes simplex Type 1 and 2 had more severe disease in sucklings than in weanlings. Myocardial lesions included focal necrosis with scant inflammatory reaction and intranuclear viral inclusion bodies in several cell types, including cardiac muscle cells. In reovirus-infected mice, gray–yellow foci were scattered in the ventricular myocardium. Histologically, multifocal nonsuppurative myocarditis was accompanied by myocardial necrosis and calcification, interstitial fibrosis, and intracytoplasmic eosinophilic viral inclusion bodies. Experimental infection of mice with vaccinia virus produced similar gross and microscopic myocardial alterations, except that inclusion bodies were not observed by light microscopy (although viral particles were seen in myocytes by electron microscopy).

Rocio virus, an arbovirus associated with outbreaks of human encephalitis in South America, produced extensive myocardial necrosis with infiltration of mononuclear leukocytes in experimentally infected suckling hamsters.[885] Damaged myocytes were seen to contain numerous virus particles by electron microscopy. Myocardial lesions have also been described with infection by St. Louis encephalitis virus in suckling hamsters[886] and by Venezuelan equine encephalomyelitis virus in newborn mice.[887]

A febrile disease with myocardial lesions developed in rabbits experimentally infected with an agent thought to be a coronavirus.[888] Grossly, multiple red foci were seen throughout the epicardium and endocardium, and hydrothorax was present. Microscopically, multifocal myocardial necrosis with minimal accompanying inflammatory reaction was observed. Electron microscopy failed to demonstrate viral particles in the hearts.

### Viral Myocarditides in Birds

A disease occurred in geese in Europe that was termed infectious myocarditis or goose influenza.[889] Intranuclear inclusion bodies were present in cardiac muscle cells. The causative virus was characterized as a par-

vovirus. A single outbreak of myocarditis, with accompanying intranuclear inclusion bodies in myocytes, was described in adult chickens at a research facility in Maryland.[890] The affected birds died unexpectedly with ascites. The hearts were pale grossly and had diffuse lymphocytic myocarditis with Feulgen-positive intranuclear inclusions in myocytes. Ultrastructural study showed virus particles 18–20 nm in diameter suggestive of parvovirus.

In chicks with experimentally induced avian encephalomyelitis, diffuse lymphocytic myocarditis was consistently present in the atria and affected the ventricular myocardium less frequently.[891]

Chicks experimentally infected with an arthritis-inducing reovirus that was recovered from an adult chicken had extensive myocarditis, with infiltration of heterophils and mononuclear leukocytes.[892]

Focal nonsuppurative myocarditis was present in chickens with experimental infection with Newcastle disease.[893]

Myocarditis was a frequent finding in an outbreak of Eastern and Western encephalitis in chukar partridges in Florida. The affected hearts had multiple pale myocardial foci grossly and, microscopically, nonsuppurative myocarditis.[894]

Turkeys with experimental influenza A infection developed multifocal myocarditis.[895] Multiple pale foci were evident grossly in the myocardium. Extensive ultrastructural alterations in myocytes were described, with myofibrillar lysis, mitochondrial alterations, and sarcolemmal disruption.

### Myocarditis in Tyzzer's Disease

Prominent myocardial lesions have been reported in several outbreaks of Tyzzer's disease in mice, rabbits, rats, and hamsters.[896–900] The gross lesions varied from bulging, large (0.2–0.5 cm in diameter) white foci in the myocardium of affected weanling Syrian hamsters to thin pale streaks in the left ventricular apical myocardium of nursing rabbits.[896,900] Microscopically, degeneration and necrosis of myocytes was accompanied by a mixed inflammatory cell infiltrate. Intact organisms of *Bacillus piliformis* were demonstrated in cardiac muscle cells by light and electron microscopy.[899]

### Toxoplasmal Myocarditis

Toxoplasmosis occurs in a wide range of animal hosts. In clinical cases, disseminated lesions are often found in the myocardium. Cardiac lesions are described most commonly in dogs and cats. Scattered pale foci are seen grossly, and the microscopic findings are necrotizing myocarditis with scattered pseudocysts.[901] In experimentally infected mice, multifocal myocardial necrosis with infiltration of mononuclear leukocytes was seen.[902]

### Trypanosomal Myocarditis (Chagas' Disease)

Trypanosomiasis (Chagas' disease) is an important disease in animals in South America and is enzootic in wild animals in the southern United States.[903] The experimental disease has been produced in mice, rabbits, monkeys, and dogs.[904–913] Affected dogs in a Texas study died with evidence of right ventricular failure.[914] The hearts had right ventricular and right atrial dilation with scattered pale foci in the myocardium. Microscopically, the lesions were those of necrotizing granulomatous myocarditis associated with scattered intracellular and extracellular amastigotes of *Trypanosoma cruzi*. In dogs with experimental chronic disease, microscopic lesions were demonstrated in the conduction system as well as in ordinary myocardium.[905,906]

In experimental infection of mice, gross findings included cardiomegaly with right ventricular dilation, mural thrombi in the right atrium and right ventricle, hydrothorax, and pulmonary and hepatic congestion.[909,911,915] Microscopically and ultrastructurally, acute myocarditis with necrosis, neutrophilic infiltration and intramyocytic pseudocysts containing amastigotes were seen until 50 days after infection (Figures 76–79). Fibrosis accompanied by histiocytic invasion was present after 50 days, with the most severe damage in the right ventricular myocardium.

## Summary

In this review we have attempted a comprehensive compilation of the cardiac morphologic changes that occur in spontaneous and experimental myocardial diseases of animals. Our coverage addresses diseases of mammals and birds and includes these diseases found in both domesticated and wild animals. A similar review of the myocardial diseases in this broad range of animal species has not been attempted previously. We have summarized and illustrated the gross, microscopic, and ultrastructural alterations for these myocardial diseases; and, whenever possible, we have reviewed their biochemical pathogenesis.

We have arranged the myocardial diseases for presentation and discussion according to an etiologic classification with seven categories. These include a group of idiopathic or primary cardiomyopathies recognized in man (hypertrophic, dilated, and restrictive types) and a large group of secondary cardiomyopathies with known causes, such as 1) inherited tendency; 2) nutritional deficiency; 3) toxicity; 4) physical injury

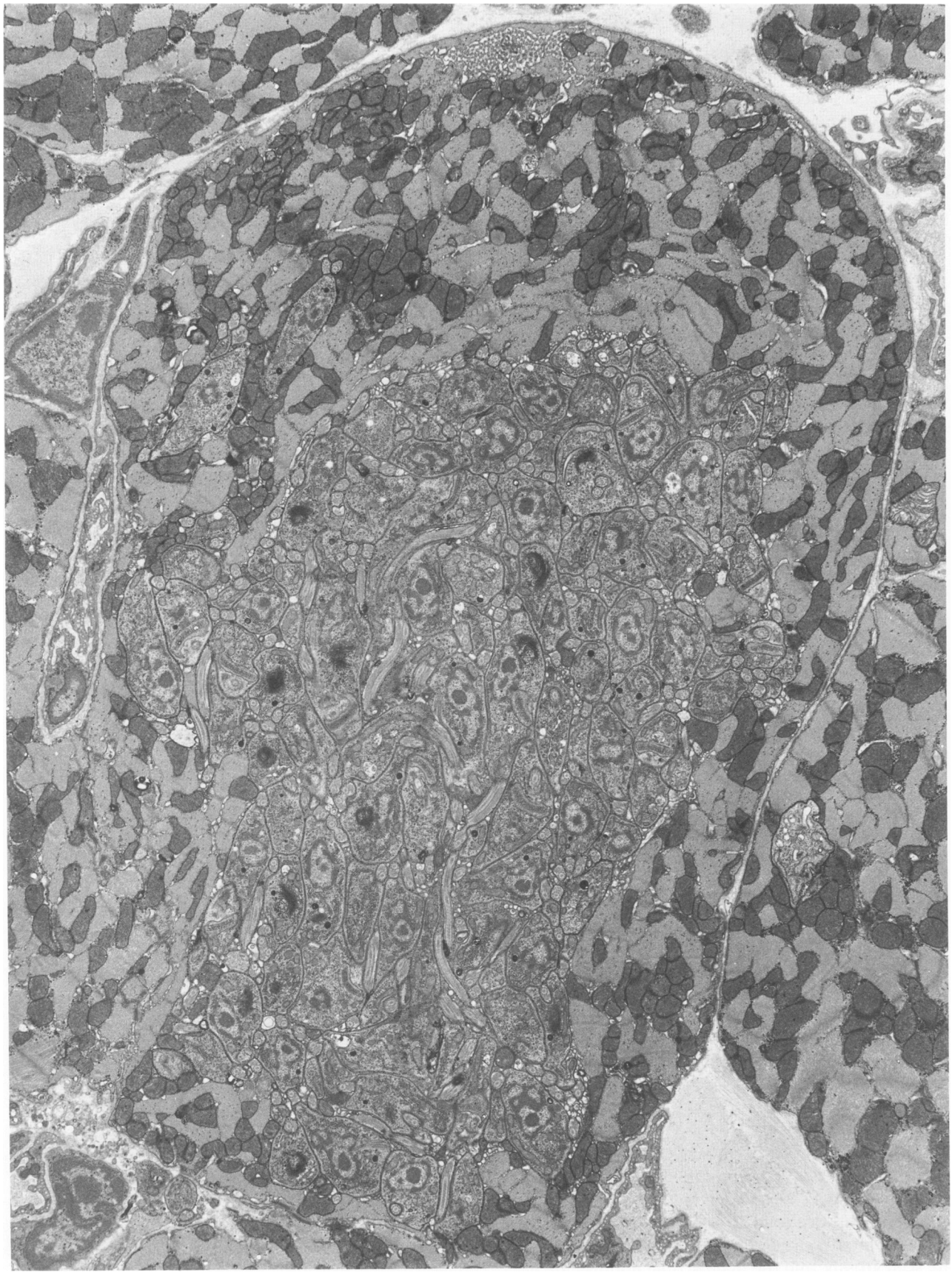

**Figure 79**—*T cruzi* myocarditis. Mouse. Low-magnification electron micrograph showing transverse section of a myocyte that contains numerous amastigotes of *T cruzi* that are beginning to differentiate into trypanosomal forms. Note the lack of structural abnormalities in cytoplasmic organelles of the invaded myocyte. One single parasite in evident in the cytoplasm of another myocyte (*lower right*). (×6000)

and shock; 5) endocrine disorders, and 6) myocarditides of viral, bacterial, and protozoal causation. Considerable overlap exists between each of the etiologic groups in the spectrum of pathologic alterations seen in the myocardium. These include various degenerative changes, myocyte necrosis, and inflammatory lesions. However, some diseases show rather characteristic myocardial alterations such as vacuolar degeneration in anthracycline cardiotoxicity, myofibrillar lysis in furazolidone cardiotoxicity, calcification in calcinosis of mice, glycogen accumulation in the glycogenoses, lipofuscinosis in cattle, fatty degeneration in erucic acid cardiotoxicity, myofiber disarray in hypertrophic cardiomyopathy, and lymphocytic inflammation with inclusion bodies in canine parvoviral myocarditis.

The myocardial diseases represent the largest group in the spectrum of spontaneous cardiac diseases of animals. Pericardial and endocardial diseases and congential cardiac diseases are seen less frequently; and, in contrast to man, coronary artery disease and myocardial ischemia are rather infrequent in animals. The present review shows clearly that the spectrum of myocardial diseases in animals is enlarging and that many newly recognized diseases are emerging and assuming considerable importance. For example, various heritable cardiomyopathies have recently been described in the KK mouse, cattle, and rats. Increasingly recognized myocardial diseases include cardiomyopathies in cats, dogs, and birds; anthracycline cardiotoxicity; furazolidone cardiotoxicity; ionophore cardiotoxicity; myocardial damage associated with central nervous system injuries; myocardial hypertrophy in hyperthyroid cats; and parvoviral myocarditis in dogs.

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