MEDICAL GRAND ROUNDS AT PARKLAND MEMORIAL HOSPITAL

May 20, 1976

MYOCARDIAL DISEASES

("Cardiomyopathy", "Myocardiopathy")

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Anatomic Types of Cardiomyopathy

(Roberts and Ferrans)

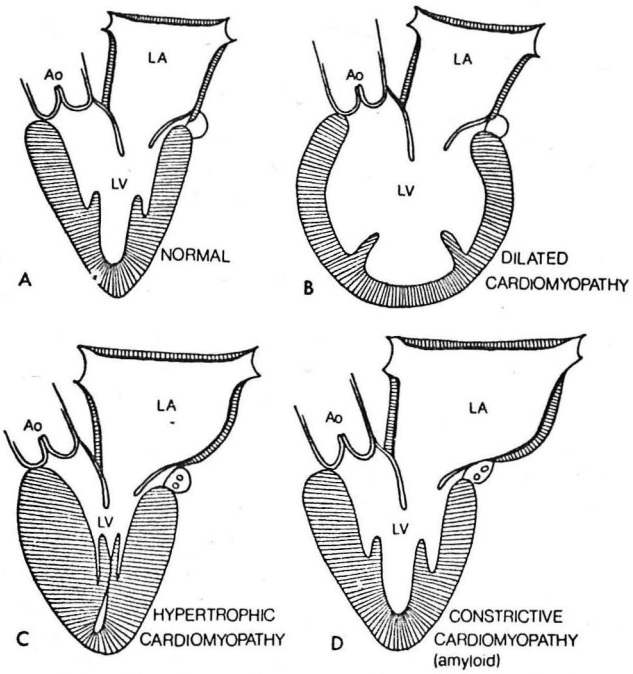

Diagram illustrating the various types of cardiomyopathies, compared to the normal, discussed herein. In the hypertrophic type of cardiomyopathy the left ventricular cavity is small, and in the constrictive variety, as illustrated by amyloidosis, the left ventricular cavity is of normal size. In the dilated type the largest circumference of the left ventricle is not at its base but midway between the apex and base.

Myocardial diseases refers to that group of disease processes in which myocardial muscle has been damaged in such a manner as to result in regional or generalized abnormalities in cardiac muscle function. For purposes of this discussion ischemic (coronary artery induced), hypertensive and primary valvular or shunt causes of myocardial disease are excluded and we will concentrate on the non coronary artery disease conditions that are generally referred to as "myocardiopathy", "primary myocardial disease", and/or "cardiomyopathy". Cardiomyopathy is defined as heart muscle dysfunction resulting from either unknown or unusual etiology, and not due to previous rheumatic fever, hypertension, coronary and/or thyroid disease or congenital heart disease. The term "cardiomyopathy" was introduced by Brigden (1) in 1957 and subsequently Mattingly (2) suggested the term primary myocardial disease to define conditions that effect the heart muscle producing abnormalities of myocardial function, but sparing other anatomic structures within the cardiovascular system. Primary myocardial disease includes diseases of both known and unknown origin, pathogenesis and/or association, and it can be divided into two major categories: inflammatory and non-inflammatory conditions. The former is generally produced by infectious agents and is called myocarditis. Other terminology which has been utilized includes the terms "primary" and "secondary" cardiomyopathies (3-6). Primary cardiomyopathy may be regarded as diseases that affect the myocardium alone and/or of unknown etiology. Secondary cardiomyopathy refers to that situation in which the heart is affected with other organ systems in a systemic disease and in which the cause is known but not always fully understood. This particular terminology of cardiomyopathies has not yet received general acceptance.

In addition to problems of terminology and classification, the difficulty of diagnosis is the major reason for our incomplete understanding and often imprecise recognition of cardiomyopathies. Clinically apparent myocardial disease may or may not be accompanied by pathognomonic histopathological changes; in many instances, however, it is impossible or difficult to obtain myocardial tissue for histological analysis. Clinicians all too frequently label heart failure as being due to hypertensive or coronary heart disease when in fact in many instances this is not the case. Goodwin (7) has differentiated four main

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1. Brigden W: Uncommon myocardial diseases. The non-coronary cardiomyopathies. Lancet II:1179-1184, 1243-1249, 1957.
2. Mattingly TW: Clinical features and diagnosis of primary myocardial diseases. Mod Concep Cardiovas Dis 30:677-682, 683-686, 1961.
3. Korb G: Heart diseases of unknown etiology. Problems of terminology and classification. In, Advances in Cardiac Structures and Metabolism, Bajusz E and Rona G with A. Brink and A. Lochner (editors), Cardiomyopathies, Vol. 2, Baltimore, University Park Press, 1973, pp 9-16.
4. Fejfar Z: Definition and classification of the cardiomyopathies. Pathol Microbiol 35:17-25, 1970.
5. Mattingly TW: Diseases of the myocardium (cardiomyopathies); the viewpoint of a clinical cardiologist. Editorial. Am J Cardiol 25:79-80, 1970.
6. Hudson REB: The cardiomyopathies: Order from chaos. Am J Cardiol 25:70-77, 1970.
7. Goodwin JF: Congestive and hypertrophic cardiomyopathies. A decade of study. Lancet I:731-739, 1970.

types of primary cardiomyopathies: the congestive, hypertrophic, constrictive (restrictive) and obliterative forms.

Congestive cardiomyopathies probably represent a multi-causal group in which low cardiac output is associated with marked dilatation of all of the chambers of the heart; hypertrophy may develop as a compensatory adjustment but it is overshadowed by generalized cardiac enlargement which is predominantly the result of dilatation. Hypertrophic cardiomyopathy has a well documented genetic background now; the hypertrophied left ventricle and reduced left ventricular cavity explain the reduced left ventricular compliance. Obstruction of left ventricular outflow may occur (idiopathic hypertrophic subaortic stenosis). In a constrictive form, myocardial rigidity results in the restriction of diastolic filling. In the obliterative cardiomyopathies, fibrosis leads to obliteration of left ventricular cavity and atrioventricular incompetence. Although the evolution of these various diseases is different, the end results are the same in all forms in that they tend to produce congestive heart failure, atrial or ventricular arrhythmias and/or pulmonary, systemic or coronary embolism. More recently, Goodwin (8) has redefined cardiomyopathies as heart muscle diseases of unknown cause but has concentrated on only two general forms, the congestive and the hypertrophic cardiomyopathies.

My personal feeling is that we should presently retain 3 separate categories for primary myocardial disease, the congestive cardiomyopathy, the obstructive cardiomyopathy (IHSS) and the restrictive or constrictive form of myocardial disease (amyloidosis, hemochromatosis, endomyocardial fibroelastosis).

The various types of myocardial disease are recognized or suspected by virtue of their producing clinical abnormalities including some of those listed in Table 1.

TABLE 1

Clinical Problems Resulting from Myocardiopathies

1. Emboli (systemic, pulmonary, coronary and/or cerebral)

2. Arrhythmias (either ventricular or supraventricular; in some instances these are responsible for a patient's demise)

3. Heart block (first degree, advanced AV junctional block and/or bundle branch block)

4. Congestive heart failure (either left or right ventricular failure, combination of the two or heart failure in which right ventricular dysfunction predominates)

5. Chest pain (in some instances this pain sounds as if it is angina pectoris, but in others is atypical chest pain that is poorly described and not specifically related to exercise, emotion, cold exposure or eating). It is important to be certain that the chest pain is not a reflection of

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8. Goodwin JF: Cardiomyopathies in England. In, Advances in Cardiac Structures and Metabolism, Bajusz E and Rona G with A. Brink and A. Lochner (editors), Cardiomyopathies, Vol. 2, Baltimore, University Park Press, 1973, pp 79-93.

pulmonary embolic disease or of pulmonary arterial hypertension occurring as a consequence of either recurrent pulmonary emboli or of severe left ventricular failure.

1. Embolization

Patients with cardiomyopathy have a definitely increased incidence of systemic arterial and pulmonary embolic disease. The incidence of recognized systemic arterial emboli is as high as 60-70% in some series. In particular, patients with "congestive cardiomyopathy" with both left and right ventricular failure and generalized cardiac enlargement (including left atrial, left ventricular, right ventricular and right atrial enlargement) may abruptly develop evidence of lower extremity arterial embolization, a cerebrovascular accident as a consequence of major cerebral arterial occlusion from embolization or an acute myocardial infarction, congestive heart failure, shock, and/or atrial or ventricular arrhythmias occurring as a consequence of coronary artery embolization. In many instances it is felt that a large dilated left atrium coupled with reduced myocardial contractility sets the stage for the development of thrombi in the left atrium. It is presumed that relatively "sluggish" flow in such a dilated heart is responsible for the development of atrial thrombosis. Some patients with cardiomyopathy also have atrial arrhythmias either intermittently or persistent ones and this may also predispose to the development of thrombus formation in the left atrium. Whether or not there is any primary alteration in platelet aggregability and/or any other important hematological or systemic factor responsible for intracardiac thrombus formation in patients with cardiomyopathy is presently uncertain.

2. Heart Block and Arrhythmias

Atrial rhythm disturbance occur in patients with the various forms of myocardial disease commonly. Its presence in a patient with a large dilated heart should make one always consider the possibility that cardiomyopathy is the etiology for heart failure and the arrhythmia. Frequent atrial premature beats, atrial flutter and/or paroxysmal tachycardia may also occur.

Frequent ventricular premature beats and death related to the development of ventricular tachycardia or ventricular fibrillation are also unfortunately all too common in patients with cardiomyopathy. Indeed, this is likely the explanation for demise in the majority of patients with heart muscle disease. The presence of frequent ventricular premature beats is a nonspecific finding, of course, and may be due to electrolyte abnormalities, blood gas abnormalities, drug excess (such as digitalis), be associated with heart failure, and/or be a reflection of the cardiomyopathy. While premature ventricular beats are relatively nonspecific in terms of their etiology when they occur with a frequency of greater than 10 per minute, when they are multifocal, when they occur on or close to the apex of the T wave and when they occur in runs (3 or more VPBs in a row represents ventricular tachycardia) they deserve drug suppression since it is known that ventricular premature beats of the types just described do represent a risk to life in patients with underlying heart disease.

Bundle branch abnormalities (left bundle branch block and right bundle branch block and/or bilateral bundle branch block) occur also with frequency in patients with cardiomyopathy. Their presence is, in most instances, a reflection of myocardial cell death or infiltration by amyloid, iron, calcium, or an inflammatory process that has interrupted either a major bundle branch or one of its fascicles. Advanced atrioventricular block including Mobitz II and complete heart block may also occur in patients with cardiomyopathy; this is often a reflection of either infiltrative or degenerative disease either in the AV junction or within the ventricle. Mobitz I heart block (Wenckebach heart block) may also occur in myocardial disease but one needs to strongly consider the possibility of digitalis excess in patients taking cardiac glycosides as a more likely possibility.

3. Congestive Heart Failure

Some of the possible mechanisms responsible for the development of congestive heart failure and for impairing myocardial contractility with cardiomyopathy are listed in Table 2.

TABLE 2

Potential Causes of Congestive Heart Failure in Patients with Myocardiopathies

1. Inflammatory destruction of cardiac muscle.

2. Infiltration and replacement of cardiac muscle by amyloid, glycogen, iron, etc.

3. Biochemical injury of cardiac muscle resulting from chemical or physical agents or metabolic deficiencies.

4. Restrictive defects interfering with relaxation and filling of the ventricles (such as might occur with amyloid or iron replacement of heart muscle or with fibrous tissue replacement of heart muscle).

5. Left ventricular outflow obstruction during ejection resulting from muscle hypertrophy particularly asymmetric septal hypertrophy (idiopathic hypertrophic subaortic stenosis or its synonymous term ASH).

6. ?? Abnormalities in excitation-contraction coupling resulting from destruction or infiltration of cardiac muscle or the consequence of biochemical injury from chemical or physical agents or metabolic deficiencies (9-13).

   a) Abnormalities of calcium transport across the cell membrane possibly resulting from alterations in "slow channel" calcium transport, alterations in the sodium, potassium ATPase cell membrane receptor, destruction of certain portions of the cell membrane, and/or alterations in serum calcium levels, systemic arterial pH, blood gases, i.e., with hypoxia and/or other electrolyte alterations.

b) Abnormalities in sarcoplasmic reticulum uptake and/or release of calcium.

c) Potentially, abnormalities in calcium accumulation at the myofilaments, myosin ATPase alterations and/or physical chemical abnormalities in actin-myosin crossbridge formation.

7. Certain cardiac rhythm abnormalities and/or heart block.

Excitation-Contraction Coupling

At this point a brief review of excitation-contraction coupling in the heart is in order. The role of calcium in normal cardiac physiology was first appreciated by Sidney Ringer (14) who reported that ionic calcium is required to sustain the beat of the heart in vitro. At the time this observation was made it was interpreted to mean that the cardiac cell membrane was calcium sensitive, but that there was an unusual dependence of heart muscle upon external calcium did not become evident until later. In 1907, Locke and Rosenheim (15) reported that the action potential of the isolated perfused heart persisted long after contractility had diminished suggesting that calcium played another role in the heart in addition to maintaining membrane competence. Subsequently, Heilbrun et al (16) demonstrated that microinjections of calcium in the muscle cells could initiate contraction. Thus, it has been evident since 1947 that excitation-contraction coupling in the heart appeared to involve calcium ions. Subsequently, other investigators have shown that peak tension in the frog heart is dependent upon external calcium in the range of 0-4 mM and that polarization of the cardiac membrane is less dependent upon calcium than upon sodium, potassium and proton concentrations (17). In 1959 Bianchi and

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9. Grossman A, Furchgott RF: The effects of various drugs on calcium exchange in the isolated guinea pig left auricle. J Pharmacol 145:162, 1965.
10. Katz AM: Contractile proteins of the heart. Physiol Rev 50:63, 1970.
11. Janke J, Jaedicke W, Fleckenstein A: Prevention of isoproterenol induced cardiac necrosis by reduction of transmembrane calcium influx with the use of potassium and magnesium salts or of calcium antagonistic inhibitors of excitation-contraction coupling. Pflügers Arch ges Physiol 319:R8, 1970.
12. Herrell WE: Beer and cobalt in cardiohepatic failure. Clin Med 74:15, 1967.
13. Klaus W, Lee KS: Influence of cardiac glycosides on calcium binding in muscle subcellular components. J Pharmacol 166:68, 1969.
14. Ringer S: A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. J Physiol 4:29, 1882.
15. Locke FS, Rosenheim O: Contributions to the physiology of the isolated heart. The consumption of dextrose by mammalian cardiac muscle. J Physiol 36:205, 1907.
16. Heilbrun LV, Wiercinski FJ: The action of various cations in muscle protoplasm. J Cell Comp Physiol 29:15, 1947.
17. Nayler WG: A study of the staircase and ventricular muscle and its relationship to the inotropic activity of certain drugs. J Gen Physiol 44:393, 1960.

Shanes (18) showed that calcium uptake studied with ^{45}Ca increased progressively in skeletal muscle during repetitive contractions. Subsequently, Winegrad and Shanes (19), Niedergierke (20), Langer (21) and Grossman and Furchgott (22) showed that the same phenomenon could be demonstrated in cardiac muscle and that in this tissue the resting uptake of calcium of 0.009 $\mu M/cm^2/sec$ could be augmented with repetitive contractions to 0.11 $\mu M/cm^2/sec$, or a twelve fold increase in calcium entry. The classical Bowditch staircase phenomenon, that situation in which contractility increases with increases in stimulation frequency, is now thought to be due to increased transfer of calcium from the extracellular to the intracellular space as a consequence of the increase in stimulation frequency, and it appears that calcium is transported in this circumstance through so-called "slow channels" (20,23). There is considerable evidence then that points to a much greater dependence by cardiac muscle upon external calcium as a source of internal calcium than is true for skeletal muscle where contractility is regulated almost solely from internal stores of calcium.

The two major contractile proteins of muscle, myosin and actin, were discovered respectively by H.H. Weber in 1934 (24) and Albert Szent-Gyorgyi (25). Myosin is a fibrous protein with a molecular weight of 500,000 and dimensions of 1500 x 30Å. It has a calcium stimulated ATPase activity which is almost completely inhibited by physiological concentrations of potassium ions. As is shown in Figure 1, it consists of 2 heavy chains of molecular weight 220,000 that traverse the entire length of the molecule and 3 light chains which are associated with a bulbous head averaging about 20,000 in molecular weight. The ATPase activity of myosin and its actin combining activity are associated with the head of the molecule and are dependent upon the presence and the integrity of the light chains (26). Myosins from different muscle types

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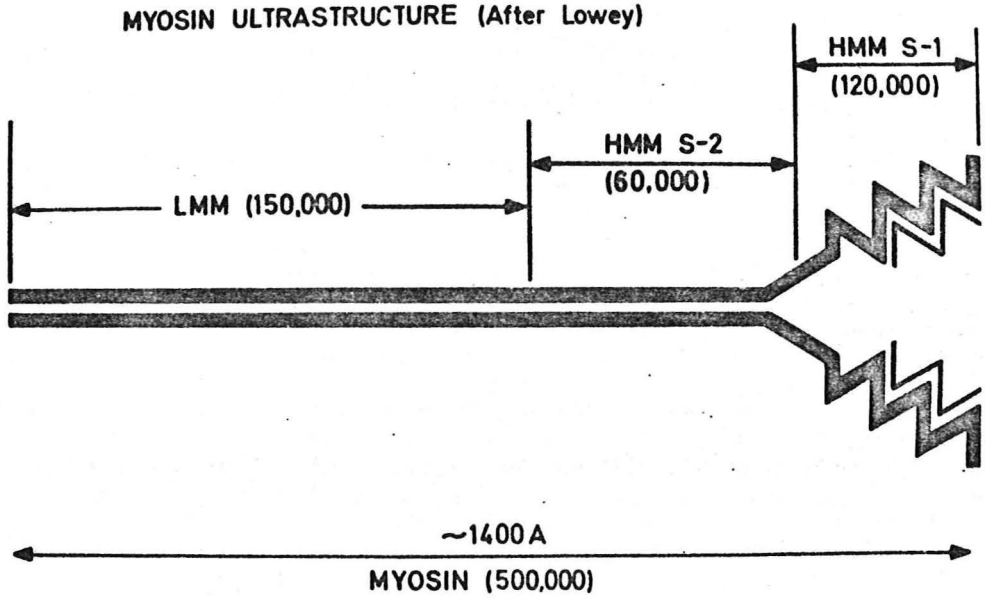
18. Bianchi CP, Shanes AM: Calcium influx in skeletal muscle at rest, during nocturity and during potassium concentration. J Gen Physiol 42: 803, 1959.
19. Winegrad S, Shanes AM: Calcium flux in contractility of guinea pig atria. J Gen Physiol 45:371, 1962.
20. Niedergierke R: The movement of calcium in frog heart ventricles at rest and during contractures. J Physiol 167:551, 1963.
21. Langer GA: Calcium exchange in dog ventricular muscle: Relation to frequency of contraction and maintenance of contractility. Circ Res 17:78, 1965.
22. Grossman A, Furchgott RF: The effects of various drugs on calcium exchange in isolated guinea pig left auricle. J Pharmacol 145:162, 1964.
23. Willerson JT, Crie S, Adcock R, Templeton GH, Wildenthal K: Influence of calcium on the inotropic actions of hyperosmotic agents, norepinephrine, paired electrical stimulation, and treppe. J Clin Invest 54:957, 1974.
24. Weber HH: The muscle proteins in the finer structure of skeletal muscles. Ergebn Physiol 36:109, 1934.
25. Banga I, Szent-Gyorgyi A: Preparation of properties of myosin A and B. In, Studies from the Institute of Medical Chemistry, University of Szeged, Basle, Vol. 1, 1941-42.
26. Lowey S, Slayter HS, Weeds AG, Baker H: Substructure of the myosin molecule. I. Subfragments of myosin by enzymic degradation. J Mol Biol 42:1, 1969.

Figure 1


MYOSIN ULTRASTRUCTURE (After Lowey)
HMM S-1
(120,000)
HMM S-2
(60,000)
LMM (150,000)
~1400 A
MYOSIN (500,000)

(red and white skeletal muscle and cardiac muscle) are identical in size, shape and physical properties, but vary in their intrinsic ATPase activity that may be regarded as a family of isoenzymes (27).

Actin, the second major contractile protein of muscle and exists in acetone powders of muscle in monomeric form (G actin), is a small globular protein with a molecular weight of 70,000. In the presence of ATP and Mg ions, G-actin polymerizes to F-actin. In F-actin the monomers appear to be spheres with a diameter of 55 Å.

Albert Szent-Gyorgyi has shown that at ionic strengths less than 0.3, similar to the intracellular milieu, F-actin and myosin combine to form a colloidal gel with a high viscosity and a molecular weight greater than 20,000,000. In the presence of Mg ion and ATP, the gel was found to contract (syneresis) and split ATP.

In 1954 studies by A.F. Huxley and R. Niedergierke (28) and H. Huxley and J. Hansen (29) by phase and electron microscopy, revealed the true nature of the ultrastructure of cardiac muscle and the intracellular distribution of the contractile proteins (30). These workers observed that 2 types of filaments exist in the myofibril. The thicker ones, about 150 Å in diameter, which coincide with the A bands of the sarcomere, are composed of an orderly array of myosin molecules (about 400 of them) with an axis of symmetry in the center of the filament so that the sense of the orientation is opposite in the two halves. Each thick filament is surrounded by 6 thin filaments which arise from the Z-line structure at each end of the sarcomere (1-2 microns apart) and project toward the center of the sarcomere. It is now known that the thin filaments are composed of a double helix of F-actin molecules, about 100 Å in diameter plus an array of regulatory proteins. Along the zone of overlap, interaction between the projecting myosin crossbridges and the actin molecules can occur. In fact, shortening of the sarcomere during muscle contraction has been demonstrated to occur by Huxley and his associates without a change in the A band length by simple sliding of the thin filaments (Fig. 2). Shortening of the sarcomere involves the making and breaking of many actomyosin bridges during shortening, presumably with the splitting of one ATP molecule at the instant of each crossbridge interaction. Thus, actomyosin formation in living cardiac muscle is a highly oriented and repetitive process.

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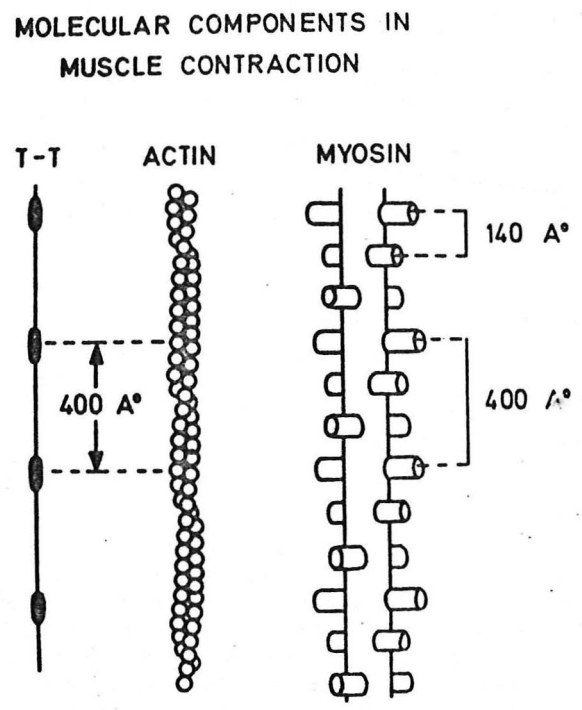
27. Mueller H, Franzen J, Rice RV, Olson RE: Characterization of cardiac myosin from the dog. J Biol Chem 239:1447, 1964.
28. Huxley AF, Niedergierke R: Structural changes in muscle during contraction. Interference microscopy of living muscle fibers. Nature (London) 173:971, 1954.
29. Huxley HE, Hansen J: Changes in the cross striations of muscle during contraction and stretch and their structural interpretation. Nature (London) 173:973, 1954.
30. Huxley HE: The mechanism of muscular contraction. Science 164:1356, 1969.

Figure 2



Ultrastructure of thick and thin filaments. The thin filament is a double helix of F-actin in the sulcus of which lies the troponin-tropomyosin (T-T) system. Myosin heads project from the thick filament at regular intervals with a spacing of 60°.

In 1951 Marsh (31) observed that the supernatant fraction obtained during the preparation of myofibrils from cardiac muscle contained a factor which could reverse contraction or syneresis. Associated with the redispersion of the actomyosin gel was a reduction in actomyosin ATP-ase activity. Many investigators subsequently contributed to the elucidation of the fact that the removal of traces of calcium appeared to be responsible for the inhibitory effects upon myofibrillar ATP-ase and relaxation in cardiac muscle, but perhaps Anne Marie Weber should receive major credit for these observations (32). Hasselbach and Makinose (33) and Ebashi and Lipmann (34) independently demonstrated that endoplasmic reticulum of the cardiac muscle cell contained an ATP-dependent calcium pump which could concentrate cytoplasmic calcium 500 times. In the presence of oxalate, a permeant anion which served as an intragranular trap for calcium, a concentration difference could read 6,000 times with a reduction in the external calcium to 0.1 μM, more than sufficient to inhibit myofibrillar ATP-ase and thus induce relaxation.

More recent studies done primarily by Ebashi's group (34) in Toyko have identified two additional proteins, troponin and tropomyosin. Troponin itself is composed of 2 dissimilar subunits, troponin A (molecular weight 18,000) and troponin B (molecular weight 30,000). Troponin A is the calcium binding subunit and binds 2 moles calcium per mole of protein. Troponin B is inhibitory to actomyosin ATP-ase in the absence of troponin A. In the presence of troponin A the inhibitory action of the B subunit is relieved. It has also been demonstrated that troponin and tropomyosin form a 1:1 complex which augments the regulatory effects of troponin upon actomyosin ATP-ase, i.e., in the presence of tropomyosin, troponin exerts maximum activation of actomyosin ATP-ase in the presence of calcium and a maximum inhibition of ATP-ase in the absence of calcium.

In summary, excitation of the contractile mechanism begins with the movement of the action potential of the muscle cell membrane down the invaginating T system to the associated longitudinal system (Fig. 3). The longitudinal reticulum which contains sequestered calcium is depolarized, its membrane becomes permeable to calcium and calcium is released into the sarcoplasm. In cardiac muscle, appreciable amounts of calcium also enter from the extracellular space. This calcium diffuses into the myofibrils combines with troponin (which in the calcium free state inhibits myosin-actin interaction) and releases this inhibition. Actin subunits of F-actin combine with myosin, ATP-ase activity appears, ATP is split and the thin filaments move along the thick ones with resultant shortening of the myofibril. As the intracellular free calcium rises from 10^{-7}M to values as high as 10^{-5}M, the longitudinal system pumps the calcium back into its lacunae and relaxation occurs.

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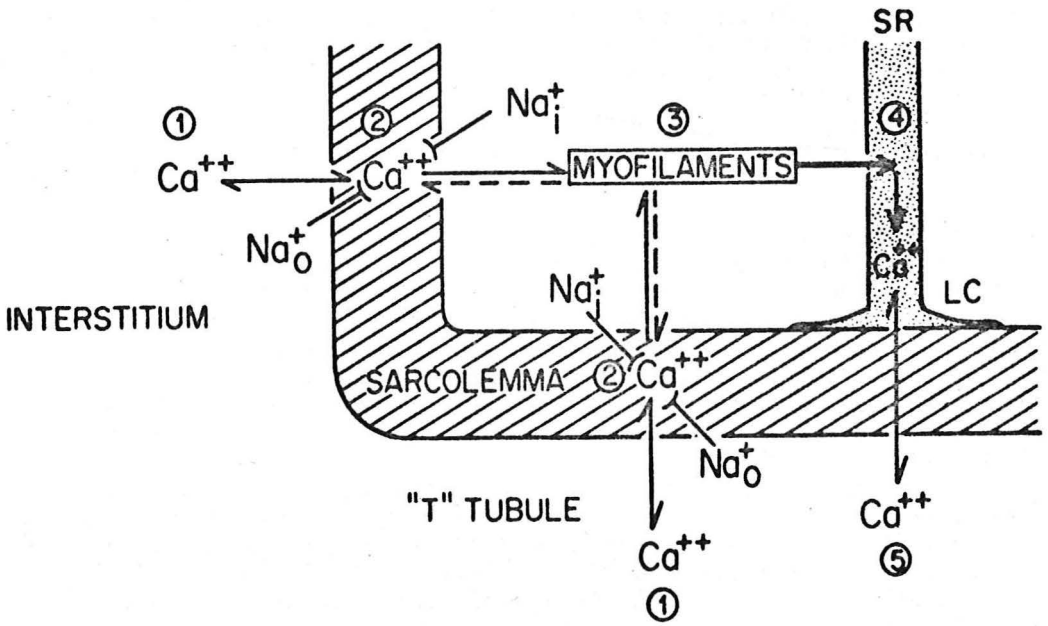
31. Marsh BB: A factor modifying muscle fiber syneresis. Nature (London) 167:1065, 1951.
32. Weber A: On the role of calcium in the activity of adenosine-5'-triphosphate hydrolysis by actomyosin. J Biol Chem 234:2764, 1959.
33. Hasselbach W, Makinose M: Die Calcium-pumpe der "Erschlaffungsrana" des Muskels und ihre Abhängigkeit von der ATP-Spaltung. Biochem Z 333:518, 1961.
34. Ebashi S, Lipmann F: Adenosine triphosphate linked concentration of calcium ions in a particulate fraction of rabbit muscle. J Cell Biol 14:389, 1962

Figure 3

Excitation Contraction Coupling

(Langer)



Schematic representation of a model for movements of calcium in mammalian myocardium. The representation Na_o-Na_i across the sarcolemma is to indicate the possible importance of tissue Na distribution in the determination of Ca exchange.

Role of Alterations in Excitation-Contraction Coupling in the Development of Heart Failure

Since 1966 a number of reports have appeared attempting to relate disorders of cardiac contraction to an altered calcium flux and more specially to a failure at one location or another in excitation contraction coupling. In 1966 Briggs and his associates (35) observed that amytal, a barbituate which can induce depression in cardiac function, was capable of depressing calcium uptake by vesicles in dog myocardium, an effect which was reversed by ouabain (36). Subsequently, this same group of investigators reported that microsomes isolated from spontaneously failing isolated perfused hearts showed a modest (27%) fall in calcium accumulation in the presence of oxalate, which was also prevented by digitalis. Harigaya and Schwartz (37) observed that the calcium uptake of reticulum from failing human hearts, made available at the time of transplantation, was lower than demonstrated by preparations from other animals with similar metabolic rates. Gertz and associates (38) have also reported an alteration in the rate of calcium pumping by the sarcoplasmic reticulum of hearts from Syrian hamsters afflicted with hereditary cardiomyopathy.

Thus, there is suggestive evidence that alterations in excitation-contraction coupling may occur in certain experimental animal models and possibly clinically in the setting of congestive heart failure. This is almost certainly a terribly important area for additional exploration in the future and in particular efforts and investigations need to be directed at determining whether the alterations in excitation-contraction coupling seen in association with congestive heart failure are primary or secondary phenomenon, i.e., whether they are causes or consequences of the congestive heart failure state. It seems highly likely that additional biochemical evaluation will help to distinguish and categorize additional as yet unrecognized forms of myocardial disease bringing some order out of present chaos. Additionally, further biochemical study of excitation-contraction coupling with various experimental models of congestive heart failure should help us understand important mechanism(s) involved in the development of congestive heart failure.

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35. Briggs FN, Gertz EW, Hess ML: Calcium uptake by cardiac vesicles: Inhibition by amytal and reversal by ouabain. Biochem Z 345:122, 1966.
36. Lain RF, Hess ML, Gertz EW, Briggs FN: Calcium uptake activity of canine myocardial sarcoplasmic reticulum in the presence of anesthetic agents. Circ Res 23:597, 1968.
37. Harigaya S, Schwartz A: Rate of calcium binding and uptake in normal animal and failing human cardiac muscle. Circ Res 25:781, 1969.
38. Gertz EW, Stam AC, Sonnenblick EH: Quantitative and qualitative defect in the sarcoplasmic reticulum in hereditary cardiomyopathy of Syrian hamsters. Biochem Biophys Res Com 40:746, 1970.

Types of Cardiomyopathy

1. Congestive cardiomyopathy: Congestive cardiomyopathy implies that the essential clinical expression of the disorder is failure of the heart as a pump. The degree of heart failure may vary from being subtle on the one hand to being an advanced congested circulatory state of biventricular failure on the other. Table 3 provides a presumptive etiologic classification to indicate several possible subgroups of myocardial disease each of which falls under the heading of congestive cardiomyopathy.

TABLE 3

Etiologic Classification of Congestive Cardiomyopathy

1. Idiopathic cardiomyopathy
2. Postpartum cardiomyopathy
3. Familial cardiomyopathy
4. Inflammatory cardiomyopathy (myocarditis)
5. Toxic cardiomyopathy
6. Metabolic cardiomyopathy
7. Nutritional cardiomyopathy
8. Cardiomyopathy associated with heredofamilial degenerative neuromyopathic diseases

Idiopathic cardiomyopathy as the name implies indicates that at the time the myocardial disease is recognized its provoking cause or causes have not been identified. Nevertheless, identifying a particular form of cardiomyopathy as being idiopathic has certain conceptual and therapeutic implications, i.e., it characterizes it as a different problem from hyperkinetic, hypertrophic, obstructive or restrictive cardiomyopathy, and thus presumably will be treated somewhat differently. In addition, at least 2 major diagnostic possibilities come to mind today as a potential explanation for "idiopathic cardiomyopathy". These 2 possibilities are further discussed below.

A. Alcoholic cardiomyopathy

Alcohol is a myocardial depressant when administered acutely (39,40). Alcoholism today is uncommonly associated with nutritional deficiency, but when

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39. Wendt VE et al: Acute effects of alcohol on the human myocardium. Am J Cardiol 17:804, 1966.
40. Gould L et al: Cardiac effects of alcohol. Am Heart J 79:422, 1970.

this occurs inadequate vitamin B_1 in the diet can lead to heart failure. In this wet beriberi there is fluid retention and cardiac dilatation coupled with a high output state. This form of hyperkinetic heart failure responds quickly to vitamin B_1 and is hemodynamically and clinically quite different from the hypokinetic low output state and poor contractile function of congestive cardiomyopathy (41). A different cause of heart failure associated with alcohol ingestion has been shown to be due to the addition of cobalt to beer to improve the stability of the "head". This has been previously shown to be responsible for the development of heart failure and death in patients who had habitually drunk several gallons of beer daily (42). The addition of cobalt to beer has now been banned and this form of heart failure is not likely to recur.

The entity of alcoholic cardiomyopathy presenting itself as congestive cardiomyopathy and not related to obvious vitamin deficiency or cobalt addition to beer is a widely accepted clinical entity, but the mechanism of production of heart failure by alcohol is uncertain (Fig. 4). The problem is compounded by the realization that since alcohol is a myocardial depressant if the heart is already ailing from any cause then the action of a myocardial depressant is predictable. If a patient with heart muscle failure is also an alcoholic, then further depression of myocardial activity could result from the alcohol. It should be recalled that congestive cardiomyopathy is uncommon in alcoholic patients with cirrhosis of the liver: this suggests that alcohol might be no more than a conditioning agent acting on already sick heart in many instances, but the biochemical mechanism through which alcohol might produce cardiomyopathy or through which it contributes to myocardial depression in the absence of vitamin deficiency or cobalt addition remains unknown today.

Alcoholic cardiomyopathy has been the subject of several recent reviews (43-45). Presenting signs and symptoms of alcoholic cardiomyopathy for 57 patients studied by Demakis and his associates are shown in the next table (44).

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41. Goodwin JF: Congestive and hypertrophic cardiomyopathies. Lancet I:731, 1970.
42. Morin Y: Quebec beer-drinkers' cardiomyopathy: Hemodynamic alterations. Canadian Med Assoc J 97:901, 1967.
43. Regan TJ et al: Ethyl alcohol and the heart. Circulation 44:957, 1971.
44. Demakis JE et al: The natural course of alcoholic cardiomyopathy. Ann Intern Med 80:293, 1974.
45. Schwartz L et al: Severe alcoholic cardiomyopathy reversed with abstention from alcohol. Am J Cardiol 36:963, 1975.

TABLE 4

Symptoms and Signs at Time of Initial Clinical Presentation in 57 Patients with Alcoholic Cardiomyopathy

Symptoms	No. of Patients
Dyspnea on exertion	55
Paroxysmal nocturnal dyspnea	30
Orthopnea	25
Ankle swelling	39
Cough	14
Chest pain	10
Fatigue	6
Complications	3
Hemoptysis	3
Signs	
Cardiomegaly	57
Rales	55
Edema	40
Hepatomegaly	33
S3	57
S4	47
Holosystolic murmur at cardiac apex	13
Ejection systolic murmur	11

These 57 patients studied by Demakis and his associates with apparent alcoholic cardiomyopathy were followed for an average of 40 months. None of the patients were treated with prolonged bed rest. During the follow-up period the clinical status improved in 15 patients, was stable in 12 and deteriorated in 30 patients. Seventy-three percent of those patients that improved abstained from alcohol, whereas in those patients that remained stable only 25% and in those that deteriorated only 13% of patients abstained. The average duration of symptoms in the patients that abstained from alcohol was 4 months which was considerably shorter than that of patients that did not improve or deteriorated (17 and 11 months respectively). Only 10 patients (17%), all in the group that abstained from alcohol, had a return of heart size to normal. Twenty four patients (42%), all in the group that deteriorated, died on an average of 36 months after being hospitalized. Thus, it appears that a short duration of symptoms before initiation of therapy and abstinence from alcohol are associated with a more favorable course. Criteria for diagnosis of alcoholic cardiomyopathy in this series were 1) congestive heart failure in patients under 50 years of age; 2) no evidence of unusual causes of heart disease to explain the clinical features; and 3) the presence of alcoholism. Alcoholism was presumed if alcoholic beverages had been used for 5 years or more and in abnormal amounts, that is a daily intake in excess of 8 ounces of whiskey or gin, 1 quart of wine or 2 quarts of beer. The majority of patients included in Demakis' series consumed far more alcohol than the amounts listed above. They were not occasional or spree drinkers, but tended to drink heavily daily

McDonald, Burch and Walsh have presented data on patients with alcoholic cardiomyopathy who were treated with prolonged bed rest (46). Of 42 patients in whom follow-up data was available 19 (45%) died. Although the heart size returned to normal in 21 (44%), in only 9 (21%) heart size continued to remain normal when patients were mobilized.

Magnesium deficiency can occur in congestive heart failure, after diuresis with furosemide, ethacrynic acid and mercurials, and with digitalis intoxication, diabetic acidosis, acute and chronic alcoholism, delerium tremens, cirrhosis, malabsorption syndromes, etc. Clinical manifestations are vague, but include the potential development of serious cardiac arrhythmias as well as weakness, tremors, stupor, coma, nausea and vomiting (47). One might also question whether magnesium deficiency could potentially cause mechanical myocardial dysfunction since magnesium is an essential component in many enzyme systems and its deficiency might be expected to produce gross changes in myocardial

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46. McDonald CD, Burch GE, Walsh JJ: Alcoholic cardiomyopathy managed with prolonged bed rest. Ann Intern Med 74:681, 1971.
47. Iseri L: Magnesium deficiency and cardiac disorders. Am J Med 58:837, 1975.

function. Although magnesium depletion may disrupt the integrity of myocardial cells, there is to date no clear evidence that it causes or even contributes in a major way to myocardial failure in human subjects (47). It should be noted, however, that cardiac mitochondria have more avidity for magnesium and are more susceptible to magnesium depletion than are liver cell mitochondria (48). Many have speculated that magnesium depletion might be an etiologic factor in the myocardial depression that occurs with alcoholic cardiomyopathy and this is a possibility that remains to be further tested in the future.

B. Postpartum cardiomyopathy

Postpartum cardiomyopathy is a term applied to idiopathic primary myocardial disease initially recognized in the postpartum period. By definition, patients with postpartum cardiomyopathy have no evidence of heart disease prior to pregnancy and no detectable cause of cardiac disease at the time they present to the hospital for delivery. Some authors include women who develop cardiac failure in the last month of pregnancy or the first 5 months after delivery. Others include only those women in whom cardiomyopathy appears between the second and twentieth postpartal weeks in order to eliminate in so far as possible occult pre-existing heart disease that becomes overt during the stress of labor and delivery. While there is little doubt that idiopathic congestive cardiomyopathy may be temporally related to the end of gestation, the nature of the relationship is not yet clear. It is interesting to note, however, that pregnancy has been shown to enhance the susceptibility of the myocardium of mice to pathological effects of encephalomyocarditis virus (49). Time and onset of the disease is somewhat variable. All writers agree that it develops in the latter months of pregnancy. Some accept, however, an onset of symptoms within the first 10 weeks of puerperium, but may be in the last trimester of pregnancy. Others have included the onset of symptoms in the last month of pregnancy or within 5 months of delivery. The exact incidence is hard to determine, estimates vary from 1 in 1300 to 1 in 4000 pregnancies. The clinical picture is one of congestive cardiomyopathy, cough, chest pain, hemoptysis and in some patients pulmonary embolism. Physical signs are those of low cardiac output, heart failure, cold blue extremities, small volume arterial pulse and increased jugular venous pressure. There is invariably a third heart sound and cardiac enlargement and often a pansystolic murmur of either tricuspid or mitral regurgitation. Atrial fibrillation occurs in 25% of patients. Pulmonary hypertension may be present. Radiographs of the chest demonstrate diffuse cardiac enlargement. The electrocardiogram shows non-specific changes including sometimes low voltage QRS complexes, flat or inverted T waves and evidence of left ventricular hypertrophy. Left bundle branch block (in contrast to congestive cardiomyopathy of other types) appears to occur, but rarely. The disease appears to be more common in black than in white patients, in multiparous older women and in the presence of twin pregnancy and toxemia (50).

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48. DiGiorgia J et al: Sarcosomes and magnesium deficiency in ducks. Biochem J 82:184, 1962.
49. Farber PA, Glasgow LA: Viral myocarditis during pregnancy: Encephalomyocarditis virus infection in mice. Am Heart J 80:96, 1970.
50. Goodwin JF: Peripartal heart disease. In, Clinical Obstetrics and Gynecology, Vol. 18, Harper and Row, 1975, p 125.

C. Familial cardiomyopathy

Familial cardiomyopathy implies the development of primary myocardial disease within a kinship. Idiopathic congestive or restrictive cardiomyopathies are seldom familial whereas positive family histories are much more common in idiopathic hypertrophic cardiomyopathy especially when obstruction to left ventricular outflow co-exists (see below). In addition, cardiomyopathy is well known in heredofamilial neuromyopathic disease (see below).

D. Inflammatory cardiomyopathy

Inflammatory cardiomyopathy (myocarditis) can be either infectious or non-infectious. It is sometimes possible to associate acute myocarditis with a specific infectious etiology, but it is often impossible to relate chronic myocarditis to a known cause. Patients with chronic myocarditis typically present as idiopathic cardiomyopathy (usually congestive cardiomyopathy) since evidence of the provoking cause has long since disappeared (51).

Myocarditis can be produced by virtually any infectious agent and viral, bacterial, rickettsial, spirochetal, parasitic and fungal etiologies have all been identified as being causative factors of myocardial inflammation (52). Myocarditis associated with infectious diseases may in some instances be ascribed to direct tissue invasion (Coxsackie B virus), to toxins elaborated by an infectious organism (diphtheria) or to an immune response (rheumatic fever) (52). Many authorities feel that viruses are the most common cause of primary infectious myocarditis in the United States today. Many types of viruses have been incriminated, but only a few seem to be clinically important in terms of prevalence, and in particular, the enteroviruses and influenza should be mentioned in this regard (51,52). It should also be mentioned that acute myocarditis, although potentially dangerous, is often clinically occult and often vanishes altogether or possibly presents years later as chronic idiopathic congestive cardiomyopathy. A viral cardiomyopathy is defined as a disease initially caused by multiplication of a virus in the myocardium, pericardium, or endocardium which temporarily or permanently affects the normal anatomy or physiological function of the heart. The myocardium, pericardium or endocardium may be involved singly or in combination. During the acute phase which usually last 7-14 days, virus is easily recoverable from the heart. Later, regardless of whether the myocardiopathy is benign or virulent, infectious virus is no longer present. The enterovirus group (Coxsackieviruses A and B, echoviruses, polioviruses) are icosahedral shaped with a particle diameter of 17-30 mμ and a ribonucleic acid core surrounded by capsid of protein. Many authors believe that the virulent cardiomyopathies are likely predominantly due to Coxsackieviruses belonging to group B, types

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51. Perloff JK: The cardiomyopathies - current perspectives. Circulation 44:942, 1971.
52. Abelmann WH: Myocarditis. N Engl J Med 275:832, 944, 1966.

1-5. Mitral valvulitis has been produced in monkeys by Coxsackievirus B4 (53). Burch and his associates (54) have shown that certain Coxsackieviruses can produce valvulitis and valvular deformities as well as pericarditis and myocarditis.

Several investigators have shown that adrenal steroids, exercise, cold, reserpine, alcohol, special genetic susceptibility of certain strains of mice, unusual virulence of the infecting virus, pregnancy, the male sex and chronic under nutrition can all lead to increased severity of myocarditis as produced by viruses (55). In addition to presentations associated with congestive heart failure, viral myocarditis can be associated with the development of complete heart block, atrial or ventricular rhythm disturbances, evidence of ST segment elevation on the electrocardiogram suggesting acute myocardial injury, coronary vein thrombosis, low voltage on the electrocardiogram, left axis deviation and T wave abnormalities (56,57). Immune or autoimmune mechanisms have been postulated as causes of some types of idiopathic myocarditis. Speculation has arisen largely because it is known that the beta-hemolytic streptococcus apparently through an immune response is known to cause myocarditis which once established can become self-perpetuating even after the infectious organism has vanished. Antibodies to heart muscle have been detected in almost 2/3 of patients with the carditis of active rheumatic fever (58). Perhaps other types of myocarditis (in particular viral myocarditis) disappear but perpetuate myocardial damage through an immune response after once initiating myocarditis. Heart muscle antibodies have also been found in idiopathic cardiomyopathy, but there is not yet evidence that such antibodies are etiologically important (59).

Toxoplasmosis may also cause myocardial dysfunction and congestive heart failure. In both congenital and acquired toxoplasmosis, hemotogenously disseminated toxoplasma gondii invade the myocardial cell where they divide and result in rupture of the parasitized cell with a subsequent mononuclear inflammatory reaction occurring and associated myocardial cell necrosis.

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53. Lou TY et al: Experimental infections with Coxsackieviruses: II. Myocarditis and cynomolgus monkeys infected with B4 virus. Arch ges Virus Forsch 10:451, 1961.
54. Sun SC, Sohal RS, Burch GE, Chu KC, Colcolough HL: Coxsackievirus B, pancreatitis in cynomolgus monkeys resembling rheumatic heart lesions. Br J Exp Pathol 48:655, 1967.
55. Lerner AM et al: Enteroviruses in the heart with special emphasis on the probable role of Coxsackieviruses, group B, types 1-5. Mod Concep Cardiovas Dis 44:7, 1975.
56. Burnside JW: Case Records of the Massachusetts General Hospital. N Engl J Med 286:1100, 1972.
57. Bell H: Cardiac manifestations of viral hepatitis. JAMA 218:387, 1971.
58. Hess EV et al: Heart muscle antibodies in acute rheumatic fever and other diseases. J Clin Invest 43:886, 1964.
59. Camp TF et al: Immunologic findings in idiopathic cardiomyopathy. Am Heart J 77:610, 1969.

The patient with toxoplasmosis may have heart failure, pericarditis, atrial or ventricular arrhythmias or even heart block; complete recovery from toxoplasma myocarditis is unusual. Adult patients with toxoplasmosis with a sinus tachycardia may have what is an otherwise unapparent myocarditis (60,61).

Myocardial involvement occurs commonly with chronic Chagas' disease. Right bundle branch block and atrial and ventricular arrhythmias occur in about 80% of patients with Chagas' myocarditis. Trypanosoma cruzi is the etiologic agent that may result in right bundle branch block, cardiac enlargement and evidence of congestive heart failure often associated with arrhythmias. Chronic Chagas' disease is the most common form of heart disease in some areas of South America effecting an estimated 7 million persons. Recovery from the acute myocarditis of Chagas' disease is possible with complete elimination of cardiac manifestations, and this usually occurs within a few months after the initial infection leaving the patient appearing in good health for the next many years. However, subsequently chronic heart disease can develop and confirmatory laboratory evidence includes a positive Machado-Guerrerio complement fixation reaction and a positive zeno diagnostic study. Patients with chronic Chagas' myocarditis often have functional mitral and tricuspid insufficiency, right bundle branch block and invariably arrhythmias which make syncope and sudden death common. There is no known therapy for the chronic form of Chagas' disease with myocardial involvement (62,63).

E. Toxic cardiomyopathy

Toxic cardiomyopathy results from myocardial injury due to exogenous or endogenous toxins. Sulfonamides, emetine, arsenic, ethylene glycol, sympathomimetic amines and alcohol have all received attention as being potential agents in the production of toxic cardiomyopathy. More recently certain cancer chemotherapeutic agents (adriamycin and daunorubicin) have also been identified as being histologically toxic to cardiac muscle when given in large amounts, long term (51).

F. Metabolic Cardiomyopathy

Metabolic cardiomyopathies are related to endocrine and electrolyte disorders and nutritional deficiencies. Hyperthyroidism is believed to effect the heart by virtue of a direct effect of thyroid hormone on the myocardium at least in part. Heart disease is known to occur in association with acromegaly in which condition hypertension, cardiomegaly and left ventricular failure occur with some frequency. Pheochromocytoma may be accompanied by myocardial disease, presumably a consequence of myocardial damage produced by high concentrations of circulating catecholamines. Gargoylism can be considered a metabolic

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60. Harvey HP et al: Myocarditis associated with toxoplasmosis. Australasian Ann Med 15:169, 1966.
61. Shee JC: Stokes-Adams attacks due to toxoplasma myocarditis. Br Heart J 26:151, 1964.
62. Laranja FS et al: Chagas' disease: A clinical epidemiologic and pathologic study. Circulation 14:1035, 1956.
63. Decourt LV et al: Chronic heart involvement in Chagas' disease. Am Heart J 33:697, 1947.

cardiomyopathy associated with diffuse infiltration of the heart by cells filled with mucopolysaccharides (64). Glycogen storage disease of Pompe is a metabolic cardiomyopathy of infancy associated with massive myocardial infiltration with glycogen (64). Eight different types of glycogen storage disease have been described and cardiac involvement occurs in types II, III and IV. Most cases of glycogen storage causing cardiomegaly belong to type II (Pompe's disease), caused by a deficiency of alph-1, 4-glucosidase, a lysosomal enzyme that hydrolyzes glycogen to glucose. Glycogen within cardiac muscle is biochemically and morphologically normal, but is present in excessive amounts both within lysosomes and free in the cytoplasm. As a result, the heart enlarges sometimes to a marked degree and congestive heart failure supervenes. Survival rarely extends beyond infancy or early childhood. Microscopically the muscle cells show a characteristic lace-work pattern, with large clear central spaces which represent the sites of glycogen deposition. Endocardial fibroelastosis in at least a portion of the left ventricle is also often present (65). Fabry's disease is a rare metabolic disorder in which glycolipid deposits are present in many organs including the heart (66).

G. Nutritional cardiomyopathy

Nutritional cardiomyopathies are characteristically congestive cardiomyopathies and they may stem from specific metabolic defects such as thiamine deficiency and the polished rice diet of oriental beriberi or be associated with a high output state related to alcohol excess described earlier. Nutritional cardiomyopathy has also been described among the adult Bantu who consume an unbalanced high carbohydrate low protein diet. Kwashiorkor, a disease of protein malnutrition in African children is also occasionally accompanied by congestive cardiomyopathy (51,64,67).

H. Neuromyopathic Disorders with Myocardial Disease

There are at least three heredofamilial neuromyopathic diseases associated with congestive cardiomyopathy. These include progressive muscular dystrophy, myotonic muscular dystrophy and Friedreich's ataxia (68). Myocardial involvement is especially common and serious in classic pseudo-hypertrophic Duchenne's progressive muscular dystrophy and in Friedreich's ataxia. Progesssive muscular dystrophy can be recognized by noting prominent R waves in leads V1 and V2 of the electrocardiogram which are the result of fibrous replacement of the posterior wall of the heart resulting in a larger R wave in anterior precordial leads than would ordinarily be expected.

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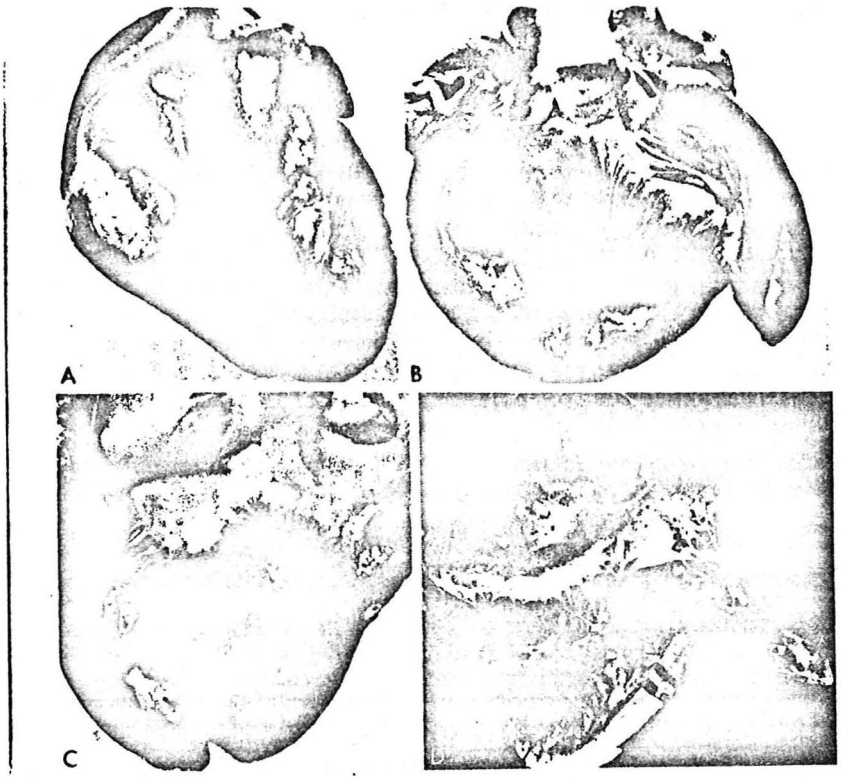
64. Perloff JK et al: Uncommon or commonly unrecognized causes of heart failure. Prog Cardiovas Dis 12:409, 1970.
65. Roberts WC, Ferrans VJ: Pathological aspects of certain cardiomyopathies. Circ Res (Suppl II) 34 and 35:II-128, 1974.
66. Ferrans VJ et al: The heart in Fabry's disease. Am J Cardiol 24:95, 1969.
67. Gillanders AD: Nutritional heart disease. Br Heart J 13:177, 1951.
68. Perloff JK: Cardiomyopathy associated with heredofamilial neuromyopathic diseases. Mod Concep Cardiovas Dis 40:23, 1971.

Figure 4

Congestive Cardiomyopathy at Post Mortem Examination

(Roberts and Ferrans)



Idiopathic dilated cardiomegaly in a 36 year old black man (A69–199), a chronic alcoholic who had been well until two years before death, when evidence of congestive cardiac failure appeared. The latter gradually worsened and various arrhythmias also appeared. Finally pulmonary infiltrates, proved to be secondary to pulmonary emboli, precipitated death. By radiography the heart was markedly enlarged. An electrocardiogram showed low voltage, Q and T wave changes suggesting old infarction, and an intraventricular conduction defect. He never had chest pain, hypertension, or a precordial murmur. At necropsy the heart with the intracardiac thrombi weighed 750 gm. "Milk spots" were present over the anterior surface of the right ventricle and at the left ventricular apex *(A)*. Thrombi were present in the apex of both ventricles *(B, C, D)* and in the right atrial appendage *(D)*. Histologically, large foci of replacement and interstitial fibrosis were seen in the left ventricular wall. Both left ventricular papillary muscles were atrophied and severely scarred. *A*, Heart as viewed anteriorly. This is better seen in Figure 4. The notch present at the junction of the left ventricular apices was considered at one time to be diagnostic of the African condition, endomyocardial fibrosis, but this is not the case as shown by this patient. *B*, Opened left ventricle, aortic valve, and aorta showing the large apical thrombus. *C*, Opened left atrium, mitral valve, and left ventricle. The mitral anulus is not dilated. *D*, Open right atrium, tricuspid valve, and right ventricle showing a thrombus at the apex of the ventricle.

Restrictive Cardiomyopathy

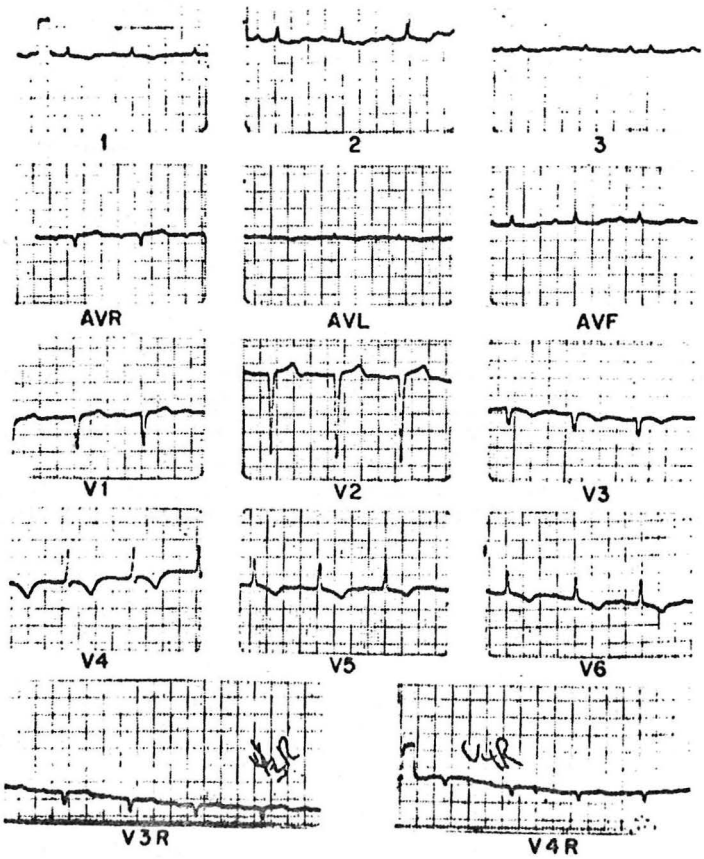
I. Cardiac Amyloidosis

This form of infiltrative heart disease ordinarily results in restriction of cardiac filling and congestive heart failure as a consequence of destruction and replacement of normal cardiac muscle. Amyloid infiltration may also occur in coronary arteries with luminal narrowing and angina pectoris and even myocardial infarction may occur as a consequence. Brandt et al found amyloid in the hearts of 90% of patients with "primary" amyloidosis (occurring without obvious associated etiology) and myeloma associated cases of amyloidosis and in 54% of cases of amyloidosis secondary to conditions such as rheumatoid arthritis, tuberculosis, osteomyelitis, bronchiectasis and lymphoma. However, cardiac dysfunction is unusual as a presenting feature except in cases of primary amyloidosis.

Patients with extensive cardiac muscle replacement by amyloid generally present with signs and symptoms of left and right ventricular failure. Some patients with extensive cardiac amyloidosis have evidence of restrictive physiology in their jugular venous pulse, i.e., a prominent A wave, elevated venous pressure and a prominent Y descent. Murmurs of mitral and tricuspid insufficiency may be present. Importantly, the electrocardiogram characteristically demonstrates low QRS voltage in the limb leads as is shown in Figure 5 in almost every patient with extensive cardiac amyloidosis. As a matter of fact,

Figure 5

ECG from a Patient with Extensive Cardiac Amyloidosis (Reference 70)



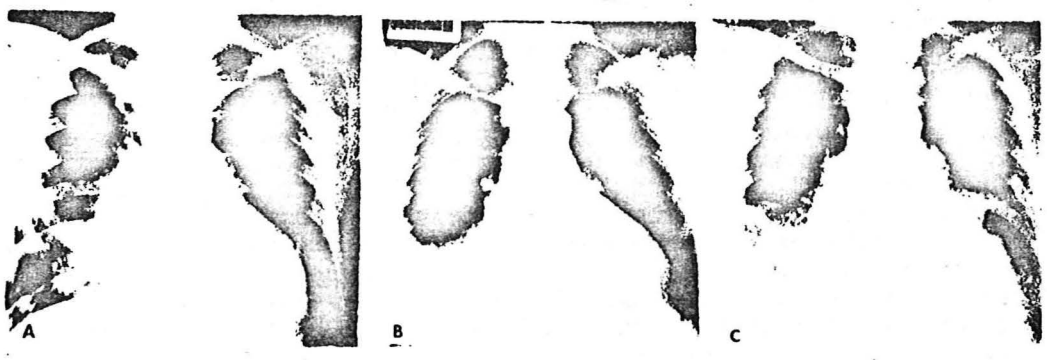
many investigators feel that in the absence of low QRS voltage in the extremity leads the likelihood of extensive cardiac muscle replacement by amyloid in an individual patient is remote. Heart size tends to be enlarged with severe cardiac amyloidosis, but ordinarily the degree of enlargement is not massive (Fig. 6). The left ventricular angiographic appearance of patients

Figure 6

Representative Examples of Cardiac Enlargement

Occurring in Patients with Cardiac Amyloidosis

(Chew et al)



Chest X-ray films of Patients 1(A), 2(B) and 3(C). All show enlargement of the cardiac shadow and pulmonary venous congestion. Patients 1 and 2 had large pericardial effusions.

with severe cardiac muscle replacement by amyloid is said to be characteristic and quite similar from patient to patient. Specifically, end-systolic ventricular contraction is reduced and there is only a slight visible reduction in volume. Trabeculation in the ventricle is prominent. In diastole the chamber sizes and shapes appear normal. The left ventricular volumes tend to be normal at end-diastole but above normal values at end-systole are found. Characteristically

there is a slight (ordinarily not terribly severe) reduction in ejection fraction to levels of approximately 40-45%. Cardiac output and cardiac index are typically reduced. From the above description it is apparent that patients presenting with severe cardiac amyloidosis usually present as "restrictive cardiomyopathy"; but it should be noted that their presentation may also occasionally simulate that seen in "congestive cardiomyopathy".

The response of patients with severe cardiac amyloidosis to digitalis and diuretics is ordinarily a modest one at best and there is usually a relatively rapid and relentless downhill course culminating in death ordinarily 1 to 1-1/2 years following the onset of congestive heart failure. Presently, there is no effective long-term therapy for this disorder. Some authorities feel that patients with extensive cardiac amyloidosis should not be given cardiac glycosides since in at least some patients sudden death or severe life threatening ventricular arrhythmias have followed the administration of what seemed to be relatively small amounts of digoxin. It is very hard for me to be sure whether or not patients with cardiac amyloidosis are indeed inordinately sensitive to cardiac glycosides in usual amounts, but my own personal feeling is that most of the instances of presumed inordinate sensitivity are explained by a physician giving more digitalis than he should have in an attempt to produce a hemodynamic response that is not possible to obtain.

The presence of cardiac amyloidosis can be suspected by considering the possibility in any patient with low QRS voltage in their limb leads coupled with evidence of either congestive or restrictive cardiomyopathy. In addition, one's index of suspicion would be increased by finding macroglossia, a history of carpal-tunnel syndrome, renal insufficiency, severe proteinuria (with Bence Jones proteinuria) and/or the demonstration of "scratch purpura" over the anterior chest or over the face especially around the eyes and on the cheeks. Endomyocardial biopsy at the time of cardiac catheterization can provide tissue from which Congo red stains can be made and amyloid identified by its "apple green" birefrigence under polarized light microscopy (69-74).

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69. Chew C et al: The functional defect in amyloid heart disease. Am J Cardiol 36:438, 1975.
70. Willerson JT, Castleman B: Relentless congestive heart failure in a 67 year old women. N Engl J Med 286:364, 1972.
71. Crockett LK: A review of cardiac amyloidosis. Am J Med Sci 264:152, 1972.
72. Schroeder JS: Cardiac amyloidosis. Diagnosis by transvenous endomyocardial biopsy. Am J Med 59:269, 1975.
73. Buja LM et al: Clinically significant cardiac amyloidosis: Clinico-pathologic findings in 15 patients. Am J Cardiol 26:394, 1970.
74. Konno S, Sakakibara S: Endomyocardial biopsy. Dis Chest 44:345, 1963.

II. Hemochromatosis

Cardiac involvement in primary hemochromatosis is well documented and it is characteristically a feature of cases presenting in childhood or early adult life (75). Often the presenting symptoms for patients with hemochromatosis are non-cardiac in the sense that skin pigmentation, testicular atrophy, sparse facial and pubic hair or diabetes mellitus may be the predominant symptoms, but in some instances obvious evidence of right heart failure coupled with signs of restrictive cardiomyopathy in the jugular venous pulse should encourage one to consider the possibility of hemochromatosis. Hemochromatosis affecting the heart typically produces diffuse cardiac enlargement with biventricular heart failure. Atrial arrhythmias are common and atrio-ventricular block may occur. The clinical presentation may closely mimick constrictive pericarditis and an exploratory thoracotomy with pericardial biopsy may be necessary in an occasional patient in order to differentiate the two conditions. However, cardiac catheterization ordinarily demonstrates a slight increase in right sided pressures, the absence of equalization of right and left sided pressures and in some instances a dip and plateau pressure contour in the right ventricular pressure tracing. Established heart failure in hemochromatosis responds poorly to conventional treatment with digitalis and diuretics and death often occurs within a year of the onset of failure if the disease process is not correctly recognized and treated. If the process is correctly recognized, however, phlebotomy over several months has resulted in considerable clinical improvement in some patients with subsequent disappearance of congestive heart failure, atrial and/or ventricular arrhythmias and the evidence of heart failure (Fig. 7) (75-77).

There are numerous pathological studies of hearts in hemochromatosis. Buja and Roberts have reviewed a large series of patients with iron deposition in cardiac muscle (76). The extent of iron deposition in atrial muscle correlated with the occurrence of supraventricular arrhythmias. All patients with grossly visible cardiac iron deposits had clinical evidence of heart failure. Buja and Roberts also pointed out, however, that extensive cardiac iron deposits can occur also in patients who receive more than 100 units of blood unless bleeding diatheses co-exist and in patients with chronic anemia and hepatic cirrhosis who receive less than 100 units of blood. Buja and Roberts also pointed out that cardiac iron deposits initially occur in the ventricular myocardium and are usually more extensive in ventricular than in atrial myocardium and that these iron deposits are always more extensive in working than in conducting myocardium.

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75. Skinner C, Kenmure ACF: Haemochromatosis presenting as congestive cardiomyopathy and responding to venesection. Br Heart J 35:466, 1973.
76. Buja LM, Roberts WC: Iron in the heart; etiology and clinical significance. Am J Med 51:209, 1971.
77. Easley RM et al: Reversible cardiomyopathy associated with hemochromatosis. N Engl J Med 287:866, 1972.

As was true for patients with cardiac amyloidosis, hemochromatosis may present as congestive cardiomyopathy or as the restrictive type of cardiomyopathy. When the presentation is as restrictive cardiomyopathy, it may as noted earlier simulate constrictive pericarditis. Hemochromatosis is more common in males than in females and when it occurs in females it is ordinarily after cessation of menses. However, it is important to keep in mind that pituitary abnormalities associated with failure of menstruation may result in even young females developing hemochromatosis. In particular, at Parkland Memorial Hospital we have recently seen a young woman (BDL) with a several year history of failure to menstruate present with cardiac hemochromatosis. Her initial presentation was with evidence of restrictive cardiomyopathy, but she subsequently developed medically refractory ventricular tachycardia and/or ventricular fibrillation. Finally, after extensive treatment by phlebotomy her recurrent ventricular arrhythmias responded to overdrive ventricular pacing and combinations of antiarrhythmic agents. With phlebotomy over the past 2 years she has become completely asymptomatic, her heart size has returned to normal, she has lost the evidence of restrictive cardiomyopathy in her jugular venous pulse, her ventricular tachyarrhythmias have disappeared and she has returned to active life and gainful occupation.

Figure 7

Serial Changes in Heart Size after Repeated Phlebotomy in a Patient with Hemochromatosis

(Skinner and Kenmure)

Chest x-rays: (a) at the time of presentation showing gross cardiomegaly; (b) after 10 months' venesection, showing reduction in cardiac size.

III. Endomyocardial Fibroelastosis

Primary endocardial fibroelastosis is a disease of infants and children predominantly. It also occurs (and/or persists) in some adults and in certain parts of Africa is the single most common etiology for cardiomegaly and heart failure. It is characterized by early cardiac failure and death resulting from idiopathic, diffuse, mainly left ventricular endomyocardial thickening. The disease process has been described in families and viruses, such as those causing mumps, have been frequently implicated as etiologic factors but never categorically proved (78-80).

Cardiac lesions similar to those found in cardiomyopathy of unknown etiology have been produced by dietary means in rats fed on tryptophan deficient diets similar to those eaten by many of the people living in areas where this disease occurs. Endocardial and myocardial lesions which appear to resemble those of endomyocardial fibrosis have been produced in guinea pigs fed on a diet consisting largely of plantains. A diet low in protein and other essential nutrients may possibly be of some importance in the development of endomyocardial fibrosis as it is known that individuals such as the Banyaruanda in Uganda exist on a high plantain and high carbohydrate diet containing only a small amount of protein and other essential nutrients have a high incidence of endomyocardial fibroelastosis.

The disease may present as either a restrictive or congestive cardiomyopathy. As noted above, it typically involves either the newborn or young children and death follows very quickly after the onset of congestive heart failure with this entity. Right and left ventricular failure, low voltage on electrocardiogram, borderline to modest heart enlargement, atrial arrhythmias (in particular atrial fibrillation), mural thrombosis and a relatively poor response to cardiac glycosides and diuretics characterize this particular form of myopathy. Endomyocardial fibrosis may also be associated with peripheral eosinophilia. Most commonly today this disease process is found in the newborn and is not infrequently the reason for demise. This disease process has been associated with other congenital malformations of the heart including severe left ventricular outflow obstruction at the level of the aortic valve, coarctation of the aorta and hypoplastic left heart syndrome. Its occurrence in adults in this country is extremely rare.

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78. Lee MH et al: Familial occurrence of endocardial fibroelastosis in 3 siblings, including identical twins. Pediatrics 52:402, 1973.
79. Somers K: Atrial arrhythmias in endomyocardial fibrosis. Cardiology 57:369, 1970.
80. McKinney B: Studies on the experimental production of endomyocardial fibrosis and cardiomegaly of unknown origin by dietary means. Am Heart J 90:206, 1975.

IV. Myocardial Fibrosis in Constrictive Pericarditis

Levine (81) has suggested that myocardial fibrosis occurs in some patients with constrictive pericarditis. In his study Levine presented evidence that myocardial fibrosis occurring in some of these patients was related to 1) direct subepicardial penetration by the inflammatory process or deposits of fat in the subepicardial myocardium; 2) compromise of coronary blood flow as a result of direct restriction of coronary arteries by scar tissue or deficient "irrigation" of subendocardial layers due to rigidity of the pericardium; or 3) a concomitant myocardial and pericardial process (lupus erythematosus, fibrosis, rheumatoid arthritis, etc.). A certain proportion of these patients then might be expected to have myocardial failure as a result of the fibrous replacement of myocardial tissue and they might present with either restrictive or constrictive cardiomyopathy. Very little additional information is available about this particular process and additional evaluation in appropriate patients needs to be made.

TABLE 5
Hemodynamics of Myocardial and Pericardial Disease (Hurst & Logue)

	Constrictive Pericarditis	Myocardiopathy
1. Left Atrial Pressure	1. Tend to equal RAP	1. 10 to 20 mm Hg > RAP
2. Right Atrial Pressure	2. Usually > 15 mm Hg with prominent Y trough	2. Usually < 15 mm Hg: normal if wedge pressure normal
3. Cardiac Output	3. Tends to normal with normal A-V difference	3. Usually low with increased A-V difference
4. Right Ventricular Pressure	4. Consistent early diastolic dip	4. Early diastolic dip may disappear with therapy
5. Diastolic Right Ventricular Pressure	5. Tends to equal or exceed 1/3 of systolic pressure	5. Usually does not equal 1/3 of systolic pressure
6. Pulmonary Artery Pressure	6. Systolic pressure usually < 40 mm Hg	6. Systolic pressure often 45 to 65 mm Hg
7. Respiratory Variation in Pressures	7. Tends to be absent	7. Usually present
8. Diastolic Pressure Plateau	8. RAP=RVDP=PADP=PWP	8. PWP > RAP

RAP, right atrial pressure; A-V, arteriovenous, RVDP, right ventricular diastolic pressure, PADP, pulmonary arterial diastolic pressure; PWP, pulmonary wedge pressure.

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81. Levine HD: Myocardial fibrosis in constrictive pericarditis. Electrocardiographic and pathologic observations. Circulation 48:1268, 1973.

Obstructive Cardiomyopathy

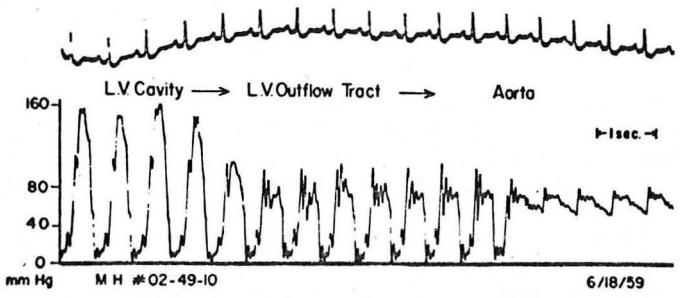
Idiopathic Hypertrophic Subaortic Stenosis, IHSS and/or Asymmetric Septal Hypertrophy (ASH)

The striking feature of hypertrophic obstructive cardiomyopathy is massive myocardial hypertrophy without dilatation of the ventricular cavity. The disease was first described by Schminke in 1907 (82) and was recognized clinically by Brock in 1957 (83). Many investigators have identified that there is massive hypertrophy of the left ventricle with the predominant hypertrophy being present in the ventricular septum resulting in an asymmetrical bulge in that region which has led to it being called asymmetrical septal hypertrophy. Massive hypertrophy is associated with a small cavity that is clearly encroached upon by the hypertrophied muscle mass resulting in left ventricular outflow obstruction. Hypertrophied muscle fibers are collected in circular fascicular "whorls" in a characteristic fashion. The myocardial fibers have a necrotic or mottled appearance and the nuclei are bizarre in shape and often have a surrounding halo (84).

A major and well established feature of the hemodynamic pattern in hypertrophic obstructive cardiomyopathy is a systolic pressure gradient between the outflow tract of the left ventricle and the aorta (Fig. 8). This gradient is

Figure 8

IHSS (ASH)



Pressure tracing recorded continuously as the catheter was withdrawn from the left ventricular cavity, through the left ventricular outflow tract, and into the ascending aorta. There is a striking "atrial kick" as well as a notch on the upstroke of the left ventricular pressure pulse proximal to the obstruction.

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82. Schminke A: Uber Linkseitige Muskulöse Conustenosen. Dtsch Med Wochenschr 33:2082, 1907.
83. Brock RC: Functional obstruction of the left ventricle. (Acquired sub-aortic stenosis.) Guys Hosp Rep 106:221, 1957.
84. Goodwin JF: Hypertrophic diseases of the myocardium. Prog Cardiovas Dis 16:199, 1973.

variable and changes from time to time in some patients under different circumstances. It can be increased by inotropic stimulation or by maneuvers that reduce the left ventricular volume either directly or as a result of peripheral vascular dilatation. The systolic outflow tract gradient is also increased after a post extra systolic beat, the compensatory pause being associated with an increase in left ventricular volume and a more powerful subsequent contraction that enhances the intracavitary obstruction. The intracavitary left ventricular obstruction has been shown to be due to the apposition of the hypertrophied septum to the anterior cusp of the mitral valve during systole in a "pinch-cock" fashion. The end-diastolic pressure in the left ventricle is usually elevated and the rate of filling of the left ventricle is reduced. The elevation of left ventricular end-diastolic pressure reflects the extent and degree of hypertrophy and the rigidity of the hypertrophic muscle with its reduced compliance and elasticity and is not necessarily the result of congestive heart failure as is true for congestive cardiomyopathy. Angiographic studies of ventricular volumes tend to demonstrate smaller than normal volumes.

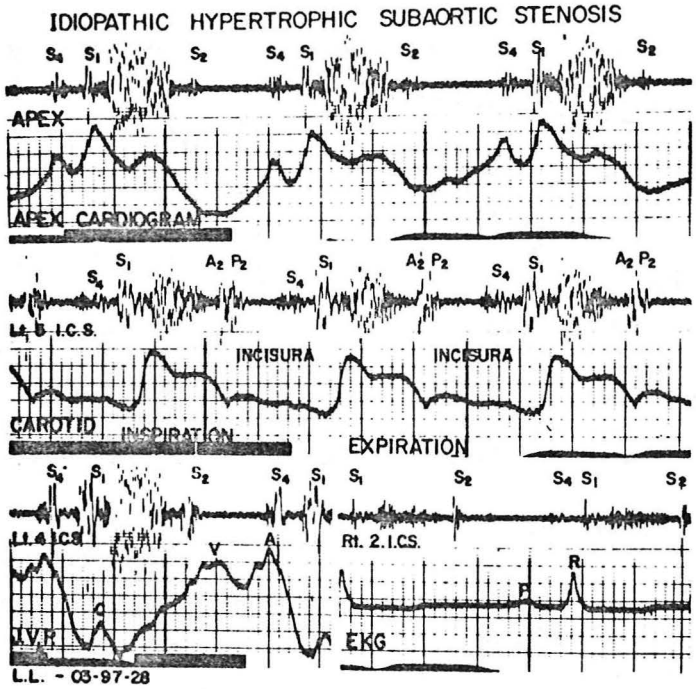
Thus, in hypertrophic cardiomyopathy the major hemodynamic disturbance is resistance to filling of the left ventricle produced by encroachment of the massively hypertrophied muscle on the ventricular cavity and the reduced distensibility of the muscle. Ventricular contraction and emptying is adequate, but the reduced compliance of the ventricle reduces the rate of filling from the atrium.

Approximately 25% of patients do not have outflow obstruction with IHSS. Though they do not have outflow tract obstruction at rest, it can often be provoked by stimuli such as those mentioned earlier. Mitral regurgitation occurs in many patients with IHSS probably as a result of anterior dislocation of the anterior cusp of the mitral valve as it moves across the cavity of the left ventricle toward the septum during systole. In a few patients severe mitral regurgitation develops ultimately requiring mitral valve replacement.

Abnormal anterior systolic movement of the anterior mitral cusp beginning with the onset of ventricular ejection has been demonstrated previously. The anterior leaflet of the mitral valve may remain apposed to the interventricular septum for up to 60% of the ejection period. Accelerated activation or contraction of the circumferentially arranged bizarre hypertrophic fibers of the left ventricular wall might account for the rapid ventricular ejection in the early non-obstructive phase of systole. Symptoms in patients with IHSS include dyspnea, angina and syncope. Angina is often due to the excessive demand of the hypertrophied myocardium for increased blood supply during effort. The coronary arteries in most patients with IHSS are large in caliber and smooth without evidence of significant obstruction. Syncope tends to occur following exercise in these patients (in contrast to valvular aortic stenosis in which syncope occurs during effort). The mechanism of the syncope in these patients is not entirely clear, but may relate to the difficulty in filling the rigid left ventricle accentuated during tachycardia by reduced diastolic filling time and further accentuated by peripheral vasodilatation occurring with exercise. Patients with IHSS typically have a rapid carotid upstroke with either a

bisferiens pulse or a "double hump" contour of the descent of the carotid. These patients have systolic ejection murmurs at the base that typically radiate poorly, if at all, into the carotids. Patients also have apical murmurs of mitral regurgitation and prominent third and fourth heart sounds (Fig. 9).

Figure 9

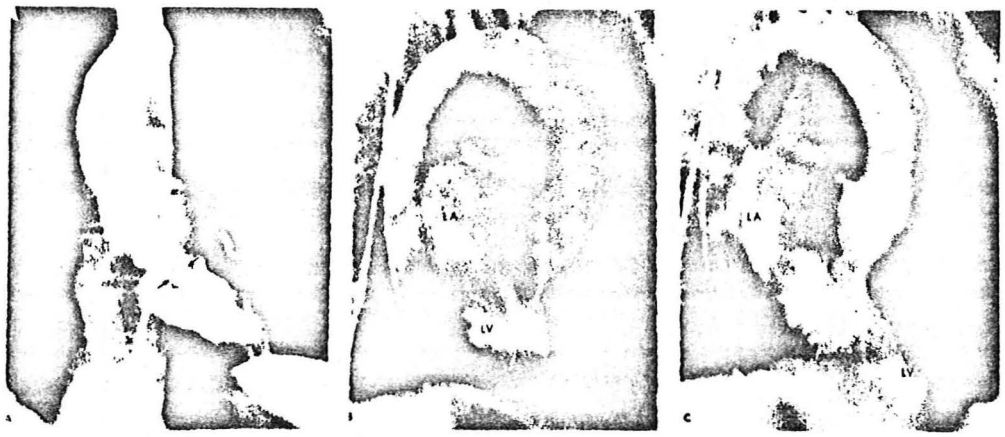


Phonocardiogram recorded at the apex, the third left intercostal space (Lt. 3 i.c.s.), the fourth left intercostal space (Lt. 4 i.c.s.), and the second right intercostal space (Rt. 2 i.c.s.). S_1, first heart sound; S_2, second heart sound; S_4, fourth heart sound; J.V.P., jugular venous pulse. Note the prominent S_4 and the presystolic expansion of the apex cardiogram, the prominent *a* wave of the J.V.P., and the rapid upstroke of the indirect carotid arterial pulse. The apex cardiogram exhibits an early systolic collapse followed by a late systolic expansion. The diamond-shaped midsystolic ejection murmur is recorded best at the apex and is less prominent along the Rt. 2 i.c.s.

The chest film ordinarily demonstrates a marked "bulge" of the left cardiac boarder suggesting a bulky mass of left ventricular muscle and slight left atrial enlargement. The heart may be enlarged, but it generally is not massively enlarged (Figs. 10,11,12). The electrocardiogram demonstrates left ventricular hypertrophy in almost every patient with IHSS.

Figure 10

IHSS (ASH)

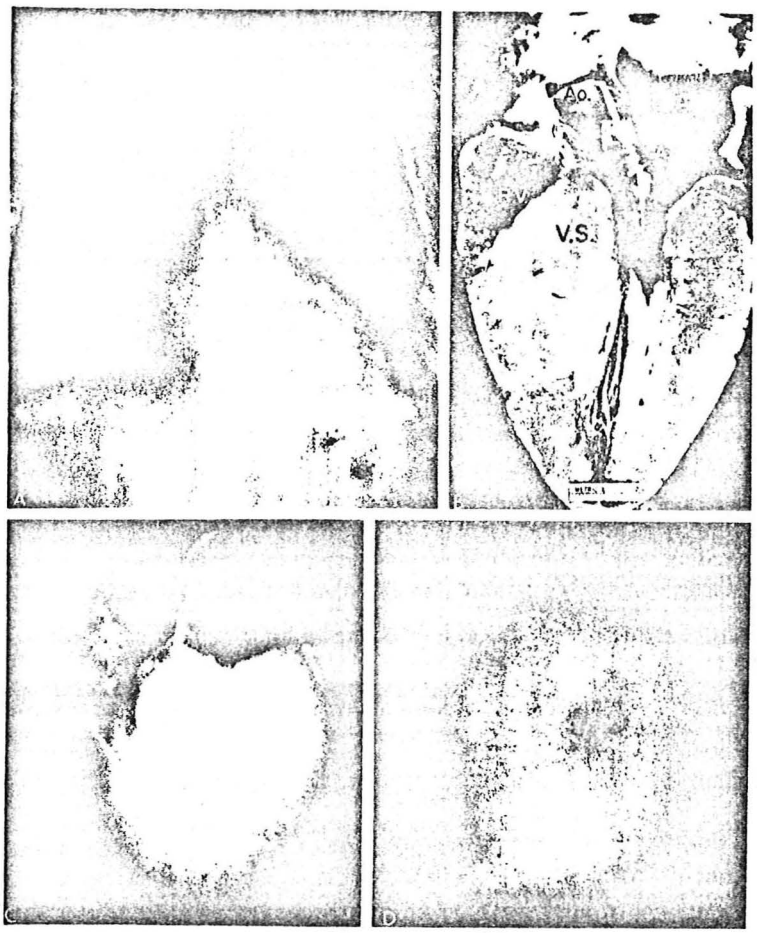


Selective left ventricular angiocardiograms in a patient with idiopathic hypertrophic subaortic stenosis, demonstrating a relatively long subvalvular area of narrowing. The film on the left was exposed in the frontal projection, and the arrows indicate the segment responsible for the obstruction. The film in the center and that on the right were exposed in the lateral projection and show the area to be narrowed during systole (center) and widened during diastole (right). There is reflux of contrast substance into an enlarged left atrium, and the left ventricular cavity is quite small during ventricular systole (center).

Figure 11

IHSS (ASH)

(Roberts and Ferrans)



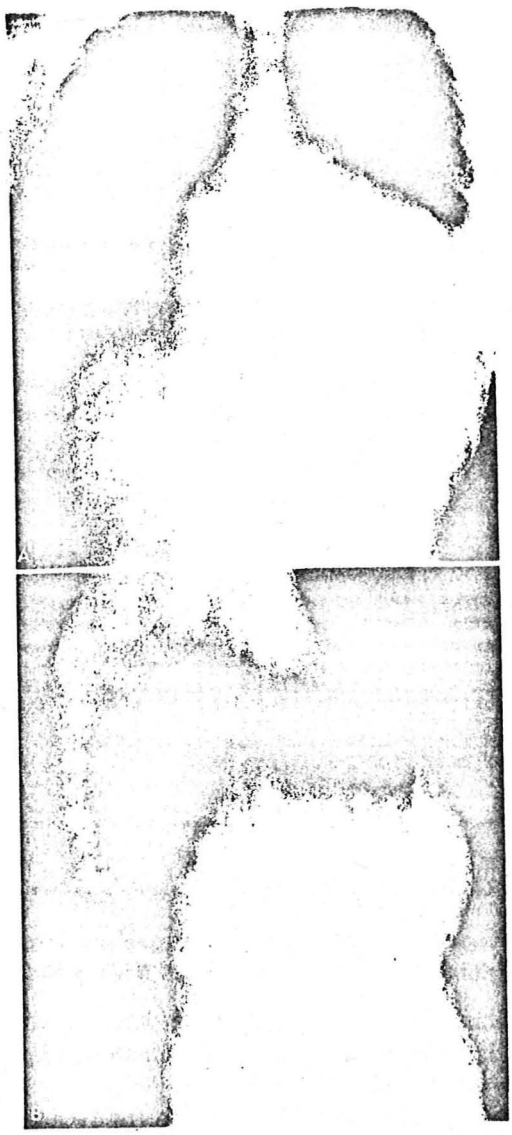
Hypertrophic asymmetric obstructive cardiomyopathy. This 36 year old woman (A67-121) developed congestive cardiac failure during her second pregnancy at age 32. When studied at age 34, she had a grade 3/6 precordial systolic murmur, loudest over the apex, and audible third and fourth heart sounds. An electrocardiogram showed bilateral bundle branch block with left axis deviation and prolongation (0.23 sec.) of the P-R interval. Catheterization disclosed a 75 mm. Hg peak systolic pressure gradient at rest between the left ventricle (160/18) and femoral artery (85/50) and a 125 mm. Hg gradient with provocation (Valsalva). The premature ventricular response was positive for idiopathic hypertrophic subaortic stenosis. She died during an episode of rapid heart action. She was known to have had multiple premature ventricular contractions on occasion. At necropsy the heart was enlarged *(A)*, weighing 450 gm., the left ventricular cavity was small *(B, C, D)*, and the ventricular septum was much thicker than the left ventricular free wall. There was little room in the left ventricular cavity for the mitral leaflets, and contact lesions (fibromas) were present on the ventricular aspect of the anterior mitral leaflet and on the adjacent left ventricular mural endocardium *(B)*. This is the typical "muscle bound" heart in which the ventricular cavities are minute in comparison to the mass of ventricular muscle. Both atria are dilated.

Figure 12

IHSS (ASH) -- Unusual Manifestation

Marked Cardiac Enlargement with IHSS

(Roberts and Ferrans)



Hypertrophic asymmetric obstructive cardiomyopathy in a 20 year old woman (A72-197). A precordial murmur had been heard at age 11, and symptoms (exertional dyspnea and palpitations) appeared at age 12 years. Catheterization at age 14 disclosed a 50 mm. Hg peak systolic pressure gradient between the left ventricle (158/10) and the brachial artery (108/57) and an abnormal premature ventricular response. A left ventricular cineangiocardiogram was consistent with idiopathic hypertrophic subaortic stenosis and showed considerable mitral regurgitation. The left ventricular cavity was small. From age 14 to 20 she had no overt congestive cardiac failure, but there were episodic palpitations and rarely chest pain relieved by rest. During this time she was functionally class II (New York Heart Association). Three months before death she had clinical, electrocardiographic, and enzymatic changes typical of acute transmural (anterolateral wall) myocardial infarction. During the period of infarction there was evidence of congestive cardiac failure. After discharge she continued to have mild dyspnea and episodic chest pain. She died shortly after the sudden appearance of features of acute pulmonary edema. The radiographs shown here were taken four years before death (age 16 years). The cardiac silhouette is massively enlarged. At necropsy the heart weighed 1250 gm. and she weighed only 47 kg. This may be one of the largest hearts ever recorded in a woman.

Frank and Braunwald in 1966 described the natural history of 126 patients with this disorder (85). Their studies showed that during a period of up to 10 years many patients remained stable, but some deteriorated symptomatically and a few even apparently improved. Sudden death was a notable feature and it was not prevented by operative correction of the left ventricular outflow obstruction resulting from the hypertrophied septal muscle mass. Atrial fibrillation occurred in some of these patients and was ordinarily poorly tolerated being associated with a marked fall in cardiac output, increase in jugular venous pressure and often the development of shock. Atrial fibrillation represents a relative medical emergency in these patients and ordinarily requires immediate cardioversion to restore hemodynamic compensation. This demonstrates the importance of ventricular filling resulting from left atrial contraction in these patients with such marked reductions in left ventricular compliance and resistance to ventricular filling.

There is a wide age range for IHSS varying from infancy to old age and there is a familial incidence suggesting that it is largely (if not entirely) an inherited disorder of cardiac muscle growth. Epstein and his associates have demonstrated using echocardiographic techniques a high incidence of abnormal septal thickness in asymptomatic relatives of patients with IHSS (86).

Recently echocardiography has been utilized as a noninvasive technique to identify the presence of IHSS. The echocardiographic identification of IHSS depends on finding increased septal muscle mass, anterior mitral valve leaflet septal muscle coaptation and the early systolic anterior motion forward of the anterior leaflet of the mitral valve (87). More recently, Bulkley and her associates have utilized thallium-201 myocardial perfusion imaging to recognize IHSS (88). The asymmetric septal hypertrophy was evident on the thallium scintigrams in patients with IHSS where a ratio of septum to left ventricular free wall of 1.7 cm compared to a normal of 1 cm was found.

Treatment of IHSS depends on utilizing beta blocking agents and typically inderal (propranolol) has been utilized. This agent reduces left ventricular outflow obstruction and decreases left ventricular end-diastolic pressure (improving compliance) by virtue of its effect to decrease left ventricular contractility as a consequence of its beta blockade. Propranolol's effect to slow the heart rate is also helpful in terms of increasing left ventricular filling. In patients that do not respond in an ideal manner to medical therapy, surgical therapy is employed and consists of surgical resection of

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85. Frank S, Braunwald E: Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on natural history. Circulation 37:759, 1968.
86. Clark CE, Henry WL, Epstein SE: Familial prevalence in genetic transmission of idiopathic hypertrophic subaortic stenosis. N Engl J Med 289:709, 1973.
87. Henry WL et al: Asymmetric septal hypertrophy: Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. Circulation 47:225, 1973.
88. Bulkley BH et al: Idiopathic hypertrophic subaortic stenosis: Detection by thallium-201 myocardial perfusion imaging. N Engl J Med 293:1113, 1975.

significant amounts of the asymmetrically hypertrophied muscle mass in the ventricular septum. Cooley has argued that prosthetic mitral valve replacement may also be helpful in many patients with IHSS, but the general consensus is that prosthetic valve replacement should be reserved for those few patients with severe mitral regurgitation (89).

It should also be noted that in addition to the physical signs described above as being highly suggestive of the presence of IHSS, that one expects to find reduced systemic arterial pulse pressure in the beat following a premature ventricular contraction since the heightened contractility occurring as a result of increased ventricular filling in the lengthy pause after a premature ventricular beat results in increased intracavitary obstruction. Typically, the systolic ejection murmur of IHSS increases in intensity with Valsalva, nitroglycerin, amyl nitrate, isoproterenol and with cardiac glycoside administration. In addition, the murmur of IHSS also tends to increase in the beat after a premature ventricular contraction (just as the murmur of valvular aortic stenosis does), but tends to decrease in intensity with squatting (as a combined result of increased venous return and an increase in systemic vascular resistance) and as systemic arterial vascular resistance and pressure is elevated by either pharmacological or physiological means (89-93).

Some confusion in the past has arisen from the fact that a small number of patients had a hyperactive cardiac apex that resulted in "catheter entrapment" at the cardiac apex and an apparent intracavitary gradient that was limited only to the extreme apex of the heart. This is now felt to be a very localized phenomenon and not suggestive of IHSS (ASH). The associated additional hemodynamic findings, the life history and the associated signs and symptoms of IHSS are not features of the hyperdynamic apex ("catheter entrapment syndrome") and thus it is only important that cardiologists and those engaged in cardiac catheterization understand this latter entity and be able to distinguish it from true IHSS.

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89. Cooley DA: Diffuse muscular subaortic stenosis: Surgical treatment. Am J Cardiol 31:1, 1973.
90. Shah PM: Idiopathic hypertrophic subaortic stenosis. Chest 68:814, 1975.
91. Stefadouros MA: Paradoxic response of the murmur of idiopathic hypertrophic subaortic stenosis to the Valsalva maneuver. Am J Cardiol 37:89, 1976.
92. Cassidy J et al: The effect of isometric exercise on the systolic murmur of patients with idiopathic hypertrophic subaortic stenosis. Chest 67:395, 1975.
93. Glancy DL, Epstein SE: Differential diagnosis of type and severity of obstruction to left ventricular outflow. Prog Cardiovas Dis 14:153, 1971.

Miscellaneous Heart Muscle Disease

I. Sarcoid Involvement of the Heart

The incidence of myocardial sarcoidosis is about 20% of patients with the disease (94). Cardiac sarcoidosis usually has a brief course. Sudden death appears to be a common occurrence. Various cardiac arrhythmias including multiple atrial, AV junctional and ventricular premature contractions as well as sustained atrial and ventricular tachycardia have been reported (95). Conduction disturbances varying from first degree AV block to advanced second degree heart block and complete heart block are also fairly common in this disease entity. Congestive heart failure either due to primary diffuse involvement of the myocardium (or in some instances secondary to chronic lung disease and pulmonary hypertension) occur in about 80% of the patients with myocardial sarcoidosis. Nonspecific ST-T wave changes due to myocardial infiltration by sarcoidosis have been described. The pericardium can also be involved in sarcoidosis resulting in recurrent pericardial effusions. Cardiac murmurs secondary to sarcoid involvement of various heart valves have been reported. Sudden mitral regurgitation has been documented in an occasional patient with myocardial sarcoidosis (94) and granulomatous involvement of the aortic valve has also been described (96).

II. "Fatty Heart"

Obesity has long been regarded as shortening the expectation of life. Hippocrates stated that fat persons were apt to die earlier than those who were slender. Laennec (1819) devoted a chapter in his essay on mediate auscultation to the "fatty heart" and established it as a cardiological entity. He distinguished between fat on the surface of the heart and fatty degeneration in which the muscular substance was transformed into fat exhibiting a yellowish pallor (97). In Dublin, Cheyne, Stokes, Adams, and others became obsessed with fatty heart as the most important form of myocardial disease and sought to identify it with clinical symptoms of Cheyne-Stokes breathing, a slow pulse and heart failure. These investigators admitted that coronary sclerosis was often present, but they maintained that fatty change in atrophy in the myocardium was the primary cause of the symptoms and that the presence of extensive fat in the heart was not necessarily accompanied by coronary disease.

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94. Zoneraich S et al: Myocardial sarcoidosis presenting as acute mitral insufficiency. Chest 66:452, 1974.
95. Porter GH: Sarcoid heart disease. N Engl J Med 263:1350, 1960.
96. Ghosh P et al: Myocardial sarcoidosis. Br Heart J 34:769, 1972.
97. Bedford E: The story of fatty heart. A disease of Victorian times. Br Heart J 34:23, 1972.

Sudden death was a frequent termination in patients with fatty metamorphosis of the heart. The exact role of fatty metamorphosis in interfering with myocardial function and producing either arrhythmias or congestive heart failure is still somewhat uncertain, but I suspect as the various types of non-coronary heart muscle disease become better elucidated there will be a role for fatty metamorphosis in altering myocardial function--perhaps it will be associated with recurrent arrhythmias and/or perhaps some patient with simply extensive fatty change in the heart will have obvious myocardial dysfunction and possibly congestive heart failure. This remains to be elucidated in the future, but I suspect it is a subject in which considerable interest will ultimately be focused once again. It should also be noted that the border zone area surrounding an area of myocardial infarction in experimental animals contains cells that have considerable fat in them, but otherwise appear structurally normal. The mechanism of this fat accumulation and its implications in terms of the type of injury that the cell has suffered and whether or not it is indeed reversible also remain to be described in the future.

III. Metastatic Disease to the Heart

Hearts may be involved by metastatic disease associated with various tumors including malignant melanoma, lymphoma, leukemia, breast and lung tumors and occasionally even by primary cardiac tumors such as rhabomyosarcomas. Despite large nodules in the heart resulting from either primary or metastatic disease, cardiac muscle dysfunction as a consequence of either primary or metastatic tumors is extremely unusual. It is more common for patients to develop premature atrial or ventricular beats and/or any of the various forms of heart block as opposed to the development of congestive heart failure secondary to malignancy that involves the heart. Thus, metastatic tumor or primary malignancies involving the heart very uncommonly result in heart muscle dysfunction, but arrhythmias and pericardial effusions occur with some frequency.

IV. Cardiac Involvement by Collagen Disease

Systemic lupus erythematosus, rheumatoid arthritis, scleroderma and/or periarteritis nodosa may all involve the heart either in the form of an arteritis (SLE and periarteritis nodosa) or in the form of nodules (rheumatoid arthritis). By involving the heart in the form of an arteritis, myocardial infarction and/or ventricular or atrial premature beats or heart block may develop. In its involvement of the heart by nodules, rheumatoid arthritis may produce atrial or ventricular arrhythmias or even various types of heart block. Frank congestive heart failure resulting from muscle replacement (and not due to myocardial infarction based on arteritis) is an extremely unusual complication of cardiac involvement by collagen disease (98).

V. Basophilic Degeneration of Myocardium

Basophilic degeneration of myocardium is a frequent finding in routine autopsies. It is found principally in the hearts of elderly persons, but

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98. Nomeir AM: Cardiac involvement in rheumatoid arthritis. Ann Intern Med 79:800, 1973.

occasionally occurs in patients of younger age. The most frequent site of cardiac involvement by basophilic degeneration is the interventricular septum, but it is usually present in more than one site of the heart and occasionally is extensive. Occasional patients have congestive heart failure during life that subsequently turn out to have extensive basophilic degeneration at the time of postmortem examination, but whether or not the latter is in any way responsible for the development of congestive heart failure is presently uncertain.

VI. Diabetes Mellitus and Myocardial Disease

From time to time scattered reports appear suggesting that diabetes mellitus is associated with the development of myocardial disease and congestive heart failure in the absence of coronary artery disease, hypertension or any other known factors that might be responsible for the development of the myocardial failure. Indeed, we have seen two or three such patients that have come to autopsy and have had myocardial hypertrophy and congestive heart failure in the absence of severe coronary artery disease. From the previous extensive discussion regarding etiologies (both known and unknown) of primary myocardial disease it should be obvious that there are many potential reasons why a patient with diabetes mellitus might develop heart muscle disease and congestive heart failure even in the absence of coronary artery disease; this realization makes it extremely difficult to be certain that there is a true association between diabetes mellitus and the development of heart muscle disease independent of coronary atherosclerosis. Critical analysis of potential patients in this category both during life and at the time of postmortem examination in the future should help to establish or refute its validity as a separate and distinct entity, but at the present time the number of patients considered to have this abnormality is quite small in relationship to the total group of patients with diabetes mellitus and with various cardiac abnormalities. Thus, I am not able to be certain that there is an etiologic relationship between diabetes mellitus and the development of myocardial dysfunction and heart failure in the absence of coronary artery disease and in the absence of any other important etiology presently.

Immunoglobulin Binding in Cardiomyopathic Hearts

Serum antibody directed against heart muscle has been reported in patients with various forms of heart disease (99-101). It has been postulated that serum antibody directed against heart muscle is the result rather than the cause of the myocardial injury in these conditions. Despite severe cardiac disability in patients with idiopathic cardiomyopathy, antibody directed against

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99. Kaplan MH et al: Immunologic studies of heart tissue. IV. Serologic reactions with human heart tissue as revealed by immunofluorescent methods; isoimmune, Wassermann and autoimmune reactions. J Exp Med 113:17, 1961.

100. Hess EV et al: Heart muscle antibodies in rheumatic fever and other diseases. J Clin Invest 43:886, 1964.

101. Dodson VN et al: Certain immunologic substances in the serum of patients with myocardial infarction and other cardiovascular diseases. Am Heart J 73:221, 1967.

human heart muscle is not found in serum in increased frequency. However, Sanders and Ritts (102) found bound gamma globulin in the hearts of 5 of 9 patients with cardiomyopathy. Das et al (103) also demonstrated bound gamma globulin by direct immunofluorescent techniques in heart tissue from three patients with severe congestive cardiomyopathy. In 2 of these 3 complement ($Beta_1$ C) was also bound to the heart muscle. Heart tissue from one of 6 patients dying after myocardial infarction showed a trace of bound gamma globulin but no bound complement. Das and his associates concluded that during life the heart in advanced cardiomyopathy may preferentially fix heart reactive immunoglobulins to specific sarcolemmal and subsarcolemmal antigens thus rendering anti-heart antibody not detectable in serum. However, the exact role of autoimmune phenomenon in the initiation and perpetuation of various types of idiopathic cardiomyopathy remains uncertain presently, but this is an area that deserves additional exploration in the future.

One Approach to the Identification and Characterization of Heart Muscle Disease in Patients

Approach to Identification of Cardiomyopathy

I. Establish etiology of congestive heart failure, i.e., is it secondary to coronary artery disease, hypertension, primary valvular heart disease, pericardial disease, pulmonary hypertension or shunt lesion (ASD, VSD, PDA)-----or is it due predominantly to heart muscle disease without any major contribution from any of the above factors?

   The answer to this question should come from:

   a) Careful and detailed history and physical examination.
   b) Exercise testing.
   c) Analysis of blood lipids and blood sugar
   d) Noninvasive tests including electrocardiography, echocardiography and radionuclide myocardial scintigraphy (myocardial imaging for presence of infarction and to look for left to right shunt, measure ejection fraction, ventricular volumes and segmental ventricular wall motion and to rule out ventricular aneurysm).
   e) If necessary and/or appropriate, invasive study by cardiac catheterization with left ventricular angiography and coronary arteriography.

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102. Sanders B, Ritts RE Jr: Ventricular localization of bound gamma globulin in idiopathic disease of myocardium. JAMA 194:171, 1965.
103. Das SK: Immunoglobulin binding in cardiomyopathic hearts. Circulation 44:612, 1971.

II. If congestive heart failure is mainly due to non-coronary artery induced heart muscle abnormalities then additional classification into either:

a) Congestive cardiomyopathy (virus, EtOH, amyloidosis, various other toxins and ??).
b) Restrictive cardiomyopathy (amyloidosis, hemochromatosis, endomyocardial fibroelastosis, myocardial fibrosis associated with constrictive pericarditis).
c) Obstructive cardiomyopathy (IHSS = ASH)
d) Myocarditis (consider infectious causes including virus and toxoplasmosis, bacterial, fungal, rickettsial, trypanosomal possibilities, etc.).
e) Miscellaneous (mainly sarcoidosis)

Distinction between any single etiology within a broad group will require appropriate chemical and/or bacteriological testing. Likely to be of additional help in the future is per venous myocardial biopsy to obtain material for histological analysis. In some instances invasive pericardial and/or myocardial biopsy may also be necessary.

Treatment of Cardiomyopathies

Obviously the treatment of the various forms of cardiomyopathy depends in large part upon their etiology. If idiopathic hypertrophic subaortic stenosis is responsible for heart failure and syncopal spells, then initial treatment with propranolol is indicated. Should this prove unsuccessful then consideration would be given to surgical correction of the left ventricular intracavitary obstruction. If hemochromatosis is responsible for congestive heart failure, then phlebotomy, diuretics and digitalis are indicated and one would be optimistic that the heart muscle dysfunction and congestive heart failure would improve dramatically with a prolonged period of phlebotomy. Thus, much depends on the initial etiology for the congestive heart failure. General recommendations, however, for the treatment of those forms of myocardial disease for which there is no specific therapy presently would include some of the following:

1) Use of diuretics and digitalis as seems proper.

2) Some consideration of the need for antiarrhythmic agents, and/or pacemaker support to treat arrhythmias and/or heart block. Obviously, this has to be highly individualized and there will be some patients who have no need for either of these, but others who will benefit substantially from their use.

3) Consideration of the use of anticoagulants. Particularly for congestive cardiomyopathy, there is an unacceptably high incidence of both pulmonary and systemic embolic disease as previously indicated and prophylactic anticoagulation would in some instances be quite helpful. However, the ability of any individual patient to take anticoagulants depends in large part upon the presence or absence of other medical

disease processes, the presence or absence of liver disease, the presence or absence of any bleeding tendency, his ability to cooperate by taking the medication as instructed and by having frequent prothrombin tests performed and his ability to avoid trauma.

4) Consideration should also be given to the possible benefits of a period of restricted activity including in some instances bed rest for a period of a few weeks. There is not terribly convincing evidence to suggest that this will be beneficial in patients with congestive cardiomyopathy, but there is some physiological rationale to consider this possibility and in the hands of others, it has been alleged to be of some therapeutic help. Thus, I think this should be considered in appropriate individual circumstances. If there is no evidence that heart size is decreasing with bed rest after a reasonable period of time, this should be abandoned.

5) Appropriate activity restriction in terms of avoiding excessively heavy manual labor in appropriate patients would also seem worthwhile.

6) Some consideration should also be given to the genetic implications of the disease process afflicting any individual and in some instances (IHSS and the neuromyopathic disorders) genetic counseling may be in order.