Editorial:
Myocardial Fiber Disarray and Ventricular Septal Hypertrophy
In Asymmetrical Hypertrophy of the Heart

E. D. WIGLE, M.D. and M. D. SILVER, M.D.

ALTHOUGH TWO NINETEENTH CENTURY French pathologists1, 2 and an early twentieth century German pathologist3 described cardiac pathological findings compatible with what we know today as "asymmetrical hypertrophy of the heart," it remained for Donald Teare to bring attention to this entity in 1958.4 In nine cases of sudden death, Teare described a marked hypertrophy and thickening of the interventricular septum at postmortem examination. In five of these cases the hypertrophic process also involved the anterior wall of the left ventricle. By contrast, the posterior left ventricular wall appeared not to be involved. The process was truly asymmetric.4 Microscopic examination of the hypertrophic areas of the myocardium revealed myocardial fiber disarray (a very bizarre form of myocardial fiber hypertrophy) and significant amounts of interstitial fibrosis. Teare's report, together with that of Lord Brock,5 opened the flood gates to voluminous literature on this fascinating, sometimes controversial, but always stimulating, entity. Much has been written on the clinical, hemodynamic, angiographic, pathophysiologic, pharmacodynamic, therapeutic and pathologic aspects. And more is yet to come.

Like a rejected lover, asymmetrical cardiac hypertrophy has been called many things. To distinguish it from other cardiomyopathies, the term hypertrophic cardiomyopathy6 seems appropriate. When obstruction to left ventricular outflow is present (hypertrophic obstructive cardiomyopathy), the terms hypertrophic7 or muscular8 subaortic stenosis have been applied. It should be noted, however, that muscular or hypertrophic subaortic stenosis may be caused not only by asymmetric cardiac hypertrophy, but also by concentric left ventricular hypertrophy.9, 10 In fact, it has recently been described in the absence of any apparent left ventricular hypertrophy.11

Until recently the presence of ventricular septal hypertrophy and/or myocardial fiber disarray on microscopy were generally considered to be specific for asymmetrical hypertrophy of the heart. Such is no longer the case. Thickening of the interventricular septum has been described in fetuses and in some newborn infants as a normal evolutionary stage.12-16 Abnormal septal hypertrophy has been described in infants of diabetic mothers,17 in association with neuromuscular diseases18 including Friedreich's ataxia,19 in olympic athletes19 and weightlifters,20 in pulmonary stenosis and pulmonary hypertension associated with right ventricular hypertrophy,13, 15, 21 in chronic hemodialysis patients,22 in coronary artery disease,23 especially in patients with hypertension and diaphragmatic myocardial infarction,24 in aortic valve disease,25 in tunnel subaortic stenosis,26 and in certain congenital heart diseases.13, 15, 27, 28 In many, but not all of these situations, septal hypertrophy appeared to be secondary to a pressure overload of either ventricle. Similarly, myocardial fiber disarray on microscopic examination of the myocardium was previously believed to be specific for hypertrophic cardiomyopathy. It is now recognized, however, that foci of myocardial fiber disarray may occur in normal hearts and in various cardiac disease states other than asymmetrical cardiac hypertrophy.13, 27-31 In normal hearts and in patients with concentric left ventricular hypertrophy, coronary artery disease or cor pulmonale, myocardial fiber disarray occurs principally in foci at the anterior and posterior ends of the ventricular septum at its junction with the left and right ventricular free walls, at the left ventricular apex, at the junction of the right ventricular inflow and outflow tracts and at the junction of the trabecular and compact muscle layers of the ventricles.13, 27-31 Recently, Van Der Bel-Kahn quantitated the amount of myocardial fiber disarray found at postmortem in the hearts of normals and infants with hypertension, coronary artery disease and cor pulmonale, by examining a whole slice of the myocardium taken 2 cm caudal and parallel to the atroventricular groove.30 In 48 of 53 hearts examined, myocardial fiber disarray involved less than 11% of the examined myocardium and no heart had more than 20% myocardial fiber disarray. In contrast, one heart with hypertrophic cardiomyopathy had more than 50% myocardial fiber disarray, involving not only the septum, but also the left ventricular free wall.30 Similarly, Maron, Epstein and Roberts have recently quantitated the amount of myocardial fiber disarray that occurred in the ventricular septum of 23 patients with hypertrophic cardiomyopathy and in 107 patients with concentric left ventricular hypertrophy.31 All patients with hypertrophic cardiomyopathy had myocardial fiber disarray and 20 of 23 had greater than 5% of the septum involved. Ten (9%) of the 107 patients with
concentric hypertrophy had myocardial fiber disarray but only four of these had greater than 5% of their septum involved. The area of the septum involved in hypertrophic cardiomyopathy averaged 50% vs 1% involvement in patients with concentric hypertrophy.34 Clearly, the amount of myocardial fiber disarray in whole horizontal slices of myocardium, or in the ventricular septum alone, is greater in hypertrophic cardiomyopathy than in the disease states compared.

Previously, Roberts, Epstein and their coworkers at the National Institutes of Health studied the distribution of myocardial fiber disarray in patients with both obstructive and nonobstructive hypertrophic cardiomyopathy, and suggested that the bizarre myocardial fiber hypertrophy is "presumably a morphologic manifestation of a genetically transmitted myocardial defect."32 33 These authors stated that hearts from patients proven to have nonobstructive hypertrophic cardiomyopathy had myocardial fiber disarray in both the ventricular septum and in the left and right ventricular free walls, whereas patients with hypertrophic obstructive cardiomyopathy had myocardial fiber disarray centered in the ventricular septum, with the fiber disarray either being absent or rarely found in the right and left ventricular free walls. As these authors have indicated, the method of examining the myocardium may have favored finding myocardial fiber disarray in the left and right ventricular free walls of the nonobstructive cases and not in the obstructive cases. Thus, six of eight nonobstructive cases were examined postmortem and the remaining two cases by myocardial biopsy. Of the 14 obstructive cases, only two were examined postmortem, while 12 underwent myocardial biopsy.32

In our own studies on the distribution of myocardial fiber disarray in 18 cases of hypertrophic cardiomyopathy, using transverse sections of the whole heart cut at 1 cm intervals from apex to base, we found that myocardial fiber disarray occurred in the ventricular septum and also in the left ventricular free wall in both the obstructive and the nonobstructive forms of hypertrophic cardiomyopathy.34 35 On gross examination, the ever-present ventricular septal hypertrophy often extended into the anterior free wall of the left ventricle,36 as described by Teare.4 At times the hypertrophy in the anterior wall exceeded that seen in the septum itself and was indistinguishable in life by plain chest x-ray.36

The investigators at the National Institutes of Health have pointed out a significant difference between the obstructive and nonobstructive forms of hypertrophic cardiomyopathy with regard to the thickness of the posterior left ventricular free wall behind the posterior mitral valve leaflet.33 This area of the left ventricular free wall is thickened in obstructive hypertrophic cardiomyopathy as a result of outflow obstruction, and becomes thinner following surgical relief of this obstruction. In nonobstructive hypertrophic cardiomyopathy this area is not thickened. It is important to emphasize, however, that other areas of the left ventricular free wall in nonobstructive hypertrophic cardiomyopathy may be hypertrophied and thickened.33 This latter observation is entirely in keeping with Teare's original report4 and with our own observations.36

In this issue of Circulation a report by Hutchins and Bulkley suggests that a catenoid shape of the ventricular septum may cause the myocardial fiber disarray and ventricular septal hypertrophy that is seen in asymmetrical hypertrophy of the heart.37 Although they use the term "idiopathic hypertrophic subaortic stenosis," we do not know whether obstruction to left ventricular outflow was present in these cases. This article is one of a series of recently published papers by these authors on the nature and distribution of myocardial fiber disarray in normals, in hypertrophic cardiomyopathy and in other conditions.13 27 These authors have demonstrated that myocardial fiber disarray, indistinguishable from that seen in hypertrophic cardiomyopathy, may be seen in infants with aortic or pulmonary atresia and intact ventricular septa, conditions in which the left or right ventricle, respectively, is believed to undergo isometric contraction.13 27 They have suggested that the altered wall stresses related to isometric contraction of the ventricles in these conditions may cause the myocardial fiber disarray.27 Based on these observations, Hutchins and Bulkley27 initially suggested that the myocardial fiber disarray seen in hypertrophic cardiomyopathy was also due to isometric contraction resulting from cavity obliteration of the left ventricle.38 If this were the case then virtually all cases of hypertrophic cardiomyopathy would have to have cavity obliteration, since virtually all have myocardial fiber disarray. In addition, the free wall of the left ventricle should be involved as much as the septum since both would undergo isometric contraction. However, these authors, in contradistinction to others,36 37 38 find no myocardial fiber disarray in the free wall of the left ventricle.37 Furthermore, cavity obliteration does not occur in all cases of hypertrophic cardiomyopathy (with or without obstruction to outflow), and in our own experience, cavity obliteration is not a sine qua non for the diagnosis of hypertrophic cardiomyopathy.39

In their current paper, Hutchins and Bulkley describe a second type of isometric contraction that, by altering the wall stresses, could cause the myocardial fiber disarray and septal hypertrophy in hypertrophic cardiomyopathy.37 From measurements on postmortem hearts studied after formalin fixation in the distended state, they describe the ventricular septum in hypertrophic cardiomyopathy to be catenoid in shape (convex to the left from apex to base, concave to the left in the horizontal plane) with net zero curvature at the left septal surface. The authors suggest that such a shape would lead to little or no myocardial shortening, i.e., isometric contraction of the septum which in turn would be responsible for the septal myocardial fiber disarray and septal hypertrophy.27 This concept would also account for the relative lack of systolic septal thickening on echocardiography.33 In
their specimens, myocardial fiber disarray was absent in the left and right ventricular free walls, a point that is compatible with their theory, but at variance with the observations of others, who have described myocardial fiber disarray in the free walls of the ventricles in hypertrophic cardiomyopathy. In addition, the catenoid septal shape theory would not account for the distinct anterior wall hypertrophy that occurs in a significant number of cases. By the nature of their studies, Hutchins and Bulkley have examined the end-stage of this condition and not the beginning. How does the septum become catenoid in the first place? In this regard, it is important to realize that the normal ventricular septum may be sigmoid-shaped in infants or adults. A sigmoid-shaped septum is convex to the left from apex to base, which is rather similar to the described catenoid shape.

The case proposed by Hutchins, Bulkley and their associates, that isometric contraction causes myocardial fiber disarray in hypertrophic cardiomyopathy, is attractive and is supported by the evidence they provide. They have suggested that isometric contraction may occur in hypertrophic cardiomyopathy by left ventricular cavity obliteration and/or because of the catenoid septal shape. We and others have indicated that there is another possible cause for isometric contraction in hypertrophic cardiomyopathy. We have studied several patients with outflow tract gradients in excess of 100 mm Hg in whom the ejection fraction varied between 50-70% (no cavity obliteration). During the last 30% of systole in these patients, the left ventricular volume was virtually unchanged in spite of there being up to 40 ml of blood remaining in the ventricle. Thus, in these hearts isometric contraction occurred at end-systole in the absence of cavity obliteration. If myocardial fiber disarray in hypertrophic cardiomyopathy is due to any form of isometric contraction, then this is potentially a third type of isometric contraction that could cause the fiber disarray.

The relationship between the gross and microscopic myocardial pathology and the clinical manifestations in hypertrophic cardiomyopathy, both in systole and diastole, bears mention. There now appears to be substantial evidence that obstruction to left ventricular outflow occurs in those cases with the thickest septa and narrowest outflow tracts at the onset of systole. A rapid, early systolic ejection passing close to the anterior mitral leaflet could draw this leaflet into the outflow tract by a Venturi mechanism and cause the obstruction to outflow and mitral regurgitation. Surgical septal myotomy and/or myectomy results in a thinning of the ventricular septum, widening of the outflow tract at the onset of systole, abolition of the systolic anterior motion of the anterior mitral leaflet, and with this, abolition of the outflow tract gradient and mitral regurgitation. This operation may also dramatically reduce left ventricular end-diastolic pressure, and it has been speculated that this might be due to a change in left ventricular diastolic filling characteristics.

Obviously, the myocardial pathology also has an important relationship to the diastolic filling abnormalities seen in hypertrophic cardiomyopathy. From the very early studies of this condition, it has been recognized that diastolic distensibility or compliance was frequently abnormal in both the left and/or right ventricles. Recent studies suggest that the left ventricular filling rate, determined by the rate of free wall thinning, may be a principle determinant of some clinical manifestations. In patients with obstruction to left ventricular outflow and abnormal diastolic filling, one or both of these abnormalities may be important in determining a given patient's symptoms. However, some authors believe that abnormal diastolic filling is the most important factor in determining symptoms, regardless of whether obstruction to outflow is present.

Knowing the clinical implications of the myocardial pathology in hypertrophic cardiomyopathy, it is important that studies of the cause and nature of the myocardial disorder continue, and that more basic studies be undertaken. For example, nonhistone nuclear proteins may play a role in genetic expression. Liew and Sole have reported distinct alterations in the composition of these proteins in the genetically determined cardiomyopathy of the Syrian hamster. More recently they have found almost identical alterations in the nonhistone nuclear proteins in myocardial tissue removed from patients with muscular subaortic stenosis at the time of surgery. Whether these findings have any relation to myocardial fiber disarray in hypertrophic cardiomyopathy is not known.

Important questions must be answered regarding the nature and distribution of the myocardial hypertrophy and myocardial fiber disarray in patients with asymmetrical hypertrophy of the heart. Is there myocardial fiber disarray in the left and right ventricular free walls? If there is, is it present only in patients without obstruction to left ventricular outflow, or is it also present in patients with obstruction to left ventricular outflow? Is myocardial fiber disarray genetically determined or is it due to isometric contraction, or could it be caused genetically in some instances and by isometric contraction in others? If myocardial fiber disarray is due to isometric contraction and is also present in the left ventricular free wall, then a catenoid shape to the ventricular septum would not in itself explain myocardial fiber disarray in the free wall. Isometric contraction due to cavity obliteration or due to inability of the myocardium to shorten toward end-systole in the absence of cavity obliteration could explain myocardial fiber disarray in the left ventricular free wall. Is it possible that myocardial fiber disarray in hypertrophic cardiomyopathy can be caused by a number of types of isometric contraction, some of which have been referred to? These and other questions must be clarified.

In the 20 years since Teare's description of asymmetrical hypertrophy of the heart and Lord Brock's recognition of the clinical entity much has been learned. Perhaps the stimulating and thought-
provoking paper by Hutchins and Bulkley in this issue of Circulation, as well as their previous work in this field, will hasten this learning process.

References
31. Maron BJ, Epstein SE, Roberts WC: Cardiac muscle cell disorganization in the ventricular septum. Evidence from quantitative histology that it is a highly sensitive marker of hypertrophic cardiomyopathy. (abstr) Am J Cardiol 41: 435, 1978
42. Wile ED: Clinical problems in hypertrophic cardiomyopathy. Lecture, 50th Scientific sessions, American Heart Association, Miami Beach, Florida, Nov 28-Dec 1, 1977
44. Henry WL, Clark CE, Griffith JM, Epstein SE: Mechanism of
left ventricular outflow obstruction in patients with obstructive asymmetric septal hypertrophy (idiopathic hypertrophic subaortic stenosis). Am J Cardiol 35: 337, 1975

Electrocardiographic Findings in Patients with Obstructive and Nonobstructive Hypertrophic Cardiomyopathy

DANIEL D. SAVAGE, M.D., PH.D., STUART F. SEIDES, M.D., CHESTER E. CLARK, M.D., WALTER L. HENRY, M.D., BARRY J. MARON, M.D., FELIPE C. ROBINSON, M.D., AND STEPHEN E. EPSTEIN, M.D.

SUMMARY One hundred and thirty-four patients with hypertrophic cardiomyopathy were evaluated by standard 12-lead electrocardiography. Normal electrocardiograms were extremely uncommon, occurring in less than 7% of each subgroup of patients (i.e., those with or without either symptoms or obstruction to left ventricular outflow), with the exception of those who were both asymptomatic and had no left ventricular outflow obstruction. Even in this subgroup, however, normal electrocardiograms occurred in only 27% of patients. Repolarization abnormalities and left ventricular hypertrophy were the most common abnormalities, occurring in 81% and 62%, respectively, of the total population. A broad spectrum of other electrocardiographic abnormalities was found, but none was unique to hypertrophic cardiomyopathy.

Patients with vs those without electrocardiographic left ventricular hypertrophy or left atrial abnormality had significantly (P < 0.005) greater mean ventricular septal thickness (22 ± 0.6 vs 19 ± 0.6 mm) and left atrial dimension (48 ± 1 vs 40 ± 1 mm) measured by echocardiography, and significantly (P < 0.01) higher mean pulmonary capillary wedge pressure (16 ± 1 vs 10 ± 1 mm Hg) and left ventricular end-diastolic pressure (20 ± 1 vs 15 ± 1 mm Hg). The high prevalence and diverse nature of electrocardiographic abnormalities suggest that any patient with an unusual and unexplained electrocardiogram should be suspected of having hypertrophic cardiomyopathy even if the physical examination is normal, as is often the case in patients without obstruction.

IN THE DECADE PRIOR TO 1968 there were numerous reports of electrocardiographic findings in patients with hypertrophic cardiomyopathy.1-10 Most of the patients were reported to have obstruction of left ventricular outflow, since the resulting murmur heard on physical examination and the gradient recorded at catheterization were the major criteria used to establish the diagnosis at that time. In the early 1970s Henry et al.16 and Abbasi et al.17 utilized asymmetric septal hypertrophy, detected by echocardiography, as a disease marker. This technique led to the recognition of a broad pathophysiologic spectrum of hypertrophic cardiomyopathy, including patients with or without either symptoms or left ventricular outflow obstruction. Little data have subsequently been published regarding the electrocardiographic findings in this group of patients.

This investigation examined the prevalence and diagnostic usefulness of electrocardiographic abnor-
Myocardial fiber disarray and ventricular septal hypertrophy in asymmetrical hypertrophy of the heart.
E D Wigle and M D Silver

Circulation. 1978;58:398-402
doi: 10.1161/01.CIR.58.3.398

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/58/3/398.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/