Myocardial disarray

A critical review

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SUMMARY Myocardial disarray or disorganisation is at present a contentious topic, not least because its value as a clinical marker for hypertrophic cardiomyopathy has changed considerably over the years. Initially observed as one of the features of asymmetric septal hypertrophy, disarray has since been promoted as its pathognomonic histological feature, regarded by some observers as the morphological manifestation of a genetically transmitted myocardial defect. Recently, however, it has become evident that myocardial disarray is not limited to hypertrophic cardiomyopathy, but is encountered in hearts with both congenital and acquired conditions, and is also observed in normal hearts. The specificity of disarray for hypertrophic cardiomyopathy is thus seriously questioned. Latterly, it has been suggested that disarray, judged from through-and-through sections of the ventricular midseptum, is a highly specific and sensitive marker of hypertrophic cardiomyopathy when considered in *quantitative* rather than *qualitative* fashion.

The present study sets out to answer the question whether disarray could be the histological expression of the normal but intricate fibre architecture of the heart, a consideration also initiated by debatable definitions of normality and abnormality of myocardial histology. Gross fibre dissections in five normal hearts showed that many sites occurred in which disarray was a natural phenomenon. In five more hearts it was found that the plane of section of a tissue block might profoundly influence the histology. In fact, tissue cubicles sampled from different faces showed a change in histology in the vast majority. Thus the diagnostic significance of myocardial disarray as a marker of hypertrophic cardiomyopathy in the clinical setting almost vanishes; a change in orientation of a tissue section may actually turn "normality" into "disarray".

The diagnosis of hypertrophic cardiomyopathy is based on a number of criteria of which asymmetric septal thickening, myocardial disarray, and systolic anterior movement of the anterior papillary muscle of the mitral valve are considered of prime importance.¹ Indeed, for clinicians and pathologists alike the diagnosis is often easily made, not least because of the obvious asymmetrical wall thickening. Septal asymmetry and a bizarre myocardial texture are not, however, always present. Moreover, the disease is not necessarily obstructive. Furthermore, it has been shown unequivocally that hypertrophic cardiomyopathy can occur under diverse clinical conditions and it has thus been suggested that the disease does not represent a distinct entity, but instead a final

common pathway.² It is on the basis of these uncertainties in finding definitive criteria for the diagnosis that in recent years much emphasis has been put on histological features, collectively termed myocardial disarray or disorganisation. In fact, myocardial disarray, in isolation, has been considered a "highly specific and sensitive marker" of hypertrophic cardiomyopathy.³⁻⁵ In our experience, however, the torrent of articles solely concerned with myocardial disarray has led to misconceptions regarding the interpretation of this histological feature. It is our purpose, therefore, to review the evolution of myocardial disarray in the articles published in an attempt to reappraise its value as a diagnostic tool in hypertrophic cardiomyopathy.

Historical review

Over recent decades the concept of myocardial disarray underlying ventricular dysfunction has excited

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cardiologists. Teare's observations in 1958⁶ that sudden death (in eight of nine patients) was associated with asymmetric septal hypertrophy, histologically characterised by a bizarre myocardial fibre architecture and conspicuous interstitial fibrosis, set the scene for relating myocardial disarray to this condition. Indeed, myocardial disarray was considered an important feature, but almost all investigators stated that when taken in isolation it was non-specific.⁷⁻¹¹

For that very reason, Van Noorden and co-workers¹² introduced a semiquantitative approach to diagnosis, which included other histological features such as the degree of hypertrophy and fibrosis. In this way they hoped to improve the specificity of the histological diagnosis of asymmetric septal hypertrophy.

Subsequent investigators, however, have singled out myocardial disarray as the pathognomonic histological feature.¹³ Some have gone so far as to consider myocardial disorganisation as the morphological manifestation of a genetically transmitted myocardial defect.¹⁴⁻¹⁶ In the mean time, it became evident that most conditions unified clinically by "idiopathic" hypertrophic cardiomyopathy presented with signs of failure of left ventricular compliance rather than with outflow obstruction.^{17,18} The promoters of disarray as the specific histological feature for asymmetric septal hypertrophy then modified their concept by stating that hearts with obstruction had myocardial disarray confined to the thickened subaortic septal area, while hearts without obstruction presented disarray in a diffuse manner throughout the ventricular free wall.^{14,15} The universality of this concept was soon disproved, not only by some of the cases reported by the same authors,^{14,19} but also by the well documented study of Edwards and co-workers.²⁰

The matter became further complicated when it was shown that asymmetric septal thickening, accompanying both acquired and congenital anomalies, could occur also in the absence of myocardial disarray.²¹ For these cases yet another term was introduced, viz. "disproportionate septal thickening" so as to distinguish these cases from those with both septal thickening and myocardial disarray (see for reviews Maron and Epstein^{1,22}). The distinction was deemed necessary since the conditions that possessed disarray presented a familial trait, while the septal thickening in the cases without disarray was considered a secondary phenomenon accompanying other diseases.

At this stage the waxing interest in hypertrophic cardiomyopathy and the possible role of myocardial disarray as its pathological substrate had led other investigators into the arena (see for reviews^{1,23-26}). It became evident that disarray was not confined to hypertrophic cardiomyopathy, but was seen in a variety of conditions including normal hearts. The specificity of myocardial disarray for hypertrophic

cardiomyopathy was seriously questioned, if not denied, thus reinforcing the opinion of the earlier investigators (see above). For example, Jones and associates²⁷ showed that the tissue specimens surgically removed from the hypertrophic infundibula in Fallot's tetralogy contained myocardial disarray indistinguishable from that present in hearts with asymmetric hypertrophy. Interestingly enough this work was presented by the same group of senior investigators who had promoted the concept that myocardial disarray was a *specific* marker for asymmetric septal hypertrophy. Van der Bel-Kahn²⁸ documented the presence of myocardial disarray in a variety of conditions, such as systemic hypertension, cor pulmonale, coronary heart disease, and normal hearts. Compared with hearts with hypertrophic cardiomyopathy the disarray encountered was similar from a histological point of view, but less extensive. Bulkley and co-workers^{29,30} documented myocardial disarray in fetal and infant hearts and in some types of congenital heart disease, such as Fallot's tetralogy and aortic and pulmonary atresia with intact ventricular septum. Beçu and associates³¹ described similar findings in hearts with isolated pulmonary valve stenosis.

These observations in congenital lesions, which incidentally could not be verified by Maron and his group of investigators,³² led Bulkley and associates²⁹ to hypothesise that the force distribution within the myocardium could play a role in the development of myocardial disarray, a concept further expanded by Hutchins and Bulkley³³ to encompass hearts with "classical" asymmetric septal hypertrophy. This point of view has recently received further support from the observation that myocardial disarray also developed in papillary muscles released from normal tension after mitral valve replacement.³⁴

The overwhelming evidence that myocardial disarray was not confined to hearts with hypertrophic cardiomyopathy has led to further studies by the Bethesda workers, who now claim that myocardial disarray is a highly sensitive and specific marker for hypertrophic cardiomyopathy only when considered in a *quantitative* rather than a *qualitative* fashion.^{3,4} In making their quantitative judgment, however, they excluded all the tissue sections from areas other than the ventricular septum. Moreover, they based their quantitative assessment solely on through-and-through midseptal sections cut in a transverse plane. St John Sutton and colleagues³⁵ recently also showed that myocardial disarray was more extensively present in the hearts of patients with hypertrophic obstructive cardiomyopathy compared with that in normal hearts or in those of patients with congestive cardiomyopathy or aortic stenosis. These authors also used full thickness sections, but they did not mention the restrictions in sampling introduced by the

Bethesda group. Furthermore, St John Sutton and his colleagues³⁵ concluded that in hearts with obstructive hypertrophic cardiomyopathy myocardial disarray did not differ much among sections from the ventricular septum or the left ventricular free wall and, moreover, appeared independent of septal and free wall thickness. Still more recently, Maron and co-workers,⁵ expanding on their earlier material, endorsed the work of St John Sutton *et al.*³⁵ and now concluded in addition that in patients with hypertrophic cardiomyopathy, not necessarily obstructive, the left ventricular free wall—when sectioned transversely—also contained more extensive disarray than it did in their reference cases. They suggested on the basis of these findings that myocardial disarray “may represent a diffuse cardiomyopathic process”, probably congenital in nature.^{5,25} It is interesting, therefore, that St John Sutton and his colleagues,³⁵ on almost the same findings, concluded that myocardial fibre disarray “probably represents an exaggeration of a non-specific common pathway for many diverse pathophysiological processes”.

The overall conclusion reached at present is that disarray is more extensively present in hearts with hypertrophic cardiomyopathy than in other conditions. This in itself is hardly a revelation, since the whole subject of myocardial disarray came into focus because it was such a striking feature in hearts with asymmetric septal hypertrophy. The practical value of myocardial disarray as a diagnostic marker, however, has almost vanished, since the criteria for evaluation cannot readily be fulfilled in a clinical setting! Indeed, the limited diagnostic value of small pieces of tissue, obtained either with endomyocardial biopsy or during septectomy, has already been shown.^{36–38} Thus, we are left with a dilemma of how to interpret myocardial disarray in ordinary histological sections, which is particularly pressing since it has unequivocally been shown that disarray can occur in hearts without any sign of myocardial dysfunction. In such cases one may wonder whether disarray represents a congenital derangement of myocardial architecture and, hence, an abnormality, or is the histological expression of a myocardial fibre architecture which can be basically normal. The latter possibility would at least explain why so many areas have to be excluded from histological evaluations in diagnosing hypertrophic cardiomyopathy.

Indeed, Streeter³⁹ and Ross and Streeter⁴⁰ suggested that the occurrence of myocardial disarray could be the simple consequence of gross fibre architecture; Fujiwara and associates⁴¹ also indicated that myocardial fibre disarray in their sections corresponded to fascicle disarray in thick sections.

In the light of these developments we have re-evaluated the histology of the myocardium so as to

investigate the occurrence of myocardial disarray at different sites in normal hearts, taking gross muscle fibre orientation as the point of departure.

Preparation of normal hearts

Ten normal hearts from patients who died of diseases unrelated to the cardiovascular and/or pulmonary system were examined. Five were studied by gross dissection of the myocardial fibres. These hearts came from patients, 1 day, and 2, 15, 18, and 75 years of age, respectively. All specimens were fixed in formalin. The dissection was carried out after removal of atria and stripping of the epicardium, fat, and the extramural coronary arteries. In two hearts (the 1 day and 15 year old cases) the myocardium was dissected using artificial cleavage planes, according to a method described by Lev and Simkins.⁴² The three remaining hearts were dissected using a step by step technique, stripping off myocardial fibres with the atrioventricular annuli as points of departure. The same sequence was followed throughout the procedures in the different specimens. Each step was photographed so that the fibre orientation could be critically compared between different hearts.

The remaining five hearts were used for a microscopical survey. These hearts came from patients 1 day, 4 months, and 4, 9, and 21 years of age. All hearts were fixed in formalin. Twelve full thickness blocks were removed for histological study (Fig. 1). The first two blocks were taken from the ventricular septum and adjacent anterior left ventricular free wall, approximately 1 cm beneath the aortic valve (Fig. 1A). Nine blocks came from a transverse slice through the heart taken approximately halfway between base and apex (Fig. 1B). The final block was taken from the left ventricular apex (Fig. 1A). Each block was removed as a cube varying from approximately 5 mm in small hearts to about 15 mm in larger hearts. All blocks were embedded in paraplast and routinely processed. Each block was then cut sequentially in three different planes, re-embedding being necessary for each of the three cuts. The first sections from each block were taken in a plane perpendicular to the long axis of the heart, that is in a transverse plane relative to the block. For the second series of sections each block was re-embedded in such a way that all blocks taken from the ventricular free walls and the anterior and posterior septal insertions were cut in a plane parallel to the endocardium. The remaining blocks from the septum and ventricular apex were cut in the frontal plane, using the anterior aspect of the block as the target. A third plane of sectioning was then parallel to the remaining uncut third pair of faces of the cube. The three different planes of sectioning were tabulated as A, B, and C,

Fig. 1 The sites of the 12 full thickness blocks removed for the histological study.

respectively.

All sections were cut at 10μ thickness and stained with haematoxylin and eosin. A total number of 180 sections was studied: one section from each of the three faces of the 12 blocks in the five hearts.

DEFINITION OF HISTOLOGICAL CRITERIA

Because of the aforementioned controversies regarding the differentiation of "disorganisation" from normality we have tried to classify myocardial histology according to the criteria set by Maron and Roberts³ and Maron *et al.*⁴ Thus, we have tried to distinguish three basic arrangements. The first arrangement which Maron and associates⁴ defined as normal, should be typified by a strictly parallel alignment of myocardial fibres (Fig. 2). The second arrangement, in which the cells did not show a rigid parallel alignment, was classified by them as a minor deviation of normality. It included different histological variants, such as branching myocardial cells and

arrangements in which small fascicles of cells were cut transversely among other muscle cells cut in a more or less longitudinal fashion (Fig. 2). We found it impossible to apply these criteria in a strict sense, since close observation of so-called parallel alignment disclosed that cellular branchings were almost always readily identified. Thus, we have considered the histology only as "parallel" when the major proportion of myocardial cells showed a parallel alignment, irrespective of the presence or absence of branching.

Finally, we distinguished myocardial disorganisation, characterised by a more complex texture of myocardial cells (Fig. 3), of which these authors already indicated that it assumed a wide spectrum of morphological appearances. Maron and Roberts³ and Maron *et al.*⁴ distinguished two major forms, further subcategorised into five histological types in alphanumerical fashion. We experienced great difficulties in recognising the often subtle differences, particularly since the different types often merged in one and the same histological section. Hence, we have abstained from introducing an elaborate subdivision, while we are primarily interested in differentiating "normal" from "minor deviations of normality" from "disorganisation". Moreover, we have not expressed the various patterns as percentages of surface area of the section, but instead have labelled a section according to its dominant histological feature, viz. the feature that captured at least 50% of the total surface area of the section.

In other words, we have used their definitions, but we have simplified the issue. Nevertheless, it is important to note that these authors state that a particular configuration (their type I), characterised by perpendicular or oblique alignment of individual cells or bundles of cells, "exclusively involves areas of septum in which cardiac muscle cells were cut longitudinally" (Maron and Roberts³: p.691).

Results

GROSS FIBRE ORIENTATION

Greenbaum *et al.*⁴³ have recently reviewed and studied gross fibre orientation in normal hearts, emphasising regional variations in ventricular wall architecture of significance for ventricular function. Our present study has extended this investigation to examine possible sites of microscopical disarray.

Like Greenbaum *et al.*⁴³ we were able to distinguish subepicardial, middle, and subendocardial layers, at the same time confirming their statement that these layers could not be considered distinct entities. Indeed, the concept of discrete muscle bundles spiralling through the ventricular walls and the septum previously has been discarded,^{42,44} emphasising the intricacy of the myocardial fibre arrangements, a gen-

Fig. 2 The histology of "normality", characterised by a parallel alignment of myocardial fibres (A), and an example of a "minor deviation of normality" (B), according to the definitions set by Maron and co-workers.^{3 4} (Haematoxylin and eosin stains; original magnifications (A) $\times 140$; (B) $\times 90$.)

erality important to recall when considering myocardial fibre texture in histological sections.

The distinction between the layers is largely based on the observation that the orientation of the fibres in what is called a layer changes less rapidly with depth than orientations encountered in a considerably deeper level of dissection (Fig. 4). Hence, the interfaces between these layers are not clearly demarcated.

Other regions of interdigitating myocardial fibres are the interventricular sulci and the right anterior atrioventricular groove (Fig. 4). The slightly deeper layers of the subepicardial zone dip into the middle layer and contribute to the formation of the main muscle mass of the ventricular septum. In doing so, these fibres intermingle with those of the middle layer and the fibre constituents derived from the right ventricular free wall. This architecture is more outspoken along the anterior interventricular sulcus than it is posteriorly, but at both sites gross fibre disarray is present as a natural phenomenon.

In the mature heart the greater part of the septum is composed of the left ventricular middle layer. The midseptal aspect, therefore, will contain muscle with its main fibre direction more or less perpendicular to

the long axis of the left ventricular (Fig. 5), while the subendocardial layers on both sides show longitudinal and oblique fibre directions.

The posterior aspect of the aortic annulus gives rise to fibres that also penetrate into the ventricular septum and run down almost in the long axis of the heart, intermingling with those that form the main septal muscle mass (Fig. 5). From the left anterior aspect of the aortic annulus, fibres arise which run parallel to those derived from the adjacent area of the mitral annulus. These fibres intermingle with the subepicardial fibres of the right ventricle which have bridged the anterior interventricular sulcus.

Likewise, gross fibre disarray is present at the ventricular apices. Subepicardial fibres from both the right and left ventricular vortices turn inward and continue into the subendocardial layers and papillary muscle groups (Fig. 5). The ventricular apices, therefore, show a rapid transition of the subepicardial "swirling" fibres into the almost longitudinal direction of fibres in the subendocardial trabeculae. A middle layer is missing from these areas. This arrangement also affects the architecture of the ventricular septum in its apical aspect.

Fig. 3 Histology of "disarray", according to criteria set by Maron and co-workers.^{3,4} (Haematoxylin and eosin stains; original magnifications (A-C) $\times 90$; (D) $\times 140$.)

A distinct difference is present in architecture between right and left ventricles. In contrast to the left ventricular wall the right ventricular free wall contains subepicardial and subendocardial layers which are closely packed together without much of a middle layer. The thin walled right ventricle will therefore almost everywhere show crossings of myocardial

fibres.

Thus, natural fibre disarray is a common feature in various sites, such as the subaortic septal region, the anterior and posterior junctional sites between the septum and the parietal wall, the subendocardial zones, the right ventricular free wall, and the ventricular apices.

Fig. 4 Heart specimen showing the intricate fibre orientation at different sites and at different levels of dissection. (A) Left anterior oblique view of the heart. The fibres that descend over the right ventricular outflow tract have an orientation different from the fibres that descend from the anterior aspect of the aortic root. Deeper dissection of the left ventricle shows yet another, more circular, arrangement (arrows). (B) The posterior aspect of the same specimen, shown with different levels of fibre dissection. The posterior interventricular groove (indicated by asterisks) shows an interdigitating fibre arrangement.

HISTOLOGY OF NORMAL MYOCARDIUM

Of the 180 sections studied, using the aforementioned criteria, only 42 showed a parallel fibre arrangement (Table). In other words, on the basis of the criteria set by Maron and Roberts³ and Maron *et al.*⁴ only 23% of the sections were judged to show normal histology. Seventy-nine sections (44%) showed a minor deviation of normality, whereas disorganisation was present in 59 sections (33%). The distribution of these findings among the five hearts according to the site of the blocks and the plane of sectioning is given in the Table. Blocks 3, 4, and 5, derived from the midportion of the ventricular septum, showed minor deviations of normality in 20 sections, disarray in 17 sections, and a parallel alignment in only eight sections.

Changing the orientation of the block produced a change in the dominant microscopical appearance in 52 of the 60 blocks (Table). In only eight blocks were the same results produced irrespective of the plane of section. In six of these eight the histology was that of minor deviation, while in the other two there was unequivocal disorganisation. Thus, a strictly parallel arrangement was never observed in one block when

sectioned in all three planes. In 15 blocks a different histology was found in each of the three planes (Fig. 6), while in the remaining 37 blocks a change in histology was found when sections were studied in two planes.

Discussion

In view of the confusion that surrounds the interpretation of myocardial disarray it is essential to appreciate that this review on myocardial disarray concerns the histology and its appraisal; it is not a dissertation of the histology in hypertrophic cardiomyopathy. In recent years various excellent reviews of the latter condition have been published.^{1 23-26} There are, however, equally confusing reports regarding the importance of myocardial disarray as a histological feature, which some consider "highly specific and sensitive for hypertrophic cardiomyopathy", while others describe this texture in different conditions, including normal hearts. It is for these reasons, in particular, that we have focused on the normal heart.

The present study shows that areas with an inter-

Fig 5 Interdigitating fibre textures. (A) Heart specimen in which the interventricular septum has been dissected and opened like a clam (indicated by arrow). The part of the septum underneath the aortic valve (AoV) shows a very different fibre orientation, as compared with the more apical area. LV, left ventricle; MV, mitral valve. (B) Heart specimen in which the interventricular septum, separating the right (RV) from the left (LV) ventricle, has been opened by blunt dissection of the fibres. The main fibre orientation is indicated by dotted lines, showing extensive intermingling in the subaortic region. RVOT, right ventricular outflow tract; Ao, aortic root. (C) The apex of the left ventricle (LV) is dissected and shows the intricacies of the fibre orientations, such as subepicardial fibres that turn inwards (arrow) to continue in subendocardial position.

weaving fibre architecture occur naturally in all normal hearts at several sites, including the ventricular septum. That this gross arrangement leads to cellular disarray at a microscopical level should therefore come as no surprise. Thus, when applying the criteria for deviations of normality and disarray, as promoted by Maron and co-workers,^{3,4} it appears that of all tissue sections examined from five normal hearts almost 44% showed a "deviation of normality", and almost 33% showed "myocardial disarray". Thus a "normal" arrangement, according to the criteria set, occurred in only 23% of the sections. We may wonder what constitutes normality, particularly, since we then found that the plane of sectioning of the tissue blocks influenced the histology. Thus, in 87% of the blocks studied the histology changed when the orientation of the block was changed. In 38% of cases the alteration was from a parallel arrangement in one plane to disarray in another. In fact, in only eight of the 60 blocks was there no alteration, but none of these contained a parallel arrangement as the dominant histology.

What then is the significance of these findings regarding the specificity of myocardial disarray in diagnosing hypertrophic cardiomyopathy?

First we must conclude that random sections have limited value in this respect, a conclusion recently reached by Maron and his co-workers.^{3,4,25} The main reason for this is that cellular disarray does indeed reflect fascicle disarray, as pointed out by Streeter,³⁹ and Ross and Streeter,⁴⁰ and Fujiwara and associates.⁴¹ Greenbaum and associates⁴³ recently re-endorsed the intricacies of the gross fibre architecture of the heart, concluding that, within a basic framework, a uniform pattern is not present. Indeed, the fibre arrangement is such that areas are produced in which disarray occurs as a natural phenomenon. Our presentation has focused on this particular aspect and has unequivocally shown that such regions are widespread. These areas, such as the junctional sites between the ventricular free walls and the interventricular septum, the apices of the ventricles, the subendocardial regions, the right ventricular free wall, and the subaortic septal region, all stand out because of a "disorderly" arranged fibre geometry. It is of interest that these sites coincide with the areas that Maron and co-workers³⁻⁵ have excluded from their recent studies on the specificity of myocardial disarray. Other workers, such as Van der Bel-Kahn,²⁸ Bulkley and associates,^{29,30} and St John Sutton and associates³⁵ have also pointed out that areas with disarray are widely dispersed and occur in hearts with congenital and acquired diseases, as well as in normal hearts, both fetal and adult. Thus, we must indeed conclude that myocardial disarray in itself is a non-specific feature; for its greater part it represents the

Table Histological patterns obtained after sectioning each of three faces of 12 tissue cubicles sampled*

Case No.	Age	Face of cubicle	Block No.											
			1	2	3	4	5	6	7	8	9	10	11	12
1	Newborn	A	P	MD	D	MD	D	D	MD	MD	MD	MD	MD	D
		B	MD	D	MD	MD	MD	MD	P	P	MD	MD	P	P
		C	D	D	P	P	D	MD	D	D	MD	P	P	D
2	4 mth	A	MD	MD	D	D	D	MD	MD	MD	D	MD	D	D
		B	D	D	MD	P	D	MD	MD	D	D	P	D	MD
		C	MD	MD	P	MD	P	MD	D	P	P	P	P	MD
3	4 y	A	MD	P	MD	MD	D	MD	MD	MD	MD	D	D	D
		B	MD	MD	MD	MD	MD	P	P	P	MD	MD	D	MD
		C	MD	D	P	MD	D	MD	D	MD	P	P	MD	P
4	9 y	A	D	D	D	MD	D	MD	MD	P	D	MD	MD	D
		B	MD	MD	D	MD	P	P	P	D	P	P	P	D
		C	MD	D	D	MD	D	D	D	D	D	D	P	MD
5	20 y	A	MD	D	MD	MD	D	P	MD	MD	P	D	D	MD
		B	MD	D	MD	P	D	MD	P	P	MD	P	P	MD
		C	D	D	D	MD	MD	MD	P	P	MD	D	MD	MD

*See text: material and methods.
The histological patterns have been designated according to the criteria set by Maron *et al.*^{3,4}: P, parallel arrangement; MD, minor deviation of normality; D, disarray (see also "definition of histological criteria").

Fig. 6 The dominant histology after sectioning the three faces of one of the tissue cubicles. (A) "Parallel" fibre arrangement; (B) "minor deviation of normality"; (C) "disarray". (Haematoxylin and eosin stains; original magnification $\times 230$.) (Reproduced from Becker A E and Caruso G. In: Paediatric cardiology Vol. 3, 1981, p 317; by permission of Churchill Livingstone.)

histological counterpart of gross fibre arrangement.
The question then remains as to how specific the myocardial disarray is for hypertrophic cardiomyopathy when it is present in the midseptal area?
The recent works of Maron and associates^{3,4} suggest that extensive occurrence of disarray in the ventricular midseptum is a "highly specific and sensitive marker for hypertrophic cardiomyopathy", though the authors also report some instances without disor-

ganisation despite the fact that these cases clinically were indistinguishable from the others.²⁵ In other words, in keeping with our own experiences, myocardial disarray is not per se a feature of hypertrophic cardiomyopathy and its absence, therefore, does not exclude the diagnosis. When present, however, disarray in over 5% of the total surface area of through-and-through sections of the midseptum is considered diagnostic for hypertrophic cardiomyopathy. We

Fig. 7 Antoni van Leeuwenhoek's drawings of the myocardium of the duck from his correspondence (letter No. 82) with the members of the Royal Society, London, April 1694. (Courtesy of Dr J James, Professor of Histology, University of Amsterdam.)

may, of course, challenge the practical significance of this approach in the clinical context, but nevertheless it is indeed true that gross fibre arrangement in the ventricular septum is such that the midsegment is the area in which the greatest regularity can be expected in normal hearts.⁴³ Sections from this site (our block 4), however, showed disarray as the leading feature in one of our five hearts, while minor deviations were present in the other four.

It is our firm belief that most of the current controversies concerning myocardial disarray relate to differences in opinion of what is normal and what is abnormal in myocardial histology. What, for instance, is the evidence that a parallel alignment of cells should be considered as normal? We thought it almost common knowledge that muscle cells in the myocardium are not aligned in parallel.⁴⁵ Indeed, a popular textbook of histology says of the myocardium that "the fibres are not simple cylindrical units but they bifurcate and connect with adjacent fibres to form a complex three dimensional network".⁴⁶

As long ago as 1694 van Leeuwenhoek,⁴⁷ in his correspondence with the Royal Society in London, beautifully portrayed different fascicle arrangements and branching cells in the myocardium of the heart of the duck (Fig. 7). According to criteria set today for normality, van Leeuwenhoek's drawings display minor deviations of normality as well as disorganisation. It could, of course, be argued that disorganisation is "normal" for ducks and that a similar architecture in man is anomalous. Some investigators have pointed out that the embryonic heart of various animal species contains myocardial disarray to a great extent,^{13 48 49} and the group from Bethesda has shown disorganisation as the histological hallmark in both

canine and feline hypertrophic cardiomyopathy.^{50 51}

Be that as it may, other investigators concerned only with the normal human heart have found replicas of van Leeuwenhoek's observations at many places in the myocardium. Indeed, our present study points out that a parallel alignment of myocardial fibres cannot be promoted as the paradigm of normality. The intricate architecture of mostly obliquely oriented layers of fibres must dictate that different orientations of sections produce histological patterns, some of which by necessity produce characteristics of "disorganisation".

The above discussion should not be construed as suggesting that myocardial disarray is not a feature of hypertrophic cardiomyopathy. What we emphasise is that disorganisation—as a microscopical feature—is by itself not necessarily an indication of an abnormality. We do not want to deny that myocardial disarray may be more extensively present in hearts with hypertrophic cardiomyopathy. Both clinician and pathologist, however, should know that a change in orientation of one and the same block of tissues may actually turn "normality" into "disarray"!

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