PATHOLOGIC STUDIES

By Eckhardt G. J. Olsen

This section is concerned with the pathology of cardiomyopathy, and is confined to the disease entity which has been defined in the previous section as "Disorder of Heart Muscle of Unknown Cause or Association."

Many classifications have been proposed for this type of myocardial disease but the clinical classification of Goodwin (1972) is of great value, because for each of the three types described a morphological counterpart can be recognised. The order of the foregoing chapter for the three types of cardiomyopathy will be followed:

Hypertrophic (with or without obstruction) (Impaired diastolic compliance).

Congestive (systolic pump failure).

Obliterative Cardiomyopathy (obliteration of the ventricular cavity).

Hypertrophic Cardiomyopathy with Obstruction

Twelve cases have been studied at post mortem. The coronary arterial tree is usually normal and widely patent. Hypertrophy of all chambers is present. On opening the left ventricular cavity a striking feature—apart from generalised hypertrophy—is the asymmetric thickening of the interventricular septum. This asymmetric hypertrophy takes the form of a bulge and often extends from the apex to the region of the aortic valve, where it comes in close contact with the anterior cusp of the mitral valve. It is composed of abnormally arranged myocardial fibres which may, to a variable extent, extend into the anterior and posterior ventricular wall. Abnormally placed anterior mitral valve cusps, as described by Bjork *et al* in 1961, have not been found in this series.

On cross section the asymmetry is particularly striking and fibrous tissue arranged in whorls can often be found varying in degree of severity. The myocardial bundle involved is usually the deep bulbospiral muscle and the overlying fasciculi of the superficial bulbospiral muscle and deep sinospiral muscle may become attenuated, often so severely as to completely disappear.

Histological examination of the asymmetrically hypertrophied area shows, on longitudinal section, disorientation of myocardial muscle fibres. In normal or hypertrophied hearts due to any other cause, long runs of myocardial fibres are found. By contrast, in patients with hypertrophic cardiomyopathy with obstruction, the normal arrangement is totally lost and myocardial fibres appear to run in all directions. An additional characteristic arrangement is the formation of myocardial whorls (Olsen 1971).

Immense hypertrophy of individual myocardial fibres is often seen. These may measure up to 100 microns diameter (normal range 5 to 12 microns, "ordinary" hypertrophy average 22 microns). Other features are also characteristic. The nuclei are usually very large, vesicular and bizarre in shape, surrounded by a clear zone—the so called "perinuclear halo." The adjacent myocardial fibrils, as they approach the perinuclear space, have a dystrophic appearance. Fibrous tissue, either interrupting the myocardial fibre or situated between adjacent fibres, is present and occasionally a large area of fibrous replacement of myocardial tissue is found. These appearances have been analysed on biopsy material from an additional 25 patients. The material was obtained at surgical operation for the treatment of the disease and has been compared with biopsy material from 47 patients with heart disease due to aortic valve disease, congenital heart disease, mitral valve disease and various other forms where hypertrophy was present. Some overlap may exist between the two groups between the individual criterion of the various histological features, but the combination of all the criteria allows diagnosis with a good degree of accuracy (Van Noorden *et al* 1971).

Histochemical evaluation has been carried out in close collaboration with my colleagues Pearse and Van Noorden. A large number of enzyme systems have been investigated. The most useful criterion for diagnosis of hypertrophic cardiomyopathy was that of glycogen accumulation, particularly in the area of the perinuclear halo, where the normal granularity of glycogen is lost and smudges of periodic acid Schiff positive material was found. Succinic dehydrogenase used for mitochondrial activity and acid phosphatase and non-specific esterases as markers for lysosomal activity has proved to be not very helpful in distinguishing this type of hypertrophy from the ordinary type.

Only occasionally has ultrastructural evaluation been helpful and the changes which were observed at histological level are reflected electron-microscopically. Disorientation of myocardial fibrils running in all directions is not infrequently found (Van Noorden *et al* 1971). These changes, however, are very patchily distributed and are not pathonomonic of this type of hypertrophy. Increased numbers of mitochondria, dystrophic myocardial fibrils, disappearing myocardial fibrils, contraction bands, Z line changes and swelling of the sarcotubular system is often found. Unfortunately the appearances are not pathonomonic and it is therefore suggested that from a diagnostic point of view ultrastructural changes are not of great help. These investigations are, however, invaluable in allowing some understanding of the physiological mechanism of the disorder.

In order to compare the various criteria enumerated, Van Noorden *et al* (1971) have devised an index allocating points for each of the features; although some overlap does exist at histological level a firm diagnosis can usually be made. As far as the histochemical index is concerned, considerable overlap exists and with regard to ultrastructural changes, almost total overlap occurred.

Hypertrophic Cardiomyopathy without Obstruction

Clinically the obstructive element may disappear any time before the patient dies, but in the majority of cases when examined at post mortem, the asymmetric hypertrophy is usually still present. Only very rarely does the bulge disappear and it is particularly important in these instances

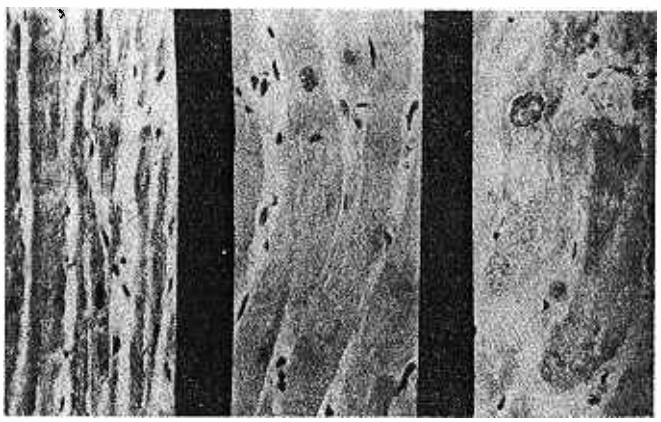

Fig. 1. Photomicrograph of coronary hypertrophy in three conditions

In the left panel, congestive cardiomyopathy showing long runs of attenuated myocardial fibres but nuclear changes of hypertrophy are present.

In the centre panel, from a patient with aortic stenosis, from the region of the left ventricular outflow tract, long runs of hypertrophied fibres and nuclear changes of hypertrophy are seen.

In the right panel, hypertrophic cardiomyopathy with obstruction showing runs of interrupted fibres, immense hypertrophy and bizarre shaped nuclei surrounded by a large perinuclear halo. Note that the myocardial fibrils have a dystrophic appearance as they approach the perinuclear space. An increase in fibrous tissue is also present.

(Each section; Haematoxylin and eosin × 350).

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that the pathologist knows exactly where to look for the abnormal fibres, as otherwise the diagnosis may easily be missed.

A number of possible causes have already been suggested by Professor Goodwin (see above). This list can be extended. Possible embryonic growth disturbance has been suggested as early as 1907 by Schminke. Teare in 1958 suggested a hamartoma of the interventricular septum. In 1964 Pearse suggested an increase in noradrenaline in the area of asymmetric hypertrophy. Subsequent work has shown that collagen also fluoresces with similar, but slightly less intensity (Van Noorden *et al* 1971). Further work is in progress to re-investigate this suggestion which would explain the benefit of beta adrenergic blockade. Lannigan in 1965 suggested a primary disorder of myocardial muscle metabolism.

Congestive Cardiomyopathy

By contrast to the hypertrophic type of cardiomyopathy, congestive cardiomyopathy has no pathonomonic features and a diagnosis can only be made by exclusion of other possible causes of heart failure.

Macroscopically, the chambers of the heart are severely dilated and nonspecific endocardial thickening is usually found. In over half the patients thrombus may be superimposed on the thickened endocardium. The thickness of the ventricular walls may fall within the normal range despite the hypertrophy which is present, this being masked by the extreme dilatation. The myocardium is usually pale and flabby and frequently fibrous replacement of the inner third of the myocardium is found. The coronary arteries are usually normal.

Histologically no pathonomonic features are present. Long runs of attenuated myocardial fibres are seen, which on measuring the diameter, fall within the normal range of thickness (5-12 microns), despite the hypertrophy. This is due to dilatation and is best seen in the inner half of the myocardium. Nuclear changes of hypertrophy such as hyperchromatism and blunting are, however, present. Not infrequently myocardial fibres run together into fine collagenous areas and can often be traced through this fibrous zone. Although not a pathonomonic feature, these changes are observed more frequently in cases with congestive cardiomyopathy.

Histochemical and ultrastructural changes reflect hypertrophy without any characteristic features. Very occasionally focal accumulation of chronic inflammatory cells are found, contributing to the suggestion that infection may play a part in the pathogenesis of this condition. Additional casually related features include the suggestion by James in 1964 that abnormalities of the small intramyocardial vessels may be found. This was not substantiated in 52 cases (Olsen 1971). Kobernick *et al* in 1963 suggested a decrease in succinic dehydrogenase. In personally examined cases an increase rather than a decrease has been found. Baimbridge and co-workers suggested in 1967 a possible infective agent but the danger of possible misinterpretation has been pointed out (Grist 1967, Van Noorden *et al* 1971). A viral aetiology has been suggested by Gardner *et al* (1967) but so far definite proof is still lacking.

Alcoholic cardiomyopathy cannot ordinarily be distinguished from congestive cardiomyopathy which has been described above, and although minor ultrastructural changes have been suggested, these changes are not sufficiently distinct to allow differentiation. Experimentally it has now been convincingly shown that alcohol has a deleterious effect on myocardial fibres (Burch *et al* 1971). In the majority of patients with congestive cardiomyopathy however, alcohol as a cause can be excluded.

Cardiomyopathy following child-birth cannot be distinguished from the cardiomyopathy above.

Obliterative Cardiomyopathy

The classical example for this type of cardiomyopathy is endomyocardial fibrosis. The disease is characterised by endocardial thickening which may affect either ventricle. Shaper *et al* in 1968 have described five patterns of endocardial thickening: apical, apical to atrio-ventricular valve, valvar, apical and valvar separated from one another and randomly scattered endocardial lesions.

Particularly in the extensive—apical to atrio-ventricular valve type—the mitral valve cusp, chordae tendineae and posterior papillary muscle are bound down by the fibrous tissue. The endocardial thickening characteristically stops abruptly as the outflow tract is approached, often ending in a thick rolled edge. Fibrous septa extending into the inner third of the myocardium may be seen on macroscopic examination. Thrombus is also superimposed in over 50% of patients.

Histological examination shows layering of the endocardial thickness. The superficial layer consists of hyaline collagen tissue in which not infrequently foci of calcification are found. Beneath that zone a fibrous layer is usually evident. The deepest layer, the so called "granulation tissue layer" contains dilated vascular and lymphatic channels and inflammatory cells, including a variable number of eosinophils. It is from this layer that the septa extend into the underlying myocardium. Brockington and I in 1972 have examined 75 patients on the majority of whom histological preparations were available. These were kindly sent to us from contributors all over the world. These include patients with various types of eosinophilia, including the idiopathic form, patients with Löffler's endocarditis parietalis fibroplastica and patients with endomyocardial fibrosis, from Nigeria, Uganda, Europeans living in Africa and from other parts of the world.

Histological examination was undertaken without knowledge of the source or original diagnosis of the material. Three types of patterns of the endocardium could be defined:

(a) necrotic
(b) thrombotic and
(c) fibrotic.

A continuous spectrum with eosinophilic myocarditis and endocarditis at the one end (showing small foci of myocardial fibre necrosis and increasing thickness of the endocardium with or without superimposed thrombi) to the fibrotic type which corresponded to the classical description of endomyocardial fibrosis. Löffler's endocarditis parietalis fibroplastica (Löffler 1936) occupied an intermediate position. On comparing the diagnosis of the "blind" study with the original diagnosis, almost complete overlap existed between the necrotic and thrombotic type and considerable overlap between the latter and the fibrotic type. None of the previously described histological criteria helped to distinguish these conditions, which also included the absence or presence of eosinophils. There is, therefore, persuasive evidence that Löffler's endocarditis and endomyocardial fibrosis are part of the same spectrum of a disease process which can be traced back to the presence of eosinophils in the myocardium.

Other aetiological suggestions concerning endomyocardial fibrosis have included: Dietary (plantain) causes, lymphatic obstruction, immunological mechanisms, filariasis, malaria and other infective causes.

SUMMARY

The clinical classification proposed by Goodwin has been adopted and the pathological material has been presented in the following order:

Hypertrophic, Congestive and Obliterative Cardiomyopathies.

The characteristic features of hypertrophic cardiomyopathy with or without obstruction have been detailed and from a diagnostic point of view it has been shown that a diagnosis can be made on adequate material histologically; as far as histochemical investigations are concerned, only glycogen accumulation was of diagnostic value. Other enzymatic investigations and ultrastructural changes were not found helpful in establishing a diagnosis. Congestive cardiomyopathy showed no pathonomonic features and a diagnosis can only be made by exclusion of other possible causes. The suggestion has been made that obliterative cardiomyopathy, endomyocardial fibrosis and Löffler's endocarditis parietalis fibroplastica are part of the same spectrum of a disease process which can be traced to the presence of eosinophils in the myocardium.

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