ISOLATED MYOCARDITIS

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Non-specific myocarditis is recognized in an increasing variety of conditions. However, myocarditis that appears to be unrelated to any other disease process is still occasionally found at necropsy. It occurs in persons of all ages, from the newborn to the very old, and is commonly known as Fiedler's myocarditis after the author who first described it in 1899. Later writers have used a variety of other names, the commonest being "isolated" (Scott and Saphir, 1929; Hansmann and Schenken, 1938; Saphir, 1942; Covey, 1942; Hertzog and Heyford, 1947; Jones and Marshall, 1948; Drennan, 1953; Conlin and Mantz, 1953; Blanshard, 1953), "interstitial" (Maslow and Lederer, 1933; Greenebaum, Felson, and Zeligs, 1941; House, 1948; Tedeschi and Stevenson, 1951), "pernicious" (Boikan, 1931; Kline and Saphir, 1960), and "giant cell or granulomatous" (Jonas, 1939; Kean and Hoekenga, 1952; Goldberg, 1955; Dilling, 1956; Gubbay, 1961; Rab, Choudhury, and Choudhury, 1963), often linked with the terms acute, subacute chronic, and circumscribed or diffuse. Some authors refer to the condition simply as "idiopathic myocarditis" (Magner, 1939; Williams, O'Reilly, and Williams, 1953), while Ware and Chapman (1947) use the elaborate terminology of "chronic fibroplastic myocarditis".

Clearly the terms are often descriptive and they give the impression of a condition or a group of conditions with an extremely varied histological appearance. The position is complicated further by attempts to differentiate between giant cell and granulomatous types (Tesluk, 1956) and between interstitial and parenchymatous types (Saphir and Cohen, 1957), the parenchymatous involving muscle necrosis. In addition Porter (1960), Long (1961), and Rab *et al.* (1963) have renewed a previous claim (Johnson and Jason, 1944) that cases of so-called giant cell myocarditis may be examples of cardiac sarcoidosis; these claims are based on observations made on single cases only.

Faced with a condition that apparently exhibits protean histological features, I have carried out a detailed examination of the heart in 18 cases of isolated myocarditis including examples of the various types referred to above. This paper presents the results of this study and the conclusions drawn therefrom.

MATERIAL AND METHODS

Because of the large spectrum of conditions said to show non-specific myocarditis, fairly rigid criteria were employed in the selection of the cases included in this study. The first of these was that the heart lesion was confined principally to the myocardium and the second that these lesions could in no way be attributed to or be part of a disease process affecting other organs. Thirdly it was considered necessary to include only those cases with lesions of fairly marked extent and severity. Not only were these assessed visually in a manner based on the ease of locating the lesions microscopically, but also according to whether they had played a major role in the cause of death. In only one case (see below) was the cardiac lesion thought not to be the primary cause of death, but the case was included because the lesions were both widespread and severe.

Because of the obvious difficulties of retrospective studies made on post-mortem material and records, it was finally decided to select cases from the 12,815 necropsies that were performed at the Radcliffe Infirmary, Oxford, from 1950 to 1963 inclusive. It was noticeable that only after 1950 did the diagnosis of isolated or idiopathic myocarditis begin to appear with any frequency, and this may be attributable to the renewed interest shown in the condition shortly before this time particularly by Saphir. The kind of circumstances that led to failure of inclusion in this study were cardiac infarcts, the true nature of which was revealed only after deeper sections had been examined, cases of idiopathic cardiac hypertrophy or cardiac fibrosis with the label healed myocarditis, and in which no evidence of active myocarditis could be found, and those showing myocarditis in the presence of other pathology, e.g. pneumoniae, uraemia, and septic conditions, etc, which are now regarded as non-specific or secondary myocarditis. Eighteen cases were finally selected and in addition to the old sections of the heart taken from the files, several others were cut from the original blocks and from new blocks made from the stored formalin-fixed material. Several sections of both ventricles and inter-ventricular septum were always examined and often sections from the atria also. Preparations of the heart muscle were stained by the following methods: hæmatoxylin and eosin (H. and E.); Masson's trichrome; Mallory's phosphotungstic-acid-hæmatoxylin (P.T.A.H.); and occasionally by the toluidine blue, periodic acid-Schiff, and the Ziehl-Neelsen methods.

Histological examination was also made of H. and E. stained sections of the lungs, liver, kidneys, spleen, pancreas, adrenals, pituitary, and thyroid, and in some cases of the brain and other organs.

Clinical Aspects. A full consideration of the clinical features is clearly beyond the scope of this paper and only a short summary is included (see also the Table).

Of the 18 cases included, 12 were male and 6 female, and their ages ranged from 11 months to 88 years; 10 had a relatively short history of illness, the longest being only three weeks; 2 of these 10 were found dead in bed having previously been in their usual health, 4 died with signs of acute heart failure, 2 had fatal Stokes-Adams attacks, and 2 died suddenly of pulmonary embolism. Of the remaining 8 cases, 7 had histories ranging from 2 months to 3 years. Of these 7, 3 died with signs of congestive heart failure, 2 others also had signs of congestive failure but died suddenly of pulmonary embolism, another known to have cardiac enlargement for some months died rapidly in acute heart failure, and the seventh succumbed after a series of Stokes-Adams attacks. In the remaining case, though severe, the cardiac lesion appeared to be coincidental to large cerebral lesions which were the immediate cause of death.

Necropsy Findings. With the exception of Case 18 in which the brain showed extensive hæmorrhage and infarction the principal findings were in the heart and in the organs affected by heart failure. Thus the lungs and abdominal organs showed acute or chronic venous congestion. The clinical impression of pulmonary embolism was verified in the 4 cases already mentioned, the emboli originating in thrombi of the leg veins in 3 and in the right ventricle in the fourth. In another case a splenic infarct was located and it was thought to be due to an embolus from recent thrombus in the left atrial appendage. The following incidental lesions were found in individual cases: chronic gastritis and polyposis; jejunal diverticulosis; carcinoid tumour of the ileum; and a partial gastrectomy.

Examination of the heart revealed the following.

Macroscopic. Detailed heart measurements were not available but the heart weight was either at the upper limit of normal or frankly increased, sometimes very much so (Table). The largest hearts belonged to those patients with the longest history, and in 3 cases could properly be described as "cor bovinum". Even in the cases with a short history and especially those in the youngest age-group an increase was often found. The heart chambers were usually dilated, sometimes grossly and sometimes more noticeably on the right side.

The appearance of the myocardium was varied. Sometimes it was deep red mottled with yellow or brown, and of a flabby consistency, and when these features were combined with dilatation of the chambers, the over-all picture was virtually diagnostic. In the largest hearts the myocardium was firm, pale, and had a granular cut surface suggesting a generalized interstitial fibrosis. Sometimes larger pale firm areas of apparent scar formation were present, particularly in the "giant cell" types (see below). In a minority the appearances passed for normal, and it is therefore important that lack of gross macroscopic abnormality should not exclude a thorough histological search.

The pericardium and valvular endocardium were significantly free from disease. In 2 cases, however, recent thrombus was found in the atrial appendages and at the apex of the right ventricle respectively. Atheroma was seen in the coronary vessels in 12 cases but was of a severe degree in only 2 and in neither of these was it producing significant occlusion of the lumen.

Microscopic. Three types of lesions were seen. (1) *Acute.* These were characterized by an infiltration

TABLE

Case No. and sex	Age (yr.)	Length of illness	Clinical features	Heart weight (g.)	C.As.	Significant extracardiac post-mortem findings	Type of myo-carditis
1 F	11/12	2 h	Rapid onset dyspnoea, cyanosis, vomiting, tachycardia, ending in coma and death	72	N	AVC	DA
2 M	17/12	24 h	Rapid onset dyspnoea, cyanosis, tachycardia, ending in coma and death	100	N	AVC	DA
3 M	49	7 d	Attacks of dyspnoea, vomiting, and later Stokes-Adams; heart block demonstrated; death during attack	480	MiA	AVC; carcinoid tumour	DA
4 F	55	24 h	Upper abdominal discomfort and pallor; death on retiring to bed	336	MiA	AVC	DA
5 M	50	3 w	Several attacks dyspnoea, chest pain, hæmoptysis; death during attack	360	MoA	DVT; PE	PA
6 M	3	6 m	Attack of bronchitis; gradual increase cardiomegaly, dyspnoea, ending in cyanosis, coma, and death	250	N	AVC	DC
7 M	38	3 y	Gradual increase in cardiomegaly; attacks of congestive failure; heart block demonstrated; sudden death	750	N	CVC; RVT; PE	DC
8 M	54	7 d	Repeated Stokes-Adams; died in attack	416	MiA	AVC	DC
9 M	57	?	Vagrant presenting with congestive failure; died on admission	530	MiA	CVC; partial gastrectomy	DC
10 M	58	3 m	Several episodes of congestive failure; final episode resulting in death	615 615	MiA	CVC	DC
11 M	66	2 y	Two episodes of congestive failure the second resulting in death	870	SA	CVC; AAT; splenic infarct	DC
12 M	70	2 m	Increasing dyspnoea; atrial fibrillation demonstrated; oedema left leg; sudden death	710	MiA	DVT; PE; jejunal diverticulæ	DC
13 F	31	?	Found dead in bed	316	N	AVC	PC
14 M	42	12 d	Dull epigastric pain increasing in severity; died with acute pulmonary oedema	540	MiA	AVC	PC
15 M	56	1 h	Sudden onset dyspnoea and cyanosis ending in death	520	MoA	AVC	PC
16 M	60	10 d	Vague illness culminating in left chest pain and sudden death	512	MiA	AVC; DVT; PE; gastric polypi	GC
17 F	70	2 m	Repeated Stokes-Adams attacks; heart block demonstrated; died in attack	290	SA	AVC	GC
18 F	88	24 h	Acute cerebrovascular episode resulting in left hemiparesis, coma, and death	480	MoA	Pontine infarct; cerebellar hæmorrhage	GC

AAT=atrial appendage thrombus. AVC=acute venous congestion. C.As.=coronary arteries. CVC=chronic venous congestion. d=days. DA=diffuse acute. DC=diffuse subacute or chronic. DVT=deep vein thrombosis. F=female. GC=giant-cell. h=hours. m=months. M=male. MiA=minimal atheroma. MoA=moderate atheroma. N=normal. PA=patchy acute. PC=patchy subacute or chronic. PE=pulmonary emboli. RVT=right ventricular thrombus. SA=severe atheroma. w=weeks. y=years.

of inflammatory cells, by oedema and vascular congestion of the interstitium, and sometimes by necrosis of the cardiac muscle fibres. A variety of inflammatory cells was seen, namely lymphocytes, plasma cells, neutrophil and eosinophil polymorphonuclear leucocytes, and cells usually regarded as cardiac histiocytes. The latter have ovoid pale nuclei with a prominent central bar of chromatin, a distinct nuclear membrane,

FIG. 1.—Diffuse acute myocarditis showing tendency of muscle necrosis to occupy areas of maximum density of inflammatory infiltrate. (H. and E. $\times 85$.)

FIG. 2.—Patchy acute myocarditis. Note area of muscle necrosis is less extensive than seen in Fig. 1. (H. and E. $\times 210$.)

and abundant, sometimes basophilic cytoplasm with indistinct margins. The relative numbers of the different types of cells varied from case to case, but when muscle necrosis was prominent there was a greater proportion of eosinophils and plasma cells. Only rarely, except when necrosis was present, did cardiac histiocytes appear.

In Cases 1, 2, 3, and 4 these changes were present diffusely throughout the myocardium, whereas in Case 5 they had a patchy distribution being especially marked in the interventricular septum. Even when the whole of the myocardium was affected the density of the infiltration was variable and there was a tendency for muscle necrosis, when present, to be located in those areas showing maximum cellularity (Fig. 1). This was also true in the cases showing scattered lesions, but the necrosis affected only a small number of fibres (Fig. 2). Necrosis was widespread in Case 3, much less so in Cases 2 and 5, and minimal in Cases 1 and 4. In H. and E. preparations the earliest stages of necrosis are not easily recognized but this is largely overcome in sections stained by the P.T.A.H. method. In these the successive stages of necrosis can be demonstrated. The earliest is one of a loss of sharpness in the appearance of the striations, followed by their gradual granular disintegration with the formation of irregular darkly staining clumps (Fig. 3). These changes are paralleled by a progressive pyknosis or lysis of the nucleus. Often the sarcoplasmic substance of the fibres seemed to undergo gradual lysis also, but sometimes there was an apparent coalescence of adjacent fibre material and an aggregation of their nuclei (Fig. 4). This change constitutes the earliest stage in the formation of myogenic giant cells. Later the vague outline of their cytoplasmic mass becomes gradually more distinct and the nuclei crowd closer together (Fig. 5 and 6). After a thorough search of numerous sections, at least one such giant cell was found in all except Cases 1 and 4 of the above, and in Case 3 they were particularly numerous. The myogenic nature of the giant cells is borne out by the presence in their cytoplasm of lipofuscin pigment when this is also present in intact fibres. Not uncommonly some of this pigment was also present in the scanty macrophages which were scattered about in the areas of muscle necrosis.

In Cases 3 and 5 evidence was present that in places the lesions were starting to heal. There was early fibrosis between some of the muscle fibres and especially in the areas showing the later stages of muscle necrosis (Fig. 7).

(2) *Subacute or chronic.* The majority of cases showed this type of lesion with the main feature being the association of inflammatory cells and fibrosis (Fig. 8). In Cases 6, 7, 8, 9, 10, 11, and 12 the ventricle,

FIG. 3.—Muscle necrosis in various stages of development. (P.T.A.H. $\times 210$.)

FIG. 4.—Earliest stage of giant cell formation. Note smudged appearance of necrotic muscle and presence of numerous cardiac histiocytes. (H. and E. $\times 210$.)

FIG. 5.—Stage of giant cell formation later than in Fig. 4. (H. and E. $\times 250$.)

FIG. 6.—Giant cell appearing as a more distinct entity than those in Fig. 4 and 5. (H. and E. $\times 210$.)

FIG. 7.—Early fibrosis in area of muscle necrosis, especially in top right of field. (H. and E. $\times 210$.)

FIG. 8.—Diffuse subacute or chronic myocarditis showing association of fibrosis and inflammatory cells. (H. and E. $\times 125$.)

interventricular septum, and the atria were affected diffusely, whereas in Cases 13, 14, and 15 the lesions had a patchy distribution with relatively unaffected areas intervening (Fig. 9).

The fibrous tissue was located between individual fibres and was often fine or reticular but occasionally hyaline. In places there was also fibrous replacement of a few muscle fibres with the formation of micro-

FIG. 9.—Patchy subacute or chronic myocarditis. (H. and E. $\times 125$.)

FIG. 10.—Single giant cell in focal scar. (H. and E. $\times 210$.)

FIG. 11.—Irregular muscle hypertrophy. Note marked differences in fibre and nuclear size. (H. and E. $\times 250$.)

FIG. 12.—Giant-cell myocarditis. Note vascular dilatation at periphery of lesion. (H. and E. $\times 125$.)

scopic scars. In these and in the rest of the fibrous tissue, a cellular infiltration was present. This was predominantly lymphocytic but with a small number of plasma cells and both neutrophil and eosinophil leucocytes, and a small increase in toluidine blue stainable tissue histiocytes.

The infiltration was exceedingly sparse in places, but in others was appreciably more dense, plasma cells and polymorphs being more numerous and an occasional cardiac histiocyte appearing. Within these

FIG. 13.—Giant-cell myocarditis showing focal granuloma. (H. and E. $\times 170$.)

denser foci there were rarely a few thin atrophic muscle fibres showing patchy loss of striation. Even more rarely, and often only after a prolonged search of the microscopic scars or of the cellular foci, a single multinucleated giant cell could be demonstrated (Fig. 10).

Another feature of the diffusely affected cases was the muscle hypertrophy which was often irregular, adjacent fibres showing obvious differences in width and nuclear size (Fig. 11).

(3) *Giant Cell*. Three remaining cases (16, 17, and 18) were distinguished by lesions showing large numbers of multinucleate giant cells. These were typically scattered haphazardly throughout areas of fibrous tissue and in some of them lipofuscin pigment could be seen. The size of the lesions varied, the largest being between 2 and 4 cm. in length. They tended to be elongated in shape with their long axis parallel to the cavities of the heart. The fibrous tissue was patchily infiltrated with lymphocytes, a few plasma cells, and scanty eosinophil or neutrophil polymorphonuclear leucocytes. Scattered throughout were also small numbers of macrophages containing lipofuscin pigment. Centrally the fibrosis was hyaline but peripherally, where the infiltration showed foci of greater density, there was evidence of fibroblastic activity and a prominence of capillaries (Fig. 12). In the centre of some of the foci of more dense cellular infiltration there was a small number of pale cardiac histiocytes and occasionally some necrotic muscle debris or one or two myogenic giant cells. Rarely such a "granuloma" was present among muscle fibres just beyond the main lesion (Fig. 13). Giant cells were not however a consistent feature of these granulomata, and appearances ranged from those shown in Fig. 13 to little more than a small collection of inflammatory cells set in fibrous tissue which had apparently replaced a few muscle fibres, these latter foci being closely similar to the lesions seen in Cases 13 to 15 in the preceding group.

It is emphasized that the majority of the giant cells were scattered throughout the fibrous tissue and were unassociated with granulomatous formations. The cardiac muscle between the lesions was histologically normal except that in Cases 16 and 18 there was evidence of muscle hypertrophy of the left ventricle.

Examination of the heart failed to reveal the presence of tubercle bacilli, *Toxoplasma gondii*, or other organisms in any of the 18 cases. Vacuolation (Lancet, 1961) and mucoid degeneration (Bishop, Campbell, and Jones, 1962) of the muscle fibres as described in cases of idiopathic cardiac hypertrophy and familial cardiomegaly were not seen.

DISCUSSION

Although each case of isolated myocarditis appears to fall into one of three broad histological groups, there are certain features that are common to all cases. This suggests an interrelationship between them despite the fact that the heart, like other organs, can react in only a limited number of ways to different noxious agents.

In the cases classified here as "acute" the heart showed many of the histological features of an acute inflammation, and the only differences between individual cases appeared to be due to differences in the degree and duration of the pathological process. The whole heart was affected in 4 of the 5 cases and death occurred after only a short illness. In these 4, the increase in heart weight was presumably due to the extensive inflammatory process, no muscle hypertrophy being detected. In Case 5, the lesions were much less extensive and the heart weight normal, death due to pulmonary embolism occurring after an illness lasting 3 weeks.

When muscle necrosis was marked then multinucleate giant cells could usually also be demonstrated. However, only Covey (1942) of the numerous authors reporting cases of acute isolated myocarditis records the presence of giant cells. This suggests that their presence in large numbers in these cases is a rarity, and there are several explanations why this is so. Muscle necrosis is a prerequisite, and this seems to be marked in only some of the severe cases. In some, necrosis was minimal but the lesions affected the whole of the heart and death occurred in the early stages of the disease. The longer that severe cases survive the more commonly should giant cells appear, there being more time for their development. In Case 3 of this series they were particularly common with a 7-day history. In Covey's case there was a 13-day history. The special circumstance for the formation of giant cells, therefore, seems to be a process severe enough to cause necrosis, but not extensive enough nor in a situation (e.g. the conducting system) where they might precipitate early death.

The other important feature of this acute group is the evidence that healing of the lesions would

result in some degree of fibrosis. It is becoming more widely appreciated that many of the smaller fibrotic lesions of the myocardium, which are found with increasing frequency as age advances, are unrelated to coronary artery disease (Schwartz and Mitchell, 1962), but that they represent healed foci of non-specific myocarditis. Such foci are seen in association with a large number of conditions (Saphir, 1941–1942, and 1942; Saphir, Wile, and Reingold, 1944; Candel and Wheelock, 1945; Marcuse, 1947; Gore and Saphir, 1947a, b; Crawford *et al.*, 1961; Kline, Kline, and Saphir, 1963), many of which are often mild and non-fatal. Moreover healing of the more extensive lesions of an “acute” isolated myocarditis could account for some of the appearances seen in the “giant cell” and “subacute or chronic” groups of cases. For example, the healing of acute lesions associated with much muscle necrosis might well result in areas of fibrosis containing giant cells. If enough cases could be examined the stages of this development could be studied. The earliest stages would be similar to those seen in Case 3 of this series and the healed stages to those in Cases 16, 17, and 18. Two cases of giant cell myocarditis are described by Goldberg (1955) and Dilling (1956) which could well represent stages intermediate to those.

Similarly a diffuse acute lesion without marked necrosis might well result in a widespread interstitial fibrosis. Moreover, as the evidence in this study suggests, various combinations of many of the features of the “giant cells” and “subacute or chronic” types of lesions could theoretically result, depending on the extent and severity of the initial process. There are, however, additional features of these lesions which cannot be explained in this way. One of these is the appearance of foci of more recent activity. Professor C. V. Harrison has described the appearance in Blanshard's (1953) case, which corresponds to the “subacute or chronic” group here, as a “smouldering myocarditis”. The lesions indeed suggest successive healing of a recurrent process.

A particular feature of the “subacute or chronic” type of case is the great weight that the heart often attains. This is due largely to the hypertrophy of the remaining muscle, the mechanism of which has recently been studied by Linzbach (1960) who also shows that in hearts weighing more than about 500 g. there is evidence that the hypertrophied muscle fibres actually undergo a longitudinal splitting. Thus there is not only an initial increase in the size of the remaining fibres but above a critical weight there is also an increase in their number.

Any discussion concerning isolated myocarditis would not be complete without a consideration of the recent claims that the “giant cell” type is in reality sarcoidosis of the heart. Cardiac involvement in generalized sarcoidosis is a well-recognized phenomenon (Johnson and Jason, 1944; Scotti and McKeon, 1948; Kirchheiner, 1960; Porter, 1960; Phinney, 1961; Forbes and Usher, 1962), and it is probable that the reported cases of so-called “giant cell” or granulomatous myocarditis in which similar lesions are seen in extracardiac sites (Jonas, 1939; Kean and Hoekenga, 1952; Tesluk, 1956; Long, 1961) are further examples of this phenomenon. Rab *et al.* (1963) consider that myocardial sarcoid can occur in the absence of lesions in other organs, and they report one such case and cite two others from the series collected by Forbes and Usher.

In the 3 cases of giant cell myocarditis studied here, occasional granulomas which bore a resemblance to sarcoid follicles were in fact present (Fig. 13). They differed from typical sarcoid lesions however in numerous details. There was a lack of epithelioid cells in the granuloma and they had a much more pleomorphic cellular composition of histiocytes, plasma cells, and polymorphonuclear leucocytes in addition to lymphocytes. Also these cells often surrounded some muscle cell debris. As a whole the lesions were different from the usual sarcoid pattern, in particular the appearance of dense areas of fibrosis in which were scattered multinucleate giant cells, some containing lipofuscin pigment and all unassociated with any apparent follicle formation. In the light of the foregoing it is therefore felt that isolated giant cell myocarditis is an entity distinct from sarcoid of the heart.

What of the aetiology of isolated myocarditis? The histological similarity of lesions is not sufficient proof that the aetiological agents responsible for them are also similar. However, from the hearts of cases that would otherwise have been grouped as acute isolated myocarditis if included in this study, viruses of the Coxsackie group have been isolated (Gear, 1958; Babb, Stoneman, and Stern, 1961; Glajchen, 1961; Butler *et al.*, 1962). It has not been possible to assess the percentage of

cases of isolated myocarditis where attempts at virus isolation have met with failure; presumably they are not frequently reported. In a case of isolated myocarditis reported by Szogi (1963) *Toxoplasma gondii* pseudocysts were seen in the myocardium. Moreover toxoplasma bodies have been recovered from cases identical to the "subacute or chronic" group of this series after injecting the heart muscle intraperitoneally into mice (Paulley *et al.*, 1954; Cathie, 1955). The smouldering nature of the lesions in this type is possibly explained by Szogi's observations that intact toxoplasma pseudocysts excite no inflammatory response but probably do so only when they rupture. Having ruptured they are no longer recognizable as such, and this may explain part of the difficulty encountered in finding toxoplasma organisms in the more chronic cases.

Appearances similar to those described in this study are regarded as non-specific myocarditis when associated with certain other disease processes, and it is also claimed that hypersensitivity to various drugs (Kline *et al.*, 1963) including the sulphonamides (French and Weller, 1942; Fawcett, 1948) can produce a similar picture. Recently Robinson and Brigden (1963) have emphasized that following muscle damage at cardiectomy, heart auto-antibody production may be induced: they also show that these antibodies are responsible for the post-cardiectomy syndrome. Primary muscle damage by a virus or toxoplasma infection may act similarly and trigger off an auto-immune reaction. This mechanism offers an alternative explanation to repeated infection with virus or toxoplasma, etc., for the appearances of a smouldering recurrent process in many of the cases of isolated myocarditis. Such cases suspected during life may have demonstrable auto-antibodies in their serum and a test such as the heart tanned red cell method of Robinson and Brigden could be of diagnostic help. Tests such as these together with serological tests for the detection of virus and toxoplasma infections, and attempts to isolate these and other organisms during life and at necropsy would undoubtedly result in a gradual decrease in the number of cases diagnosed rather unsatisfactorily as isolated myocarditis.

SUMMARY

The histological appearance of the heart in 18 cases of isolated myocarditis is described and the relation between the three different types of lesions found and their possible aetiology is discussed. Giant cell myocarditis is thought to be an entity quite separate from sarcoid of the heart. It probably evolves under special circumstances as the result of an initial acute process associated with muscle necrosis. As more cases of myocarditis of obscure origin are more fully investigated, the diagnosis of isolated myocarditis should become increasingly uncommon.

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REFERENCES

- Babb, J. M., Stoneman, M. E. R., and Stern, H. (1961). Myocarditis and croup caused by Coxsackie virus type B5. *Arch. Dis. Childh.*, **36**, 551.
- Bishop, J. M., Campbell, M., and Jones, E. W. (1962). Cardiomyopathy in four members of a family. *Brit. Heart J.*, **24**, 715.
- Blanshard, T. P. (1953). Isolated diffuse myocarditis. *Brit. Heart J.*, **15**, 453.
- Boikan, W. S. (1931). Myocarditis perniciosa. *Virchows Arch. path. Anat.*, **282**, 46.
- Butler, N., Skelton, M. O., Hodges, G. M., and MacCallum, F. O. (1962). Fatal Coxsackie B₃ myocarditis in a newborn infant. *Brit. med. J.*, **1**, 1251.
- Candel, S., and Wheelock, M. C. (1945). Acute non-specific myocarditis. *Ann. intern. Med.*, **23**, 309.
- Cathie, I. A. B. (1955). Myocardial toxoplasmosis. *Lancet*, **1**, 149.
- Conlin, G. J., and Mantz, F. A. (1953). Isolated myocarditis in infants. *J. Pediat.*, **42**, 414.
- Covey, G. W. (1942). Acute isolated myocarditis (Fiedler's myocarditis). *Amer. J. clin. Path.*, **12**, 160.
- Crawford, S. E., Crook, W. G., Harrison, W. W., and Somerville, B. (1961). Histoplasmosis as a cause of acute myocarditis and pericarditis. *Pediatrics*, **28**, 92.
- Dilling, N. V. (1956). Idiopathic giant-cell myocarditis. *J. Path. Bact.*, **71**, 295.
- Drennan, J. M. (1953). Acute isolated myocarditis in newborn infants. *Arch. Dis. Childh.*, **28**, 288.
- Fawcett, R. M. (1948). Myocardium after sulfonamide therapy. *Arch. Path.*, **45**, 25.
- Forbes, G., and Usher, A. (1962). Fatal myocardial sarcoidosis. *Brit. med. J.*, **2**, 771.
- French, A. J., and Weller, C. V. (1942). Interstitial myocarditis following the clinical and experimental use of sulfonamide drugs. *Amer. J. Path.*, **18**, 109.

- Gear, J. H. S. (1958). Coxsackie virus infections in the newborn. *Progr. med. Virol.*, **1**, 106.
- Glaichen, D. (1961). Myocarditis due to Coxsackie virus infection in an adult. *Brit. med. J.*, **2**, 870.
- Goldberg, G. M. (1955). Myocarditis of giant-cell type in an infant. *Amer. J. clin. Path.*, **25**, 510.
- Gore, I., and Saphir, O. (1947a). Myocarditis: a classification of 1402 cases. *Amer. Heart J.*, **34**, 827.
- , and — (1947b). Myocarditis associated with acute nasopharyngitis and tonsillitis. *Amer. Heart J.*, **34**, 830.
- Greenebaum, J. V., Felson, W., and Zeligs, M. (1941). Acute interstitial myocarditis in an infant. *J. Pediat.*, **18**, 799.
- Gubbay, E. R. (1961). Idiopathic giant-cell myocarditis. *Canad. med. Ass. J.*, **85**, 349.
- Hansmann, G. H., and Schenken, J. R. (1938). Acute isolated myocarditis. *Amer. Heart J.*, **15**, 749.
- Hertzog, A. J., and Heyford, W. D. (1947). Acute isolated myocarditis (Fiedler's myocarditis). *Minn. Med.*, **30**, 54.
- House, R. K. (1948). Diffuse interstitial myocarditis in children. *Amer. J. Path.*, **24**, 1235.
- Johnson, J. B., and Jason, R. S. (1944). Sarcoidosis of the heart. *Amer. Heart J.*, **27**, 246.
- Jonas, A. F. (1939). Granulomatous myocarditis. *Bull. Johns Hopk. Hosp.*, **64**, 45.
- Jones, H. E., and Marshall, A. G. (1948). Isolated (Fiedler's) myocarditis. *Arch. Dis. Childh.*, **23**, 201.
- Kean, B. H., and Hoekenga, M. T. (1952). Giant cell myocarditis. *Amer. J. Path.*, **28**, 1095.
- Kline, I. K., Kline, T. S., and Saphir, O. (1963). Myocarditis in senescence. *Amer. Heart J.*, **65**, 446.
- , and Saphir, O. (1960). Chronic pernicious myocarditis. *Amer. Heart J.*, **59**, 681.
- Kirchheiner, B. (1960). Sarcoidosis cordis. *Acta med. scand.*, **168**, 223.
- Lancet (1961). Cardiomyopathy. **1**, 1214.
- Linzbach, A. J. (1960). Heart failure from the point of view of quantitative anatomy. *Amer. J. Cardiol.*, **5**, 370.
- Long, W. H. (1961). Granulomatous (Fiedler's) myocarditis with extracardiac involvement. *J. Amer. med. Ass.*, **177**, 184.
- Magner, D. (1939). A case of subacute fatal myocarditis of unknown etiology. *Amer. J. med. Sci.*, **198**, 246.
- Marcuse, P. M. (1947). Nonspecific myocarditis. *Arch. Path.*, **43**, 602.
- Maslow, H. L., and Lederer, M. (1933). Interstitial myocarditis in a child nineteen months of age. *Amer. J. Dis. Child.*, **45**, 807.
- Paulley, J. W., Jones, R., Green, W. P. D., and Kane, E. P. (1954). Myocardial toxoplasmosis. *Lancet*, **2**, 624.
- Phinney, A. O. (1961). Sarcoid of the myocardial septum with complete heart block. *Amer. Heart J.*, **62**, 270.
- Porter, G. H. (1960). Sarcoid heart disease. *New Engl. J. Med.*, **263**, 1350.
- Rab, S. M., Choudhury, G. M., and Choudhury, A. R. (1963). Giant-cell myocarditis. *Lancet*, **2**, 172.
- Robinson, J., and Brigden, W. (1963). Immunological studies in the post-cardiotomy syndrome. *Lancet*, **2**, 706.
- Saphir, O. (1941-1942). Myocarditis. *Arch. Path.*, **32**, 1000, and **33**, 88.
- (1942). Isolated myocarditis. *Amer. Heart J.*, **24**, 167.
- , and Cohen, N. A. (1957). Myocarditis in infancy. *Arch. Path.*, **64**, 446.
- , Wile, S. A., and Reingold, I. M. (1944). Myocarditis in children. *Amer. J. Dis. Child.*, **67**, 294.
- Schwartz, C. J., and Mitchell, J. R. A. (1962). The relation between myocardial lesions and coronary artery disease. I. An unselected necropsy study. *Brit. Heart J.*, **24**, 761.
- Scott, R. W., and Saphir, O. (1929). Acute isolated myocarditis. *Amer. Heart J.*, **5**, 129.
- Scotti, T. M., and McKeown, C. E. (1948). Sarcoidosis involving the heart. *Arch. Path.*, **46**, 289.
- Szogi, S. (1963). Isolated toxoplasma myocarditis in a child. *Acta path. microbiol. scand.*, **58**, 399.
- Tedeschi, C. G., and Stevenson, T. D. (1951). Interstitial myocarditis in children. *New Engl. J. Med.*, **244**, 352.
- Tesluk, H. (1956). Giant cell versus granulomatous myocarditis. *Amer. J. clin. Path.*, **26**, 1326.
- Ware, E. R., and Chapman, B. M. (1947). Chronic fibroplastic myocarditis. *Amer. Heart J.*, **33**, 530.
- Williams, H., O'Reilly, R. N., and Williams, A. (1953). Fourteen cases of idiopathic myocarditis in infants and children. *Arch. Dis. Childh.*, **28**, 271.