Myocarditis and Myocardosis

A Clinicopathologic Appraisal

By M. A. Blankenhorn, M.D., and Edward A. Gall, M.D.

Search of 3,141 autopsies found 108 examples of myocardial disease of which 77 were inflammatory (nonrheumatic) and 31 noninflammatory but degenerative and not due to sclerosis or hypertension. These are designated myocardosis. Myocarditis was associated with infections in a manner often described; myocardosis was associated with a variety of noninfectious disorders. A discussion of the use of this term is elaborated. Clinical records also were studied to find what part such lesions played in causing death and how such myocardial lesions could be diagnosed with more certainty.

A significant renewal of clinical interest in myocarditis and other disorders of cardiac muscle has become manifest in recent years. Much of the impetus has stemmed from an increasing awareness that pathologists were frequently encountering intrinsic myocardial abnormalities in patients in whom these had been unsuspected during life. Also of contributory significance have been the growing use of the electrocardiograph and the development of therapeutic measures for the control of serious acute infections. The latter has led indirectly to the unmasking of evidences of myocardial dysfunctions previously considered manifestations of the underlying febrile disorder. The combination of these factors has served to overcome a popular reluctance to consider myocardial disease a valid clinical entity.

The term "myocarditis" came into disfavor at the turn of the century; a reflection of its misuse as a basket category into which were placed sundry conditions for which no pertinent pathologic evidence was forthcoming.1-3 The recognition in 1912 of the significance of coronary occlusion and its associated myocardial alterations all but eliminated primary disease of heart muscle from clinical teaching. Indeed, Sir Thomas Lewis sounded the prevailing note with the remark that the diagnosis "myocarditis" was not justified, save in relation to rheumatism and then "carditis" served a more representative purpose. On the other hand, Christian4 (1950), among others, persisted in emphasizing the importance of primary myocardial disease in certain instances of heart failure. Confirmatory support for this stand has emerged during the past 10 years, in good part initiated by the large scale studies of Saphir (1941) and Gore (1947, 1948). Others have claimed an autopsy incidence as high as 10 to 15 per cent and have expressed the belief that most persons experience fleeting attacks of myocarditis in the course of various acute infectious disorders.1,4

The present study was made to discover the incidence of myocarditis at autopsy in the Cincinnati General Hospital and further to evaluate the pathologic findings in relation to the clinical signs. An added purpose was the investigation of cases of "cardiac catastrophe," thus disclosed. A cardiac catastrophe is defined as a situation in which death resulted from myocardial insufficiency but in which this possibility was not recognized during life. It is not pertinent to this arbitrary definition that a correct diagnosis would necessarily have benefited the patient. It is rather considered a catastrophe not to know what could have been known.

Material

The autopsy records of 3,141 cases examined during the five-year period, 1949 to 1953, were searched. Patients of all age groups were included. From this source were culled those cases with myocardial disease exclusive of that due to coronary artery insufficiency and rheumatic fever. There were no cases with diphtheritic heart disease in this period but there were 11 individuals with active rheumatic myocarditis.

From the Departments of Medicine and Pathology, University of Cincinnati and the Cincinnati General Hospital, Cincinnati, O.
The group thus gathered numbered 108 cases. Only routine sections of the heart were available for microscopic study and these ranged from two to eight per case, the average being three sections. Usually the right and left ventricles were represented. The lesions encountered were divisible into two major categories: Myocarditis, characterized by inflammatory exudates of varying intensity; and myocardosis in which cellular exudate was absent and the significant alterations were of retrograde or degenerative nature as defined in Dorland and used by American authors for a quarter of a century or more.6-8 Seventy-seven cases comprised the myocarditis group and 31 cases were classified as myocardosis.

The clinical records in all of these cases were critically surveyed by one of us (M. A. B.), the autopsy findings were independently investigated by the other (E. A. G.). Each attempted, from the data available to him, to determine whether or not death was attributable to the myocardial disorder. A remarkable degree of conformity was attained on this score.

Pathologic Lesions

The lesions of myocarditis have as a common denominator the presence of a cellular exudate in the myocardium. Although Christian10 pointed out that the suffix “itis” in a classical sense had little limiting connotation, it has become customary to utilize it as an indication of inflammation alone.9 Unfortunately in the press of conservative interpretation of pathologic alteration of the myocardium, many have ignored the distinction between degeneration and inflammation. As a result such terms as toxic myocarditis and fibrous or fibroplastic myocarditis, intended to indicate noninflammatory lesions, have introduced a confusing note into the literature.1, 2, 6, 7, 11-13 In our own studies we have held to the minimum requirement of inflammatory cell infiltration as a basis for the recognition of myocarditis. The character of the exudate was found to vary in respect to cell type, intensity and extent. No effort was made, however, to classify the lesion save to estimate whether it was of significance in contributing to the death of the patient. This was arrived at by evaluating both the myocardial process and the extracardiac findings disclosed by the autopsy.

In some of the cases, the lesions were widely distributed; in others, they were relatively spotty. In one instance coalescent, noncaseating tubercles of sarcoid constituted the outstanding feature. In most specimens the exudate was located in the interstitium, but replacement of myocardial fibers was also encountered. Varying degrees of muscle necrosis occurred. In view of Saphir’s observation of a doubled yield in the incidence of myocarditis when 25 heart sections were prepared, it is assumed that a significant number of cases were missed in this investigation. Whether or not this error was of the order of 100 per cent, however, is open to considerable question. It is felt that relatively few cases in which the myocardial lesion actively contributed to death were not detected.

Myocardosis, a term coined by Riesman,8 has not had wide usage in this country and is not remarked in most of the standard works in cardiology.10 As a means of categorizing noninflammatory disorders of the myocardium and those degenerative conditions unrelated to coronary disease the term has found wider application in European publications.11, 12, 14-16 Both clinical and experimental observations have justified the separation of these retrograde states from infectious and commonplace anoxic lesions.17-26 In establishing a given alteration as a definitive lesion it is naturally necessary to avoid including banal postmortem changes. This has been done insofar as possible. Included as indicative of myocardosis have been such lesions as pronounced interstitial edema; swelling, lamination and proliferation of stroma; amyloidosis; shrinkage and irregularity or cloudy swelling, opacification, granulation and loss of striation of muscle fibers; hyalinization, over fragmentation; fatty degeneration and, in extreme instances, necrosis.27

Incidence

In the absence of a precise definition of myocarditis and a uniform method for histologic survey there is not much comparable meaning to the figures cited in the literature. Saphir28 found myocarditis in 4.3 per cent of all autopsies at the Michael Reese Hospital (9 per cent when more elaborate methods were used), de la Chapelle5 recorded 3.3 per cent at Bellevue
Hospital and Gore and Saphir\textsuperscript{3} observed 3.5 per cent at the Army Institute of Pathology. This constitutes a surprising degree of agreement and our own figure of 3.4 per cent is quite in keeping.

Others, however, have claimed an incidence of 10 to 15 per cent.\textsuperscript{3, 4} On the other hand, there are many reports indicating a negligible appearance of myocarditis\textsuperscript{29-31} in relatively large series of cases.

The different studies cited have had little uniformity in the types of cases excluded in arriving at a determination of the occurrence rate of myocarditis. Many have not considered newborn and stillborn cases, those dead on arrival, and those with valvular or coronary vascular disease. There has been much variation in the inclusion of cases with active rheumatic carditis and diphtheria. We have not considered it necessary to exclude any but the cases with rheumatic heart disease since it has not been possible in these to distinguish between death due to myocardial failure and that attributable to concomitant valvular distortion.

\textbf{Clinical Studies}

Viewed according to distribution of hospital services, the 108 cases were:

<table>
<thead>
<tr>
<th>Service</th>
<th>Myocarditis</th>
<th>Myocardosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>55</td>
<td>24</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Surgical</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Contagious</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dead on arrival</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

\textit{Myocarditis}

In inflammatory myocarditis much has been made of the association of specific infections with myocarditis, this being the usual and sole proof of specific etiology. Saphir's major contribution was to show what specific infections were associated with, and hence etiologically related to, myocarditis in a vast number of situations. Following his technic, which is the simplest method available, we find much the same relations.

In 77 instances of inflammatory myocarditis there were 46 with recognized infectious disease:

13 found with pneumonia—lobar or lobular;
12 found with septicemia—not specified nor defined by cultures;
6 found with staphylococcal septicemia;
4 found with meningococcal septicemia;
3 found with virus diseases (2 polio, 1 neuritis);
2 found with subacute bacterial endocarditis;
1 each with Friedlander pneumonia, tuberculosis, pyocyanous infection, amebic abscess with secondary E. coli contamination, syphilitic aortitis, meningitis—organism not determined—and sarcoidosis.

As might be expected, the clinical picture of the patient found with myocarditis is dominated by systemic infections as shown above or by some associated organ system disease. The latter diseases are listed here in the order of frequency and are somewhat simplified for reporting:

\textbf{Neurologic disorders (including cerebrovascular accident—many with associated pneumonia).} \textsuperscript{20} 20
\textbf{Malignant neoplasm (including lymphoma).} \textsuperscript{9} 9
\textbf{Acute and chronic lung disease.} \textsuperscript{8} 8
\textbf{Trauma and poisoning.} \textsuperscript{5} 5
\textbf{Diabetes.} \textsuperscript{4} 4
\textbf{Kidney disease.} \textsuperscript{3} 3
\textbf{Liver disease.} \textsuperscript{3} 3
\textbf{Disseminated lupus.} \textsuperscript{3} 3
\textbf{Neerotizing angitis, periarteritis and hypersensitivity angitis.} \textsuperscript{3} 3
\textbf{Congenital heart disease.} \textsuperscript{1} 1
\textbf{Peripheral vascular disease.} \textsuperscript{1} 1

Myocarditis was found to be accompanied by some other form of heart disease in 29 out of 79 instances. Listed in order of frequency were the following:

\textbf{Acute endocarditis.} \textsuperscript{8} 8
\textbf{Bacterial.} \textsuperscript{6} 6
\textbf{Nonbacterial.} \textsuperscript{2} 2
\textbf{Subacute bacterial endocarditis.} \textsuperscript{3} 3
\textbf{Hypertensive heart disease.} \textsuperscript{4} 4
\textbf{Chronic inactive valvular heart disease, rheumatic.} \textsuperscript{3} 3
\textbf{Coronary artery disease.} \textsuperscript{3} 3
\textbf{Pericarditis, acute.} \textsuperscript{3} 3
\textbf{Cor pulmonale.} \textsuperscript{2} 2
\textbf{Congenital.} \textsuperscript{1} 1
\textbf{Syphilitic aortitis.} \textsuperscript{1} 1
\textbf{Idiopathic hypertrophy.} \textsuperscript{1} 1

Electrocardiograms were not made on many of these 77 patients. In the 21 records available, the following abnormalities were reported.
from interpretations done in the official cardiographic laboratory of the hospital:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspecific myocardial abnormalities</td>
<td>11</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>2</td>
</tr>
<tr>
<td>Left ventricular strain</td>
<td>2</td>
</tr>
<tr>
<td>A-V heart block</td>
<td>1</td>
</tr>
<tr>
<td>Old myocardial infarct</td>
<td>1</td>
</tr>
<tr>
<td>Digitalis effect</td>
<td>1</td>
</tr>
<tr>
<td>Auricular flutter</td>
<td>1</td>
</tr>
</tbody>
</table>

One, only, was reported normal. In this latter instance cor pulmonale had been diagnosed and also chronic lung disease. The amount of myocarditis was not great.

In the 29 instances where other forms of heart disease were found present among the 77 cases of myocarditis, heart disease of some sort had been diagnosed clinically in 24, that is 24 of 29 patients, either previous to the final illness or in its course. The significance of such diagnosis is best comprehended by an opinion on whether myocarditis was the cause of death or contributed to death. This opinion was formed by each of the writers separately, as stated above. The clinical study was especially concerned to learn whether congestive failure was diagnosed, whether orthopnea, rapid pulse or low blood pressure was described and whether death was sudden. There was remarkably good agreement in the two separate opinions about the significance of the myocardial disease.

Among the 77 myocarditis cases heart disease was found to be the primary cause of death in 17, to be a contributing factor in 25, and to have no apparent relationship in 35 instances.

Among the 17 patients where myocarditis was the primary cause of death, five could be classed as cardiac catastrophes, as defined above. Essential details of these patients were briefly as follows:

Case 1, No. 160515, was a male, age 53. Cause of death was acute gastritis; heart failure. Heart disease was not diagnosed clinically although orthopnea, gallop rhythm with obscure heart sounds and dependent edema were found. No electrocardiograms were made. The heart weighed 570 Gm. and exhibited acute, severe myocarditis microscopically.

Case 2, No. 115839. Another such catastrophe was in a man of 65 who was being studied on the Surgical Service for a mass in the region of the liver. Heart disease was not diagnosed and no electrocardiograms were made, although there were obscure heart tones and orthopnea. There was evidence of nutritional failure and of peripheral neuropathy. The heart was described as grossly normal but the site of severe acute and chronic myocarditis. The abnormal mass proved to be a chronic amebic abscess. The patient had not received emetine.

Case 3, No. 267704, a male age 39, was in the hospital less than two hours, having collapsed while at work as a "helper around a bar". He was in circulatory collapse; heart disease was not diagnosed although there were obscure heart tones and orthopnea. He was considered to be ill with acute gastritis and nutritional cirrhosis, and no electrocardiograms were made. The heart was described as flabby, weighing 390 Gm. The cut section showed a striking mottled appearance. Microscopically there was hydropic degeneration of the myocardium thought to be indicative of beriberi heart disease. There was also, however, profuse diffuse infiltration of polynuclear leukocytes in interstitial spaces. The lesion was classified as acute myocarditis. There was nutritional cirrhosis and possible beriberi.

Case 4, No. 231080, a 28 year old male, was dead on arrival. At autopsy the heart weighed 445 Gm. and showed extensive severe infiltration with tubercles characteristic of sarcoid. There was similar involvement of lungs and liver but no evidence of congestive failure. He had been thoroughly studied on the Dermatological Service two years previously but no electrocardiograms were made and no heart disease diagnosed. It may be straining a point to class this as a catastrophe, but the patient was not followed in clinic nor advised about limitation of activity.

Case 5, No. 126799, a male 70 years old, was in the hospital less than 24 hours. Chronic lung disease and spontaneous pneumothorax were diagnosed. A tube thoracotomy was done and there was only transitory improvement. Heart disease was not diagnosed although there were obscure heart tones, orthopnea and edema. The electrocardiogram showed only atrial tachycardia. The heart was not grossly abnormal at necropsy. Atheromatous plaques were described in the coronary arteries. Microscopically there was severe subacute myocarditis.

Myocardosis

The 31 patients with myocardosis at autopsy were of about the same age and sex distribution as the 77 with myocarditis.

The association with infections is quite different, being almost with no relation, as follows: one with meningitis, one with pertussis, one or two with doubtful staphylococcal sepsis, also
postoperative sepsis. There were none with positive blood cultures—ante mortem or post mortem.

As to associated disease, the pattern is much the same as with myocarditis but with more of metabolic disorders than of infections. The associated diseases can be summarized somewhat loosely rather than clearly because several such associated diseases were coexistent and the relative value hard to define.

Pneumonia ...................................... 5
Nutritional cirrhosis .................................. 5
Renal disease ...................................... 4
Generalized arteriosclerosis .......................... 4
Renal disease ...................................... 4
Lung disease ....................................... 2
Poisoning (lye ingestion, CO) ...................... 2
Amyloidosis, secondary .............................. 2
Blood dyscrasias, agranulocytosis, thrombocto-
penia .................................................. 2
Obesity .................................................. 2
Trauma .................................................. 1
Periarteritis nodosa (not of heart) .............. 1
Toxemia of pregnancy ............................... 1
Myxedema ............................................. 1
Diabetes ................................................ 1

There was relatively little associated heart disease of other category. There were two with hypertrophy and one with chronic valvular heart disease, probably sclerotic.

Electrocardiograms were made in 12 of these 31 patients. Eight were described as nonspecific changes, two with atrial fibrillation, one left ventricular strain and one sinus tachycardia. None was normal.

In this group heart disease was diagnosed 10 times during life. One, being suspected of hypokalemia, was treated with potassium chloride by mouth and later found with 12.8 mEq., but the cardiograms were not characteristic of potassium poisoning. Two with chronic renal disease had cardiograms not suggestive of potassium retention.

The significance of myocarditis in this group, as determined at autopsy and by clinical study, was: Primary cause of death, 10; secondary cause of death, 3; and no apparent relationship, 18.

There are six examples of cardiac catastrophe among these 29 patients with myocarditis.

Case 6, No. 261303, a female age 44, was known to be a chronic alcoholic and diagnosed as Wernicke’s syndrome and nutritional cirrhosis, being in the hospital four days. No specific cardiac disorder was diagnosed although she was suspected of having mild congestive failure. The patient was examined by four physicians but no electrocardiograms were made. At autopsy the heart weighed 500 Gm. and was described as extremely flabby with pale brown myocardium. Microscopic study showed interstitial edema with vacuolization of muscle fibers considered consistent with beriberi heart disease.

Case 7, No. 280042, was a woman, age 52, with myxedema in whom heart disease was not diagnosed although there were obscure heart tones, orthopnea and edema. This patient was in the hospital but five hours and received no treatment. The heart weighed 400 Gm. and was not grossly abnormal except for considerable coronary sclerosis. Microscopic examination showed myocardial fibers widely separated by edematous interstitial tissue. Immediate cause of death was right heart failure.

Case 8, No. 19123, was a man of 49 with “chronic pneumonia” in whom heart disease was not diagnosed. Heart tones were obscure and gallop rhythm present. Electrocardiogram suggested right heart strain. Death was sudden and unexpected.

Case 9, No. 292482, a male age 81, was in a confused state but not with overt heart disease. Pleural fluid was found to contain type 3 pneumococcus. This later developed into frank empyema which was repeatedly tapped, being treated meanwhile with penicillin. The patient died suddenly immediately after a thoracentesis. The heart was not grossly abnormal but there was coronary sclerosis of considerable degree. Microscopic examination showed amyloidosis of the heart, widespread. Heart disease was not diagnosed clinically although there were obscure heart tones, gallop rhythm and orthopnea. Electrocardiograms showed sinus tachycardia and occasional ventricular premature contraction.

Case 10, No. 177767, was a woman of 35. Autopsy diagnosis was acute thrombocytopenic purpura and she was being treated for an obscure anemia with fever. She apparently had transfusion reaction but correct matching and grouping were reconfirmed. The myocardium showed extensive platelet thrombosis of capillaries. There were focal areas of necrosis and fibrosis and there was interstitial edema and fibrosis. Grossly the heart was normal. Electrocardiogram was normal. Pulse and blood pressure were not remarkable. No heart disease was diagnosed clinically although it is quite apparent that heart failure was the principal cause of death.

Case 11, No. 64569, was a woman, age 54, who died 15 minutes after being returned from the operating room where extensive surgery was done. She was described as “returned to the ward in good condition.” When transferred from the cart to the
bed, she suddenly developed difficulty in breathing and the pulse was found slow and faint. She could not be revived. She had been ill over a year with rectal stricture and had been nine months with colostomy. Autopsy showed scanty findings. The heart weighed 375 Gm. with good coronary arteries and valves. Microscopic examination of the heart showed marked cloudy swelling and interstitial myocardial edema, slight myocardial fibrosis consistent with beriberi. Before operation systolic and diastolic murmurs had been described and the blood pressure was 170/100. No electrocardiograms were made. The final episode is typical of syncope reaction commonly seen in beriberi heart disease. It is suggested that the chronic gastroenteric disease was responsible for nutritional failure as shown in the myocardium.

Summary

A five year study at the Cincinnati General Hospital disclosed 108 cases of "myocarditis" in 3,141 autopsies from all services including newborn and stillborn and those dead on arrival; patients with rheumatic fever and diphtheria were excluded. This incidence, 3.4 per cent, is in keeping with reports from similar hospitals in New York and Chicago and from the Army Institute of Pathology.

In this study a distinction is made between inflammatory and degenerative myocardial disease, and the term myocardosis applied to the latter, of which there were 31 among the 108 total. A brief discussion of histologic criteria for diagnosis of myocardosis and somewhat about the history of this usage is given.

Inflammatory disease, i.e. myocarditis, was found associated with infections in much the same pattern as reported by others.

Myocardosis was usually unassociated with acute infections, but with a variety of intoxicants or metabolic diseases; prolonged pneumonia, nutritional type cirrhosis and renal disease were most frequent. Myocarditis was associated with other forms of heart disease in 29 of 77 instances. Myocardosis was seldom so associated. Electrocardiograms of both groups were abnormal with one exception and were interpreted variously—usually "nonspecific myocardial abnormality".

It was estimated that among the 77 patients with myocarditis, heart disease was the primary cause of death in 17, a contributing factor in 25, and unrelated in 35. Among 31 with myocardosis, heart disease was the primary cause of death in 10, a contributing factor in 3, and unrelated in 18. In the total series "cardiac catastrophe," i.e. where heart disease might have been diagnosed but was not, was found 11 times. Brief clinical notes about these are given, from which it is suggested that attention to certain physical signs might have led to diagnosis.

Summario in Interlingua

Un quinente studio al Hospital General Cincinnati revelava 108 casos de "myocarditis" inter 3141 autopsias ab omne brancas de servicio, includente neonatos e mortenatos e personas morte al arrivar sed exclusente casos de febre rheumatic e diphtheria. Iste proporcion (3,4 pro cento) se trova de acordo con reportos ab simile hospitales in New York e Chicago e ab le Instituto de Pathologia del Armea Statounitese.

Nos distingue in nostre studio inter morbo myocardiac inflammatore e degenerative. Le typo degenerative, que nos designa como myocardosis, es representante per 31 in le total de 108 casos. Es presentate un breve discussion del criterios histologic applicable al diagnostic de myocardosis, insimul con alicun remarca super le historia de iste termino.

Le morbo inflammatore, i.e. myocarditis, se trovava associate con infecciones in plus o minus le mesme maniera e al mesme grado como in le reportos de altere autores. Myocardosis esualsemente non-associate con infecciones acute sed con un varietate de intoxicantes o morbos metabolic. Le plus frequente inter istos esseva prolongate pneumonia, cirrhosis del typo nutritional, e morbo renal. Myocarditis esseva associate con altere formas de morbo cardiac in 29 inter 77 casos. Myocardosis rarmente mostrava un tal association. Electrocardiogrammas in ambe gruppos esseva anormal con un exception. Illos esseva interpretate in varie manieras, usualmente como "non-specific anormalitate myocardial."

Il es estimate que inter le 77 patientes con myocarditis, morbo cardiac esseva le causa primari del morte in 17 casos; illo esseva un factor contributente in 25 casos; e illo habeva nihil a facer con le morte in 35 casos. Inter
le 31 patientes con myocardosis, le correspondentem numeros esseva 10, 3, e 18. “Catastrophe cardiae”—i.e. morte in casos in que morbo cardiac haberea esite diagnosticabile sed in que nulle tal diagnoste esseva estabilite—occurrvea 11 vices in le serie total. Nos presenta breve notas clinic in re iste casos e conclude que un plus alte grado de attention prestate a certe signos physic haberea poteste stabile le diagnoste.

REFERENCES

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