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Isolated myocarditis : a review : with emphasis on the question of etiology

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ISOLATED MYOCARDITIS

A REVIEW,
WITH EMPHASIS ON THE QUESTION OF ETIOLOGY

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I. ISOLATED MYOCARDITIS DEFINED

Isolated myocarditis was first described by Fiedler [1] in 1890, but in the United States attention was not directed to this unusual form of myocarditis until 1929 by Scott and Saphir. [2] The disease has been described under various names, but it is generally agreed that isolated myocarditis is a rare form of heart disease which presents both clinically and pathologically a picture different from that seen in other inflammatory lesions of the myocardium. The clinical picture in all recorded cases is clearly one of progressive myocardial failure, rapid in some cases, more gradual in others, but unassociated with any of the better known factors leading to heart failure. Saphir [3] said, in a review of the literature, that one is justified in accepting the occurrence of isolated myocarditis in the sense of a more or less diffuse inflammatory lesion if every known cause for this type of myocarditis is ruled out and if the myocarditis is found in the absence of any major pathologic condition involving either the endocardium and pericardium or the entire body. Saphir reached this conclusion after studying 240 instances of myocarditis, among which were found 15 cases of isolated myocarditis of the type just mentioned. Anatomically the disease is not a specific form of myocarditis but

is classified as a separate entity largely because the etiology is unknown.[4]

There has, however, been disagreement in the extent of pathologic involvement included under the term isolated myocarditis. It has been pointed out[5] that not all authors have excluded, as Fiedler did, cases in which myocarditis was not the sole lesion. "Many were complicated by systemic infection or by other kninds of heart disease. Those in which infection was present might not differ greatly from cases of myocarditis following diphtheria, scarlet fever, severe burns, or influenza."

Cases with pericardial involvement have been described. In a case presented by Simon and Wolpaw,[6] the posterior aspect of the epicardial surface showed small irregular depressed areas over which a small amount of fibrin was seen. Covey[7] reports localized fibrinous pericarditis in a case of isolated myocarditis.

Throughout the literature, isolated myocarditis has been reported under a galaxy of terms. Acute isolated myocarditis was proposed by Fiedler. Later, other synonyms were applied, and terms such as acute interstitial isolated myocarditis, acute, subacute, and chronic isolated myocarditis, myocarditis perniciosa, and granulomatous myocarditis have appeared in reviews and case reports of this condition. The eponym

of Fiedler's myocarditis was naturally applied, and the condition has sometimes been referred to by such quasi-descriptive terms as primary, interstitial, circumscribed, diffuse, isolated myocarditis; productive myocarditis; eosinophilic myocarditis; idiopathic myocarditis; or myocarditis of unknown etiology. It seems logical and more convenient to refer to the condition simply as isolated myocarditis, although individual cases may vary highly in duration, and the prefix acute, subacute, or chronic in these instances seems justified.

II. HISTORY OF ISOLATED MYOCARDITIS

The first clear account of this disease was given by Fiedler in 1890, although two years earlier Steffen [8] reported two cases of acute myocarditis which probably fall in this classification. Sellentin [9] was the first to name the disease isolated myocarditis because, as a rule, changes are not found in other parts of the heart or in other organs. The earliest histologic description was made by Schmorl, [10] who examined Fiedler's cases.

Isolated myocarditis is rare. Engelhardt and Bruno, [11] in an historical survey reported in 1943, found nine reported cases of this entity in the American literature. In the world literature, they were

able to find at least 46 cases that conform to the pathologic criteria consistent with this syndrome. Since this survey, at least five cases of isolated myocarditis have been reported in the United States.

III. INCIDENCE

Isolated myocarditis is characteristically a disease of young persons, and the sex ratio has been greater than two males to each female affected. [12] While the disease may occur at any age, the most common period of involvement is twenty to fifty years. In a survey reported by Bailey and Andersen, 40% of the patients were in the third decade and 70% were between 21 and 50 years of age.

Isolated myocarditis, however, has also been reported in infancy and childhood. A series studied by Smith and Stephens [13] included two infants, 10 and 13 months old, respectively. Singer's [14] patients were 6 and 13 months of age. Lindberg [15] reported a patient 11 months old; Blühdorn [16] presented a case in a one and one-half year old child. Maslow and Lederer [17] reported an instance in a 21 month old white male hospitalized eleven days, who expired suddenly following dyspnea and rapid, feeble heart action. Kenney and Sanes [18] reported two cases in infants which they called parenchymatous myocarditis. One patient,

a girl one year of age, had bronchopneumonia six weeks before the onset. She had been well for two weeks, then dyspnea and cyanosis were noted, and she died in ten days. The other patient was a boy six months of age. The only preceding illness was stomatitis of three days duration some months before. He became dyspneic and cyanotic and died in a few hours.

IV. CLINICAL CLASSIFICATION

Boikan [19] attempted to classify the forms of isolated myocarditis into three groups.

"The first group embraces the acute forms of isolated myocarditis, the type probably originally described by Fiedler. This form usually causes death but may undergo healing with much new formation of connective tissue.

The second group included the truly chronic forms which invariably cause death of the patient after disease of several months. The left ventricle is particularly affected, and occasionally also the left auricle. Almost invariably the changes are present in the inner half of the ventricular wall, starting just beneath the endocardium. The initial changes are round cell infiltrations, the cells either localizing in groups or more diffusely infil-

trating the interstitial tissues. The capillaries are conspicuously dilated. Later eosinophilic leukocytes are seen, and the muscle fibers become necrotic. Gradually granulation tissue is formed, and eventually foci of fibrosis replace the destroyed muscle fibers.

The third group is characterized by the simultaneous presence of recent and old inflammatory changes. Because this is a progressive disease culminating invariably in the death of the patient with the clinical picture of progressive cardiac failure, the term 'pernicious' was applied."

The validity of this classification is doubtful, inasmuch as the terms acute, subacute, and chronic isolated myocarditis have probably been more generally used, and also because there is frequently considerable difficulty in correlating the clinical and pathological pictures. Some of the cases have undoubtedly gone unrecognized over long periods.

V. CLINICAL COURSE

The onset of isolated myocarditis in the majority of cases is abrupt and may be accompanied by a chill. Engelhardt and Bruno [11] believe the disease may be initiated by upper respiratory symptoms, such as cough, dyspnea, hemoptysis, generalized weakness and precordial distress, although it seems apparent

that these complaints are better explained on the basis of acute congestive failure.

Among patients in which the down-hill course is rapidly progressive, dyspnea and weakness are the outstanding symptoms, with cyanosis and tachycardia the most frequently found signs. In patients who run a longer course, the story is usually one of dyspnea, weakness and palpitation, with the gradual development of cyanosis, anasarca, and ascites, death usually being preceded by severe congestive failure. [12] In either case, precordial pain may be present.

In one survey, [12] in none of the cases did examination of the heart during life give any clue as to the type of lesion present. In practically all the heart was enlarged with an increase in the area of cardiac dullness, and the sounds were usually described as being of poor quality. None had murmurs suggesting endocardial lesions. In most of them the pulse was weak and rapid, and there is frequently low arterial pressure.

Simon and Wolpaw [6] and Engelhardt and Bruno, [11] in later reviews, however, reported the occurrence of occasional apical systolic murmurs.

Physical examination may reveal no findings of any consequence. [11] There has been in some instances a slight but definite increase of temperature for which no explanation was evident. Some cases have

presented evidence of focal infection of varying severity. Hansmann and Schenken [5] have pointed out, however, that acute isolated myocarditis is not to be confused with acute toxic myocarditis, for the former is not accompanied by the misleading protean manifestations of the generalized infectious process. Jonas [20] has also stated that isolated myocarditis is not to be confused with the acute myocarditis occurring during the course of pyogenic infections, acute respiratory infections, and severe burns.

The duration of the disease is highly variable, and has been reported as brief as one day and as extended as 27 months from the beginning of symptoms. [11] An extended period of involvement, however, is not the general rule, and in the usual case the disease will have run its course after a few months. It is noteworthy that in only a few instances was the correct diagnosis made during the life of the patient. [3] Clinically no constant progression of symptoms and signs that is diagnostic of this pathologic entity is known. [11] Isolated myocarditis is most frequently mistaken for coronary thrombosis, pericarditis or acute rheumatic myocarditis. The clinical diagnosis is made by exclusion. In a young person with a history of rapid, progressive myocardial insufficiency, the exclusion of the ordinary etiological factors, especially rheumatic fever, should lead one to consider

acute isolated myocarditis as a clinical diagnosis. [21] It has been further suggested that acute isolated myocarditis should be considered in cases of prolonged tachycardia in infants and children in whom no other cause can be found. [22]

In summarizing the status of isolated myocarditis, Bailey and Andersen stated that the variety of clinical pictures presented by the cases reported leads one to the conclusion that the disease is a pathological rather than a clinical entity. This is further borne out, they conclude, by the fact that in no instance has the correct diagnosis been made before death.

De La Chapelle and Graef, [23] in 1931, were the first to employ the electrocardiograph to demonstrate severe impairment of conduction in a case of isolated myocarditis. They found a prolonged P-R interval, complete intraventricular block and low voltage in all leads with a normal sinus rhythm. Scott and Saphir, [2] however, had earlier showed left ventricular preponderance in two cases with the electrocardiograph.

Most of the reported tracings have shown either prolonged P-R or QRS intervals with inverted T waves in one or more leads. Any combination of these abnormalities may be encountered, [21] and no diagnostic criteria have been established for the condition. [11]

The following is a case reported by Schenken and

Heibner, [4] which may be considered more or less typical of the diffuse type of acute isolated myocarditis:

"A 16 year old, white, American male of Jewish descent was admitted to the hospital December 24, 1942, at 7:20 p. m. and died December 25, 1942, at 10:20 a. m. His chief complaint was pain in the chest. On the afternoon of admission while playing basketball, the patient suddenly experienced great difficulty in breathing, saw spots before his eyes, became dizzy, and fell to the floor. He had never had any serious illnesses before, had been a regular member of the basketball team, and had been able to perform strenous tasks without difficulty.

Physical examination revealed that the skin was cold and clammy. His blood pressure was 70/40, pulse rate 110 per minute, and temperature 98 degrees F. He was given immediately 1,000 cc. of 10% glucose intravenously, and, following this infusion, his blood pressure rose to 90/70. Examination of the heart at this time revealed that the pulmonic second sound was louder than the aortic second sound. The mitral first sound was prolonged, but no murmurs were heard. Examination of the lungs revealed crepitant râles and a wheezing expiration. Eight hours after admission the patient was still in shock. The pulse was rapid and thready, the neck veins were distended,

and the nail beds as well as the skin over the face and neck were cyanotic. He intermittently beat his chest with his hands and cried, 'The pain is killing me.' Coarse rales were heard over both lung bases. Just before death, which occurred about eighteen hours after the onset of illness, large amounts of pink, frothy material poured forth from the nose and mouth.

Laboratory Examination. —— An x-ray film of the chest was made shortly after admission, and the following report was given: 'There is a slight increase in the transverse diameter of the heart. No shift of the mediastinal structures can be detected. The vascular markings are accentuated throughout both lungs and there is a mottled clouding of the parenchyma, the impression being that of pulmonary congestion and edema. A flat plate of the abdomen reveals marked gastric dilatation.' No other laboratory examinations were made.

Post-mortem Examination. —— The body was that of a well-developed and well-nourished white male, measuring 165 centimeters in length and weighing 54.5 kilograms. A pinkish-white froth filled the nasal and oral cavities. The superficial veins of the neck were markedly distended. The skin of the face and neck, the mucous membranes, and the nail beds were deeply cyanotic. There was no edema of the

extremities or the back.

The peritoneal cavity contained about 40 cc., each thoracic cavity contained 500 cc., and the pericardial sac contained about 50 cc. of a clear, straw-colored fluid. No exudate was present upon the serous membranes.

The right lung weighed 620 grams and the left, 460 grams. Each lung showed similar findings. Pinkish-white froth filled the large bronchi, and clear fluid poured forth from the cut surface. There was no evidence of consolidation. The liver weighed 1,212 grams. The capsule was smooth, the margins sharp, and the cut surface revealed normal color and markings. The gall bladder and bile ducts were normal. The spleen weighed 150 grams, and its capsule was smooth. The cut surface was irregular and deep purple in color; the pulp was softer than normal, but the markings were preserved. The right kidney weighed 112 grams, and the left, 125 grams. A moderate degree of congestion was the only finding of note. The pancreas, suprarenal glands, urinary bladder, gastro-intestinal tract, and testes appeared normal.

The heart weighed 225 grams. The chambers of the heart appeared to be moderately dilated. The endocardium was smooth and glistening, and the valves appeared normal. The myocardium was somewhat flabby. The cut surface of the left ventricle and the left

ventricular side of the interventricular septum showed a zone of brownish-red muscle directly beneath the endocardium. This zone, which extended from apex to base and measured 0.5 to 0.6 centimeters in thickness, did not reach the endocardium at any point but remained about 0.1 to 0.2 centimeters beneath it. The myocardium of the right ventricle did not show these changes. The coronary vessels were carefully inspected by serial cross sections and were widely patent throughout.

Microscopic Examination. —— The lungs showed large quantities of fluid mixed with varying numbers of red blood cells in the alveolar sacs. No exudate was present. No macrophages were noted. The alveolar capillaries were dilated but there was no evidence of interstitial inflammation. The only finding in the liver was a separation of the sinusoidal walls from the liver cords. There was no evidence of chronic passive congestion. The spleen showed a moderate congestion of the pulp with an increased number of polymorphonuclear leukocytes. One Malpighian corpuscle in each section showed a central area of reticulum cell hyperplasia and necrosis. The remaining organs appeared normal.

Although the lesions in the heart were present predominantly in the mottled zone beneath the endocardium, changes in the myocardium were present

throughout the entire thickness of the musculature from the pericardium to the endocardium. Neither of these surfaces was inflammed. The location and distribution of the lesions were quite irregular.

The areas showing the alteration in the muscle fibers were distributed in a patchy fashion. Some of these patches were surrounded by normal appearing muscle fibers. The changes in the muscle fibers were, for the most part, degenerative changes with the preservation of the general contour. In some areas there were irregular thickenings of the muscle fibers due to localized points of hyalinization, whereas in other areas rather long lengths of muscle fibers showed a loss of cross and longitudinal striations as the result of a rather uniform hyalinization. In both areas, however, the fibers stained more deeply than normal with eosin. In some areas the fibers showed an increase in the granularity, often revealing irregular, coarse granules and irregular, thick intercalated disks, as well as pale staining granular areas alternating with deep red staining hyalinized areas.

Inflammatory cell infiltration was associated with these degenerative changes. In most areas this infiltration was rather mild, consisting largely of rows of polymorphonuclear leukocytes and a few macrophages between the muscle fibers. In other areas,

however, very tiny foci of inflammatory cells were present at a point where there was obviously a defect in the continuity of the muscle fiber. None of these areas was large enough to be classified as an abscess. The densest points of accumulation of inflammatory cells were in the relatively loose supporting tissue in the region of the large blood vessels. In some areas there was hyalinization of the muscle fibers associated with very little cellular infiltration. In general, however, the degree of cellular infiltration was dependent upon the severity of the degenerative process. In many areas, marked hemorrhage was associated with degeneration and rupture of the muscle fibers. There was no evidence of pre-existing disease.

Bacteriologic Studies. —— No ante-mortem bacteriologic studies were made. Blood taken from the heart at autopsy was inoculated into brain broth, and no bacterial growth occurred. The splenic pulp was cultured on brain broth and was sterile. A block of myocardium, measuring about one square centimeter, was placed in acetone for one minute in order to destroy the contaminating surface organisms. It was then transferred to a sterile mortar and triturated with sterile sand and broth. Portions of this material were then inoculated into brain broth, Brewer's fluid thioglycollate medium, and upon a blood agar plate.

A pure culture of micro-aerophilic Streptococcus hemolyticus was isolated. No contaminating organisms appeared in any of the media."

VI. PATHOLOGICAL CONSIDERATIONS

The foregoing case selected from the literature is an excellent example of clinical and pathological findings in a typical case of the diffuse type of acute isolated myocarditis. Although the diffuse type is more common, [3] another variety has been repeatedly described——that characterized by the presence of granulomatous lesions.

The granulomatous type, which may show a proliferative inflammatory reaction of the myocardium with giant cells and sometimes caseation, suggests the picture seen in tubercles or gummas. Taussig and Oppenheimer [24] reported a case of myocarditis during antisyphilitic therapy in a six year old child which died suddenly of acute cardiac decompensation. Tubercle-like coalescent foci of necrosis with giant cells were noted in the myocardium, liver, lungs, and lymph nodes. The authors concluded that the lesions were probably due to syphilis, although exhaustive attempts to demonstrate spirochetes gave negative results.

Magner [25] presented a case in which sudden death

after subtotal excision of a simple colloid goiter was found to have been associated with myocarditis of an unusual type. Microscopic examination of the myocardium revealed many small foci of subacute inflammation in which muscle fibers had disappeared. Giant cells were prominent among the mononuclear inflammatory cells and proliferating fibroblasts in these areas.

Hansmann and Schenken [5] found myocardial lesions in various stages of development in a 48 year old colored woman dying suddenly after complaints of weakness, shortness of breath, and fever. "The most recent lesions consisted of fractured hyalinized muscle fibers which had lost their striations, and in these areas definite hemorrhages were observed. Others which appeared to be further developed revealed, in addition to the muscle injury and hemorrhage, numerous polymorphonuclear leukocytes. Still others contained remnants of hydropic and fatty muscle fibers and many lymphocytes and large mononuclear cells. Many of the latter contained hemosiderin. There were also areas of quite well-developed scar tissue which was arranged in a columnar pattern as if it had replaced individual muscle fibers. A few myocardial giant cells were present in some of these areas, and here and there exudate extended into the interstitial tissue." The coronary vessels were

normal, there was but slight atheromatous change in the aorta, and the remaining organs showed only acute edema and congestion.

Jonas [20] described three cases, all of them having extensive, severe granulomatous myocarditis, but numerous other organs were also involved in a similar granulomatous process. Two of the cases died in acute myocardial failure; death in the third case was sudden and did not occur while the patient was under observation. The histological picture in all three cases was characterized by a diffuse granulomatous process containing giant cells and showing a tendency toward tubercle formation. There was slight disposition toward caseation. All showed necrosis of tissue with replacement by collagen and resultant scarring, as well as involvement of the vessel walls by focal subintimal lesions unlike the perivascular lesions of syphilis. The lesions did not resemble those of rheumatism and no Aschoff bodies were found. In Jonas' words, "Syphilitic and tuberculous myocarditis, despite their rarity, were the conditions which these cases brought to mind." There was, however, no evidence in support of such an etiology. Although Saphir [3] included these cases in his survey, the question arises whether or not they should be considered isolated myocarditis in the presence of extracardiac granulomatous lesions. Saphir had previously said that the conditions

of isolated myocarditis are fulfilled only if the myocarditis is found in the absence of any major pathologic condition involving either the endocardium and pericardium or the entire body.

Similar granulomas have been reported by Magner, [25] Šikl, [26] Sidorov, [27] and Miller. [28] Earlier reports in the foreign literature were made by Baumgartner, Saltykow, and Gierke. [3]

The other histological type of isolated myocarditis, that characterized by a more diffuse type of inflammation without the formation of granulomas, is more commonly described in the literature. There is usually an interstitial infiltration of the myocardium, which is chiefly due to lymphocytes, monocytes and, to a certain extent, neutrophils, eosinophils, and plasma cells. Areas of necrosis are not infrequently found in the muscle fibers. This injury is diffuse throughout the myocardium. In some cases, hemorrhages have been described, due in all probability to the rupture of hyalinized muscle fibers. In the more chronic cases these areas are replaced by acellular fibrous scars. There may be actual granulation tissue with new capillary formation and fibroblastic proliferation. [11] It has been noted that in most of the cases of more than one month duration there are mural thrombi in the left ventricle, [12] and cases have been reported with large antemortem

thrombi in three chambers of the heart. [21]

Some of the confusion that has arisen from pathological reports of isolated myocarditis may be due to the fact that varied stages in the same disease process have been described, starting with very cellular stages and culminating in extensive fibrosis.

Schultz [29] reported the occurrence of myogenic giant cells without the formation of granuloma in the myocardium of a 21 year old soldier showing diffuse interstitial myocarditis. The muscle fibers were more or less destroyed and were replaced by loose connective tissue and inflammatory cells, and a number of multinucleated cells were also found.

Mittelbach [30] presented a case showing both endocardial and pericardial lesions in addition to changes in the myocardium, which would properly exclude this case from a classification of isolated myocarditis. It has been suggested that the lesions seem more likely to have been rheumatic in origin, but the possibility of subacute isolated myocarditis in a heart that happened to be the seat of old rheumatic endocarditis cannot be ruled out. The findings included an old slight endocarditis of the aortic, mitral and tricuspid valves, and a recent hemorrhagic pericarditis. "The myocardium was firm and had a peculiar shiny appearance, resembling amyloid. The myocardium showed thickening of medium-sized and smaller arteries

with absence of nuclei and presence of a homogeneous mass with destruction of the elastic lamellas and occasionally proliferation of the intima. Not rarely giant cells were found in the periphery or close to the masses. The myocardium showed a number of foci of fibrosis and atrophy of heart muscle fibers. Here and there small lymphocytic infiltrations were found with occasional intermingled mast cells. In spite of the fact that the patient had had scarlet fever, measles, and typhoid fever, it was not considered that these infectious diseases had produced the myocardial changes."

VII. ETIOLOGY

The disease entity termed isolated myocarditis was first called by that name because, as a rule, changes are not found in other parts of the heart or in other organs. When first described, the etiology was uncertain. An infectious or toxic etiology was suggested by Aschoff, [31] and von Gierke [32] believed the lesion in his case to be a syphilitic manifestation. Throughout the history of the disease its etiology remained obscure, and the term isolated myocarditis was generally applied only in the presence of a more or less diffuse inflammatory or granulomatous lesion when every known cause for this type of

myocarditis could be ruled out. [33] At the present time there is still no general agreement as to the etiologic agent responsible, but at least two recent investigations have gone far toward clarifying much of the pre-existing confusion.

Because of the histologic differences of the two types of isolated myocarditis, it seems possible that the etiologic agents may also be different. Saphir [3] has suggested that the granulomatous type may very well be caused by a specific organism of unknown variety or one that was not found at the time of the examination. Thus he concluded that either syphilis or tuberculosis may be the underlying cause and that the granulomas signify either miliary gummas or tubercles. Jonas [20] and Taussig and Oppenheimer [24] expressed similar views. Saphir, however, went on to point out that there are instances on record of granulomatous myocarditis caused by other organisms than the tubercle bacillus or Treponema pallidum, citing the Blastomyces reported by Baker and Brian [34] and the pasturella of tularemia as suggested by Lillie. [35]

Magner [25] thought that the group of diseases classified under isolated myocarditis is a heterogeneous one, including atypical varieties of tuberculous, syphilitic and rheumatic myocarditis as well as certain other inflammatory conditions of unknown and

probably variable causation. He concluded, however, that the attribute of obscurity cannot be considered as a justification for grouping these conditions together as manifestations of a single disease.

In regard to the more diffuse type of isolated myocarditis, the question arises whether or not this is a special anatomic entity or whether a variety of diseases of known or unknown origin may not occasionally involve the myocardium in the absence of recognizable changes in either the endocardium or the pericardium.[3] Schenken and Heibner[4] suggest it is possible that the two types of isolated myocarditis may represent disease processes of different etiology, but since their separation on anatomic grounds alone is not justified they are still considered as variants of the same disease. Norris and Pote,[36] who reported four cases dying of unexplained hypertrophy and dilatation of the heart, concluded that isolated myocarditis appears to be a group which includes various disease entities, the etiology of which is uncertain.

A survey of the literature reveals that a wide variety of etiologic factors have been incriminated by being observed in connection with this disease. In the individual case reports carbuncles, burns,[37] gonorrheal urethritis,[38] upper respiratory infections,[7] influenza,[39, 40] "rheumatism," rheumatic

fever, [33] status thymicolymphaticus, [16] pyogenic skin infections, [41] toxemias, [37] allergies, [42] and injuries of the myocardium brought about by chemicals, [43] have been described as being associated in patients found at autopsy to have isolated myocarditis. Engelhardt and Bruno [11] believed these findings to be coincidental, but very recent investigations place certain theories on much firmer footing.

Chamberlain [44] reported the case of a patient with a history of alcoholism who at necropsy was found to have isolated myocarditis. Myocarditis unrelated to endocarditis or to pericarditis has also been shown to occur during the course of pneumonia and other acute infectious diseases, such as scarlet fever and typhoid fever. As early as 1921, Schmincke [40] reported isolated myocarditis in instances of influenza. Myocarditis has been found in the hearts of patients with trichinosis in the absence of larvae in the myocardium. Saphir [3] has pointed out that these myocardial lesions, though in some instances at variance, often give practically identical histologic pictures. Thus, he concludes, it seems possible that the scope of the term isolated myocarditis must be broadened to include not only those conditions so labeled by the respective authors, but also those known to occur occasionally in a wide variety of infectious diseases. Schenken and Heibner [4] readily

agree that the pathologic lesions in many cases of myocarditis where the etiology is known are indistinguishable from those in acute isolated myocarditis, but Hansmann and Schenken, in an earlier article, stated that acute isolated myocarditis differs etiologically from the acute toxic myocarditis which is caused by infectious diseases only in that the origin of the infectious agent is obscure. [5]

Saphir also points out that there are instances on record of isolated myocarditis in patients who gave no history of infectious diseases that could have caused the inflammatory changes in the myocardium. This, of course, may have been due to an inadequate search for the etiologic agent. He suggests that a number of cases reported as instances of isolated myocarditis would not fall into this group, and segregation of true isolated myocarditis, excluding the granulomatous form, would not be based on histologic criteria but on clinical histories and observations.

It seems obvious that much confusion has existed in descriptions of the disease entity called isolated myocarditis, and it appears logical to believe that if the term is to be applied correctly to isolated myocardial lesions where the etiologic agent is obscure, it must remain purely on a pathologic basis.

It should be mentioned that a few instances have

been recorded in which the disease was attributed to etiologic agents of an unusual nature. Šikl [26] reported that two patients dying from severe acute myocarditis had been treated for syphilis with bismuth compounds and neoarsphenamine. One patient possibly had syphilis, the other was in the primary stage of syphilis, and in both a dermatitis developed. Šikl believed that the myocarditis may have been of an allergic nature due to an idiosyncrasy to either bismuth or neoarsphenamine. Stöckenius [45] reported four patients with syphilis in whom a dermatitis developed in the course of arsphenamine treatment. Two of these patients revealed myocarditis at autopsy. As in Šikl's cases, there were granulomatous lesions in the myocardium. Though Stöckenius expressed the opinion that these lesions were the result of rapidly spreading syphilis in spite of the absence of spirochetes, Šikl, after restudy of the pertinent sections, concluded that the myocardial changes, just as the lesions of the skin, could be better explained as a result of a peculiar hypersensitivity to arsphenamine.

Similarly, Nelson [46] reported a patient in whom a myocarditis of the interstitial type developed while exfoliative dermatitis due to neoarsphenamine was present. Nelson was the first to single out arsenical dermatitis as a possible etiologic factor, although cutaneous infection in general had been implicated as

a cause of the myocardial injury by Bailey and Andersen three years before.

A case strikingly similar to the foregoing was also reported by Brown and McNamara.[42] Theirs was a 34 year old white male who had an acute exfoliative dermatitis following neoarsphenamine therapy for syphilis, dying of acute interstitial myocarditis six days after the onset of the rash. Cultural studies of the blood or myocardium unfortunately were not made in this case. The most highly inflammatory focus in this patient was the myocardium, and bacteria were not demonstrable at this site by specific tissue stains. These authors commented that since arsenical exfoliative dermatitis is considered to be an allergic manifestation on both clinical[47] and experimental[48] grounds, it is reasonable to assume that complicating visceral lesions may have a similar pathogenesis.

Bailey and Andersen[12] have emphasized the association of infection, especially pyogenic infections of the skin, and interstitial myocarditis in eleven of the 32 cases reviewed by them. In all cases of acute myocarditis due to arsphenamine reviewed to 1940, a generalized dermatitis has preceded the symptoms of cardiac insufficiency for between six and twenty days. In the cases of Taussig and Oppenheimer[24] there was a relatively mild cutaneous reaction, while in all the others the reaction was apparently severe. The constant

anticipation of the myocardial changes by the dermatitis and their development in patients not receiving arsphenamine favor but do not establish the hypothesis that a factor associated with the dermatitis causes the subsequent myocarditis, Brown and McNamara concluded. In this concept the role of the drug is merely that of instigating the severe dermatitis, with the subsequent development of bacterial allergens. The possibility of an allergen arising from a combination of dermal infection and the arsenical must also be entertained.

Warthin [49] reported a series of eight cases of cardiac incompetency terminating in death which he attributed to syphilis. There was a known clinical history of syphilitic infection in half the cases. He pointed out that in all cases the ages are too early for marked senile vascular changes, or for cardiac lesions due to age alone. This clinical feature, in itself, he concluded, should indicate the existence of cardiac disease of an infective or toxic nature.

Any discussion of acute myocardial inflammation found in a syphilitic person should include reference to the cases of malignant myocardial syphilis reported by Warthin in two of his other articles. [50] In these much of the exudative involvement was perivascular, and miliary gummas could be identified frequently.

In addition to these, Boyd [51] has noted collections of neutrophils containing spirochetes in the left ventricular myocardium of a patient considered by him to have acute myocardial syphilis. In the case reported by Brown and McNamara [42] the ventricular exudate was diffuse and acute and lacked any perivascular arrangement. Syphilitic myocarditis, they concluded, would seem unlikely after apparent disappearance of general symptoms following initial neoarsphenamine therapy.

It is interesting to note that French and Weller [52] report an interstitial myocarditis, rich in eosinophil cells, found in the hearts of 126 patients whose sole common factor was that one or more of the sulfonamide drugs had been administered shortly before death. No involvement was found in cases where the drugs had been discontinued for more than thirty days prior to death. All cases were excluded from the series in which some condition was present which might produce an interstitial myocarditis. Wells and Sax [53] have recently reported a case of isolated myocarditis probably of sulfonamide origin.

A similar eosinophilic interstitial myocarditis has been produced in mice and rats by the daily intraperitoneal injection of neoprontosil, sulfanilamide, sodium sulfapyridine and sodium sulfathiazole in amounts computed to be less than comparable to the

usual human dosage. Eosinophilic infiltrations were seen also in the lungs, livers and kidneys of both the human cases and of the experimental animals. The bone marrow, spleen, and lymph nodes likewise showed increased eosinophil cells in some instances. [52]

Franz [43] discussed a patient who for a number of years had been treated with epinephrine because of bronchial asthma. At necropsy the myocardium showed foci of fibrosis with a few lymphocytes and fibroblasts, and in some fields the connective tissue spread in the form of a network, leaving some of the muscle fibers preserved within the holes of the net. Franz suggested that the heart muscle fibers may have been primarily damaged as a result of the administration of epinephrine or possibly because of a definite hypersensitivity toward this substance.

It should be mentioned in this connection that Hansmann and Schenken [5] in their report on acute isolated myocarditis remarked that in the experimental production of acute myocarditis the best results were obtained by the method, among others, of combining sparteine with epinephrine. They stated, however, that the lesions produced are not comparable in severity with those of acute isolated myocarditis.

In reviewing these findings, Saphir [3] suggested that these observations are extremely interesting because they suggest a common etiologic factor, possibly

a peculiar hypersensitivity (allergy) to chemicals or perhaps, though not likely, syphilis.

Miller [28] reported a case of so-called granulomatous myocarditis in a Chinese male age fifty who had been suffering from an ill-defined infection of seven months duration. He agreed with Boikan that there is a disease entity due to an as yet undiscovered micro-organism which shows a special affinity for the heart muscle, producing there lesions of a subacute inflammatory type.

It remained for Schenken and Heibner, [4] in 1945, to conclusively prove the presence of a micro-organism in the myocardium of a patient dying from acute isolated myocarditis. The case referred to was presented earlier as a typical clinical example (page 10). A pure strain of micro-aerophilic streptococcus hemolyticus was isolated in this case. The authors suggest that syphilis is admittedly responsible for a number of cases of myocarditis, but is certainly not the cause of the majority of cases of isolated myocarditis. Among the cases reported in the literature, they point out, organisms were searched for in three cases. In the case reported by Rindfleisch, [54] staphylococcus citreus was isolated from the myocardium, but abscesses were not found and hence its etiological relationship remains in doubt. In the other two cases reported by Scott and Saphir, [2] organisms

were searched for by staining the tissue and not by culture. Schenken and Heibner question whether this method of examination would reveal the presence of small numbers of organisms. Using a Gram's method which stains organisms very well in control tissues, they were unable to find organisms in the myocardium in their case. They conclude that the search for a causative infectious agent has been inadequate because the disease is difficult to recognize clinically and macroscopically at necropsy.

That the problem still remains unsettled, however, is indicated by the fact that certain recent cases have been more or less convincingly attributed to a virus. Covey [7] reported the case of a young male attacked by a cold in the midst of which an acute process involving the myocardium intervened and caused death. The process in the heart muscle was apparently primarily one of necrobiosis of muscle cells rapidly followed by lysis and reaction of the surrounding tissue indicated by infiltration with a variety of cells usually associated with an inflammatory process. There were, however, pathologic findings in the central nervous system and lungs often associated with, if not absolutely characteristic of virus infection of these organs. The case reported by Hansmann and Schenken [5] showed explosive necrobiotic lesions without cellular infiltration in every way comparable to

those shown in this report.

In the literature Covey noted that the one disease most commonly mentioned as immediately preceding the onset of the myocarditis is influenza. According to him, this is the only preceding infectious process escept syphilis which is listed in the reviews more than once. Influenza or similar respiratory infection is said to have been present in six of the fourteen of those cases reviewed by him in which the preceding or accompanying infections were known.

This review receives support from the observations of Pearce [55] on the effects of inoculation of various viruses into rabbits after a preceding intravenous injection of a solution of acacia. In these experiments, edema, atrophy, necrosis and calcification of heart muscle fibers were observed, and there was also cellular infiltration.

At about the same time that Schenken and Heibner isolated the streptococcus as an etiologic agent of isolated myocarditis, Helwig and Schmidt [56] described a filter-passing agent producing myocarditis in anthropoid apes and small animals. The substance was obtained from hydrothorax fluid of a gibbon which dropped dead, and from similar fluid and spleen of a chimpanzee dying very suddenly. Grossly both animals had dilated hearts, pericardial effusion, pulmonary edema and bilateral hydrothorax and histologically

pulmonary edema and an intense diffuse interstitial myocarditis strikingly similar to that in human acute interstitial myocarditis of unknown etiology.

The filter-passing agent was passed through a series of 122 mice, and with rare exception regularly produced paralysis followed by death or apparent recovery after a week or two. At necropsy interstitial myocarditis was found in almost all the animals. In some it was very severe; in others limited to small foci of necrosis and inflammation. In those animals that recovered from their paralysis and appeared to be approaching normalcy, the microscopic myocardial lesions varied, often showing marked calcification in the zones of necrosis, fibroblastic replacement of muscle and early scar tissue formation. These older lesions were always accompanied, however, by varying degrees of leukocytic reaction.

The agent produces myocarditis in guinea pigs and rabbits, also. It is potent and specific when introduced intravenously, intraperitoneally, subcutaneously, intracranially, and by nasal instillations, and is present in the nasal washings of inoculated animals. It is completely destroyed by heating to 70 degrees Centigrade for 20 minutes, but withstands heating to 56 degrees Centigrade for 20 minutes, losing some of its potency, but not its specificity. It passes Berkefeld and Seitz filters and has been

transplanted to seven day chick embryos and again passed through Berkefeld filters without losing its potency or specificity. Extracts of organs of companion chimpanzees dying of other conditions have uniformly failed to produce any lesions in mice. Such an agent has not been previously described, and strongly suggests that isolated myocarditis of humans may well also be, among others, a virus disease.

There is good evidence, however, that isolated myocarditis may be more than just a virus disease. Ware and Chapman, [57] in 1946, reported two cases of young women dying of what they termed chronic fibroplastic myocarditis. The exact cause of the underlying pathology was obscure, and they believed the cardiac hypertrophy and fibrosis represented the healed end result of a previously existing acute myocarditis, or Fiedler's myocarditis, which may have been the result of some former acute illness.

Scherf and Boyd [58] have asserted that with the frequency of acute infectious diseases and miscellaneous infections, there are but few persons who, during a lifetime, do not have inflammatory myocardial foci. Alterations in the electrocardiogram, asthenia, slight precordial discomfort, and breathlessness occurring shortly after acute infectious diseases should be considered as possible indications of myocarditis, they suggest. From the preceding it can be seen that

acute myocarditis may follow, or be associated with, a wide variety of diseases of both acute and chronic nature. The cases of chronic myocarditis with cardiac hypertrophy and fibrosis of apparently unknown etiology could be ascribed to many acute or chronic infections that the individual may have had early in life.

It will be remembered that Saphir [3] has suggested that the granulomatous type may very well be caused by a specific organism of unknown variety or one that was not found at the time of the examination. Schenken and Heibner [4] proved this same hypothesis by isolating a pure strain of micro-aerophilic streptococcus hemolyticus in a case of the diffuse type. Their thesis appears to be sound logic——that many cases of acute isolated myocarditis are probably due to an infectious agent, but the failure to recognize the condition clinically or grossly at necropsy has prevented proper bacteriologic studies.

Magner, [25] in 1939, believed the group of diseases classified under isolated myocarditis is a heterogeneous one, and Norris and Pote [36] later concluded that isolated myocarditis appears to be a group which includes various disease entities. The problem of etiology in isolated myocarditis is probably the most compelling aspect of this disease. A definitive deduction is extremely difficult, especially when so many views

of a conflicting nature continue to appear in the literature. Additional opinions, unless confirmed by careful study of the problem clinically and at the autopsy table, only add to the confusion. It seems probable that the answer lies somewhere along the lines just discussed, that isolated myocarditis may be the end result of several disease processes, not all of which have been unmistakably identified.

VIII. CONCLUSION

In summary it may be stated that isolated myocarditis often causes rapidly progressive myocardial failure or sudden death. The disease may be divided into two types, one characterized by the presence of granulomatous lesions, and the other by a more or less diffuse inflammatory lesion, of the myocardium. The granulomatous form presents a clearly outlined anatomic picture, resembling other known types of granulomas.

Various etiologic agents have been held responsible for these granulomatous lesions. Often syphilis or tuberculosis has been suspected. Recently, a special form of hypersensitivity, particularly that to arsphenamine, has also been held responsible. As long as the origin of this form is not known the term "granulomatous" seems adequate. Whether or not

the diffuse inflammatory type of myocarditis should be set aside and marked specifically is questionable, since histologically similar types of myocarditis occur in various infectious diseases. [3] Perhaps as Gouley, McMillan and Bellet [59] have stated, the term "isolated myocarditis" as used for the diffuse type is little more than a convenient name for myocardial inflammations that do not fall into standard classifications. As Wells and Sax [53] have suggested, there is good reason to believe that there are a variety of causes for the cases now published under this name. Therefore, it should be used purely as a pathologic term and not as the name of a disease entity. As each new cause for the myocarditis is proved, it should be given a separate classification. The greatest step toward solution of the existing problem undoubtedly lies in the direction of careful bacteriologic studies, especially at autopsy, in an attempt to isolate the causative organisms. Then, not only can the disease be properly classified, but probably effectively treated in certain cases as well.

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