Viruses and Heart Disease:
A Problem in Pathogenesis*

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ABSTRACT

Identification of viral myocarditis offers problems; pathologists fail to agree on the definition of the disease and biopsy-proven cases documented in the English literature are still few in number. Though endomyocardial biopsy is becoming a standard procedure at many medical centers, tissue sampling, especially in cases of patchy myocarditis, can result in further diagnostic difficulties. While conventional wisdom holds dilated cardiomyopathy the end-stage of chronic viral myocarditis, a history of preceding viral infection is usually unobtainable. Some research suggests that myocardial necrosis is a cell-mediated immune process and chronic myocarditis an autoimmune disease.

Understanding the true relationship between viruses and heart disease will require further research.

Introduction

Although the term "myocarditis" had been used earlier, Fiedler11 first described idiopathic interstitial myocarditis in 1897, and Saphir's autopsy studies14 in the 1940s suggested it was probably a significant disease. As diagnosis of viral diseases became routine, it appeared that viruses were responsible for a large percentage of myocarditis. It had long been thought that mumps and influenza viruses were the most frequent offenders, but improved diagnostic techniques have shown that the ribonucleic acid (RNA) viruses, especially the picornaviruses, are cardiotropic for the newborn, young, and adult human popula-

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years has tissue diagnosis by endomyocardial biopsy become relatively commonplace in the larger medical centers, allowing serial monitoring of cardiac pathology. Feneley emphasizes the contribution endomyocardial biopsy can make to both a definitive diagnosis of acute myocarditis and the monitoring of drug therapy to modify the course of the disease. Fenoglio has classified myocarditis into acute, rapidly progressive and chronic stages by means of endomyocardial biopsy to give a clinically useful diagnosis (table I). Yet, Fowles found only 25 percent of clinically diagnosed myocarditis cases had histologic evidence on biopsy; sampling is an acknowledge problem owing to the frequent patchy distribution of the disease. Recovery of the virus from heart tissue or pericardial fluid is reported only in the first few days of the disease, and the "active excretion of the virus has already ceased" by the time of clinical diagnosis. Autopsy cases are infrequent and often incompletely documented. Techniques, including the use of monoclonal and polyclonal antibodies tagged by fluorescent antibody or immuno-peroxidase markers for identification of viral antigens in heart tissue, give variable results in different hands. "Foot prints".

### TABLE I

<table>
<thead>
<tr>
<th>MYOCARDITIS</th>
<th>CORRELATION OF CLINICAL HISTORY, ENDOMYOCARDIAL BIOPSY AND OBSERVED OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIAGNOSTIC GROUPING BY CLINICAL AND HISTOLOGIC FINDINGS</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td><strong>ACUTE MYOCARDITIS</strong></td>
<td>7</td>
</tr>
<tr>
<td>history of viral-like illness 1-3 weeks preceding sudden onset of congestive heart failure in all patients</td>
<td></td>
</tr>
<tr>
<td>interstitial inflammatory infiltrate and extensive acute cell damage</td>
<td></td>
</tr>
<tr>
<td><strong>RAPIDLY PROGRESSIVE MYOCARDITIS</strong></td>
<td>18</td>
</tr>
<tr>
<td>history of viral-like illness in 8 patients and pregnancy in 1, preceding sudden onset of progressive congestive heart failure in all patients</td>
<td></td>
</tr>
<tr>
<td>Patchy acute and healing cell damage and fibrosis</td>
<td></td>
</tr>
<tr>
<td><strong>CHRONIC MYOCARDITIS</strong></td>
<td>9</td>
</tr>
<tr>
<td>vague history of viral-like illness in 4 patients and pregnancy in 4 preceding congestive heart failure in all patients</td>
<td></td>
</tr>
<tr>
<td>Focal inflammation and cell damage</td>
<td></td>
</tr>
</tbody>
</table>

*VALUES ARE EXPRESSED AS MEAN ± S.D.

^aGross autopsy findings in four examinations: four-chamber dilation of slightly to moderately enlarged heart

^bSpontaneous recovery, asymptomatic

^cGross autopsy diagnosis in 11 examinations: idiopathic congestive cardiomyopathy

^dResidual cardiac dysfunction

remaining in chronic disease can do no more than suggest that a specific virus might have been the inciting agent. Diagnosis by fourfold change in viral antibody titers is often ignored for a single one-tube dilution difference in titer or a single "high" titer with no reference to the prevalence of the disease or the titer range in the prevailing population. Relatively little is factually known about the role viruses play in heart disease, yet conventional wisdom attributes a congestive cardiomyopathy to an earlier viral episode. Reliable statistics have not been compiled; the National Center for Health Statistics does not code from death certificates for "viral heart disease", and neither the Epidemiology and Biometric Program of the National Heart, Lung and Blood Institute, National Institutes of Health (NIH), nor The Centers for Disease Control is able to furnish information relating to the prevalence, incidence, morbidity, and/or mortality of viral heart disease.

Interest in the association of human heart disease and viral infection is, however, remarkable. In 1983, The International Society and Federation of Cardiology met for a workshop on viral heart disease and published, sometimes seemingly contradictory, reports. "Folklore" has it that at the November 1984 American Heart Association meeting in Dallas, pathologists were locked in a room till they had agreed on histologic criteria for a diagnosis of acute myocarditis: a "process characterized by an inflammatory infiltrate of the myocardium with/without necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary heart disease."* Dissatisfaction with this definition has led to the continuation of multiple definitions, and proceedings have yet to be published. In September 1985, the NIH and the College of Physicians and Surgeons hosted a workshop, "Pathogenesis and Pathophysiology of Myocarditis", in order to promote collaboration, evaluate various disease models, and identify research tools and topics to assist in the better understanding and treatment of acute and chronic myocarditis. One participant wondered if enough was factually known to even identify areas of probable break-through for targeted research!

**Acute and Chronic Myopericarditis**

Olsen's definition of myocarditis is typical: "The presence of inflammatory cells in the myocardium, with evidence of fraying of adjacent myocardial fibers but with concomitant sequential necrosis", the latter barring ischemic heart disease. These non-specific changes are found, irrespective of specific virus. Although most cases of acute myocarditis recover without sequelae, the progressive chronic disease reportedly results in an end-stage heart, similar to that of specific, non-viral, acute myocarditides, from rheumatic fever to malaria. However, few cases have been followed and recorded in which acute viral myopericarditis developed into a dilated cardiomyopathy.

Dilated cardiomyopathy is expressed as a hypertrophied, overweight heart, usually with all four chambers exhibiting dilatation of such a degree that both atrial and ventricular walls are normal in thickness. The endocardium is variously thickened and may have a superimposed thrombus. The myocardium exhibits fibrous replacement for the loss of myocardial fibers, and this may be limited to its inner third alone. The epicardium, pericardium, and coronary vessels are usually non-remarkable. Histologically, the myocardial fiber diameter may be increased or even normal owing to

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stretching, with an increase of interstitial fibrous tissue or small foci of subendocardial fibrosis.28

Fuster, in 1981, reviewing 104 Mayo Clinic patients with a diagnosis of idiopathic dilated myocardiopathy, followed for 6 to 20 years, found a history of heavy alcoholic intake in 21 percent; the event of a flu-like (viral) syndrome in the 60 days preceding the clinical manifestation in 20 percent; a record of previous rheumatic fever without value involvement in eight percent; and various other diagnoses in the remainder. "Idiopathic dilated cardiomyopathy", Fuster wrote, "remains a challenge because the cause is unknown, the natural history is ill-defined, and the response to therapy is generally unsatisfactory."

In one study, with matched controls for 50 patients with diagnosed dilated cardiomyopathy, 15 patients and only one control exhibited viral antibodies by microneutralization in Vero cells and reciprocal dilution titers (≥)24. Endomyocardial biopsy of these 15 patients showed no evidence of active or old myocarditis. Earlier viral "sensitization", absence thereof, or lack of a well-selected control group, is utilized to suggest explanations for variable results reported in the literature.15,23

The significance of the label, "dilated myocardial infarction", is underscored by the accelerated course to death of 77 percent of the patients, two-thirds occurring within two years' time of the diagnosis.13

Viral Infections and Myocardial Infarctions

Coxsackie B virus has been identified as the most common virus agent in human myocarditis and, consequently, has been studied widely.32,34 It has also been implicated in myocardial infarctions.

A report from Glasgow, Scotland, cites four cases mimicking coronary artery disease but held by the authors to be due to a Coxsackie B virus.31

In a controlled, prospective study of 228 consecutive patients admitted to a London coronary care unit for chest pain, admission and discharge serum samples (usually 10 days apart) were tested for Coxsackie B virus antibodies by microneutralization. Each patient was queried for a history of a preceding flu-like illness. Titers and histories of patients with proven myocardial infarction did not differ significantly from the control group.15

However, a similar prospective study, conducted in Finland with 101 patients diagnosed as having acute myocardial infarction, showed 15 percent of the patients had evidence of a recent Coxsackie B virus infection as compared with only 2.6 percent of controls. Interestingly, all patients had negative Coxsackie B virus cultures on admission. Throat washings and fecal samples grew no virus, supporting the concept that, by the time damage to the heart is evident, the virus is no longer present and should therefore be considered an inciting but not necessarily effecting agent for the pathological changes.

Viral Infections and Cardiac Aneurysms

A single case history and post-mortem examination of a four-week-old newborn dying from cardiac arrest reported a large, thin-walled, left ventricular, apical aneurysm and a segmented, partially organized and recanalized thrombus occluding the left anterior descending coronary artery. Since typical cytomegalic inclusions were widespread in various tissues, the author favored an "association" of disseminated cytomegalovirus infection with the sequence of a coronary artery vasculitis, resulting in thrombosis, apical myocardial infarction, cardiomalacia, and eventual aneurysmal dilation.

Other authors have also suggested that certain human cardiac aneurysms are a
result of viral infection, and one case is reported of multiple ventricular aneurysms in a 17-year-old Nigerian woman.

Experimental laboratory animals have developed cardiac aneurysms following viral infections. Three of 10 Syrian golden hamsters which survived acute infection with Coxsackie virus B (with accompanying electrocardiographic evidence of myocarditis) showed single or double ventricular aneurysms upon sacrifice. In the hamster, myocardial necrotic lesions and minimal antibody titers occurred at the height of the infection while the virus could still be isolated from myocardial tissue. Suckling Swiss Webster mice, inoculated with Coxsackie virus (types 1 or 4), also developed cardiac aneurysms with one animal exhibiting two. The infective agent was recovered from blood and minced heart tissue on days two through seven, with minimal necrotizing myocarditis found in tissues from days three to five. Using 647 mice (three strains) infected with encephalomyocarditis virus, Matsu­mori reported 1.1 percent developed aneurysms of the right ventricle.

Immunity and Cardiac Damage

An immunological mechanism recently has gained more prominence in the explanation of myocardial damage from viral disease. One proposal put forth for the Coxsackie viral infection suggests the stimulus for the lesion could be the virus capsid itself or a neoantigen consistent with fibrin and gamma globulin present in autopsied hearts.

Continuing work with Woodruff’s BALB/c mouse model and Coxsackie B3 as the infecting virus, Huber and colleagues have shown that the peak virus titer in heart tissue occurs on day three, at which time hyper eosinophilic myofibers are seen, suggesting direct injury to heart muscle by the virus. However, if the animal is immunosuppressed, an observed increase in viral titers at day three is accompanied by widespread necrosis. Histologic myocarditis may persist well past the complete elimination of the virus by 10 to 14 days (figure 1).

In response to viral replication, the body produces interferon: this (1) prevents spread of infection to other cells, (2) causes activation of macrophages, and (3) stimulates production of killer cells to lyse preferentially the infected cells and halt production of progeny virions.

But elimination of the virus appears dependent on humoral antibodies. Virus-specific IgM can be identified in the mice at day two, peaking at day four, and decreasing slowly as the virus is eliminated. The activated macrophage’s importance is attested by the death of suckling mice with Coxsackie B infection, unless these mice are supplied macrophages from viral-immune syngeneic mice. It was further found that T-lymphocyte-deficient mice do not develop histologic myocarditis after Coxsackie B infection despite viral titers consistent with infected, immune-competent controls. Thus, T-lymphocytes appear responsible for the histological lesions of myocarditis. (Since other strains of mice may have equally high titers with infection but only minimal...
inflammation, it is suggested that the host’s genome is of singular importance in disease determination.)

Controlled tests proved that killer lymphocytes effected significant lysis of infected neonatal mouse cardiocytes while antibodies did not. Further experiments showed that, following equal initial cytolysis of infected and uninfected cardiocytes by T cells at days four to six, a transition to preferential cytolysis of infected cardiocytes by anti-virus-specific lymphocytes occurred, with overall peak cytolysis at day seven. Further work separated the immune T-cell population into subsets, one able to lyse only uninfected cardiocytes (cardiocyte-specific antigen) and the other, infected cardiocytes (virus-specific antigen). Huber’s conclusion was that immune T-cells can lyse uninfected cardiocytes and, consequently, T-cell-mediated insults to the myocardium can last well after the virus is no longer detected: thus proposed is a classical auto-immune disease, independent of the virus causing the initial infection.

Investigation of the immunological regulatory and effector systems in man\(^7\) has shown an increased target cell-specific, cytolitic component in patients with a viral heart disease. Bolte’s\(^2\) continuing work points to the development of dilated cardiomyopathy in association with binding of immunoglobulin to the myocardium and the presence of humoral antibodies against myocardium. Maisch’s group\(^22\) suggests that the inflammatory stage of myocarditis allows autologous epitopes to be recognized as non-self, leading to the secondary immunopathogenesis effected by the same “organs” as the primary immune response. Thus, a number of investigators\(^2,7,22\) have suggested that “a secondary immunopathogenesis seems likely in protracted forms of myocarditis and in some patients with postmyocardial dilated heart disease.”

**Summary**

In spite of some splendid work, the generally variable clinical, pathological, and immunological reports\(^2,3,5,8,13,19,22,29,35\) (which may merely reflect normal differences owing to techniques, age, sex, species, strains, hormonal, immunologic states, etc.) indicate medical science is still far from understanding the interaction and effect of viruses on the heart. And we may indeed be viewing not a single disease, but one of mixed etiology.

**Note**


**References**

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