Pericardial and Myocardial Disease Associated with Serological Evidence of Infection by Agents of the Psittacosis–Lymphogranuloma Venereum Group (Chlamydiaceae)

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SUMMARY

Nine patients with acute pericarditis or myocarditis, or both, were found to have serological evidence of concurrent infection by a psittacosis agent. Three patients had conclusive epidemiological and clinical evidence of complicating pulmonary psittacosis and demonstrated that psittacosis agent does produce inflammatory heart disease in this geographic area.

Six patients had imperfect corroborative evidence of psittacosis and their clinical manifestations were atypical. Indeed, half of these patients were initially believed to have some form of idiopathic myocardial disease. Studies of these patients suggest that psittacotic infection may be causal in certain forms of heart disease commonly designated primary myocardial disease.

Additional Indexing Words:
Pericarditis, acute  Myocarditis, acute  Radioisotope precipitation test
Epidemiological studies  Idiopathic myocardial disease

Numerous infectious agents may cause perimyocarditis in human beings, but evidence of cardiac involvement by agents of the Chlamydiaceae family group (Bedsoniae, Miyagawanella, Psittacosis-lymphogranuloma) is rarely sought since these agents have not been isolated from the heart, and their causative relationship to human perimyocarditis is unproven. Nevertheless, many reports1–8 inferentially link pulmonary psittacosis or serological evidence of infection, or both, by a member of the Chlamydiaceae family† to perimyocardial disease.

Adamy in 19301 first commented on the development of postinfectious myocardial degeneration associated with psittacosis. This and other reports prompted Lyon9 in 1956 to include psittacosis in his monograph dealing with infectious agents considered capable of affecting the cardiovascular system. Subse-

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*This family is referred to hereinafter as psittacosis.

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sequently, psittacosis infection has been implicated in the production of perimyocardial disease in reports from Germany,10 the United States,11–18 Japan,14 and Scotland.15 Grist and McLean15 stated that “enlargement and failure of the heart is a recognized feature of psittacosis.”

Therefore, historical precedent combined with the chance detection of two patients with apparent acute psittacosis pericarditis prompted us to investigate the role of this agent in acute pericardial and myocardial disease. A complement fixation (CF) test for psittacosis agent antibody was included in the battery of CF tests performed on sera from 599 patients suspected of having acute pericarditis or myocarditis, or both. Serological evidence implicating the psittacosis agent was obtained in nine patients and comprises the substance of this report.

Methods

Study Population

A series of 599 patients with suspected acute perimyocarditis was developed from two sources: in study group I, 400 patients suspected of having acute viral disease involving the heart had one or more specimens of serum submitted to the Viral Laboratories of the State of Illinois during the years 1959 through 1965; and in study group II, 199 patients considered to have acute or chronic primary myocardial disease (PMD) were studied at Cook County Hospital, Chicago.

If CF antibody to psittacosis agent antigen was found and if either a fourfold rise or fall in titer, or two or more sequential titers of 1:16 or greater were present, the patient was examined for historical or physical evidence of inflammatory pulmonary or heart disease, or both. The criteria used to establish the diagnosis of pericarditis and myocarditis16 were reviewed recently (see Table 3). The criteria used to establish the diagnosis of primary myocardial disease associated with alcoholism or pregnancy and to include or exclude hypertensive, arteriosclerotic, rheumatic, and other forms of heart disease, have been published.17, 18

Patient Studies Included

History. Age, sex, race, places of residence (rural versus urban), occupation(s), pregnancies, contacts with birds or animals, prior disease (that is, trachoma, cat-scratch disease, lymphogranuloma venereum (LGV), Hodgkin's disease, syphilis, pneumonia, or carditis), and season, date of onset, and details of the current illness were obtained.

Physical Examination. Symptoms and signs of pulmonary (rales or dullness), pleural (friction rubs or effusion), and pericardial inflammation (friction rub, effusion, or positional pain-relief) were sought. All evidence of heart failure (edema, elevated venous pressure, audibility of the third or fourth cardiac sound, cardiomegaly, tachycardia) or other significant disease was recorded.

X-ray. Acute or chronic pulmonary infiltrates, pulmonary congestion, pericardial or pleural effusion, or both, and abnormal cardiac contour or cardiomegaly were noted from serial 2-m postero-anterior and lateral chest x-rays.

Electrocardiogram. Serial 12-lead electrocardiograms were recorded and analyzed according to the criteria of the New York Heart Association for: (1) disturbances of rhythm or conduction, (2) changes of ventricular hypertrophy, damage, myocarditis, or infarct, and (3) evidence of acute pericarditis.

Ancillary Laboratory Procedures. These included white blood cell count, antistreptolysin-O (ASO) titers, and Kahn or Venereal Disease Research Laboratories (VDRL) test in all cases. Blood samples were drawn from all patients of study group II (PMD) but only irregularly from study group I) for determination of fasting and postprandial blood sugar values, cholesterol, serum glutamic oxalacetic transaminase, cephalin flocculation, thymol turbidity, total protein, and for serum and hemoglobin electrophoretic studies. Additional studies included urinalysis, venous pressure, circulation time, and search for lupus erythematosus cells by plasma clot method.

Serological Studies. Serial CF tests for antiviral antibodies were done using appropriate serum controls, initially by the macro technique, but subsequently by the micro-titer method.20, 21 The antigens included: mumps (soluble), poliomyelitis, herpes simplex,22 adenovirus,23 Q-fever, Coxsackie B2,3,4,5, influenza A24 and B,25 parainfluenza 1, 2, and 3, and, when indicated, respiratory syncytial (RS).26 Unless otherwise stated, serological tests for psittacosis were done with Psittacosis Human Diagnostic Antigen* (purified elementary bodies from the allantoic fluid of hen's eggs infected with the DD34 strain of psittacosis agent).

Representative serum specimens were periodically checked for comparative purposes with two other psittacosis antigens: Psittacosis Complement

*Markham Laboratories, Chicago, Illinois.
Fixation Antigen* (Cat. no. 75-0231), and Psittacosis Diagnostic Antigen† (the Hamilton strain propagated in chick embryo yolk sacs and harvested by heat and extraction).

Twelve samples of serum from four patients displaying CF antibody titers (>1:16) to psittacosis were also evaluated by the radioisotope precipitin test (RIP) for psittacosis group antibody. This test was performed by Dr. R. K. Gerloff.

**Control Population**

To serve as a frame of reference, specimens from three adult control populations were tested for complement-fixing antibody to psittacosis.

One thousand serum specimens were obtained from apparently healthy individuals in Freeport, Illinois, during the year 1961-1962.

Forty serum specimens were obtained from patients hospitalized at Cook County Hospital for miscellaneous noncardiac diseases. The patients in this group had similar ethnic and socioeconomic backgrounds, were from the same geographic area of northeastern Illinois, and were hospitalized during the same season of the same year (1963-1964) as the majority of patients in the study population.

Six thousand three hundred sixty-seven specimens from patients suspected of having viral respiratory disease were received by the Viral Laboratories of the State of Illinois between 1962 and 1965.

**Results**

**Control Populations**

Of 1,000 routine serum specimens from nonhospitalized residents of Freeport, Illinois, 4.6% contained antibody for psittacosis but no titer exceeded 1:8.

In the Cook County Hospital population antibody for psittacosis was found in three of 10 patients with liver disease, five of 18 patients with bacterial pneumonia, and six of 18 patients with traumatic injuries, but the highest titer recorded was 1:16.

Among the 6,367 specimens from patients with suspected noncardiac viral disease, 141 (2.2%) showed fourfold titer rises, or titers >1:32. In 35 of these 141 cases clinical data compatible with the diagnosis of lymphogranuloma venereum, cat-scratch disease, or febrile upper respiratory illness (URI) were obtained. Detailed information concerning these 35 patients is presented in table 1. Most patients had bird (parakeet, turkey, and pheasant) or animal (cat, dog, and rabbit) contact; the clinical diagnoses included lymphogranuloma venereum—one, cat-scratch disease—four, viremia or fever of undetermined origin (FUO)—six, upper respiratory illness (URI) or bronchitis—eight, and pneumonia—16. Sequential serum specimens were obtained in 32 patients; single specimens were obtained in three, but in each of these CF antibody titers exceeded 1:32. A fourfold or greater rise of fall in CF antibody titer was observed in 13 patients. Twenty patients had titers of 1:16 or greater. Significant evidence of infection by other agents was not found.

**Study Population**

Among the series of 599 patients investigated, nine had epidemiological, clinical, and laboratory evidence suggestive of acute infection by agents of the psittacosis group and

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*Communicable Disease Center, Diagnostic Reagents Division, Atlanta, Georgia.
†Lederle Laboratories, American Cyanamid Company, Pearl River, New York.
perimyocardial disease (table 2). Five were men and four were women. Five were Negro and four were Caucasian. Ages ranged from 32 to 60 years. The occurrence of illness was nonseasonal and no epidemiological factors suggested a common source of infection. In four patients cardiac disease other than acute

<table>
<thead>
<tr>
<th>Subgroup A</th>
<th>Subgroup B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3</td>
</tr>
<tr>
<td>Age (yr):</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>33</td>
</tr>
<tr>
<td>Maximum</td>
<td>60</td>
</tr>
<tr>
<td>Average</td>
<td>38</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>1</td>
</tr>
<tr>
<td>Coexisting cardiac disease:</td>
<td></td>
</tr>
<tr>
<td>Primary myocardial disease</td>
<td></td>
</tr>
<tr>
<td>Post partum</td>
<td>0</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>0</td>
</tr>
<tr>
<td>Arteriosclerotic heart disease with myocardial infarction</td>
<td>0</td>
</tr>
</tbody>
</table>

pericarditis or myocarditis was also suggested by clinical data: arteriosclerotic heart disease with myocardial infarction, not recent in one; and primary myocardial disease associated with alcoholism in two and with pregnancy in one.

The nine patients were divided into subgroups A and B (table 2) on the basis of diagnostic criteria for infection by agents of the psittacosis group (table 3). Clinical data for these subgroups are listed in table 4 and the results of serological studies on sequential serum specimens are found in table 5.

**Table 3**

Epidemiological, Clinical and Laboratory Evidence Indicative of Infection by Psittacosis Agent in Two Subgroups of Patients

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Subgroup B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3</td>
</tr>
<tr>
<td>Fourfold or greater rise in CF antibody titer</td>
<td>3</td>
</tr>
<tr>
<td>Parakeet exposure</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
</tr>
<tr>
<td>Complete clinical recovery</td>
<td>3</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>1</td>
</tr>
<tr>
<td>Response to antibiotics</td>
<td>3</td>
</tr>
<tr>
<td>Fourfold fall in antibody titer</td>
<td>0</td>
</tr>
<tr>
<td>Multiple antibody titers of 1:16 or greater</td>
<td>0</td>
</tr>
<tr>
<td>Other Chlamydiaeae disease*</td>
<td>0</td>
</tr>
<tr>
<td>Chronic illness</td>
<td>0</td>
</tr>
<tr>
<td>Acute perimyocarditis</td>
<td>3</td>
</tr>
</tbody>
</table>

*Other disease due to Chlamydiaeae agents: Lymphogranuloma venereum, trachoma, inclusion blennorhea and Hodgkin’s disease.10

Three patients fulfilled the following criteria: (1) exposure to parakeets; (2) acute, radiologically documented pulmonary infiltrates; (3) concomitant fourfold or greater rise in CF antibody titer to routine psittacosis antigen; (4) complete clinical recovery; (5) favorable response to antibiotic therapy; and (6) no serological or historical evidence of trachoma, cat-scratch disease, lymphogranuloma venereum, or Hodgkin’s Disease.10

Two of these patients were men (one a physician), ages 33 and 45, and one was a woman, age 60 years. None had had antecedent cardiac or pulmonary disease (table 2). Each presented with evidence of acute
Table 5

Serial Changes in Reciprocal of Complement Fixation (CF) Antibody Titer to Psittacosis Antigen* in Each of Two Subgroups of Patients

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Complicating CV disease†</th>
<th>Serological observation (wk)</th>
<th>Time and sequence of CF tests expressed as months after clinical onset of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup</td>
<td></td>
<td></td>
<td></td>
<td>1/2 1 2 3 4 5 6 7-12 13-24 25-60</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>45</td>
<td>None</td>
<td>4</td>
<td>4 8 64</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>None</td>
<td>11</td>
<td>0 32 16 16</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>None</td>
<td>3</td>
<td>3 32 256</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>None</td>
<td>13</td>
<td>0 256 32</td>
</tr>
<tr>
<td>Subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>PMD-PP</td>
<td>145</td>
<td>0 32 32 16 16-32 32-16 32</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>PMD-AL</td>
<td>168</td>
<td>8 256 32 32-0 64-16-0-32</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>ASHD</td>
<td>5</td>
<td>8 32 256</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>PMD-AL</td>
<td>148</td>
<td>8 8 32-0 64-16-0-32</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>None</td>
<td>5</td>
<td>0-32 32-32 0</td>
</tr>
</tbody>
</table>

*Psittacosis Human Diagnostic Antigen, Markham Laboratories, Chicago, Illinois.
†Key: CV = cardiovascular disease; PMD-AL = primary myocardial disease, post partum; ASHD = Arteriosclerotic heart disease with myocardial infarction.
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Table 6
Comparison of Complement Fixing Antibody Titer to Psittacosis Antigen* and Radioisotope Precipitation (RIP) Test for Chlamydia Group Antibody in Four Patients

<table>
<thead>
<tr>
<th>Case no.</th>
<th>No. sera tested</th>
<th>0</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>64</th>
<th>128</th>
<th>256</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup B</td>
<td>5</td>
<td>2</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>13</td>
<td>63</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>62</td>
<td>55</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>35</td>
<td>33</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Psittacosis Human Diagnostic Antigen, Markham Laboratories, Chicago, Illinois.
†Corrected P values = Percentage of radioactivity of meningopneumonitis particles labeled with $P_{32}$ precipitated by test serum. Normal limits: -20 through +20.

Two patients (cases 4 and 9) displayed both a fourfold rise and fall in CF titer and in three patients (cases 5, 6, and 8) persistent high titers have been detected for about 3 years. These three patients (cases 5, 6, and 8) are considered to have primary myocardial disease.

Five patients recovered and are in apparent good health. One alcoholic patient (case 8) with primary myocardial disease has had recurring evidence of congestive failure for 4 years. Histological examination of his pericardium and myocardium obtained by biopsy 2 months after the onset of disease and after tetracycline therapy disclosed an active, chronic nonspecific inflammatory process without inclusion bodies; cultures of myocardium, blood, stool, and sputum for infectious agents were negative.

No patient had historical or serological evidence of syphilis; none had lymphogranuloma venereum, trachoma, cat-scratch disease, or Hodgkin's disease.

Discussion
Agents of the psittacosis family cause widespread disease in birds, animals, and man. Diseases recognized in human beings are psittacosis, ornithosis, lymphogranuloma venereum, cat-scratch disease, trachoma, and inclusion blennorrhea. These infectious agents can be identified by light microscopy, a method used in diagnosis of trachoma and inclusion blennorrhea. Isolation and identification of the agent from sputa in pulmonary psittacosis and ornithosis are the most accurate means of diagnosis but are successful in only five to 10% of cases. The entire psittacosis-LGV group share a common antigen, and an increasing concentration of CF antibody to this antigen during disease is the basis for serological diagnosis. In psittacosis characterized by atypical pneumonia and bird exposure, a fourfold rise in CF antibody titer to 1:64 or greater develops by the third week of the disease. The titer subsides slowly over several months. Antibiotic therapy may suppress or delay antibody response or hasten subsidence. Latent or chronic infection may develop, and chronic pulmonary infection of 8 years' duration has been documented by Meyer.  

Subgroup A
Subgroup A patients present epidemiological, clinical, and serological evidence of psittacotic infection and complicating perimyocarditis. Psittacosis perimyocarditis has been described. Indeed, Levinthal discovered the inclusion bodies bearing his name in the pericardial fluid of infected birds and the disease in turkeys is predominantly a myocarditis. Two reports furnish histological or cultural confirmation of myocardial involvement in man by psittacosis infection. Jannach described psittacosis myocarditis in a human infant and demonstrated characteristic inclusion bodies in the heart, lungs, and liver identical with those demonstrated in a bird contact. Sheldon and associates isolated the
agent from a supraclavicular node in a man with pericarditis and systemic lymphogranuloma venereum.

Subgroup B

The validity of relating the acute perimyocarditis of these patients to infection by psittacosis family agents depends chiefly upon serological evidence. Corroborative epidemiological and clinical evidence of recent past or intercurrent psittacosis infection was lacking; but we consider it unlikely that these serological changes are fortuitous for the following reasons:

1. The serological response of subgroup B patients of the study group was similar to that of the 35 patients in the third control group.
2. The sera of 1,042 controls (1,000 apparently healthy persons and 42 patients hospitalized with nonviral noncardiac disorders) displayed no CF titer to psittacosis greater than 1:16; all subgroup B patients displayed higher titers.
3. Eleven of 12 specimens of serum from four patients, of study subgroup B (cases 4, 5, 6, 8) examined by the radioisotope precipitation (RIP) test had abnormally high levels of antibody. This test is a very sensitive, group-specific detector of antibody. It is two to 32 times more sensitive than CF, probably detects antibody qualitatively different from that detected by CF, and detects antibody in many sera negative by CF test. This may explain why one of 12 sera showed no correspondence between CF and RIP tests. Since the antigen employed in the RIP test is the Cal. 10 strain of meningopneumonitis agent cultivated on mouse fibroblasts, the problem of cross reactivity with hen's egg yoke as encountered in the CF test is eliminated.

Three additional factors contribute to the difficulties encountered in assessing the significance of rising CF antibody titers in the absence of bird exposure, typical clinical findings, or recovery of the agent. They are as follows:

1. Enhancement of CF titer to psittacosis antigen has been reported with other diseases such as brucellosis, Q fever, and hepatitis. Such antibody titers are usually low and subside rapidly.

2. Since two of these patients had primary myocardial disease and alcoholism, the antibody titers to routine psittacosis antigen might be attributed to an altered immune mechanism associated with liver disease. However, no patient had clinical or laboratory evidence of hepatic involvement.

3. Demonstration of a serological response to psittacosis agents does not necessarily indicate this agent to be causal in perimyocarditis despite coincident appearance. The agent may be merely a passenger and some other agent or factor may have caused the cardiac involvement. Thus, our current failure to demonstrate the agent in secretions, blood, pericardial fluid, or myocardium detracts from our thesis that psittacosis agent caused the heart disease in subgroup B patients. Yet, the failure to isolate the agent from biopsied myocardium or pericardial fluid, attempted in two patients, may well have been due to delay in obtaining specimens, and use of HeLa cell culture media.

In spite of these limitations, we believe psittacosis agent is responsible for heart disease in the nine patients described. Increasing knowledge has modified the necessary criteria for diagnosis. Bird contact is not essential. Kemmer and associates have commented on the difficulty in obtaining admission of bird contact; since patients may be afraid of losing pets. Furthermore, this agent can be transmitted from man to man, and from domestic animals to man. Clinical manifestations are not always in the classic mold; psittacosis infection produces a spectrum of illness, subclinical to severe. Gerlach isolated the agent from five asymptomatic individuals and concluded that human psittacosis is not invariably accompanied by recognizable clinical signs and symptoms, that human beings are subject to subclinical latent psittacosis and are carriers, and that man-to-man infections occur frequently. Ward and associates described several asymptomatic
patients with high CF titers among families with other members who had respiratory illness and significant CF titers. Harding\textsuperscript{31} noted demonstrable antibody in 41% of 275 parakeet owners with no history of acute febrile respiratory illness. Fraser and co-workers\textsuperscript{45} detected serological evidence of infection in 11% of 2,175 naval recruits without bird contact; 41% of these recruits had no history of respiratory illness. Thus, attention must be given to the possibility of chronic psittacosis infection, and to the presumption that a titer of 1:32 or higher sustained for 2 or more months indicates recent and continued activity of the agent. Such titers are not found in normal persons; such titers are associated with typical clinical cases, and persistent high titers occur with recrudescent LGV or with chronic pulmonary psittacosis.\textsuperscript{32}

Thus, prior observations and our experience suggest that human infection by psittacosis agents is rather frequent and produces a spectrum of disease. Subgroup A patients had acute perimyocarditis and typical epidemiological, clinical, and serological evidence of psittacosis. This group of patients is manifest evidence of the existence of psittacosis heart disease in this geographic area. The subgroup B patients may have even greater significance. Studies of these patients suggest that psittacosis infection may be causal in some forms of myocardial disease previously designated idiopathic.

Acknowledgment

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References


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