Myocarditis in Acute Infectious Diseases
A Clinical and Electrocardiographic Study

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Serial clinical and electrocardiographic studies were carried out on 84 patients suffering from a variety of acute infectious diseases. About one-third were found to have myocarditis on the basis of abnormal electrocardiograms. Abnormal physical findings were usually present. Evidence of congestive heart failure was uncommon. A group of patients subjected to artificial fever therapy did not manifest similar abnormalities.

Myocarditis associated with acute infectious disease has been described frequently in the literature. Most of the reports, however, are incomplete, either because of lack of essential data (such as the age of the patient, existence of previous heart disease, serial clinical and electrocardiographic studies) or because of the variability of criteria used (both clinical and pathologic). None of these papers has described the use of unipolar leads in detecting myocarditis.

This study was undertaken with several purposes in mind: (1) to determine the frequency of myocarditis in a variety of infectious diseases as demonstrated by significant electrocardiographic abnormality; (2) to investigate the extent and nature of these electrocardiographic changes; (3) to attempt a correlation of clinical and electrocardiographic findings; (4) to attempt an estimate of the functional disturbance of the cardiovascular system produced by Infectious disease.

The Frequency of Myocarditis in Infectious Disease

Burnett and Piltz\(^1\) took serial electrocardiograms on 55 adults and 45 children, all of whom were having, or had recently had, an acute infectious disease—influenza, pneumonia, tonsillitis, otitis media and mastoiditis, poliomyelitis, or tuberculous peritonitis. Significant electrocardiographic abnormalities, consisting essentially of partial A-V heart block and inverted T waves, were shown by 20 of the adults and 8 of the children.

Masters and Jaffe\(^2\) took daily electrocardiograms on patients with acute infectious diseases and found abnormalities in a large number. The authors gave no information as to the nature of the T-wave and RS-T abnormalities noted, nor whether the deviations reverted to normal.

Saphir\(^3\) collected data on 5626 autopsies on patients who had died from a wide variety of unrelated diseases, including infections such as bacterial meningitis, pneumonia, and tuberculosis. He found that myocarditis occurred in approximately 4 per cent of the cases. Saphir, Wile, and Reingold\(^4\) in a study of 1420 routine autopsies on children who had died of poliomyelitis, diphtheria, pneumonia, meningitis, pyemia, tuberculosis, bacterial endocarditis, or rheumatic fever found myocarditis in 6 per cent. The authors stated that the most significant single sign of myocarditis is a tachycardia out of proportion to temperature, since this phenomenon was present in one-half the patients in their series. Symptoms of cardiac failure were almost exclusively confined to patients with rheumatic heart disease or bacterial endocarditis. They concluded that myocarditis produces no characteristic symptoms, but that its presence should be suspected in any patient suffering from an acute infectious disease who, suddenly and without apparent reason, becomes worse.

In a recent study, Saphir\(^4\) described the characteristic heart in myocarditis as enlarged, with a soft, greyish yellow myocardium and a few yellowish streaks or minute areas of hemorrhage. Because often the disease process can

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be detected only by histologic examination, he emphasized the need for careful scrutiny of a number of tissue slides. Gore and Saphir reported that of 1402 instances of myocarditis collected at the Army Institute of Pathology over 90 per cent were nonrheumatic.

Neubauer stated that acute infectious disease is the most important cause of myocarditis. He stressed the belief that the electrocardiogram can demonstrate this condition when clinical signs are slight, doubtful, or absent. In his study of 200 patients with infectious diseases, such as diphtheria, scarlet fever, pertussis, and measles, a diagnosis of myocarditis was made on clinical grounds alone in 55 per cent and on electrocardiographic evidence alone in 24 per cent. The author considered the clinical signs to include pallor, listlessness, vomiting, albuminuria, cardiac enlargement, bradycardia, tachycardia, gallop rhythm and hypotension, with the principal sign a first heart sound of poor quality. He found the earliest electrocardiographic sign was a flattened T wave, which later became isoelectric and eventually inverted. Depression of the S-T segment and low voltage of the QRS complex often were present. The duration of myocarditis in his patients was from 2 weeks to 4 months. In 75 per cent of the subjects, its termination could be determined only by electrocardiograms.

FREQUENCY OF MYOCARDITIS IN SPECIFIC INFECTIOUS DISEASES

Diphtheria. Myocarditis in diphtheria is well recognized as occurring frequently.

Streptococcal Infections. Recently, emphasis has been placed on scarlet fever as another common cause of myocarditis. Two studies of acute beta-hemolytic streptococcal respiratory infections (Rantz and associates and Watson, Rothbard, and Swift) revealed that electrocardiographic changes of a transient nature often occurred during the height of the infection. The electrocardiogram became normal as the acute infection subsided; there was no relation to the late "phase III" illness which is indistinguishable from rheumatic fever. In the post-streptococcal state, Rantz, in a recent report, advised caution in interpreting post-streptococcal myocarditis as different from rheumatic myocarditis. Similar findings were described by Gore and Saphir.

Pneumonia. A number of reports on the incidence of myocarditis in pneumonia have appeared (Stone, De Graff and associates, Saphir, Master and co-workers, and Thompson and associates).

Typhoid Fever. Serial clinical and electrocardiographic observations of myocarditis in typhoid fever were made by four groups of investigators, Thayer, Brow, Porter and Bloom, and Rachmilewitz and Braun. Their results indicated a higher incidence of myocarditis in this disease than had been suspected previously.

Meningococcic Meningitis. Saphir, in a series of ten autopsies on patients who had died of meningococcal infection, found two instances of myocarditis caused by actual seeding of the organisms in the myocardium. Lowe and Diamond reported a case of meningococcic meningitis in a 13-year-old girl. During the disease, necrotic skin lesions, pericarditis, cardiac dilation, heart failure, and peripheral edema developed. Characteristic electrocardiographic changes were noted. An operation was performed, during which lesions were seen on the pericardium. It was suggested that their course had paralleled that of the cutaneous lesions.

Tuberculosis. Wallgren concluded that tuberculous heart disease is rare. In his opinion, pericarditis associated with this disease is often a tuberculous-allergic phenomenon. Auerbach and Guggenheim in 10,165 autopsies on adult tuberculous patients found the myocardium involved in 0.28 per cent. In autopsies on 973 children, the incidence of myocarditis was found to be 3.9 per cent.

Mumps. Rosenberg reported on 2 patients whose mumps were accompanied by complete heart block, and who developed precordial pain and faintness. Both patients recovered completely. Wendkos and Noll studied 15 cases of mumps and found one instance of myocarditis as evidenced by transient partial A-V block and flat T waves.

Influenza. Hyman reported 3 cases of heart block in influenza, but suggested that many cases were missed because of lack of electrocardiographic studies.
and Joliffe described 2 instances of death from influenza infections in which extreme degrees of diffuse myocarditis were seen at autopsy.

Atypical Pneumonia. Painton, Hicks, and Hartman took electrocardiograms during the acute illness and convalescence of 63 patients with atypical pneumonia. While 12 subjects showed electrocardiographic evidence of myocardial and pericardial involvement, only 2 of the 12 presented clinical evidence of cardiac abnormality.

Infectious Hepatitis. Dehn, Feil, and Kinderknecht studied 11 cases of infectious hepatitis during an epidemic. Electrocardiographic changes were minor and cleared during convalescence.

Infectious Mononucleosis. Evans and Graybiel examined serial electrocardiograms in 100 cases of infectious mononucleosis; 4 proved cases were described in detail.

Measles. Degen performed a series of autopsies on patients who had died from measles. In 91 hearts, he found 4 instances of cellular infiltrations in the myocardium, including 2 with exudative pericarditis.

Poliomyelitis. Gefter studied 467 patients with poliomyelitis. Electrocardiograms taken on 226 of the 467 subjects showed abnormalities in 32 (14.2 per cent). Saphir and Wile found an interstitial myocarditis with perivasculcar foci of lymphocytes in the hearts of 6 of 7 patients who had died of poliomyelitis. Dublin and Larson found 2 instances of acute myocarditis at autopsy in 12 patients who had died of poliomyelitis. Peale and Lucchesi demonstrated changes characteristic of myocarditis in the hearts of 7 of 9 patients dying of bulbar poliomyelitis. Two of the patients exhibited rapid, thready pulse and cyanosis before dying.

Epidemic Encephalitis. Ungar reported a case of diffuse interstitial myocarditis in epidemic encephalitis. He concluded that myocarditis occurs during this disease more frequently than is realized.

Scrub Typhus. Säyen found pathologic, clinical and electrocardiographic evidence of myocarditis in a series of persons with scrub typhus. All the patients who died showed extensive myocardial damage at autopsy. Sokolow and Garland and Levine, in follow-up studies of scrub typhus, concluded that the heart of a patient who survives the acute phase of the disease eventually shows complete return of function. In his monograph on typhus fever, Wolbach and associates described the typical vascular lesions of the disease and demonstrated that such lesions were not uncommon in the myocardium. Woodward and Bland studied 40 patients with typhus fever and concluded that peripheral rather than central circulatory collapse was the main clinical problem.

 SUBJECTS AND METHODS

An intensive study was made of 84 patients who were suffering from a wide variety of acute infectious diseases. Representative cases of varying severity were selected. Patients with pre-existing cardiac disease and those harboring beta-hemolytic streptococci in the throat, unless these organisms were considered to be the primary pathogenic agent, were excluded from the series.

A clinical evaluation of the cardiovascular system of each patient was made daily. It included determinations of temperature, pulse rate, arterial blood pressure, heart size, quality of the apical first heart sound, relationship of the intensity of the aortic and pulmonic second heart sounds, cardiac rhythm, and the presence of murmurs, gallop rhythm, dispersion of the neck veins, pulmonary abnormalities, cyanosis, edema, enlargement of the liver, and dyspnea. In most instances any significant clinical findings were checked by at least two of us.

Determination of circulation time and venous pressure was made every other day on patients old enough to cooperate. Alpha lobelin was used to determine the circulation time in comatose patients, magnesium sulfate and saccharin were used in all others. Venous pressure determinations were done with the zero level considered to be 5 cm. below the angle of Louis. A water-filled spinal fluid manometer attached to a three-way stopcock was used. A venous pressure greater than 12 cm. water and a circulation time greater than 12 seconds with alpha lobelin and 16 seconds with magnesium sulfate or saccharin were considered abnormal. Blood counts and sedimentation rates were done on each patient at entry and were repeated as indicated.

Electrocardiograms were taken on each patient from 1 to 24 hours after his entry to the hospital and, in most cases, were repeated every other day during his entire stay. Standard leads I, II, and III and unipolar leads aVL, aVR, V1, V2, and V3 were used routinely. Other unipolar precordial leads were taken when indicated. Criteria for abnormality were as follows:

1. Diphasic or inverted T waves (except in rare instances where low to flat T waves were present
with tall R waves (an R/T ratio of greater than 10:1), provided they became normal on serial observation.

2. Abnormal contour of T waves which persisted in serial observations. (This phenomenon was always accompanied by other abnormalities in the electrocardiogram.)

3. RS-T deviation greater than 0.5 mm. in Lead I and greater than 1.0 mm. in all other leads.

4. Complete atrioventricular dissociation, dropped beats, or a P-R interval over 0.21 second in adults or over the upper limits for age and rate in children as defined by Ashman and Hull. In serial records, a change of 0.04 second or more in the P-R interval, unless the interval exceeded 0.20 second, was required.

5. Arrhythmias, such as nodal rhythm, ventricular ectopic beats at a heart rate greater than 120, auricular fibrillation, and other ectopic rhythms.

6. Intraventricular conduction defects where the QRS duration exceeded 0.11 second. The upper limits of Q-T interval were determined according to age and rate as defined by Ashman and Hull using Bazett’s formula.

A normal electrocardiogram of each patient, taken at some time during the course of his illness, was used as a control. Usually the electrocardiogram became normal during convalescence, although in some instances it was normal at the time of the first record and became abnormal later. No patient was included in the series unless a normal control observation was available.

Results

In the 84 cases accepted for evaluation, serial electrocardiograms were definitely abnormal in 28 patients (33 per cent), borderline in 5 (6 per cent), and normal in 51 (61 per cent) (table 1). Abnormal T waves were present in 20 patients, prolongation of the P-R interval in 8, significant RS-T deviation in 3, and abnormalities in rhythm in 6. Prolongation of the QRS interval was noted in only 4 patients. Figures 1, 2, 3, and 4 illustrate typical electrocardiographic changes found.

Abnormality of the T waves (table 2) proved the most frequent and sensitive indication of myocarditis. The use of unipolar leads was of considerable value in demonstrating this aberration. In 12 of the 20 patients manifesting abnormal T waves, the significant changes were shown in the unipolar limb or precordial leads, or both, whereas the standard leads showed either normal or borderline patterns. In only two instances where the T waves in standard Lead I were abnormal did the unipolar leads fail to reflect the change.

Alterations in the contour of the T waves were often significant. Many patients demonstrated flat-topped broad T waves which, in serial records, gradually became sharply peaked and normal in shape (fig. 3).

| Table 1.—Electrocardiographic Diagnoses in 84 Cases of Infectious Disease |
|-----------------------------|---|---|---|---|
| Disease                    | Total | Normal | Abnormal | Borderline |
| Diphtheria      | 16 | 8 | 8 | 0 |
| Tuberculous meningitis | 9 | 8 | 1 | 0 |
| Typhoid fever    | 8 | 0 | 7 | 1 |
| Measles         | 8 | 6 | 0 | 2 |
| Infectious mononucleosis | 7 | 7 | 0 | 0 |
| Scarlet fever   | 6 | 3 | 2 | 1 |
| Streptococcal pharyngitis | 5 | 4 | 1 | 0 |
| Lobar pneumonia | 5 | 2 | 3 | 0 |
| Meningococcal infections | 5 | 2 | 3 | 0 |
| Viral infections | 4 | 4 | 0 | 0 |
| CNS unknown etiology | 1 | 0 | 1 | 0 |
| Pneumococcal meningitis | 1 | 0 | 1 | 0 |
| Influenzal meningitis | 1 | 0 | 1 | 0 |
| Streptococcal meningitis | 1 | 0 | 0 | 1 |
| Acute brucellosis | 1 | 1 | 0 | 0 |
| Poliomyelitis    | 1 | 1 | 0 | 0 |
| Vincent’s pharyngitis | 1 | 1 | 0 | 0 |
| Psittacosis      | 1 | 1 | 0 | 0 |
| Chicken pox     | 1 | 1 | 0 | 0 |
| Total            | 84 | 51 | 28 | 5 |

The abnormalities in rhythm and conduction included bundle branch block, partial A-V block with and without dropped beats, complete A-V dissociation, and nodal rhythm with and without A-V block. With the exception of partial A-V block in several patients and dropped beats in a patient with mumps (fig. 4), these abnormalities in conduction and rhythm occurred only in the patients with diphtheritic myocarditis.
Abnormalities first appeared in the electrocardiograms from 1 to 19 days after the date of onset of the disease, with the majority occurring within the first 10 days. In scarlet fever abnormalities usually became apparent during the second and third weeks, presumably when toxicity was greatest.

Twenty-five patients were febrile and 3 were afebrile at the time the first abnormalities were seen in the electrocardiograms. In general, the abnormalities appeared in the electrocardiogram during the acute febrile phase of illness.
and persisted for a short time into convalescence. Eventually, all the electrocardiograms became normal.

*Clinical Manifestations of Myocarditis (Table 3)*

Of the 28 patients with abnormal electrocardiograms, 13 (46 per cent) manifested an apical heart sound of poor quality. Of the 51 with normal electrocardiograms, only 2 patients (4 per cent) demonstrated a poor apical heart sound on serial examination. Both patients were comatose at this time and died shortly thereafter.

The poor quality of the first heart sound was first noted from 1 to 44 days after the onset of the infection. This sign persisted from 1 to 38 days. In the group with abnormal electrocardiograms, this auscultatory evidence did not vary more than 4 days in either direction from the first appearance of electrocardiographic abnor-

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**Fig. 4.** M. S., female, age 5 years. Mumps. Onset March 9, 1948. Illustrating partial A-V block with dropped beats and serial changes in contour of the T waves in leads I, aVL and aVF. A. March 15, 1948. B. March 17, 1948. C. March 29, 1948.
seen in the electrocardiogram. A first heart sound of poor quality, although difficult to describe, has a distinctive muffled, distant or weak quality. There was little disagreement among us as to when the apical first heart sound was of poor quality.

Table 2.—T-Wave Abnormalities Found in 84 Cases of Infectious Disease

<table>
<thead>
<tr>
<th>T</th>
<th>Low</th>
<th>Diphasic</th>
<th>Inverted</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>T2</td>
<td>5</td>
<td>3</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>TVL</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TVF</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>TVA</td>
<td>3</td>
<td>3</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>TVh</td>
<td>5</td>
<td>2</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>11</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.—Clinical Manifestations of Myocarditis in the Present Series of 84 Cases

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Total Number</th>
<th>Patients—Abnormal ECG</th>
<th>Patients—Normal ECG</th>
<th>% With Abnormal ECG</th>
<th>% With Normal ECG</th>
<th>Ratio % Abnormal to Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor quality M1</td>
<td>15</td>
<td>13</td>
<td>2</td>
<td>46.6</td>
<td>3.7</td>
<td>~12:1</td>
</tr>
<tr>
<td>Drop in systolic blood pressure 20 mm. or more</td>
<td>11</td>
<td>8</td>
<td>3</td>
<td>28.6</td>
<td>6.0</td>
<td>~5:1</td>
</tr>
<tr>
<td>Gallop rhythm</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>28.5</td>
<td>7.2</td>
<td>~4:1</td>
</tr>
<tr>
<td>Systolic murmur</td>
<td>26</td>
<td>12</td>
<td>14</td>
<td>42.8</td>
<td>25.9</td>
<td>~2:1</td>
</tr>
<tr>
<td>Pulse rate greater than 125</td>
<td>22</td>
<td>11</td>
<td>11</td>
<td>39.3</td>
<td>21.6</td>
<td>~2:1</td>
</tr>
</tbody>
</table>

Of the group with abnormal electrocardiograms, 8 (20 per cent) showed a decrease in systolic blood pressure of 20 mm. or more, as compared to control convalescent blood pressure levels. Of the group with normal electrocardiograms, only 3 (6 per cent) had a comparable fall in blood pressure.

Of the 28 individuals with abnormal electrocardiograms, 8 (28.5 per cent) developed a diastolic gallop rhythm sometime during the course of the disease. In 6 of these patients, it was heard within four days after the first abnormalities appeared in the electrocardiogram; in 3, its onset coincided exactly with the date of their appearance. This sign was heard from 8 days before to 25 days after the last abnormalities were seen in the electrocardiogram; it persisted from 1 to 60 days. Of the 54 patients with normal electrocardiograms, only 4 (7 per cent) developed a gallop rhythm. In all 4, the abnormal rhythm was heard for only one day during the course of the disease.

Apical systolic murmurs of varying intensity were heard in 12 (43 per cent) of the patients with abnormal electrocardiograms. The murmurs were first noted from 9 days before to 5 days after the abnormalities were first apparent. In 5 of the 12 patients, their occurrence coincided with the appearance of the first aberrations in the electrocardiogram. The murmurs persisted from 1 to 60 days. They were last heard from 25 days before to 10 days after the last abnormalities were seen in the electrocardiogram, disappearing, in most cases, 2 to 3 days before or after this event. Of the 53 with normal electrocardiograms, 14 patients (26 per cent) developed murmurs.

Pulse rates greater than 125 per minute were noted in 11 (39.3 per cent) of the group with abnormal electrocardiograms and in 11 (21.6 per cent) of the group with normal electrocardiographic patterns. This pulse rate was selected arbitrarily; it is apparent that under certain circumstances a pulse rate of 125 may be considered perfectly normal.

Thus, it may be concluded that an apical heart sound of poor quality is by far the most reliable clinical sign of myocarditis. The next most dependable signs are, in order of importance: a drop in systolic blood pressure of 20 mm. or more, gallop rhythm, systolic murmur, and a pulse rate greater than 125 per minute.

Table 4 summarizes the distribution of these clinical signs in the patients with abnormal electrocardiograms. Twenty-four of the 28 patients with myocarditis had at least one of the five clinical signs. Of these, 3 had an apical first heart sound of poor quality as a single
manifestation, 3 had systolic murmurs alone, and 2 had pulse rates greater than 125 alone. Six patients demonstrated both an apical heart sound of poor quality and gallop rhythm. Five patients had a combination of apical heart sound of poor quality, gallop rhythm and a murmur. In 2 patients, the venous pressure was elevated; in 3 patients, the circulation time was prolonged.

None of the patients with normal electrocardiograms developed elevated venous pressure or prolonged circulation time.

Eleven of the patients studied died: 1 of post-measles encephalitis, 1 of Staphylococcus aureus lobar pneumonia, 1 of typhoid fever, 3 of diphtheria, and 5 of tuberculous meningitis.

The patient who died of post-measles encephalitis had T waves bordering on the abnormal. The patient with Staphylococcus aureus pneumonia had a normal electrocardiogram, although clinical signs pointed to congestive failure. Neither of these patients was autopsied. The patient with typhoid fever revealed myocarditis, both clinically and electrocardiographically, and at autopsy showed toxic degeneration of the muscle fibers and interstitial myocarditis (fig. 5). All 3 patients with diphtheria showed bizarre electrocardiographic abnormalities before death. The 2 who were examined at autopsy manifested definite toxic degenerative

### Table 4.—Clinical Signs in 28 Patients with Abnormal Electrocardiograms

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Disease</th>
<th>Poor M</th>
<th>Drop in Systolic BP 20 mm. or More</th>
<th>Gallop Rhythm</th>
<th>Systolic Murmur</th>
<th>Pulse Rate More than 125 per Min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.P.</td>
<td>11</td>
<td>Meningococemia</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C.F.</td>
<td>7</td>
<td>The. meningitis</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>A.X.</td>
<td>31</td>
<td>Mening. meningitis</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>L.W.</td>
<td>21</td>
<td>Typhoid fever</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>H.C.</td>
<td>7</td>
<td>Typhoid fever</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>J.H.</td>
<td>3</td>
<td>Typhoid fever</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>L.Y.</td>
<td>50</td>
<td>Typhoid fever</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>J.K.</td>
<td>9</td>
<td>Typhoid fever</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B.J.</td>
<td>61</td>
<td>Strep. meningitis</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
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<tr>
<td>L.B.Y.</td>
<td>10</td>
<td>Scarlet fever</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>G.R.</td>
<td>24</td>
<td>Typhoid fever</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>H.V.</td>
<td>?</td>
<td>Diphtheria</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>M.S.</td>
<td>5</td>
<td>Mumps</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
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<tr>
<td>A.C.</td>
<td>32</td>
<td>Typhoid</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
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<tr>
<td>J.H.</td>
<td>40</td>
<td>Diphtheria</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
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<tr>
<td>J.S.</td>
<td>43</td>
<td>Pneumonia</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
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<tr>
<td>J.M.</td>
<td>26</td>
<td>Scarlet fever</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>F.S.</td>
<td>51</td>
<td>Meningococemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>L.M.</td>
<td>74</td>
<td>Diphtheria</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
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<tr>
<td>L.I.</td>
<td>31</td>
<td>Pneumo. meningitis</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>E.D.</td>
<td>48</td>
<td>Diphtheria</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>O.O.</td>
<td>49</td>
<td>Diphtheria</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C.F.</td>
<td>37</td>
<td>Diphtheria</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>I.E.</td>
<td>33</td>
<td>Typhoid fever</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>D.P.</td>
<td>11</td>
<td>Scarlet fever</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>H.B.</td>
<td>42</td>
<td>Infl. meningitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H.S</td>
<td>49</td>
<td>Pneumonia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>J.S.</td>
<td>31</td>
<td>Strep. throat</td>
<td>0</td>
<td>0</td>
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</table>
mal both by clinical and electrocardiographic evidence. These last 4 patients showed no evidence of myocarditis at autopsy.

**Fig. 5.** Typhoid fever. Toxic degeneration of muscle fibers and interstitial myocarditis. (Hematoxylin and eosin × 100)

**Fig. 6.** Diphtheritic myocarditis. Marked toxic degeneration. (Hematoxylin and eosin × 100)

**Effect of Artificial Fever Therapy on the Heart**

As stated previously, most of our patients were febrile when the first abnormalities appeared in the electrocardiogram, but became afebrile before the electrocardiographic patterns returned to normal. In order to determine the effect of fever and tachycardia per se on the heart, we studied an additional 18 patients who were receiving artificial fever therapy. All subjects, according to history and physical examination, were free of pre-existing cardiac disease.

The 18 patients were kept at 105 to 106°F by means of bakers and blankets for six hours. Each patient was given 500 cc. of 3 per cent sodium chloride intravenously immediately before therapy, and sedation as needed. Electrocardiographic, clinical and hemodynamic studies (the same described for the patients with acute infectious diseases) were made after each patient had one or two treatments. Control studies were made before therapy was begun and were repeated immediately after treatment, while the temperature was still at 106 degrees.

There have been several previous descriptions of the effect of fever on the electrocardiogram. According to these reports, only an occasional patient receiving pyrotherapy showed significant electrocardiographic deviations; the majority demonstrated no electrocardiographic abnormalities.

The results of our study were in agreement with these observations. In the 18 patients studied, minor S-T deviation, usually depression, and a slight lowering of the R and T waves were fairly common. No clinical signs of cardiac disturbance were present, with one exception. One patient showed significant changes in the
electrocardiogram; the T wave in Lead II became diphasic and in aVp became inverted. He seemed to be in a shocklike state and manifested tachycardia and hypotension. In this patient, the venous pressure rose from 4.5 cm. of water before therapy to 11.0 cm. after therapy. The circulation time increased from 16 to 21 seconds, whereas all the other patients showed a definite decrease. The pulse rate rose from 83 to 136 per minute; blood pressure fell from 140/90 to 96/54. Embryocardia and an apical first heart sound of poor quality were present.

**DISCUSSION**

In diphtheria and scarlet fever, the myocardium probably is affected by toxins circulating in the blood stream. This also may be true in typhoid fever, acute streptococcal disease, bacterial pneumonia, and other infectious diseases characterized by toxemia.

In certain other infectious diseases, different elements may contribute to the derangement of myocardial function. A specific infection of the myocardium is known to occur in rare cases of tuberculosis and in pyemia from various causes. In benign virus diseases, such as mumps, influenza A, and measles, it is possible that the myocardium is directly attacked by the virus. Schmidt isolated a virus from a chimpanzee dying of interstitial myocarditis which produced a myocarditis and encephalitis when injected in mice, hamsters, and guinea pigs. It could not be identified with any variety of known viruses.

It also is possible that electrolyte and fluid imbalance may contribute to the electrocardiographic changes characteristic of myocarditis. The acidosis and electrolyte imbalance of diabetic coma often results in electrocardiographic changes. Barker, Shrsder, and Ronzoni studied the effects of alkalosis and acidosis in man as reflected in the electrocardiogram. Alkalosis was produced by hyperventilation and ingestion of sodium bicarbonate, and acidosis by ingestion of ammonium chloride. Alkalosis resulted in a definite reduction in the amplitude of the T waves, while acidosis caused a striking increase in their height.

Alterations of the serum potassium can lead to T wave, RS-T, and conduction abnormalities. Tarail, in a report on a patient with uremia associated with hyperpotassemia, described peaked T waves of large amplitude and brief duration in Leads I and II, delayed intraventricular conduction, prolonged P-R interval, some tendency of the P waves to disappear, development of a deep Q in CF2, abnormal S-T elevation, and an inclination to left ventricular strain. Other reports have described the chief changes in hypopotasssemia as low to flat T waves, depression of RS-T, and prolongation of the Q-T interval. Reduction of the ionized serum calcium produces typical changes with prolongation of the Q-T interval, sharply pointed positive T waves, and a long isoelectric course of S-T. Dehydration can cause flattening of the T waves and depression of the RS-T segments.

Another hypothetic cause of myocarditis in infectious diseases might be an allergic factor similar to that presumed to produce rheumatic lesions. The presence of myocarditis early in the illness would militate against this possibility.

Rachmilewitz and Braun, in a study of typhoid fever, gave two reasons for concluding that the abnormalities in the electrocardiograms of their patients were not due to myocarditis: (1) the pathologic changes in the heart were not sufficiently severe, (2) there was no clinical evidence of myocardial involvement. They gave 23 of their patients 300 to 600 mg. of niacin each day. The daily electrocardiogram returned to normal in 6 patients after two days, in 12 patients after three to five days, and in 4 patients after six to ten days. In 12 patients from whom niacin was withheld, the electrocardiographic patterns gradually improved, becoming completely normal in an average of 12½ days.

Weiss and Wilkins have shown that abnormalities in the T wave and the Q-T interval are common in conditions due to thiamin deficiency. Feil, in a report on 38 patients with pellagra, found that approximately one-half showed sinus tachycardia, S-T segment abnormalities, inversion of the T waves, or prolongation of the Q-T interval.
Simonson, Henschel, and Keys studied young men who underwent 24 weeks of semi-starvation. During this period, the electrocardiograms of the majority of subjects became abnormal and statistically, showed highly significant changes in the electrocardiographic components. The Q-T interval and the mechanical systole increased during semistarvation and shortened again during rehabilitation. The amplitude of all deflections (P wave, QRS complex, and T wave) decreased continuously and considerably during semistarvation and increased during rehabilitation. Most electrocardiographic components were back to control values within 32 weeks.

Our patients, in most instances, received two to three times the minimum daily requirement of all vitamins known to be essential to human nutrition (A, D, C, B, B2 and niacin). Vitamin deficiencies probably contributed little, if any, to the abnormal findings.

Therapeutic agents also must be considered as a possible cause of myocarditis. One of our patients was excluded from the series when it became necessary to give him emetine for the treatment of amebic lung abscess. Many of our patients received sulfonamides. French and Weller examined the hearts of 238 patients who had received sulfonamide drugs and found significant myocarditis in 126 (44.5 per cent). These workers gave therapeutic doses of sulfonamides to 60 mice and 47 rats, following which 38 of the mice and 33 of the rats developed interstitial myocarditis. McKinley described a case of allergic carditis, pericarditis, and pleurisy during serum sickness. The electrocardiogram showed variable flat and negative T waves, with the major changes occurring after asymptomatic recovery. Other observers also have noted carditis in serum sickness. In our series, three patients with diphtheria developed serum sickness but showed no clinical or electrocardiographic evidence of carditis.

It is difficult to estimate the importance of myocarditis in infection. It is well known to be a cause of death in diphtheria. In most other fatal infections, since potentially lethal disturbances of systems other than the cardiovascular also are present, death appears to be due to a summation of many causes. The data of Saphir, Stone and others suggest that myocarditis is a common occurrence in patients dying of infectious diseases, but its presence does not mean that it is the most important cause of death. Our observations indicate that myocarditis rarely produces even a slight degree of congestive heart failure. Yet, sudden death from myocarditis may occur, although the usual picture of progressive heart failure is lacking. Thus, while many individuals dying of infectious diseases have myocarditis, most persons who develop myocarditis during an infectious disease survive. It is even unlikely that such acute myocarditis causes any important residual effects. The heart of every surviving patient in this series became normal, according to both clinical and electrocardiographic signs, before he was discharged from the hospital.

**SUMMARY AND CONCLUSIONS**

1. Serial clinical and electrocardiographic studies were made on 84 patients suffering from a variety of acute infectious diseases.

2. Of the patients, 33.3 per cent demonstrated electrocardiographic abnormalities as compared with their own normal control records. An additional 5.9 per cent manifested border-line electrocardiographic aberrations.

3. The majority of patients with abnormal electrocardiograms demonstrated clinical signs considered to represent myocarditis.

4. Physical findings generally associated with electrocardiographic abnormality were, in order of frequency: abnormality of the apical first heart sound, drop in systolic blood pressure of 20 mm. Hg, apical systolic murmurs, and a pulse rate greater than 125 per minute.

5. Myocarditis, as determined by clinical and electrocardiographic evidence, did not seem to be decisive in determining the survival of the patient, except in diphtheria. The patients in general were unaware of its presence.

6. Examples of myocarditis in typhoid fever, diphtheria and tuberculosis as determined at autopsy are presented.

7. The fever and tachycardia of pyrotherapy did not produce clinical or electrocardiographic signs of myocarditis in 17 of 18 patients who
were studied in the same manner as the 84 patients with infectious diseases.

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IRVING FINE, HENRY BRAINERD and MAURICE SOKOLOW

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