A Study of the Cardiac Stigmata in
Prolonged Human Thiamine Deficiency

By DAVID T. ROWLANDS, JR., M.D., AND CARL F. VILTER, M.D.

Eight clinically proved cases of prolonged thiamine deficiency were evaluated by routine pathologic study. The microscopic features were evaluated by comparison with sections of myocardium obtained from normal individuals and individuals suffering from cardiac diseases of other varieties. No specific transitory or permanent alterations were demonstrable. It is concluded that beriberi heart disease is largely the result of a reversible biochemical abnormality and is not characterized by specific pathologic lesions.

Most of the early studies of beriberi were carried out in the Orient\(^1\)-\(^3\) and the occurrence of the disorder is well recognized in populations in whom milled rice constitutes a large portion of the diet. In the United States it was considered little more than a medical curiosity until the studies of Weiss and Wilkins\(^4\),\(^5\) in the late 1930's. These authors indicated a surprisingly high incidence of beriberi heart disease (1 case in each 160 medical admissions to a large charity hospital in Boston). In many of these patients the disorder was considered to be very mild; in most instances alcoholism was a prominent feature in its pathogenesis.

During the 1940's the concept of beriberi heart disease in this country changed considerably, in some measure through the efforts of Blankenhorn,\(^6\) who suggested relatively simple criteria for its recognition. He indicated that the disease is somewhat more common in the United States than had previously been recognized. Particular attention was directed to the common occurrence of a chronic form of cardiac failure rather than acute, high-output failure as a manifestation of beriberi heart disease. It was emphasized that other forms of cardiac disease often were complicated by the deficiency disorder. The clinical requirements for the appreciation of beriberi heart disease listed by Blankenhorn\(^6\) were (1) enlarged heart with normal rhythm, (2) dependent edema, (3) elevated venous pressure, (4) peripheral neuritis or pellagra, (5) nonspecific alterations in the electrocardiogram, (6) no other evident cause for heart disease, (7) gross deficiency of diet for 3 months or more, and (8) improvement of symptoms and reduction of heart size after specific vitamin replacement, or (9) necropsy findings consistent with beriberi.

The cardiovascular lesions have been investigated at necropsy in human beings and in experimental animals.\(^4\),\(^7\) The gross pathologic features are characterized by normal or increased heart weight with dilatation and hypertrophy of one or more of the chambers. The microscopic lesions, although numerous, are nonspecific.\(^8\) Myocardial fibers show either no alteration or varying degrees of hydropic degeneration. Striations are usually intact. Intercellular edema, congestion, hemorrhage, and swelling of connective tissue are seen. Interstitial and replacement fibrosis is also encountered.

Although it is generally agreed that complete recovery may result if beriberi heart disease is corrected at an early date, it is also maintained that recovery may be incomplete if scarring of the myocardium has resulted from the degenerative disorder.\(^8\) The ultimate fate of the heart in treated but recurrent beriberi has not been extensively investigated.\(^9\)

During the last 20 years a number of patients suffering from what appeared to be prolonged thiamine deficiency were examined at necropsy in the Cincinnati General Hospital. All had had heart failure at some time during their illnesses. In some, when suitably treated,
the cardiac failure was followed by apparent remission. In others, the recurrent episodes of heart failure continued. In some, the heart failure constituted a terminal event. It is proposed to record the pathologic alterations encountered in the hearts of patients known to have had severe thiamine deficiency for prolonged periods, as indicated below. This study stemmed from the desire to determine whether or not there were permanent alterations supervening upon the apparently reversible lesions of the acute form.

Materials and Methods

The diagnostic files of the Departments of Medicine and Pathology of the Cincinnati General Hospital were culled for cases coded as either "beriberi" or "myocarditis" on a clinical or pathologic basis. Among these there were 29 patients considered to have had vitamin B deficiency in whom necropsy examination had been performed.

The criteria proposed by Blankenhorn were employed as basic requirements in our clinical evaluation. In view of the desire to investigate the nature of the lesions induced by long-standing deficiency, a modified criterion of 6 months' duration of deficiency (instead of 3 months) was employed. In addition, in order to be certain that the cases were truly examples of pure beriberi heart disease, those displaying severe anemia or cardiac arrhythmia were excluded. Only 8 of the 29 cases were found to meet these limitations. These were selected for detailed clinical and pathologic survey. Despite the small number, these were unquestionable examples of beriberi heart disease from the clinical standpoint, and therefore comprised a suitable group for pathologic analysis. In 4 instances, there had been frank beriberi heart disease for more than 6 months and in the remaining 4, manifestations of heart failure had existed for less than this period although thiamine deficiency was known to have been present for 6 months or more.

Table 1 lists the salient clinical data from the 8 cases deemed suitable for this investigation. The average age at death among these patients was 50 years, with a range of 41 to 67 years. Six patients were male; all had had manifestations of heart failure and an unequivocal history of prolonged dietary deficiency. Alcoholism was a contributing factor in all but 1 patient (J.C.); psychosis was believed responsible for his poor nutrition. Three patients manifested mild elevation of venous pressure. In 2 of these the venous pressure returned to normal during hospitalization; in 1 instance (G.E.) this improvement was attributed to effective thiamine therapy. In 3 cases venous pressure had not been recorded, and in 2 it was within normal limits. Evidences of peripheral neuritis or pellagra were encountered in 7 patients. There were nonspecific electrocardiographic abnormalities in 7 instances. Five of the patients showed moderate hypertension, which, however, was not considered to militate against the diagnosis of beriberi in view of the overwhelming clinical evidence of the latter. Indeed, the hypertension tended to be variable. Cardiac failure or the transient "hypertension" common on admission blood pressure readings often accounted for the high values. On the other hand, in case G.E., there was persistent hypertension after clinical recovery from beriberi.

In 5 patients, treatment with thiamine effected an improvement of symptoms. In 1 patient (C.B.) no treatment was given. Failure of response in 2 cases is not an unusual experience. One patient (J.C.) was given thiamine in a dose of 20 mg. twice a day but for only 4 days prior to death. Another patient (W.L.C.) received 100 mg. of thiamine intramuscularly every 6 hours but treatment was not begun until the day of death.

Pathologic data were gathered by a review of the descriptions of the heart recorded by the pathologists and examination of the available tissue sections. The majority of the latter had been fixed in Zenker's solution with 5 per cent acetic acid; in a few instances, 10 per cent formalin had been used. The tissues were sectioned after embedding in paraffin and stained with hematoxylin and eosin; 1 to 6 samples of myocardium were available in each instance (2 cases, 1 section; 1 case, 2 sections; 3 cases, 3 sections; and 2 cases, 6 sections.) Trichrome and van Gieson stains were performed in each instance to determine the extent of fibrosis. Fat stains were carried out in 3 cases in which stored, formalin-fixed, wet tissue was available. Periodic acid-Schiff stains with and without previous digestion by malt diastase were done on sections of heart from 7 of the cases of beriberi and on a group of 14 controls (4 cases of arteriosclerotic heart disease, 3 cases of hypertensive cardiovascular disease, 4 cases of rheumatic heart disease, and 3 normal individuals).

An attempt was made to quantitate the microscopic features that have, in the past, been considered significant in the cardiac lesions of beriberi (vacuolization, interstitial edema, interstitial fibrillation, replacement fibrosis).
**Clinical Data**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Patient</th>
<th>Age at death</th>
<th>Enlarged heart</th>
<th>Dependent edema</th>
<th>Peripheral neuritis or pellagra</th>
<th>Electrocardiogram</th>
<th>Other cause for heart disease</th>
<th>Duration deficiency of diet</th>
<th>Duration of heart disease</th>
<th>Improvement after vitamin therapy</th>
<th>Venous pressure em. water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G.E.</td>
<td>53</td>
<td>+</td>
<td>1+</td>
<td>+</td>
<td>low voltage T-waves</td>
<td>0*</td>
<td>Simultaneous with onset of failure</td>
<td>18 yr.</td>
<td>+</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>W.L.C.</td>
<td>47</td>
<td>0</td>
<td>1+</td>
<td>+</td>
<td>low voltage sinus arrhythmia</td>
<td>hypertensive and arteriosclerotic, mild</td>
<td>10 years</td>
<td>1 yr.</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>H.R.</td>
<td>41</td>
<td>+</td>
<td>1+</td>
<td>+</td>
<td>low voltage T-waves, Prolonged A-V conduction</td>
<td>hypertension, mild</td>
<td>6+ years</td>
<td>10 mo.</td>
<td>+</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>J.B.</td>
<td>48</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>prolonged intraventricular conduction; T to low voltage and diphasic</td>
<td>0</td>
<td>6+ months</td>
<td>1 mo.</td>
<td>4 days’ treatment without effect; death 2 days later</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>J.C.</td>
<td>67</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>low voltage QRS and T-waves</td>
<td>hypertension, mild</td>
<td>many years</td>
<td>6 wk.</td>
<td>No effect—treatment for 4 days</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>C.B.</td>
<td>44</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>premature ventricular beats</td>
<td>hypertension, mild</td>
<td>?</td>
<td>2 yr.</td>
<td>No treatment</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>H.S.</td>
<td>42</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>?</td>
<td>10 years</td>
<td>acute failure, death in a few hours</td>
<td>Initial</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>H.M.</td>
<td>58</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>complete A-V block</td>
<td>complete A-V block</td>
<td>2 years</td>
<td>2 mo.</td>
<td>Slight</td>
<td>12</td>
</tr>
</tbody>
</table>

*Patient G.E. developed hypertension after recovery from her initial episode of beriberi heart disease.
As controls, sections of myocardinum from 60 patients of comparable age were selected from the necropsy files. All of these patients were without clinical evidence of vitamin deficiency. In 20, the hearts were considered normal. Fifteen examples, each of hypertensive cardiovascular disease and inactive rheumatic heart disease, were chosen. There were 10 cases in which the underlying disease was coronary arteriosclerosis without hypertension.

The sections were repeatedly examined as unknowns and the degree of alteration was appraised in each instance. The examiner was consistently able to arrive at an identical estimate in each section.

**Results**

Specific pathologic examination of the hearts included those features that appeared important in excluding other forms of heart disease as well as those characteristics considered indicative of beriberi. The weights of the hearts varied from 225 to 675 Gm. (table 2). Four hearts were considered hypertrophied by weight (one of these was from the patient (G.E.), who had persistent hypertension) and 2 hearts were only slightly enlarged; the weights of 2 hearts fell within normal limits. On the basis of measurements of the thickness of the ventricles, there was marked hypertrophy of both left and right ventricles in 2 (1 with hypertension). In the other 6, the thickness of at least one ventricle was within the normal range. Observable ventricular dilatation was found in 4 cases; atrial dilatation alone was a feature of 2 others. Since the prosector’s note constituted the only basis of this determination, his failure to indicate the state of the chambers did not necessarily mean that they were not dilated.

Microscopic examination revealed no significant epicardial lesions. In only 1 case was an endocardial alteration noted; this consisted of a recent mural thrombus. Vacuolization proved to be of hydric nature (fig. 1); interstitial edema was a constant feature (fig. 1) and was often accompanied by fine interstitial fibrillation (fig. 1). Coarse fibrosis and frank collagenization were rare. Occasional infiltration with lymphocytes was observed in most cases, but they were present in only very small numbers. It was noted that there was

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**Table 2**

**Gross Pathologic Findings in Eight Cases of Beriberi**

<table>
<thead>
<tr>
<th>Case</th>
<th>Heart weight (Gm.)</th>
<th>Right atrium</th>
<th>Right ventricle</th>
<th>Left atrium</th>
<th>Hypertrophy*</th>
<th>Other diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.E.</td>
<td>530</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>W.J.C.</td>
<td>400</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>H.R.</td>
<td>675**</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>---</td>
</tr>
<tr>
<td>J.B.</td>
<td>495</td>
<td>yes</td>
<td>yes</td>
<td>---</td>
<td>---</td>
<td>(4)</td>
</tr>
<tr>
<td>J.C.</td>
<td>400</td>
<td>yes</td>
<td>yes</td>
<td>---</td>
<td>---</td>
<td>(5)</td>
</tr>
<tr>
<td>C.B.</td>
<td>500</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>H.S.</td>
<td>310</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>(3)</td>
</tr>
<tr>
<td>H.M.</td>
<td>225</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>(4)</td>
</tr>
</tbody>
</table>

*Measurements are in millimeters.

**Weighed with ‘‘some excess tissue at the base.’’**

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considerable variation in the severity of muscle vacuolization, interstitial edema, and fibrosis from field to field, probably because of the mechanics of myocardial function and structure. On the other hand, the controls frequently showed changes as great as those seen in cases of beriberi (table 3).

Figures 1 and 2 represent sections of heart from cases of beriberi. Little scarring was found. Figure 3 illustrates a section of heart from a patient with hypertensive cardiovascular disease, figure 4 is from a patient with no cardiac abnormalities, and figure 5 shows the microscopic appearance of the myocardium in a patient with coronary occlusive disease. Figures 3, 4, and 5 disclose a close similarity to figures 1 and 2 in degree of interstitial edema and hydropic degeneration.

Both fat and periodic acid-Schiff stains were used in an attempt to determine the identity of the substance comprising the myocardial vacuoles. In none of the cases in which these were employed was either lipid or glycogen demonstrable. In 1 case (W.L.C.) a
significant amount of perinuclear lipid was observed. In the remaining 2 (C.B. and G.E.) small droplets of fat were found within the muscle fibers. This group of 3 cases is believed to be too small to permit accurate conclusions regarding the significance of accumulation of intracellular fat in beriberi heart disease. The connective-tissue stains verified the presence of fibrous tissue of the type and extent recorded in table 3. A summary of additional pathologic features in these patients is presented in table 4.

**Discussion**

The clinical criteria employed in selection of these patients were, in general, those proposed by Blankenhorn. Patients suffering from disease that might simulate beriberi heart disease and those with complicating conditions that might significantly damage the myocardium were excluded. The failure of some patients to respond to thiamine is not unprecedented. Moreover, the dose of thiamine in these patients was usually quite low and treatment was of short duration.

No evidence was adduced in this series to indicate a specific morphologic alteration in beriberi. On gross examination there was appreciable variation in the degree of cardiomegaly. Dilatation of cardiac chambers appeared as a more outstanding feature than an anticipated increase in weight. Indeed, the 2 hearts in this group with normal weights were described as having atrial dilatation and increase in thickness of the ventricles.

The microscopic data failed to disclose a lesion that might be called characteristic or would provoke suspicion that a lesion was of prolonged duration. It is thus apparent that one may not adequately discriminate histologically between those cases of thiamine deficiency that have had overt cardiac failure early in their course and those in whom this is only a late manifestation. Furthermore, it is not possible to discern microscopic characteristics in the myocardium of cases of beriberi significantly different from those seen in other cardiac diseases or in essentially normal hearts.
<table>
<thead>
<tr>
<th>Case</th>
<th>Lungs</th>
<th>Liver</th>
<th>Alimentary tract</th>
<th>Genitourinary system</th>
<th>Nervous system</th>
<th>Other</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.E.</td>
<td>Atherosclerosis, moderate; infarction</td>
<td>Passive congestion</td>
<td>--</td>
<td>Renal infarction; leiomyomatous uteri</td>
<td>Normal</td>
<td>--</td>
<td>Ventricular fibrillation, hypertension with cardiac failure</td>
</tr>
<tr>
<td>W.L.C.</td>
<td>Congestion; multiple emboli; marked fibrosis; emphysema; inactive tuberculosis</td>
<td>Passive congestion; central lobular necrosis</td>
<td>Leiomyoma-esophagus (10x5x4 mm.)</td>
<td>--</td>
<td>Cavernous hemangiomata of lungs, (5 mm. diam.)</td>
<td>Anasarca; ascites</td>
<td>Pulmonary edema due to beriberi</td>
</tr>
<tr>
<td>H.R.</td>
<td>Infarctions, 2; congestion and edema, moderate</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Undetermined, cardiac failure</td>
</tr>
<tr>
<td>J.B.</td>
<td>Hydrothorax (700 and 400 ml.); lobular pneumonia, severe</td>
<td>Fatty infiltration; Congestion, acute</td>
<td>--</td>
<td>Pyelonephritis, acute and chronic; benign prostatic hypertrophy; Multiple areas of ependymomalacia</td>
<td>--</td>
<td>--</td>
<td>Lobular pneumonia</td>
</tr>
<tr>
<td>J.C.</td>
<td>Hydrothorax (700 and 1,100 ml.); emboli, multiple; infarctions, 3; congestion; pneumonia; lobular, early</td>
<td>Central lobular necrosis</td>
<td>--</td>
<td>Benign prostatic hypertrophy</td>
<td>Not done</td>
<td>Axillary vein thrombosis</td>
<td>Pulmonary emboli, lobular pneumonia, cardiac failure due to beriberi</td>
</tr>
<tr>
<td>C.B.</td>
<td>Congestion; lobular pneumonia</td>
<td>Fatty infiltration</td>
<td>--</td>
<td>Nephrosis, toxic</td>
<td>Cerebral edema and congestion</td>
<td>Peripheral edema; peripheral neuritis; slight edema and congestion</td>
<td>Lobular pneumonia, congestive cardiac failure due to beriberi</td>
</tr>
<tr>
<td>H.S.</td>
<td>Lobular pneumonia; congestion and edema</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Pulmonary edema, lobular pneumonia</td>
</tr>
<tr>
<td>H.M.</td>
<td>Hydrothorax (600 and 400 ml.); congestion; early pneumonia</td>
<td>Posthepatitic cirrhosis; chronic hepatitis</td>
<td>Chronic pancreatitis, interstitial; gastric ulcer, active, penetrating; cholelithiasis, chronic</td>
<td>Hydronephrosis, left; pyelitis, acute</td>
<td>--</td>
<td>--</td>
<td>Congestive cardiac failure due to beriberi</td>
</tr>
</tbody>
</table>
THIAMINE DEFICIENCY

In the cases described, fibrosis was not a significant feature of the chronic form of the disorder. The absence of fibrosis was certainly significant in the 4 cases with prolonged cardiac failure. Follis stated that severe cardiac alterations may be produced by thiamine deficiency in swine. These lesions consisted principally of necrosis that healed by scarring if thiamine was restored to the diet. Benchimol and Schlesinger indicated that the myocardial damage in human beriberi was usually reversible in its initial stages. They believed, however, that in cases of long standing, the changes might be permanent and be characterized by progressive myocardial fibrosis. This fibrosis, however, could be similar to, if not identical with, that seen in other forms of heart disease. Weiss stated that the myocardium could develop hypertrophy, "hydropic" degeneration, and interstitial deposition of collagen. He implied that prolonged thiamine deficiency could cause progression from an easily reversible to an irreversible condition. It is possible that scarring of the heart associated with beriberi may be the result of coexistent diseases such as coronary insufficiency. Hydropic degeneration and interstitial collagenization and edema are common in beriberi heart disease, but they are by no means specific. As noted above, they are present with equal prominence in a variety of other cardiac conditions and in normal hearts as well.

Therefore, it appears that human beriberi heart disease is largely a biochemical abnormality affecting the myocardium without inducing necrosis or other pathognomonic lesions. In each instance the patient manifested cardiac failure for which neither inflammatory, vascular, nor valvular lesions were responsible, thus justifying the designation "myocardosis." Any tissue is relatively limited in its morphologic responses to injury. Identical alterations may be encountered as a result of damage stemming from many different causes. Therefore, it is not surprising that a specific pathologic array does not present itself for beriberi heart disease.

Figure 4
Section of heart from a patient with no known cardiac abnormalities. It demonstrates a striking similarity to figures 1, 2, and 3. (H & E stain, × 160.)

Figure 5
Microscopic appearance of heart muscle in a patient dying with coronary occlusive disease. Many of the features noted in beriberi are also present. (H & E stain, × 160.)
Since only 1 patient among those studied had adequate therapy for beriberi, followed by recurrence of the ailment, this study is inadequate to indicate the effect on the heart of treated but recurrent beriberi. However, in view of the absence of significant pathologic lesions in untreated cases of prolonged duration, it seems unlikely that such damage would occur in treated but recurrent beriberi.

Summary and Conclusions

Eight patients with clinically recognizable chronic thiamine deficiency and beriberi heart disease were investigated from a pathologic point of view in an effort to establish the presence and the extent of characteristic morphologic stigmas. In these cases there were no pathognomonic cardiac alterations at necropsy. Individuals with cardiac failure of short duration and those with prolonged heart failure manifested identical pathologic lesions.

It is concluded that beriberi heart disease is largely the result of a reversible biochemical abnormality and is not characterized by necrosis, fibrosis, or other irreversible damage to the myocardium, even after prolonged periods of cardiac failure.

Summario in Interlingua

Octo patientes con chronic carentia de thiamina de clinicamente recognoscibile severitate e morbo cardiac de beriberi esseva investigate ab un puncto de vista pathologie con le objectivo de estableir le presentia e le intensitate de characteristic stigmas morfoligique. In iste casos nulle alterationes cardiacae de character pathognomonic esseva constatate al necropsia. Individuus con decompensation cardiacae de breve duration e individuus con decompensation cardiacae prolongate manifestava le mesme lesiones pathologie.

Es concludite que morbo cardiac de beriberi es in grande mesura le resultato de un reversible anormalitiae biochemical e es characterize con necrose ni per fibrose o altere irreversibile stigmas del myocardio, mesmo post prolongate periodos de discompensation cardiacae.

References

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