Thiamine Deficiency in Organic Heart Disease

By Michael G. Wohl, M.D., Charles R. Shuman, M.D., Richard Turner, M.D., and John J. Fittipaldi, Jr., M.D.

Since cocarboxylase, derived from thiamine, is necessary for normal utilization of pyruvate by heart muscle, the importance of adequate body stores of thiamine in patients with chronic heart disease is quite obvious. In order to investigate the occurrence of subclinical thiamine deficiency in patients with chronic heart disease, the thiamine was determined in the four-hour specimen of urine after loading dose in 33 male patients with congestive heart failure and compared with thiamine excretion in 17 persons free from cardiase disease. It was found that the noncardiac group had a significantly higher excretion of thiamine after a loading dose than patients with heart disease. Nine patients with severe heart failure receiving mercurial diuretics in the course of treatment were studied using 24-hour urine collections before, during and after the injection of the mercurial. The 24-hour urinary thiamine content was measured, demonstrating significant increases in thiamine excretion with mercurial diuresis.

That thiamine deficiency may be a primary cause of serious cardiac disturbances is well established. However, it is not generally recognized that organic heart disease, per se, constitutes a conditioning factor in the development of thiamine deficiency. Such a possibility fits in quite well with the symptoms and signs accompanying chronic heart disease. These include anorexia associated with congestive failure or drugs used in its treatment, venous stasis of the gastrointestinal tract and hepatic congestion and dysfunction. All these are factors of cardinal importance in restricting the intake of food rich in thiamine and/or impairing absorption and utilization of thiamine. Another factor which may further deplete the already decreased stores of thiamine in the body is the conventional use of mercurial diuretics in patients with chronic heart disease. Since cocarboxylase derived from thiamine is essential for normal utilization of pyruvate by heart muscle, the clinical importance of inadequate thiamine stores is quite obvious. Therefore research was recently initiated on certain phases of thiamine metabolism in persons with chronic heart disease. This preliminary communication deals with the incidence of subclinical thiamine deficiency in patients hospitalized for treatment of cardiac failure. The effect of mercurials on thiamine excretion will be briefly summarized here. Details of this study will be reported elsewhere. Other phases of a larger study of this problem will be reported on from time to time.

For determination of subclinical thiamine deficiency, the method of Hochberg and Melnick was chosen as the most convenient, and it compares favorably with the procedure used by Robinson, Melnick and Field.

Method and Material

The method for determination of thiamine in the urine is based on the reaction between the vitamin and diazotized aminoacetoephone as developed by Melnick and Field and Melnick and Hochberg.

The thiamine excretion was determined on a four hour urine specimen from persons who had had no food for 12 hours and who received 0.35 mg. of thiamine per square meter of body surface intramuscularly. In many of the patients the determination of thiamine was performed in duplicate. According to Hochberg and Melnick, when a person excretes in four hours less than 100 micrograms of thiamine after the load test, thiamine deficiency is present. The four hours urine method was employed for two reasons. First, some difficulties were encountered in getting accurate 24 hour urine collections on patients in a general medical ward, and second, it has been shown that when thiamine is administered parenterally most of the total amount excreted is found in the first four-hour urine sample.

Thirty-five male patients were selected from the medical wards of the Philadelphia General Hospital. The patients were hospitalized for treatment of cardiac failure. The causes leading to cardiac failure were hypertension, arteriosclerotic coronary artery...
disease, and rheumatic heart disease. Alcohol addicts and patients with disorders known to lead to avitaminosis were eliminated from the study.

The ingested daily diet of the patients contained on the average 0.9 mg. to 1 mg. thiamine and provided 1800 to 1900 calories. The calculations were based on tables compiled by Bowes and Church. The patients were on such a diet for a period of 10 days prior to the thiamine clearance determination. An effort was made to have the patients under study consume the daily allowed food. However, in some instances a portion of the food was not eaten. We are fully aware that this factor may contribute to low levels of thiamine excretion. But the validity of the results of the over-all study is not impaired since our object is to evaluate the status of thiamine nutrition in cardiac patients as they are observed in a general hospital under the ordinary hospital care. The food intake of our patients represents probably the usual dietary experiences of hospitalized cardiac patients. Supplementary vitamins were discontinued for six days prior to and during the study. Digitalis was continued; mercurial diuretics, however, were omitted for six days prior to and during the study.

**Controls.** Seventeen persons free from cardiac disease served as controls. Thirteen were hospitalized patients of similar age and sex distribution as the cardiac group; they were served the same food as the cardiac patients and did not receive supplemental vitamins; four subjects in the control group were interns; their diet was more liberal and contained on the average 1.2 mg of thiamine and 2000 to 2200 calories.

**The Effect of Mercurials on Thiamine Excretion**

The effect of mercurial diuresis upon thiamine excretion was investigated in a group of nine patients with chronic congestive heart failure. Each of these had been under treatment with digitalis, mercurials, and salt restricted diets for periods ranging from six months to four years; most of these patients had been given supplemental vitamins during the treatment period. Included in the group were five patients with hypertensive heart disease, three with arteriosclerotic heart disease, and one with mitral stenos's. Prior to the collection of urine, vitamin supplements and mercurials were stopped and the majority of patients were maintained on a 1800 calorie diet providing approximately 1.0 mg. of thiamine daily. After several days on this preparatory regimen and prior to mercurial injections the 24 hour urine collections were made as control for the urine collections obtained on the day of the mercurial and the day immediately following the mercurial (Thiomerin or Mercuhydrin, 2 cc. intramuscularly). The daily urine samples were measured, a 200 cc. aliquot was acidified and kept refrigerated until the thiamine determinations were made by the method described.

The data were analyzed to determine whether any relationship existed between the volume of urine and the urinary thiamine content, the volume of urine excreted on control days and the days of mercurial injection as well as the day following the mercurial. The principal interest of this phase of the study centered about the comparison of the thiamine excretion in absolute terms as well as in micrograms per cubic centimeter between the control and mercurial periods. The results are reported in table 3.

**Results**

Table 1 and figure 1 present results of the four-hour thiamine clearance in both cardiac patients and control subjects. The mean for the 35 cardiac patients was 40.6 micrograms with a standard deviation of 24.9 micrograms; the mean for the 17 control subjects was 139.5 micrograms with a standard deviation of 73.5 micrograms. The difference between the means was tested by means of the t test, which showed a probability of less than 0.001. Hence it may be concluded that noncardiac subjects have a significantly higher mean excretion of thiamine than cardiac cases. The difference between variances was tested by means of the F test, which showed a probability of less than 0.001. If all subjects are kept, this would mean

<table>
<thead>
<tr>
<th>Microgram/4 Hrs.</th>
<th>Number of Cases</th>
<th>Percentage of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Cardiac Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-24</td>
<td>9</td>
<td>25.7</td>
</tr>
<tr>
<td>25-44</td>
<td>15</td>
<td>42.9</td>
</tr>
<tr>
<td>45-64</td>
<td>3</td>
<td>8.6</td>
</tr>
<tr>
<td>65-84</td>
<td>6</td>
<td>17.1</td>
</tr>
<tr>
<td>85-104</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control Male Noncardiac Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-89</td>
</tr>
<tr>
<td>90-109</td>
</tr>
<tr>
<td>110-129</td>
</tr>
<tr>
<td>130-149</td>
</tr>
<tr>
<td>150-169</td>
</tr>
<tr>
<td>170-189</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
that noncardiacs are significantly more variable than cardiac cases (table 2).

It was noted, however, that two noncardiac subjects were "unusual" in that they contributed an excessive proportion of the total variance. When these two subjects (with values of 250.8 and 379.3 micrograms) were eliminated, the mean for the 15 remaining non-
cardiac subjects was reduced to 116.1 micrograms and the standard deviation to 30.4 micrograms. This mean was still significantly higher than the mean for cardiac patients (probability of $t$ less than 0.001), but the variance for the noncardiac group did not differ significantly from that of the cardiac group (probability of $F$ greater than 0.05). From table 1 and figure 1 it becomes apparent that the lowest thiamine excretion of the 68.6 per

cent of the cardiac patients ranged in four hours from 4.5 to 44.5 micrograms, while the lowest values of the 66.6 per cent of the control noncardiac patients ranged from 69.5 micrograms to 129.5 micrograms of thiamine.

In 12 other cardiac patients and seven control subjects both the fasting thiamine excretion and the four-hour urinary excretion after the test dose of thiamine were determined. The fasting urinary thiamine in the cardiac patients varied between 7 micrograms and 57.6 micrograms. The higher excretion levels were in the females. In the control cases the fasting thiamine excretion varied between 33.5 micrograms and 119.9 micrograms.

It is not definitely known whether the amount of urinary thiamine excreted after an intramuscular load test, or, for that matter, the blood thiamine level is a valid measure of tissue storage of the vitamin. However, the extremely low urinary levels in our cardiac patients tend to indicate that the nutritional status of the patients with respect to thiamine was subnormal. There is cogent evidence to suggest that a marked subnormal thiamine status is associated with thiamine tissue depletion. It is to be noted that there were marked individual differences in the urinary thiamine excretion. However, the four-hour thiamine excretion in the same individual tended to remain on the same low level from day to day while the four-hour urinary excretion in the control group varied considerably among individual patients and in the same individual from day to day. The number of cases in which fasting urinary thiamine excretion was determined is too small to permit any conclusions. A larger number of determinations may prove it to be a good routine laboratory screening test. This agrees with the conclusions of Lowry. Daily fluctuations of thiamine excretion are much smaller when thiamine intake is low than when thiamine intake is high. The chances of misdiagnosing thiamine deficiency on a one-day excretion are therefore also less.

**Effect of Mercurials on Thiamine Excretion**

The results of the thiamine excretion studies as affected by mercurial treatment were of
considerable interest. It was initially determined that among individuals there was no evidence that a high volume of urine was associated with an elevated absolute amount of thiamine in the urine. It is to be noted that on the day of mercurial administration and the following day the mean volume of urine was 1374 cc. and 1557 cc., respectively; the mean volume of the urine on the control day was 847 cc. Thus it is apparent that the mean volume of urine during mercurial administration was significantly greater than on the control day (the probability of \( t \) equals less than 0.01 and 0.02, respectively).

### Table 3.—The Mean Urinary Thiamine Excretion and Urine Volumes for Nine Patients During Control Periods and Following Administration of Mercurial Diuretics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Control Day</th>
<th>Day of Mercurial</th>
<th>Day Following Mercurial</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. M.</td>
<td>280.7</td>
<td>500</td>
<td>.561</td>
</tr>
<tr>
<td>E. R.</td>
<td>86.9</td>
<td>1260</td>
<td>.069</td>
</tr>
<tr>
<td>S. G.</td>
<td>54.1</td>
<td>1035</td>
<td>.049</td>
</tr>
<tr>
<td>F. B.</td>
<td>247.4</td>
<td>370</td>
<td>.669</td>
</tr>
<tr>
<td>M. M.</td>
<td>156.4</td>
<td>1290</td>
<td>.121</td>
</tr>
<tr>
<td>S. S.</td>
<td>91.1</td>
<td>858</td>
<td>.106</td>
</tr>
<tr>
<td>V. M.</td>
<td>61.0</td>
<td>700</td>
<td>.087</td>
</tr>
<tr>
<td>J. M.</td>
<td>213.4</td>
<td>450</td>
<td>.054</td>
</tr>
<tr>
<td>L. M.</td>
<td>211.8</td>
<td>1102</td>
<td>.192</td>
</tr>
<tr>
<td>Mean of all subjects</td>
<td>134.9</td>
<td>847</td>
<td>.212</td>
</tr>
</tbody>
</table>

As to the effect of mercurial therapy on thiamine excretion, the results recorded in table 3 indicate that on the day of mercurial administration the mean value of thiamine excretion was 403.2 micrograms per 24 hours and the following day 419 micrograms per 24 hours as compared with the mean value of 134.9 micrograms per 24 hours for the control days. The probability of \( t \) for these values was 0.01. However, the mean concentration of thiamine per cubic centimeter of urine was not significantly different when mercurials were administered as compared with control values.

The difficulties encountered in collecting 24-hour urine specimens necessary for this study are appreciated. However, if collection errors were randomly distributed throughout the groups, the largest losses should have occurred in those periods wherein urine volumes were greatest. This gives added significance to the thiamine losses observed during and immediately after the mercurial administration. The data demonstrate that marked urinary excretion of the water soluble vitamin occurred as a result of the mercurial diuresis.

### Discussion

There are several references in the literature to the occurrence of thiamine deficiency in hospital patients in England and in this country. However, records of studies on thiamine deficiency in cardiac patients are limited and do not provide a basis for statistical treatment. Goodhart and Sinclair, using the amount of the coenzyme determined in the blood as a method for estimating thiamine deficiency, found significantly low values in 6 out of 13 subjects with cardiac failure. One diabetic patient with congestive heart failure had a low value (1.0 microgram) of coenzyme which increased considerably (5.5 micrograms) after therapy with vitamin B₁₂.

In this country Robinson and co-workers found excretion of thiamine less than 7 per cent of an oral 5 mg. test dose in six out of seven patients with cardiac decompensation. These low excretion values were interpreted as indicating thiamine depletion. Goldsmith, using the lactate-pyruvate ratio as a method of determining thiamine deficiency, found low...
lactate-pyruvate ratios in four out of nine patients with heart disease and considered this to be indicative of thiamine deficiency. The reports of these investigators and our findings suggest that thiamine deficiency in association with cardiac disease is more than a coincidence.

The question arises as to the factors responsible for the thiamine deficiency in patients with chronic heart disease. Doubtless there are many reasons for it. It is quite likely that the anorexia and low thiamine intake in the diet play an important role.

Another factor involved in disturbed thiamine metabolism is the anoxia associated with heart disease. Anoxia of the intestinal tract because of passive congestion may interfere with absorption of the small amount of thiamine supplied by the inadequate food intake. A further cause of thiamine depletion in chronic cardiac disease is probably the conventional use of mercurial diuretics. Although mercurial diuretics are most effective in controlling edema of congestive heart failure, their effect upon excretion of thiamine has not been generally appreciated. Williams and Bissell\textsuperscript{14} observed marked urinary loss of thiamine following injection of Mercuphyline in two patients with congestive heart failure. Our results tend to demonstrate that the levels of thiamine excretion following administration of mercurials are significantly increased over the levels observed on the control days. Because the over-all analysis does not reveal a direct correlation between urine volume and urinary thiamine concentrations, we are led to suspect that the loss of thiamine occurs as a result of the influence of the mercurial diuretics upon the renal tubular mechanism for thiamine reabsorption. The lack of a satisfactory method for measurement of blood thiamine renders the study of renal mechanism for thiamine excretion difficult.

The patients considered in these studies did not manifest clinical signs of thiamine deficiency. The probable explanation for the absence of clinical findings of vitamin B\textsubscript{1} deficiency is the fact that in patients of the type used in this study the caloric intake is generally reduced to a level at which subnormal thiamine supplies may be adequate for non-appearance of gross clinical manifestations. Furthermore, there is a possibility that thiamine deficiency may occur in the cardiac muscle, since it is peculiarly sensitive to deprivation of thiamine,\textsuperscript{14} whereas other organs may be free of that deficiency. Investigation of this problem is indicated.

**Summary**

Thirty-five patients under treatment for chronic heart failure were given loading doses of thiamine, using 0.35 mg. per square meter of surface area, following which the four-hour urinary thiamine content was measured by the method of Hochberg and Melnick. Seventeen control subjects selected from patients with noncardiac disease whose nutritional status was good or from the hospital personnel were studied by the same method. The mean thiamine excretion of the group with congestive heart failure was 40.6 micrograms with a standard deviation of 24.9 micrograms. The mean excretion of the control group was 139.5 micrograms with a standard deviation of 73.5 micrograms. Statistical analysis of the data indicated that the noncardiac group had a significantly higher excretion of thiamine after a loading dose than the patients with heart disease.

Nine patients with severe heart failure who were receiving mercurial diuretics in the course of treatment were studied, using 24-hour urine collections before, during and after the injection of the diuretic. The 24-hour urinary thiamine content showed significant increases in thiamine excretion with mercurial diuresis.

**Acknowledgments**

We are indebted to Dr. H. Menduke for statistical treatment, Mr. Martin Brody for technical assistance, Drs. Henry P. Schwarz and Carl Alper for advice and supervision of the laboratory work, Miss Elizabeth Blake for dietetic assistance and Drs. Thomas Durant, William G. Leaman and David Kremer for permission to use their clinical material.

**SUMARIO ESPAÑOL**

Como la cocarboxilasa derivada de la tiamina es necesaria para la utilización normal del piruvato por el miocardio, la importancia de las reservas de tiamina del cuerpo en pacientes...
con enfermedad crónica cardíaca es muy obvia. Para poder investigar la incidencia de deficiencias subclínicas de tiamina en pacientes con enfermedad cardíaca crónica, el nivel de tiamina se determinó en especímenes de orina a las cuatro horas de habersele dado a 35 pacientes varones con decompensación cardíaca una dosis de carga y comparando la excreción de tiamina con la de 17 personas libres de enfermedad cardíaca. Se encontró que el grupo no cardíaco tuvo una excreción de tiamina significativamente más alta luego de la dosis de carga que los pacientes con enfermedad cardíaca. Nueve pacientes con decompensación cardíaca severa recibiendo diuréticos mercuriales durante el curso del tratamiento, fueron estudiados usando la colección de orinas por 24 horas antes, después y luego de la inyección del mercurial. El contenido de tiamina en el especimen de orina de 24 horas se determinó, demostrándose un aumento significativo en la excreción de tiamina con la diuresis mercurial.

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