4. Some Problems upon the Interrelationship between Wuhrmann's Myocardosis and Hegglin's Syndrome with the Special Reference to their Clinical and Pathological Diagnosis

YOSHIKI INAGAKI
[The 2nd Clinical Department of Internal Medicine (Director: Prof. Dr. Soroku Saitoh), School of Medicine, Chiba University]

KIYOSHI TERAO
[Department of Pathology (Director: Prof. Dr. Nobujiro Takizawa), School of Medicine, Chiba University]

Based upon the clinical cases which were fully examined in our laboratories since these ten years, the problem of overlapping of Wuhrmann's myocardosis and Hegglin's energetic-dynamic heart insufficiency was studied not only on the clinical date intra vitam, but also on the pathologic findings.

A. CLINICAL OBSERVATIONS

evaluation of prognosis but also as a direct cause of death due to cardiac insufficiency.

Abnormal electrocardiographic findings in hepatic diseases are more closely related to dysproteinemia than to dyselectrolytemia.

The occurrence of a positive anoxia test is high in hepatic diseases and it is second only to coronary disease. Moreover, the anoxia positive rate was as high as 28% in the group with normal electrocardiograms at rest.

It can be considered that the origin of a positive Levy's test in hepatic disease is due more to dysfunction of myocardial oxygen uptake than to a dysability of coronary vascular reaction.

Acknowledgement
The author wishes to express sincere gratitude to Prof. K. Hara for his guidance.

REFERENCES
liver disease group consisted of 7 cases of hepatitis (15 observations), 9 of cirrhosis (16 observations) and 15 of hepatoma (24 observations). Almost simultaneously observations were aided by Tissellius' electrophoretical determination of plasma protein fraction, Beckmann's flame photometric analysis of serum electrolytes, metabolic electrocardiographical analysis by Wuhrmann-Niggli and cardio-vascular dynamical analysis by Blumberger-Holldack's and Wezler's methods.

According to the criteria of the Japanese Electrophoresis Society, the grades of dysproteinemias were classified as follows: (+) meant the patients whose albumin fraction was less than 50%; (++) cases whose albumin fraction from 40 to 50% and β-globulin fraction from 20 to 30%; (+++), cases of the more advanced hypoalbuminemia and hyperglobulinemia. In addition to this, decrease in the total protein (Hypop-roteinemia) was also expressed as (+) in this paper. The patients with paraproteinemia were all excluded.

Fig. 1 shows the relationship between the ratio TH/B by Wuhrmann-Niggli's metabolic electrophersis and the grades of dysproteinemias. As dysproteinemias was advanced, proportional increase of the signs of diffuse myocardial metabolic disturbances (Wuhrmann-Niggli) was observed, i.e. the cases of the ratio TH/B less than 1 or 0.5, was increased in their number. It was examined if the change of these values could be related to the presence of dyselectrolytemia in 66 observations, in which protein-fractions and electrolytes in serum were simultaneously determined. As shown in Tab. I, the patients with dyselectrolytemia in the dysproteinemias groups from (−) to (+++) revealed the ratio TH/B less than 1.0 or 0.5 in relatively higher percent age. Such a tendency, however, could not be found in the more advanced (+++) and (++++) dysproteinemias group. Judging from the above results, the decrease in the ratio TH/B appeared to be affected by the presence of dyselectrolytemia as well as the extent of dysproteinemias. However, diagnostic reliability of the ratio TH/B was limited to a certain extent and should be carefully evaluated, especially in the conditions of hyperpotassemia, as Ogawa reported.

The relationship between the extent of dysproteinemias and the time difference of QT-QII was studied. As dysproteinemias was progressed, the percentage of the difference QT-QII more than +20σ (shown in Fig. 2 as the dotted and black parts of circles) appeared to increase in number, but in the cases with QT-QII longer than +40σ no definite tendency was found as seen in Fig. 2. The similar observations were performed under the presence of dyselectrolytemia about 120 times. As shown in Tab. 2,
TABLE II  DISPROTEINEMIA, DYSSELECTROLYTEMIA  
and QT-QII  
<table>
<thead>
<tr>
<th></th>
<th>QT-QII (σ)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 0</td>
<td>0~19</td>
<td>20~39</td>
<td>&gt;40</td>
<td></td>
</tr>
<tr>
<td>Dyselectrolytemia (+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;4&gt; &lt;4&gt;</td>
<td>n:14</td>
<td>29%</td>
<td>14</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>&lt;4&gt; &lt;4&gt;</td>
<td>n:31</td>
<td>36</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>&lt;4&gt; &lt;4&gt;</td>
<td>n:6</td>
<td>25</td>
<td>37</td>
<td>13</td>
</tr>
<tr>
<td>Dyselectrolytemia (-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;4&gt; &lt;4&gt;</td>
<td>n:8</td>
<td>64</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>&lt;4&gt; &lt;4&gt;</td>
<td>n:30</td>
<td>50</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>&lt;4&gt; &lt;4&gt;</td>
<td>n:9</td>
<td>45</td>
<td>22</td>
<td>33</td>
</tr>
</tbody>
</table>

the patients with the difference QT–QII above +20σ as well as +40σ were dominantly found in the groups complicated with dysselectrolytemia. These results persuaded us that the incidence of the patients with difference QT–QII longer than 20σ depended upon the presence of dysselectrolytemia more than that of disproteinemina.

Fig. 3. showed the summary of 44 cardio-vascular dynamical analyses of the cases of Wuhrmann’s myocardosis. The patients with QT–QII longer than +40σ, those with shortened QII and those with prolonged QT were found less than 50% of all the patients respectively. However, the normal cardio-vascular dynamics was found less than 40% of the patients.

II. About Hegglín’s energetic-dynamic heart insufficiency

Since 1937, Hegglín has emphasized the existence of a heart failure independent from the dynamic cardiac insufficiency, in which the myocardial energetic metabolism was severely disturbed; this type of heart failure was named by Hegglín as the energetic-dynamic heart insufficiency of which the characteristics consisted of prolonged QT and shortend QII. As a matter of fact, the further concrete diagnostic criteria could not be fully elucidated even in Hegglín’s original paper published in 1949 or in his hitherto reported literatures. In 1957, Jaeger examined his own 1100 cases basing upon Hegglín’s monograph issued in 1947, in which the criterion for the diagnosis of Hegglín’s syndrome was suggested as follows; the difference QT–QII should be longer than +40σ. At first we screened up 343 cases of disproteinemina or dysselectrolytemia according to this criterion. The cases of the difference QT–QII above +40σ and those +40σ cases with the absolutely prolonged QT were relatively frequent, i.e. they occupied more than 15% in the group of hepatic disease, malignant neoplasma or metabolic disorders respectively, whereas they were found less than 8% in the group of hypertension, coronary disease or valvular disorders. As a whole, those cases were seen nearly 13% in 343 patients. However some of those cases did not show the clinical signs and symptoms insisted by Hegglín, for example transitory dysselectrolytemia due to administration of chlorothiazide derivatives showed QT–QII abnormalities as well as the recovery state of acute nephritis. Therefore the definition of the literally energetic-dynamic heart insufficiency, in our opinion, demanded for its certain diagnostic criteria in evaluation of QII shortening. As shown in Fig. 4, the approximate formulae \( y = ax^\frac{1}{2} \) and \( y = b^x \) were assumed from the distribution of QII corresponding to RR intervals of 150 normal subjects. By means of the least square method the coefficients were calculated, and then, by means of the recurrent analysis the normal range of QII time

![Fig. 3. Cardiovascular Dynamics of 44 Observations with Wuhrmann’s Myocardosis](image)
PROBLEMS UPON INTERRELATIONSHIP BETWEEN WUHRMANN' MYOCARDOSIS & HEGGLIN' SYNDROME

was determined. From these results the formula
\[ y = 39.7 \sqrt{x} \pm 40 \sigma \] was obtained. The QT-formula was calculated by the same method on the same subjects and the formula QT = 12.41/RR ± 38σ was gained as shown in Fig. 5.

Actually, it was found entirely equal to Hegglin-Holzmann's QT-formula. The normal variations of QT calculated by Hegglin-Holzmann's and our formulae were ±40 and ±38 respectively. The difference between these two formulae was negligible. Therefore we thought our QII-formula credible, and the diminution of QII more than one half of 40σ (the standard deviation of QII-formula which had 68% of the reliability) was considered to be "absolute" shortening. About the same time when we were studying in 1959, Hegglin reported in Cardiology the standard of absolute diminishing of QII as the guiding remark of the energetic-dynamic heart insufficiency. Applying Hegglin-Holzmann's QT-formula he proved the measurement value of QT-QII less than 20σ as a temporal standard of the shortening. When judged the absolute shortening of QII by our QII-formula and the absolute prolongation of QT and clinical findings taken into account, 18 patients who satisfied the criteria of us only occupied 5% of the total observations. We considered these cases Hegglin's syndrome in the strict sense or the literally energetic-dynamic heart insufficiency. It might be necessary to separate these cases from Hegglin's syndrome in the broad sense because the criteria of the difference QT-QII longer than +40σ alone could include simple transitory Hegglin's syndrome.

SUMMARY

From the results above described, the overlapping of Wuhrmann's myocardosis and Hegglin's energetic-dynamic heart insufficiency was summarized in Fig. 6. The energetic-dynamic heart insufficiency was found in 5% of 343 cases. 78% of this 5% did not have the primary cardio-vascular diseases (Wuhrmann). 93% of this 78% were diagnosed as the myocardosis. On the other hand, Wuhrmann's myocardosis was found in 35% of 126 observations on the cases without primary cardio-vascular diseases. In 32% of this 35% the energetic-dynamic heart insufficiency was observed. Thus, the incidence of Wuhrmann's myocardosis was found more frequent than that of the energetic-dynamic heart insufficiency, which appeared in about one third of the former. On the other hand, the energetic-dynamic heart insufficiency was complicated with the myocardosis (Wuhrmann) in most cases.

B. PATHOLOGICAL OBSERVATIONS

The ventricular myocardium of 62 autopsied
cases, half of which showed Wuhrmann's myocardiosis and/or Hegglin's energetic-dynamic heart insufficiency, was examined on 9 portions (Fig. 7). Each specimen was fixed with formalin and stained with hematoxyline-eosin, PAS, Azan-Mallory, and also with phosphorus-tungsten acid-hematoxyline in some cases. Observation was mainly directed to some degeneration of myocardium. This degeneration has been well known as basophilic degeneration\(^3\) in hematoxyline-eosin staining since 1910 and was identified by Umeda\(^4\) with the mucoid degeneration in 1941. By hematoxyline-eosin staining, retention of basophilic substances was observed among myofibriles which seemed to be elbowed aside by the substances and nuclei showed markedly degenerative atrophy. These substances were also stained violett-red with PAS staining (Fig. 8). The number of this mucoid degeneration per unit area was calculated by measuring an area of each microscopic section. The upper column of Tab. III showed a mean

![Fig. 7] Schematic representation of a longitudinal and a transverse section of heart to show portions in which histological observation were made.

1. left Ventricular Wall
2. ant. Papillary Muscle of 1. Ventricle
3. post. Papillary Muscle of 1. Ventricle
4. right Ventricular Wall
5. ant. Papillary Muscle of r. Ventricle
6. post. Papillary Muscle of r. Ventricle
7. Ventricular Septum (transverse Section)
8. Ventricular Septum (longitudinal Section)
9. Apex

![Fig. 8] Mucoid Degeneration of Muscle Fibers
(PAS-reaction, ×400)

### Table III: Distribution of Mucoid Degeneration in Myocardium
(The upper column showed a mean value in each portion of 60 hearts.)

<table>
<thead>
<tr>
<th>Portion</th>
<th>Dysprotei- Hypopro- Myocardosis</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyrnemia</td>
<td>teinemia</td>
</tr>
<tr>
<td>Mean</td>
<td>6.2</td>
<td>6.0</td>
</tr>
<tr>
<td>1.2</td>
<td>83.3</td>
<td>87.0</td>
</tr>
<tr>
<td>3.4</td>
<td>162.4</td>
<td>177.6</td>
</tr>
<tr>
<td>5.6</td>
<td>10.9</td>
<td>46.7</td>
</tr>
<tr>
<td>7.0</td>
<td>4.6</td>
<td>18.7</td>
</tr>
<tr>
<td>9.1</td>
<td>305.0</td>
<td>223.9</td>
</tr>
<tr>
<td>6.2</td>
<td>100.0</td>
<td>120.0</td>
</tr>
<tr>
<td>3.4</td>
<td>41.5</td>
<td>78.3</td>
</tr>
<tr>
<td>5.6</td>
<td>40.0</td>
<td>114.6</td>
</tr>
<tr>
<td>7.0</td>
<td>38.8</td>
<td>109.5</td>
</tr>
<tr>
<td>9.1</td>
<td>35.0</td>
<td>25.6</td>
</tr>
<tr>
<td>I.S.</td>
<td>12.0</td>
<td>5.8</td>
</tr>
<tr>
<td>N.K.</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>H.K.</td>
<td>0.8</td>
<td>1.7</td>
</tr>
<tr>
<td>N.M.</td>
<td>1.1</td>
<td>5.3</td>
</tr>
<tr>
<td>K.Y.</td>
<td>0.8</td>
<td>1.7</td>
</tr>
<tr>
<td>U.K.</td>
<td>1.1</td>
<td>5.3</td>
</tr>
<tr>
<td>M.M.</td>
<td>0.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Numbers/cm²

---

*Japanese Circulation Journal Vol. 28, March 1964*
value in each portion of 60 out of 62 hearts. The lower column outlined a scattered determination in the older age (over 60 years). Two hearts of case I. S. and case N. M. were excluded from the statistics because of enormous deviation of the values. The mucoid degeneration was found more frequently in the left ventricle than in the right ventricle. The mucoid degeneration was found several times frequent in the patients over 60 years of age who had dys- and hypoproteinemia. All these cases were diagnosed intra vitam as Wuhrmann’s myocardosis. In the cases diagnosed free from myocardosis there existed no hypoproteinemia and the number of mucoid degeneration was less than the average. In other words, when a patient over 60 years of age was complicated with dysproteinemia and hypoproteinemia, the mucoid degeneration was considered to play a significant rôle on the occurrence of the myocardosis. The interstitium in these hearts were characterized by edema or the fibrosis of the adventitia of small arteries.

The relationship between the mucoid degeneration and the serum protein fractions was examined on 20 dysproteinemic cases above 50 years of age (Fig. 9). As a contrast, it was also findings for myocardosis except the mucoid degeneration has not ascertained yet.

Only 14.3% of the cases of energetic-dynamic heart insufficiency showed the mucoid degeneration more than the average (Fig. 10). The swelling of myofibriles and the lightening in color of perinuclear area were rather the frequent findings in the myocardium of energetic-dynamic heart insufficiency. One of the cases of energetic-dynamic heart insufficiency showed noticeable mantle-edema (Linzbach) in the right ventricle as well as in the intraventricular septum. “Lamellae Auflöckung” of the adventitia of vessels in the inerstitium described by Takizawa[6] was also observed in most of the cases. Furthermore, relatively acute interstitial edema was found in almost all the cases (Fig. 11).
**Summary**

The senile cases of myocardosis complicated with hypoproteinemia showed always the abundant mucoid degeneration in the myocardium. The cases of energetic-dynamic heart insufficiency showed the mucoid degeneration less frequently than those of the myocardosis, however, the former showed the more marked interstitial edema than the latter.

**References**


Discussion Fig. 1. U. K. 66, m. Cancer of Biliary Duct and Liver Metastasis

Discussion Fig. 2. U. K. 66, m. Cancer of the Biliary Duct with Liver Metastasis