Experimental Studies on the Beriberi Heart
III. Correct Treatment Doses of Thiamine for the
Beriberi Heart Disease and Effects of
Vitacampher and Norepinephrine

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With regards to treatment dosage of thiamine for beriberi heart
disease, there is no definite standard and in many papers there are great
differences in prescribing doses. But the doses of thiamine is an im-
portant problem when using thiamine as drug.

We carried on experimental studies in order to clarify this problem
by using thiamine deficient rats.

In our previous papers, we have reported on the cardiac lesions in thiamine
deficient rats and on the effect of starvation and role of vagus nerve. The
present paper is a report on the study with regards to treatment of beri-
beri heart.

There had been many experimental studies on the physiological thiamine
requirement in men and for a long time about 1 to 2 mg. has been com-
monly recognized as human requirement.

On the other hand, as regards the curative dosage of thiamine, in other
words, the thiamine dosage used as medicine, there is no definite standard

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Fig. 1. Repetition method of thiamine deficiency and cure.

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even today. In fact, although many textbooks\textsuperscript{4)-27)} concerning treatment doses show wide differences (several mg. to 400 mg.), most of them do not state the experimental or theoretical basis of such doses. Such wide difference as that in the thiamine treatment dose cannot be seen in prescriptions of any other medicines and as such we consider that this is an important problem that should be clarified.

Furthermore, from long ago it has been said that Epinephrine,\textsuperscript{4), 5), 28)} Digitalis and Strophantine\textsuperscript{4), 5), 15), 25)-33)} are practically ineffective for beriberi heart and no reason for it is given even today.

From the above points of view, experimental studies on the correct treatment doses of thiamine and effects of vitacampher and norepinephrine (heretofore have not been experimented with) were carried on.

**Methods**

1. To each group of rats in each week of thiamine deficient progress, vitacampher, norepinephrine and thiamine injections were given in the right fore leg and at every 10 to 30 min. thereafter electrocardiographic examinations were carried on for 60 to 240 min. to observe the effects of the injections.

2. In the experiment to study the correct treatment dosage of thiamine we used repetition method (thiamine deficiency, cure and repeat) as shown in Fig. 1. The rats in the final stage of thiamine deficiency were divided into 4 groups of thiamine injection; 0.05 mg., 0.1 mg., 0.2 mg. and 0.5 mg. To each group the respective prescribed dosage of thiamine was injected once (intramuscularly) and thereafter the general thiamine deficient symptoms and electrocardiographic findings\textsuperscript{1)} were observed on the 24th, the 48th hours, the recovery progress and then on the 2nd time deficiency progress at intervals of 1 to 3 days. At the end stage of the 2nd thiamine deficiency same injection dosage was given and foregoing observations were carried on. The above experiments were repeated again and again.

The single injection method was adopted because the rats die in about 24 hours if the injection was ineffective as the injection is given at the final stage of thiamine deficiency. In other words, whether the injection is effective or not (live or die) depend on this single injection.

When thiamine deficiency and single thiamine injection are repeated, some rats finally die inspite of thiamine injections in about 24 to 48 hours. That is, although the injections were slightly effective, they were insufficient as a cure and therefore the foregoing rats we have taken as ineffective cases of thiamine injection. Rats that died soon after the injection were excluded from data as experimental failure because the injection time was too late.

Therefore in this experiment the most important thing is to determine the end stage of thiamine deficiency owing to the fact that when rats are given thiamine injection at too early stage they all recover whereas they all die when given too late. With this in view the following chart was prepared:

(1) Food intake:
  great decrease, about 2 to 3 Gm. or less.
(2) General findings:
decrease in vitality, inactive, great decrease in body weight, hair becomes stained reddish brown here and there, marked paralysis of extremities.

(3) Electrocardiographic findings:
   extreme bradycardia (in 200ths or less), extreme abnormal pattern (block, ST and T-wave abnormalities).
   From these 3 items we decided the final stage of thiamine deficiency.

RESULTS

I. a) Effect of vitacampher injection:
In some rats in the 2nd to 4th week of thiamine deficiency there were slight increase in heart rate for about several minutes after injection, but there was no effect in electrocardiographic complexes.
   In some cases arrhythmia showed slight improvement 10 to 20 min.

Fig. 2. 23rd day of thiamine deficiency, 61.5 Gm., heart rate 91-80.

Fig. 3. 30 min. after vitacampher injection, rate 91-81.
after injection but in many cases no effect was observed.

No effect of injection was observed in rats after the 5th week of thiamine deficiency.

Marked effect was observed after thiamine injection when vitacampher showed no effect. Fig. 2 to 6 are one of the examples. Vitacampher showed no effect in extreme bradycardia and arrhythmia but when thiamine was injected 60 min. thereafter, arrhythmia began to improve after 30 min. and 90 min. after injection it disappeared. Bradycardia also greatly improved as time progressed.

b) Effect of norepinephrine injection:
In rats in each week of thiamine deficiency there were almost no effects on heart rate and on electrocardiographic changes after injection.

In some cases arrhythmia showed slight improvement 10 to 20 min. after injection but in many cases no effect was observed.

Marked effect was observed after thiamine injection when norepinephrine showed no effect. Fig. 7 to 10 are one of the examples. Norepinephrine showed no effect in extreme bradycardia, ST elevation and T-wave elevation but when thiamine was injected 60 min. thereafter, great improvement was observed 45 min. later and thereafter as time progressed marked improvement took place. Fig. 11 shows bradycardia, right axis deviation and negative T-wave. Norepinephrine showed no effect but when thiamine was injected

![Figure 7](image_url)

Fig. 7. 22nd day of thiamine deficiency, 54 Gm., rate 187.

![Figure 8](image_url)

Fig. 8. 10 min. after norepinephrine injection, rate 181.

![Figure 9](image_url)

Fig. 9. 30 min. after norepinephrine injection, rate 177.

![Figure 10](image_url)

Fig. 10. 45 min. after thiamine injection, rate 184.
60 min. thereafter, improvement began 30 min. later and negative T-wave became positive 60 min. after injection.

c) Effect of thiamine injection:

We have already reported a part of this problem in our previous paper. In cases of from the 2nd to 4th week of thiamine deficiency, bradycardia, arrhythmia and abnormal electrocardiographic changes (ST, T-wave abnormalities) began to improve 15 to 30 min. after thiamine injection and as time progressed there were marked improvements.

The following show some of the examples; Fig. 12 and 13 show ST elevation and slight bradycardia. Fifteen min. after thiamine injection (1 mg.),
Fig. 14. 20th day of thiamine deficiency, 76.5 Gm., rate 273.

Fig. 15. 2 hours after thiamine injection (0.5 mg.), rate 410.

Fig. 16. 29th day of thiamine deficiency, 75.5 Gm., rate 242–210.

improvement began and 60 min. after ST became normal. Fig. 14 and 15 show bradycardia, ST depression and negative T-wave. Thirty min. after thiamine injection (0.5 mg.) improvement began and 2 hours after these
became almost normalized. Fig. 16 and 17 show bradycardia, arrhythmia, ST elevation and T-wave elevation. Two hours after thiamine injection (0.5 mg.) these became almost normalized. Fig. 18 to 20 show bradycardia and
ventricular premature beat. Fifteen min. after thiamine injection (0.2 mg.) there was marked improvement and ventricular premature beat disappeared 30 min. after injection.

Fig. 21 to 23 show a case in which the approximate normal requirement dosage of thiamine (2.5 µg.) was administered orally in thiamine deficient rats. Some improvements in bradycardia and arrhythmia were observed after 24 hours but 48 hours later again became worse. That is, the foregoing dose was good to certain extent for one day only.

As mentioned above in rats from the 2nd to 4th week of thiamine deficiency for the first time, marked effect was always observed by administration of various doses of thiamine (1 to 0.0025 mg.).

In cases of after the 5th week of thiamine deficiency, there were some that recovered rather quickly after injection while some showed great improvement on the 2nd day.

In cases in which they were greatly emaciated in the final stage of thiamine
Fig. 22. 24 hours after oral administration of thiamine (2.5 µg.), rate 409.

Fig. 23. 48 hours after thiamine administration, rate 346–325.

Fig. 24. 30th day of thiamine deficiency, 79 Gm., rate 136–97.
injection (even a large dose) was ineffective. Fig. 24 to 26 are one of the examples. Thiamine injection (1 mg.) showed almost no effect in extreme bradycardia, arrhythmia and flat T-wave 30 min., 1, 2 and 3 hours later and after 4 hours the rat died showing ventricular automatism. From the foregoing experiments it was found that if thiamine injection was given too late it was ineffective for thiamine deficient heart failure.

II. Treatment doses of thiamine (experiments in repetition method of thiamine deficiency and cure):

a) Thiamine 0.05 mg. injection group:

Most rats died after the 3rd injection as it had no curative effect as shown in Fig. 27. Fig. 28 is one example in which the rat recovered the most number of times in this group but finally died after the 5th injection. In both figures the number of days of effectiveness of 0.05 mg. injections decreased as injections were repeated.
Fig. 27. 0.05 mg. injection.

Fig. 28. 0.05 mg. injection.

Fig. 29. 0.1 mg. injection.
b) Thiamine 0.1 mg. injection group:
Effectiveness was almost the same as in the (a) group. All rats died after the 3rd to 4th injections. Fig. 29 is one of the examples.

c) Thiamine 0.2 mg. injection group:
In many rats injection was not effective after the 4th injection but there were 3 rats (33%) that recovered after the 5th injection. Fig. 30 is a case in which the 4th thiamine injection was ineffective. Here, the number of days of injections decreased as injections were repeated. Fig. 31 is a case in which the 5th thiamine injection was also effective. Here, the number of days of effectiveness of injections did not decrease as injections were repeated. And as injections were repeated body weight increase gradually improved. (However, the end stage came when the body weight was at a rather high level.)

d) Thiamine 0.5 mg. injection group:
Table I. Thiamine Dosage of Single Injection, Number of Times of Injection, Number of Deaths

<table>
<thead>
<tr>
<th>Injection frequency (mg.)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Over 8</th>
<th>Total case</th>
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<tbody>
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<td>0.05</td>
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<td>4</td>
<td>2</td>
<td>1</td>
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<td>10</td>
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<td>0.1</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>0.2</td>
<td>2</td>
<td></td>
<td>4</td>
<td>3*</td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
<td>2**</td>
<td>1</td>
<td>6***</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

* killed for histological examination. ** deaths owing to abscess. *** 5 were killed for histological examination.

In most rats thiamine injection was effective for more than 6 times. However 2 rats died after the 4th injection owing to abscess caused by high summer temperature. In this group there were 2 subgroups. In one group in which there were more rats as injections were repeated, body weight increase gradually improved as shown in Fig. 32. In the other group inspite of repetition of injections there were almost no changes in body weight increase as
shown in Fig. 33. Rats of both groups were kept for more than 6 to 8 months.

Table I shows the frequency of thiamine injections and number of deaths in each group.

**DISCUSSION**

I. a) Vitacampher injections:

Clinically vitacampher is sometimes used as stimulant in cases of acute cardiac weakness. The ineffectiveness of camphor for beriberi heart has been known clinically from long ago but as there is no report on vitacampher (vitacampher is a more effective derivative of camphor) we have studied on the effect of vitacampher on it experimentally.

As stated above although vitacampher had hardly any effect on the electrocardiographic changes of thiamine deficient rats marked effect was observed when thiamine was injected in them. From this, it became clear experimentally that vitacampher like camphor is hardly effective for beriberi heart.

b) Norepinephrine injections:

It has been known from long ago that epinephrine is not only ineffective but sometimes worsens beriberi heart and should not be used clinically. Moreover there is an experimental report that epinephrine had no special effect on electrocardiographic changes in thiamine deficient rats. On the other hand, as there is no report on norepinephrine, we have studied the effect of norepinephrine experimentally.

As stated above although norepinephrine had hardly any effect on the electrocardiographic changes of thiamine deficient rats marked effect was observed when thiamine was injected in them. From this result, it became clear experimentally that norepinephrine is hardly effective for beriberi heart.

C) Thiamine injections:

There are some reports that yeast extracts or thiamine have marked effect on bradycardia and electrocardiographic changes in thiamine deficient animals but most of these experiments were carried on only on one stage (when bradycardia was at medium degree) and not on the whole stage of thiamine deficient progress or on various degrees of deficiency. Furthermore, the effectiveness of the various doses of thiamine had not been investigated in these experiments. Accordingly these experiments did not clearly show the relation between the difference of thiamine effect and difference of thiamine deficient degree (the fact that when thiamine deficient degree is light thiamine effect is marked and when thiamine deficient degree is heavy thiamine effect is slight) and the correct curative dosage depends on the degree of deficiency symptoms.
Therefore we have experimented on the effect of various doses of thiamine on the thiamine deficient rats every week of the deficient progress and at their final stage. As stated above each dose of thiamine had marked effect up until the 4th week of deficiency but after the 5th week in some rats it has immediate effect whereas in others it was slow. In greatly emaciated rats in the end stage each dose showed no effect.

From these findings, it became clear that the effect of thiamine for thiamine deficient cardiac failure depends on the time of injection. That is, thiamine effect is connected with degree of thiamine deficient cardiac lesions. Furthermore, from speed of recovery, it could be considered that electrocardiographic changes in thiamine deficient rats are mainly due to functional (biochemical) disturbances until the 4th week, whereas the changes thereafter are mainly due to organic (histological) disturbances. This quite agreed with the histological findings we have previously observed that myocardial degeneration occurs after the 5th week.1)

Thiamine given at the stage of mainly functional disturbances showed marked effect whereas thiamine given at the stage of organic disturbances showed almost no effect. These experimental results are well applicable to human cases. For example, thiamine has marked effect on cases such as, human thiamine deficient experiments,4),5),41)-47) infantile beriberi,4),5),28),29),48)-50) or new beriberi in adults for the first time.4),5),28)-30),51)-56) On the other hand, in cases where men have died owing to ineffectiveness of thiamine, histologic myocardial changes are observed,4),5),28),29),32),57)-60)

In the Western countries, "thiamine administration is effective" is generally accepted as one of the diagnostic standards of beriberi heart.30)-32),50),51),53),55)-63) Although it is said that it must be used carefully, the foregoing our findings reveal clearly that it should be applied with much caution. In other words, when thiamine is effective the cardiac failure can be
diagnosed right away as beriberi heart but just because thiamine is ineffective it is not always correct to rule out beriberi heart.

Next, when approximate normal requirement dosage of thiamine was given to thiamine deficient rats it had some effect for only one day but when 1 mg. of thiamine was injected once the effect was marked and continued for about 2 weeks in all cases (Fig. 34). This gave the experimental basis for clinical usage of thiamine that the larger the dose the more effective it is than normal requirement dose. Details on this is given in the next chapter of treatment dosage of thiamine.

II. Correct treatment dosage of thiamine for the beriberi heart:

As mentioned in the preface there is as yet no clear criteria in the usage of thiamine for beriberi heart, only a general idea that a small dose may be used for mild case and a large dose may be used for severe case. As such there is a wide difference in the practical prescription of thiamine usage.

The textbooks\textsuperscript{4-11} that prescribe small dosage (several mg. to few tens mg. daily) are mainly based on thiamine deficient experiments on animals and humans and on mild human beriberi. In fact, in thiamine deficient experiments on animals and humans small doses (several $\mu$g. to few tens $\mu$g. in animals, about 1 to several mg. in humans) quickly cured the symptoms. Furthermore, in infantile beriberi and new beriberi in adults, administration of several mg. to about 10 mg. quickly cured them. In view of the foregoing it can be said that for beriberi heart treatment small doses (about physiological requirement dose or several times of it) is probably enough.

On the other hand, textbooks\textsuperscript{19-27} that prescribing large dosage (to about 100 mg.) are mainly based on clinical treatments of severe beriberi, it seems. In fact, in severe or repeated chronic beriberi quite large doses (even 100 mg. or more) were necessary but even then these were not always effective. Moreover, as our experiments proved in greatly emaciated rats in thiamine deficient end stage, even a large dose as much as 1 mg. (when calculated in terms of human dosage this amounts to several hundreds to 1,000 mg.) had no effect. In view of this it can be said that larger doses might have shown better effect.

The marked difference in the above 2 facts brought about the great difference concerning the clinical treatment dosage of thiamine for beriberi heart. To eliminate this gap further investigation is necessary to bridge the basic curative experiments with the clinical experiences logically.

When we look into the heretofore basic curative experiments almost all of the thiamine deficient experiments (on animals and on humans) were on one-time deficiency only and curative tests were carried on it. These curative tests may be applied to treatment of new beriberi only in humans.
(they are not applicable to repeated chronic or severe beriberi). This is clearly shown by the fact that similar response (almost same quick improvement can be observed by administration of almost same dosage) as that of the experiments can be observed by thiamine administrations to infantile beriberi and new beriberi in adults. That is, almost all the curative experiments up to now were only experimental studies on treatment of new or acute beriberi. Accordingly it is natural that there was a wide gap between the thiamine effect in these experiments and in severe cases observed in clinic.

As stated above because there was no experimental method corresponding to repeated chronic beriberi heart in human beings we tried a new experimental method; thiamine deficiency and cure repetition. By applying this method we studied the correct treatment dosage of thiamine for beriberi heart.

As stated above although thiamine injections of doses less than 0.2 mg. had no curative effect at the 3rd or 4th injection, 0.5 mg. injection had curative effect even more than 6 times. However, up until the 3rd thiamine deficiency there was hardly any noticeable difference between the curative effect of 0.05 mg. and of 0.5 mg. On the other hand, as stated in I. (c) at the first-time thiamine deficiency, approximate normal requirement dosage (2.5 μg.) was able to improve the electrocardiographic changes somewhat only (that the minimum curative dosage for the first-time thiamine deficiency is about 5 μg., was stated in our first report1) but even as large a dose as 1 mg. had no effect for the greatly emaciated rats in the final stage.

These experimental results of ours suggest that the clinical treatment dosage of thiamine for beriberi heart is as follows;

a) Clinical treatment dosage of thiamine should be considered apart from physiological requirement dosage.

b) For infantile and new beriberi heart even small doses as were said up to now (several mg. to about 10 mg., i.e. about several times of physiological requirement dosage) should be effective.

c) However, for repeated chronic or severe beriberi heart quite large doses (0.2 to 0.5 mg. for rats, i.e. several hundreds mg. for human beings) should be used immediately parenterally (by oral administration there is a problem concerning absorption of thiamine in digestive canal). Naturally, corresponding to the degree of improvement thiamine dosage can be gradually decreased to about several tens mg.

d) For far advanced beriberi heart with great myocardial changes, any large doses of thiamine will have no effect. Accordingly the most important thing for clinical physicians is to discover beriberi heart at an early stage and give adequate amount of thiamine immediately.
Lastly, we shall briefly state on the use of other drugs for beriberi heart.

There are papers which state that digitalis (and strophanthine)\textsuperscript{4), 5), 15), 25)-33) caffeine,\textsuperscript{4), 5), 28) camphor,\textsuperscript{4), 5), 28) epinephrine\textsuperscript{4), 5), 28) and diuretics\textsuperscript{4), 5), 15), 26), 28), 30)-32) are hardly effective for beriberi heart and from our experiments, it can be considered that vitacampher and norepinephrine are also hardly effective.

On the other hand there are papers which state that digitalis and diuretics\textsuperscript{24), 25), 27), 53), 55)-58), 61) are used together with thiamine. However, in these cases it is difficult to determine to what extent digitalis and diuretics themselves were effective.

At present it is difficult to determine clearly the effectiveness of cardiac drugs for beriberi heart. This problem is connected with the great clinical problem that cardiac drugs are generally ineffective for cardiac failure caused by metabolic disturbances and this must await further study.

In our next paper we shall report the relation between the electrocardiographic changes of thiamine deficient rats and some chemical substances in blood.

**Summary**

As there is no definite standard on the treatment dosage of thiamine for beriberi heart we carried on experiments on thiamine deficient rats.

1) Vitacampher and norepinephrine had hardly any effect on electrocardiographic changes.

2) Each dose of thiamine showed marked effect until the 4th week of first-time thiamine deficiency but after the 5th week there was a difference in the effectiveness. Even a quite large dose had no effect on greatly emaciated rats in the final stage.

3) From these findings, it became clear that thiamine effect is remarkable in the mainly functional disturbance stage but it is less effective in organic disturbance stage. That is, thiamine effect depends on the degree of myocardial lesions.

4) We tried a new experimental method to study the treatment doses of thiamine for beriberi heart; repetition method of thiamine deficiency and cure by single thiamine injection.

5) There was hardly any noticeable difference between the curative effect of small dosage and of large dosage until the 3rd-time thiamine deficiency. However, after the 5th-time deficiency unless the dosage was as large as 0.2 to 0.5 mg. (when calculated in terms of human dosage this amounts to several hundreds mg.) it had no curative effect.

6) From the above experiments we were able to determine the following:
a) Small dosage of thiamine (several mg. to about 10 mg. daily) is probably enough for mild or new beriberi heart.
b) For repeated chronic or severe beriberi heart quite large doses (several hundreds mg. a day) should be given parenterally immediately. Corresponding to the degree of improvement thiamine dosage can be gradually decreased to about several tens mg. daily.
c) For far advanced beriberi heart with great myocardial changes, any large doses of thiamine will have no effect.

References