AN EFFICACIOUS APPLICATION OF GENTIAN VIOLET TO
THE TREATMENT OF HUMAN STRONGYLOIDIASIS

BY

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INTRODUCTION

Since heavy infestation of Strongyloides stercoralis (Bavay, 1876) was dis-
covered by Yoshino (1932) in Okinawa, the southwest islands of Japan were
known as the infesting foci of this parasite. In recent years epidemiological
studies have been made by Tanaka (1957, 58), Sasa et al. (1958) and Shiroma
(1959) on the Amami and Okinawa Islands. In paralleling with the discovery
of the severe cases of this disease, choice of therapeutic medicament, however,
became a problem for the practical doctors at the infesting localities.

The treatment of strongyloidiasis is still difficult, though various drugs have
been indicated to this disease. Among the drugs used in the treatment of
strongyloidiasis, methylrosaniline (gentian violet) was found to be effective by
De Langen (1928), Faust (1930, 32) and Yoshino (1939). In recent years,
however, doubt has sometimes been directed to the effect of gentian violet,
because eradication of Strongyloides was not attained in certain cases, and because
reappearance of the larvae in the stool occurred in many cases after transient
disappearance of the larvae (Jones 1950, Matsubayashi 1955).

The present authors compared various drugs and experienced that per
oral administration of gentian violet tablets was most satisfactory when the drug
was used under appropriate conditions. In the course of this study, heavily
infected patients were selected. And the effect of the drug was checked with
two indications; the reduction of the number of larvae in the stool and the
evacuation of parasitic females**** after administration of the drug. The
discharge of the parasitic females in the course of treatment has not so far been
paid much attention. It occurred only when gentian violet or dithiazanine
was used, and the present study has been concentrated to the observation of
the course of the evacuation of parasitic females applying gentian violet. It
was proved in the present study that gentian violet has satisfactory vermicidal action to the parasitic females and also has the therapeutic effect to the severe cases of strongyloidiasis with the application of the suitable tablets and with the controled adjustment of the dose and the time of administration.

Parts of this study have been already published in Japanese by Shiroma & Tanaka (1959) and Shiroma (1959). The present paper deals with the revision of the previous reports and new informations of further studies.

**Method**

Most cases of the strongyloidiasis were patients at Yonobaru, Okinawa and one on Miyako Island, Ryukyus. Patients harboured many *Strongyloides stercoralis* and discharged larvae in a density as more than 50 larvae in a smear specimen under 18 mm square cover glass. The course of treatment was observed, daily counting the number of larvae in the stool by smear method. As 3 to 5 mg of the stool were contained in a single smear specimen, the number of the larvae in a specimen was roughly correlated to the value of E. P. G. The main checking points of the present study were the remarkable reduction of the larvae after administration of the drug, therefore the difference of the discharged larvae was measured enough by the observation of the smear specimen in routine procedures.

Three kinds of gentian violet tablets used in the treatment were commercial products obtained in Okinawa and were made in foreign countries. The kinds of products were differentiated with marks L, M and M’ in the following chapters. One of those tablets, however, was apparently made for the anthelmintic to pinworms and the others were also supposed to be originally made for the same purpose. The tablets originally prepared for the treatment of strongyloidiasis were not available. The types of coating of each product were presented in the following chapter.

The volume of the drug administered was principally 195 mg (3 grains) daily, 1 grain t.i.d., and was increased up to 390 mg (6 gr.) in persistent cases. The drug was administered at three different times for comparison; 30 minutes before meal, immediately after and 30 minutes after meal.

**Clinical Cases with Successful Treatment**

Patients examined and treated were all suffered from severe strongyloidiasis of chronic stage or acute exacerbation. By the difference of the tablets and the time of administration, anthelmintic effect of gentian violet seemed to be varied. Among three kinds of tablets (L, M and M’), tablet M in general showed successful results. The following cases show the various courses of successful treatment with gentian violet.

*Case 1:* 14 year old boy on Miyako Island. In March 1956, a clinical change was found in lung by the examination of Roentgen picture and treatment was given under the diagnosis of lung tuberculosis till August, 1957. Since diarrhea,
abdominal swelling and pressing abdominal pains on the right lower quadrant occurred in May 1957, treatment was directed under the diagnosis of intestinal tuberculosis until January 1958. The patient, not being cured by the treatment of tuberculosis, ceased to go to school because of physical weariness and emaciation and took rests at home from September 1957. In October 1957, severe diarrhea, vomiting and tenesmus lasted for several days. In 1958, the frequency and intensity of diarrhea increased, the patient discharged semiliquid stool 5 to 6 times daily and he was becoming emaciated accompanied with anorexia. In May 1958, anemia was found and treatment of hookworm was given. In September 1958, Strongyloides stercoralis was detected by the fecal examination at the Health Center. At the examination in November 1958, he was absolutely emaciated with mummy like appearance, weighing 17.25 Kg and 121.0 cm in height (Fig. 2). The larvae of Strongyloides were detected in fecal smear approximately 500 under 18 mm square cover glass in an average.

The treatment with gentian violet tablets (M) began from 1st Nov.. Tablets, each containing 33 mg (1/2 grain) of methylrosaniline, were administered 30 minutes before meals, 97 mg daily for the first two days and 195 mg for the succeeding 12 days. During the course of the treatment, fecal examinations were made daily and the change of the evacuated number of the larvac was observed. The results were presented in Table 1 and illustrated in Fig. 1. The number of larvae on the table is the average calculated from the observation of 5 specimens. The larvae suddenly diminished on the 3rd day and after the 5th day almost none of larvae was detected. On the other hand, parasitic females were evacuated and observed in the fecal specimens on the 1st, 2nd, 3rd and 5th days, the greatest number of the parasitic females being

Table 1. A course of treatment with gentian violet. Case I. T. T. 14 year old boy on Miyako Island, Administration of tablet M 30 minutes before meals

<table>
<thead>
<tr>
<th>Days elapsed</th>
<th>Nos. of worms in stool*</th>
<th>Gentian violet mg per diem</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Larvae</td>
<td>Parasitic females</td>
</tr>
<tr>
<td>0</td>
<td>470.2</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>600.9</td>
<td>1.25</td>
</tr>
<tr>
<td>2</td>
<td>204.2</td>
<td>1.50</td>
</tr>
<tr>
<td>3</td>
<td>14.3</td>
<td>0.83</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0.75</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>9-12</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Nos. of worms show the average counts of 6 fecal smear specimens under 18 mm square cover glass
Nos. of parasitic females and larvae are presented by the same method as in Table 1.

Fig. 1. A course of treatment with gentian violet, Case 1. T. T. 14 year old boy

1.5 in 18 mm square cover glass in an average (Fig. 2).

A fecal smear specimen usually contains 3 to 5 mg of stool and the volume of the daily discharge of stool is 120 to 180 g. If 5 mg of stool is in a fecal smear and the discharged volume of stool is 100 g, the total number of the parasitic females in a day is calculated as at least 20,000 times the number of the average in a fecal smear specimen. By this calculation, the total daily output of the parasitic females on the 2nd day of this case seemed to be at least 30,000. And at the same time, gentian violet was proved to have the activity to discharge so many numbers of parasitic females. The females evacuated were all dead.

After one course of the treatment, his physical conditions became well, the growth had been restored as shown in Fig. 2 and Table 2, and he could spend the ordinary school life in 1959.
Fig. 2. Evacuated parasitic female in a fecal specimen

Table 2. The growth of the patient after treatment
Case 1. born on 1st March 1944

<table>
<thead>
<tr>
<th>Date</th>
<th>Body weight (Kg)</th>
<th>Height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Nov. '58</td>
<td>17.3</td>
<td>121.0</td>
</tr>
<tr>
<td>13 Dec.</td>
<td>22</td>
<td>121.4</td>
</tr>
<tr>
<td>10 Mar. '59</td>
<td>23</td>
<td>122.7</td>
</tr>
<tr>
<td>12 June</td>
<td>25.5</td>
<td>123.4</td>
</tr>
<tr>
<td>11 Aug.</td>
<td>26</td>
<td>125.0</td>
</tr>
</tbody>
</table>
Table 3. A course of treatment with gentian violet. Case 2. N.T. 44 year old woman. Administration of tablet M immediately after meals

<table>
<thead>
<tr>
<th>Days elapsed</th>
<th>Nos. of worms in stool*</th>
<th>Gentian violet mg per diem</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Larvae</td>
<td>Parasitic females</td>
</tr>
<tr>
<td>0</td>
<td>500</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>500</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>500</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

* The same as Table 1

Counts of worms are observed by the same method as in Table 1

Fig. 3. A course of case 2, N.T. 44 year old woman
Case 3. A. Y. 46 year old man

195 mg
325 mg
\[ \text{gentian violet 390 mg} \]

\[ \text{larva} \]

no. of parasitic female

\[ \text{parasitic female} \]

day

0 5 10 11 15 20

Case 4. K. O. 60 year old man

\[ \text{gentian violet 195 mg} \]

\[ \text{larva} \]

no. of parasitic female

\[ \text{parasitic female} \]

day

0 5 10

Case 5. T. M. 42 year old man

\[ \text{gentian violet 292 mg} \]

\[ \text{larva} \]

no. of parasitic female

\[ \text{parasitic female} \]

day

0 5 10 11 15 20 30

Fig. 4. Courses of cases 3–7. Nos. of worms are counted as in Table, 1
Case 2: 44 year old woman. Chief clinical manifestations were diarrhea and anemia. In this case, the course of treatment was similar to that of case 1. Gentian violet (M) was administered immediately after meals 292 mg daily for 6 days. The fall of the evacuated number of larvae occurred on the 4th day and the parasitic females appeared in stool on the 2nd to 6th days (Table 3 & Fig. 3). Peculiar to this case, the evacuation of the parasitic females was greatest in number among examined cases, being 7 in a fecal specimen in an average. By the calculation mentioned above, the number of the parasitic females evacuated seemed to be at least 140,000 in the 4th day and be 290,000 in the whole course. And the patient was also clinically cured. And in this case
Fig. 5. Cases with relapse after successful treatment. Nos. of worms are counted as in Table 1
Table 4. Comparison of the effect of gentian violet among different kinds of tablets and the times of administration

<table>
<thead>
<tr>
<th>Kinds of tablets</th>
<th>Times of administration</th>
<th>Nos. of cases</th>
<th>Successful cases</th>
<th>Cases with side reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nos.</td>
<td>%</td>
<td>Nos.</td>
</tr>
<tr>
<td>L</td>
<td>30 min. before meals</td>
<td>7</td>
<td>3</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>30 min. after meals</td>
<td>8</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>M</td>
<td>30 min. after meals</td>
<td>3</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>immediately after meals</td>
<td>20</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>30 min. after meals</td>
<td>6</td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td>M'</td>
<td>immediately after meals</td>
<td>3</td>
<td>1</td>
<td>33</td>
</tr>
</tbody>
</table>

of gentian violet were mostly similar to those of cases 1 and 2 and are illustrated in Fig. 4. In those cases, gentian violet (M) was administered immediately after meals. Daily dose was adjusted case by case so that little side reaction suffered the patients. The daily dose was principally 195 mg but was often increased to 390 mg per diem, and the largest quantity tolerable to each patient was used. For example, as neither evacuation of the parasitic females nor diminish of larvae were attained at the initial dose in cases 3 and 7, the larger volume of the medicine was used and gave successful results.

*Cases 8 and 9:* are the samples of the reappearance of the larvae after one course of successful treatment (Fig. 5). In those cases, larvae were found in stool again 1.5 or 2 years after the disappearance of the larvae from stool.

**Comparison of the Effect by the Different Methods of Administration**

The effect of three kinds of tablets was compared, changing the time of administration. When the larvae disappeared from the stool and the parasitic females were discharged, the method of administration was denoted as effective. The results of the experiment are shown in Table 4. Among those combinations, the administration of tablets M immediately after meals presents the highest effect. The side reaction, on the other hand, appeared only at the use of this tablet M. The side reaction of gentian violet is believed to appear, when the tablet releases the chemical in stomach. So the tablet L and M' are not thought to release the ingredient at the part of the stomach. While tablet M seems to do at that part. Considering the combination of effect and side reaction, it is concluded that such tablets as release partially their contents at the stomach have remarkable activity for elimination of *Strongyloides.*

**Solubility Test of Tablets**

The tablets used were all enteric coated. But the types of coating of these
tablets differed each other. The solubility test of these tablets was made using the method defined in Japanese Pharmacopoeia VI (1955). The standard of enteric coated tablets determined in J. P. is as follows; more than 1 out of 6 tablets should not be dissolved in simulated gastric fluid within 2 hours and then in succeeding test more than 5 out of 6 should be dissolved in simulated intestinal fluid within 1 hour. The test should be done using the special apparatus and the fluid be kept at 37±2°C, similar to that determined in U. S. Pharmacopoeia XV. The times required for dissolution of tablets are shown in Table 5. All tablets were not fitted to the standardization of the enteric coating in J. P. VI, tablets L and M being coated much thicker than the standard, and tablet M being partially thicker and partially thinner. Amongst them, however, the tablet M, which showed the most effective results, was coated in the closest resemblance to the standard of the enteric coating defined in J. P. From the results, the type of coating is the important factor to make the gentian violet effective for the elimination of Strongyloides, and also the choice of the suitable kind of tablet should be carefully made in the treatment of strongyloidiasis.

Table 5. Solubility test of tablets, time required for dissolution

<table>
<thead>
<tr>
<th>Kinds of tablets</th>
<th>gastric fluid</th>
<th>Intestinal fluid*</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>Insoluble within 6 hr.</td>
<td>2 to 3 hr.</td>
</tr>
<tr>
<td>M</td>
<td>2 to 3.5 hr.</td>
<td>0 to 1.5 hr.</td>
</tr>
<tr>
<td>M'</td>
<td>Insoluble within 6 hr.</td>
<td>4 hr. 20 min. to 5.5 hr.</td>
</tr>
<tr>
<td>Standard in J. P.</td>
<td>Insoluble within 2 hr.</td>
<td>within 1 hr.</td>
</tr>
</tbody>
</table>

* After tablets were immersed in gastric fluid for two hours

**Discussion**

Therapeutic activity of gentian violet to strongyloidiasis was reported for the first time by De Langen in 1928, and Faust (1932) clarified that larvae of Strongyloides were disappeared with gentian violet in 45 cases out of 47. Furthermore, Yoshino (1939) found the discharged parasitic females in fecal specimens in 4 cases out of 16 patients, and be presumed that the activity of gentian violet was the actual discharge of the parasitic females, consequently diminishing the larvae from the stool. Yoshino's presumption was experimentally proved in the present paper through many clinical cases. In the present study, gentian violet itself has been proved to be a valuable anthelmintic on strongyloidiasis, and also the efficacious method of application was revealed.

The parasitic females have been sometimes detected in the stool. But discharge of them was recognized as the accidental affairs and so far little signified. The evacuation of them was observed as a sign of effective application of the drug in the present study, and as it was readily observed at the treatment of the heavily infected patients, such patients were gathered and examined.

The type of the coating of the tablets was the most important factor to
exert an influence to the activity of gentian violet. The results of the present study indicate that the tablet should be prepared so that gentian violet is released at the upper part of residing site of *Strongyloides* in the alimentary tract. As the residing site is the upper part of the intestine, such ideal conditions of coating are required, as the tablet should not be dissolved in the stomach and release the contents immediately after passing through the stomach. Probably considering those relationships, Faust (1949) recommended the use of 1.5 hour Seal-Ins enteric coated tablets. The tablets, however, are not usually available in any locality of the world, and furthermore such standardization of enteric coating is not generally accepted in the present days. In general, the tablet coated thinly seems to be better than the thickly coated ones, and the latter usually hides the effect of gentian violet. Though the tablets coated nearly the same thickness as the standard of the enteric coating in J. P. were most effective in the present study, much better type of coating is thought to exist.

By the comparison of the times of administration of tablet M, the best result was gained when the tablets were given immediately after meals. The time of administration really influenced the effect, but the best time of administration of tablet M was not always thought to be applicable to other kinds of tablets. The suitable time of administration should be determined considering with the type of coating of tablets used. As gentian violet shows side reactions when it touches to stomach mucosa, administration immediately after meal is recommended because of the reduction of the reaction. In a case to which the tablet M had been administered 30 minutes before meal in vain for long period of days, the same tablets showed dramatic effect when they were taken immediately after meal.

In refractory cases, transduodenal intubation of gentian violet solution has been usually recommended. In the practice of treatment, when intubation was applied, gentian violet was sometimes pushed back into stomach due to contra peristalsis, and the patient was suffered from vomiting. Even to such cases, per oral administration of the tablets was applicable. In such cases as vomiting, continuous watery diarrhea and emaciation occurred, per oral administration of tablets would usually be hesitated. However, gentian violet was given perorally to those patients in the present study. Although vomiting took place in high frequency in those cases, certain quantity of the drug seemed to pass through stomach, elimination of the parasitic worms was successfully attained and clinical manifestations were recovered. The administration was often interrupted by the occurrence of side reaction in severe cases but was soon able to continue after an interval of a few days, associating with the improvement of clinical symptoms of *Strongyloides* itself and of the side reaction.

Occurrence of relapse or reappearance of the larvae in stool after a course of treatment has been giving a suspicion about the effect of gentian violet. In fact, relapse was sometimes experienced, but if relapse occurs, gentian violet is not valued as out of choice in the treatment of strongyloidiasis, for its apparent vermicidal activity was proved in the present study. Relapse seems to take place from two origins; migrating larvae, to which gentian violet gives
no effect, and a certain number of the worms remained in a course of the treatment. Relapse may be prevented by the further improvement of application method of the effective medicament.

Using the similar method of experiment as applied to gentian violet, the effect of other chemicals was tested. The drugs tested were carbarson, diethylcarbamazine, tetrachloroethylene, 1-bromonaphthol-2, piperazine hydrate, stibophen, sodium antimonyl tartrate, quinacrine hydrochloride and dithiazanine. Except for dithiazanine, little anthelmintic action was observed in any drug. Dithiazanine was applied as an anthelmintic on strongyloidiasis by Swartz-Welder et al. (1957, 58) and given such high removal rate as 89 per cent of patients. In the use of dithiazanine, the same vermicidal action as gentian violet was revealed in the successful cases of the present study. Dithiazanine, however, should be further studied to enable the readily and satisfactory practical use; considering its activity and toxicity in comparison with gentian violet. The problem with gentian violet is to find out the suitable type of coating of tablets and also dose, time and period of administration to prevent the relapse.

Summary

1. Several kinds of drugs were compared in the therapeutic effect of strongyloidiasis. And gentian violet showed the most specific anthelmintic action. With the use of per oral administration of gentian violet tablets, parasitic females were evacuated, and larvae in stool were suddenly diminished in successful cases. The course of treatment of 9 cases were illustrated in the present paper.

2. The number of removed parasitic females at a patient was estimated as at least 140,000 in a day and 290,000 in a course of treatment. More or less number of parasitic females were also discharged from the other patients, and the vermicidal action of gentian violet was proved.

3. The activity of the drug was much influenced by the difference of the tablets used. In comparison of three kinds of products (L, M & M’), the most satisfactory effect was obtained with administration of tablet M, of which coating was thinnest and was thought to be partially dissolved in the stomach because side reaction appeared in the highest rate.

4. More or less occurrence of side reaction is thought unavoidable in the use of the gentian violet tablets which are expected to realize the effective treatment. To apply gentian violet effectively in the treatment of strongyloidiasis, choice of the suitable tablets, adjustment of dose and the time of administration are of importance so as the drug to release from the coating of tablets at the upper part of residing site of the parasite.

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**LITERATURE**


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* Japanese text.