Studies on the Treatment of Leprosy with a Synthesized Thiocarbanilide Derivative L-4

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ABSTRACT

A total of 62 leprosy patients, 47 lepromatous type, 9 tuberculoid, 5 borderline group and 1 indeterminate group, have been treated with a synthesized thiocarbanilide L-4, and the effectiveness of L-4 administration in the treatment of leprosy is evaluated on the basis of clinical and bacteriological improvements. The results are summarized and concluded as follows:

1. L-4, contained in gelatin capsule, can be safely administered orally to the patients through slow induction, from initial dosages of 50 mg to 100 mg daily to the therapeutic maintenance levels of 200 mg to 300 mg daily, for a period of time.

2. L-4 administration has brought apparent and remarkable improvement in clinical symptoms of the patients after a relatively short period of medication compared with that of DDS administration.

3. Changes of SFG values caused by L-4 administration were much speedier than, (or, at least, equivalent to) the effect caused by DDS. The changes of SFG values, in general, synchronized fairly well with clinical improvement of the patients.

4. Lepromatous cases with leprosy reaction or sulfone allergy responded well to L-4 medication with remarkable clinical improvement, and prolonged administration of L-4 did not provoke such a precipitating action to leprosy reaction as did DDS.

INTRODUCTION

Though Chaulmoogra oil (Mouat 1854) had been used empirically in the treatment of leprosy from ancient times, the very beginning of modern chemotherapy of leprosy was initiated by the work of Paget et al. (1943) who originated the Promin treatment of leprosy. Promin was a less toxic derivative of the parent sulphone, i.e., DDS (Diaminodiphenyl sulphone) which was synthesized by Fromm and Whittmann (1908). However, Promin itself was too toxic to be given orally or subcutaneously, and therefore, it had to be given only intravenously. By the introduction of other derivatives of DDS such as Sulfoxone sodium, U.S.P. (Diasone sodium), Solapsone, B.P. (Sulphetrone), Aceto-sulphone (Promacetin) and Thiazolsulphone that could be given orally in similar doses with safety, Promin was eventually replaced by these drugs.

Meanwhile, the pioneering work done by Cochrane et al. (1949), Lowe and Smith (1949) and Lowe (1950) firmly established that DDS, the parent sulphone of those derivatives, did possess activity against Mycobacteria, and DDS
has become the choice of drug in the treatment of leprosy since then.

Today, it is well recognized that DDS is the drug having the virtues of low cost, general efficacy, suitability for outpatient treatment, rarity of drug resistance, and prophylactic effectiveness. However, as Davey (1964) pointed out, DDS has still many limitations such as 1) its rather strong toxicity, 2) the existence of idiosyncrasy, 3) the precipitation of hypersensitive state, 4) the development of leprosy reactions, 5) the prolonged time of medication, 6) occasional occurrence of non-responding patients etc. Those limitations of DDS indicate that it could not be the sole nor the ideal antileprosy chemotherapeutic agent.

Efforts (Buu-Hoi 1954, 1955a, 1955b, Buu-Hoi et al. 1955a, Buu-Hoi et al. 1955b, Buu-Hoi et al. 1955c, Mayer 1941, 1954, Mayer et al. 1953, Mayer et al. 1959) have been made to produce alternative ideal drugs that would exert lesser toxicity, speedier action, and smoother progress during the treatment in addition to the virtues of DDS. The following representatives of several classes of various organic compounds have been discovered and have been shown to possess activity against Mycobacterium leprae at more than one institute throughout the world; Diaminodiphenylsulfoxide (Buu-Hoi et al. 1955a) Sulfamethoxypyrazine (Lederken; Schneider et al. 1958, Schneider et al. 1960), Sulfamethox Diazine (Barclay and Wilkinson 1963), Acetylsulphamethoxypyrazine (Schneider and Languillon 1963), P-acetamidobenzaldehyde thiosemicarbazone (Amithiozone or TBI/689; Ryrie 1950, Lowe 1952, Lowe 1954, Dharmendra and Chatterjee 1932), 4-butoxy-4'-dimethylaminodiphenyl thioures (DPT or Ciba 1906; Davey and Currie 1956, Davey et al. 1958, Davey 1960) and Diethylthiolumisophthalate (Ditophal or Eitisul; Davey and Hogerzeil 1959).

All those chemical compounds have been developed in the hope that they could be administered singly or in combination with DDS to surpass or to improve the limitations of DDS. Recently, there have been some reports which provided additional data in support of the general efficacy and advantages of DDS administration for the treatment of patients and for the control of leprosy. Such reports include the effectiveness of low dose DDS treatment and its advantages (Browne 1965, Leiker and Carling 1965, Ramu and Ramanujam 1965), and the sensitivity of Mycobacterium leprae to low levels of DDS in mice (Shepard et al. 1966).

Choi and Lew (1965) synthesized a series of thiocarbanilide derivatives in the efforts of developing new antileprosy and antituberculosis chemotherapeutic agents. Among the synthesized derivatives, L-4 was shown to possess a significant activity against murine leprosy (Choi and Lew 1965). Following their original study, Kim and Lew (1967) demonstrated that L-1 exerted potent antifungal activity in in-vitro experiment, and Chang and Lew (1967) also reported that the activities of L-1 and L-4 against mycobacteria and superficial mycoses were specific and selective ones.

These evidences clearly indicated the possibility of clinical treatment of leprosy with L-4, a synthesized thio-carbanilide derivative.

In this study, domiciliary leprosy patients who had registered at the World Vision Leprosy Treatment and Research Center were included. The results of clinical trial of L-4 in the treatment of leprosy patients were assessed clinically and bacteriologically in comparison with patients under ordinary DDS treatment.

**MATERIALS AND METHODS**

**A. The drugs used**

1. A synthesized thio-carbanilide derivative, L-4.

L-4 was synthesized at the Department Detailed procedures and data of the syn-
thesis will be published elsewhere.

2. DDS

Local products of DDS were purchased and the content of DDS in a given sample was analysed by the methods of Pharmacopeia of U.S.A. (1965) and other’s (Lee 1962).

B. Patients

1. Selection of the patients

A total of 62 patients have been included for clinical trial of L-4. They consisted of new and old patients registered at the World Vision Leprosy Treatment and Research Center. Table 1. shows the types of disease included for trial with L-4, and Table 2 their age and sex distribution.

As shown in Table 1, 22 patients out of 47 lepromatous type had received no antileprosy treatment prior to L-4 trial. Through the course of L-4 treatment, 8 out of 22 patients were excluded from the trial; 6 due to causes other than leprosy (Waters et al. 1967), 1 of suicide and 1 with side effects of L-4.

2. first experiment

A total of 16 patients were included in the first experiment, 15 cases of lepromatous type and 1 of reational tuberculoid. Among them, three of lepromatous type (Patient No. 3358, 3397 and 3618 in Table 4) and 1 reational tuberculoid were new cases who had no previous antileprosy treatment and they were treated with L-4 from the beginning of this experiment. However, the remaining 12 cases in the first experiment had been treated with DDS or other drug when they were included in the first experiment.

3. The second experiment

In the second experiment, the fresh lepromatous cases were included exclusively.

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Lepromatous</th>
<th>Tuberculoid</th>
<th>Indeterminate</th>
<th>Borderline</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>0~4</td>
<td>32</td>
<td>15</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>5~9</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10~14</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>15~19</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>20~24</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>25~29</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>30~34</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>35~39</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>40~44</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>45~49</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>50~54</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>55~59</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>60~</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>15</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 3. Criteria of evaluation of L-4 treatment

<table>
<thead>
<tr>
<th>Clinical improvement</th>
<th>Decrease in bacterial index</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>−</td>
<td>−</td>
<td>Worse</td>
</tr>
<tr>
<td>±</td>
<td>± or ±</td>
<td>Stationary</td>
</tr>
<tr>
<td>+ or ±</td>
<td>± or +</td>
<td>Good</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>Better</td>
</tr>
<tr>
<td>++</td>
<td>++</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

for accurate comparison of the activity of L-4 against Mycobacterium leprae with that of DDS. The patients had no previous treatment with any kind of antileprosy remedy, and the bacteriological examination of skin smears revealed strong positivity in relation to Bacterial Index and SFG value (Ridley 1964).

C. L-4 administration

1. Routine laboratory examinations

Before the initiation of L-4 administration the following laboratory examinations were completed and results recorded.

a) Detailed clinical and photographic records of the cases.

b) Bacteriological examinations of the skin by skin scraping method and calculation of Bacterial Index and SFG values (Ridley 1964).

c) Lepromin skin test with the trypsin-purified Lepromin antigen (Lew and Carpenter 1955) and the result of 4 week reaction.

d) Routine hematological examinations including total counts of RBC and WBC, differential count and the determination of hemoglobin level.

e) Urinalysis including microscopic examination of the sediment and the tests for sugar and protein in the urine.

These laboratory examinations, except the Lepromin test, were repeated at regular intervals through the course of the experiment.

2. Administration of L-4

a) L-4

L-4 was contained in gelatin capsules in the amount of 50 mg to 100 mg, given by mouth to the patients. For the adult, the

Table 4. Results of the L-4 treatment to the non-reactional Lepromatous cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Chart No.</th>
<th>Age</th>
<th>Sex</th>
<th>Type of dis.</th>
<th>Bact. index</th>
<th>Lepromin</th>
<th>Type of Lepra reaction</th>
<th>React. cont.</th>
<th>Medication</th>
<th>Starting date of L-4</th>
<th>Duration of L-4</th>
<th>Dosage of L-4/day</th>
<th>Evaluation of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 3,269</td>
<td>44</td>
<td>34</td>
<td>M</td>
<td>L</td>
<td>4+</td>
<td>4+</td>
<td>−</td>
<td>No reaction</td>
<td>D. D. S. L-4</td>
<td>Mar. 12 1955</td>
<td>8 m</td>
<td>100 mg—2 w</td>
<td>200 mg—2.5 m</td>
</tr>
<tr>
<td>2 3,312</td>
<td>26</td>
<td>19</td>
<td>M</td>
<td>L</td>
<td>3+</td>
<td>2+</td>
<td>−</td>
<td>No reaction</td>
<td>D. D. S. L-4</td>
<td>Mar. 26 1955</td>
<td>11 m</td>
<td>100 mg—1 m</td>
<td>150 mg—1.5 m</td>
</tr>
<tr>
<td>3 3,358</td>
<td>51</td>
<td>48</td>
<td>M</td>
<td>L</td>
<td>4+</td>
<td>4+</td>
<td>−</td>
<td>No reaction</td>
<td>L-4</td>
<td>Mar. 26 1955</td>
<td>11 m</td>
<td>100 mg—1 w</td>
<td>200 mg—1 m</td>
</tr>
<tr>
<td>4 3,397</td>
<td>21</td>
<td>18</td>
<td>F</td>
<td>L</td>
<td>5+</td>
<td>4+</td>
<td>−</td>
<td>No reaction</td>
<td>L-4</td>
<td>Apr. 14 1965</td>
<td>8.5 m</td>
<td>100 mg—2 w</td>
<td>200 mg—2 m</td>
</tr>
<tr>
<td>5 3,518</td>
<td>14</td>
<td>11</td>
<td>F</td>
<td>L</td>
<td>6+</td>
<td>8+</td>
<td>−</td>
<td>No reaction</td>
<td>L-4</td>
<td>Aug. 6 1965</td>
<td>8 m</td>
<td>25 mg—1 w</td>
<td>50 mg—2 w</td>
</tr>
<tr>
<td>6 3,262</td>
<td>43</td>
<td>39</td>
<td>M</td>
<td>L</td>
<td>4+</td>
<td>3+</td>
<td>−</td>
<td>No reaction</td>
<td>D. D. S. L-4</td>
<td>Feb. 19 1965</td>
<td>8 m</td>
<td>100 mg—1 m</td>
<td>150 mg—2 w</td>
</tr>
</tbody>
</table>
Table 5. Results of the L-4 treatment to lepromatous cases with Erythema Nodosum Leprosum

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Chart No.</th>
<th>Age</th>
<th>Sex</th>
<th>Type of dis.</th>
<th>Lepro-</th>
<th>Type of Lepra reaction</th>
<th>React. cont.</th>
<th>Medication</th>
<th>Starting date of L-4 R</th>
<th>Duration of L-4 R</th>
<th>Dosage of L-4/day</th>
<th>Evaluation of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>516</td>
<td>62</td>
<td>F</td>
<td>L</td>
<td>5+</td>
<td>E.N.L.</td>
<td>4 y</td>
<td>D.D.S. Prednisonone I.N.H. L-4</td>
<td>Feb. 19 1965</td>
<td>10.5 m</td>
<td>100 mg-2 w, 200 mg-2 m, 300 mg-4 m, 600 mg-2 m</td>
<td>Excellent</td>
</tr>
<tr>
<td>8</td>
<td>418</td>
<td>20</td>
<td>M</td>
<td>L</td>
<td>5+</td>
<td>E.N.L.</td>
<td>5 m</td>
<td>D.D.S. B.T.: L-4</td>
<td>Apr. 12 1965</td>
<td>11 m</td>
<td>100 mg-1 w, 200 mg-2 m, 300 mg-3 m, 400 mg-5 m</td>
<td>Better</td>
</tr>
<tr>
<td>9</td>
<td>2,428</td>
<td>20</td>
<td>F</td>
<td>L</td>
<td>5+</td>
<td>E.N.L. Neuritis</td>
<td>3 y</td>
<td>D.D.S. I.N.H. SU-1960 Operation L-4</td>
<td>Jun. 8 1964</td>
<td>1 y</td>
<td>100 mg-2 m, 300 mg-4 m, 600 mg-2 m</td>
<td>Good</td>
</tr>
<tr>
<td>10</td>
<td>1,691</td>
<td>36</td>
<td>M</td>
<td>L</td>
<td>5+</td>
<td>E.N.L. Neuritis</td>
<td>5 m</td>
<td>D.D.S. I.N.H. SU-1960 Operation L-4</td>
<td>Dec. 4 1964</td>
<td>1 y</td>
<td>100 mg-2 w, 200 mg-3 m, 300 mg-6 m, 400 mg-2 m</td>
<td>Excellent</td>
</tr>
<tr>
<td>11</td>
<td>910</td>
<td>27</td>
<td>F</td>
<td>L</td>
<td>2+</td>
<td>E.N.L. Progressive Lepra reaction</td>
<td>1 y</td>
<td>D.D.S. Prednisonone I.N.H. L-4</td>
<td>Mar. 5 1965</td>
<td>7 m</td>
<td>100 mg-1 w, 200 mg-2 m, 300 mg-3 m, 400 mg-5 m</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

*) B.T.: Blood transfusion

Table 6. Results of the L-4 treatment to the lepra reaction cases other than E.N.L.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Chart No.</th>
<th>Age</th>
<th>Sex</th>
<th>Type of dis.</th>
<th>Type of Lepro-</th>
<th>Type of Lepra reaction</th>
<th>React. cont.</th>
<th>Medication</th>
<th>Starting date of L-4 R</th>
<th>Duration of L-4 R</th>
<th>Dosage of L-4/day</th>
<th>Evaluation of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>3,248</td>
<td>33</td>
<td>M</td>
<td>L</td>
<td>5+</td>
<td>Sulfone allergy</td>
<td>1 m</td>
<td>D.D.S. L-4</td>
<td>Jun. 22 1965</td>
<td>1 y 2 m</td>
<td>150 mg-1 w, 300 mg-1 m</td>
<td>Stationary</td>
</tr>
<tr>
<td>13</td>
<td>3,522</td>
<td>28</td>
<td>F</td>
<td>L</td>
<td>5+</td>
<td>Sulfone allergy</td>
<td>2 w</td>
<td>D.D.S. (2 w) L-4</td>
<td>Aug. 27 1965</td>
<td>4.5 m</td>
<td>100 mg-1 w, 200 mg-3 m, 300 mg-1 m</td>
<td>Excellent (Suicide)</td>
</tr>
<tr>
<td>14</td>
<td>3,589</td>
<td>28</td>
<td>M</td>
<td>L</td>
<td>3+</td>
<td>Sulfone allergy</td>
<td>2 m</td>
<td>D.D.S. (1 m) I.N.H. L-4</td>
<td>Dec. 17 1965</td>
<td>4 m</td>
<td>50 mg-3 w, 100 mg-1 m, 150 mg-2 m</td>
<td>Good</td>
</tr>
<tr>
<td>15</td>
<td>2,562</td>
<td>31</td>
<td>M</td>
<td>L</td>
<td>4+</td>
<td>Neuritis</td>
<td>9 m</td>
<td>D.D.S. SU-1960 Operation L-4</td>
<td>Nov. 19 1965</td>
<td>4 m</td>
<td>100 mg-2 m, 200 mg-2 m</td>
<td>Better</td>
</tr>
<tr>
<td>16</td>
<td>3,520</td>
<td>20</td>
<td>M</td>
<td>T</td>
<td></td>
<td>React. tuberc</td>
<td>2 m</td>
<td>L-4</td>
<td>Aug. 18 1965</td>
<td>7 m</td>
<td>100 mg-2 w, 200 mg-2 m, 300 mg-3 m</td>
<td>Good</td>
</tr>
</tbody>
</table>

*) B.T.: Blood transfusion
initial dose of L-4 was 50 mg to 100 mg per
day, and therapeutic maintenance doses of
200 to 300 mg per day were gradually
attained through the slow induction course
that is routine in antileprosy treatment,
particularly with DDS.

b) DDS

The initial dose of DDS was 25 mg to 50 mg
per week and the doses were gradually in-
creased to the level of therapeutic main-
tenance, i.e., 300 mg to 350 mg per week.

D. Evaluation of treatment of leprosy
with L-4

1. The first experiment

The bases for the evaluation in the first
experiment were the clinical improvement
and the changes of the Bacterial Indices
after the period of L-4 administration.
Table 3 summarises the criteria used for
the evaluation of the experiment.

2. The second experiment

In the second experiment, the bacterio-
logical changes, i.e., decrease in Bacterial
Indices and changes of SFG values were
carefully followed through the course of L-4
administration to the patients in association
with the clinical improvement. For comparison,
a similar follow-up study of bacteriological
changes was made with the patients who
were given DDS as control.

RESULTS

A. The results of the first experiment

For convenience of evaluating the results of
the clinical trial with L-4, 16 patients included
in the first experiment were divided into 3
groups as follows:

Group I; 6 cases of lepromatous type
without any form of reaction or allergic
manifestation.

Group II; 5 cases of lepromatous type who
were in a state of ENL or ENL with
some other condition.

Group III; 4 cases of lepromatous and 1 of
tuberculoid who were in a state of
sulfone allergy, neuritis, or reactional
tuberculoid.

On the basis of the criteria shown in Table
3, the results of the first experiment were
evaluated (Table 4, 5 and 6). By the criteria,
the majority of the patients responded to L-4
treatment with remarkable progress, i.e., 6 cases
of Excellent, 3 Better, and 6 Good through the
course of the treatment with L-4, ranging from
4 months to 1 year and 2 months. Only one
case (Pt. No. 2248) out of 16 patients included
in the first experiment could be graded as
Stationary.

1. Clinical improvement

In general, clinical improvement observed
after the initiation of L-4 treatment was
much more evident than the decreases in
Bacterial Indices. Clinical improvements
included better general conditions, and
subsidence or decrease in the extent or
number of skin lesions and nodules, and
alleviation or disappearance of reactional or
allergic manifestations.

2. The decreases in Bacterial Indices

The decreases in Bacterial Indices were
observed in 9 cases out of 15 lepromatous
types included in the first experiment. Those
changes of Bacterial Indices were most
prominent in Group II and III, and (2+) decrease in Bacterial Indices in 6 cases out
of 9 lepromatous type included was observed.

B. The results of the second experiment

In the second experiment, the changes of
Bacterial Indices and of SFG values were
carefully followed during the course of L-4
administration in association with clinical
improvements. Similar observations were made
with the patients who were given DDS as a
control drug for comparison.


As shown in Fig. 1, 2, 3, 4, 5 and 6, there occurred decreases in Bacterial Indices such as (6+) to (3+) in 1 case, (6+) to (4+) 2 cases, (5+) to (4+) 1 case, (4+) to (3+) 1 case and (3+) to (3+) 1 case at the end of a relatively short period of L-4 administration, the shortest 4 months and the longest 9 months. Meanwhile, the changes of SFG values observed in the same patients through the period of L-4 administration were much more significant. In patients No. 4067, 4010, 4139 and 4098 (Fig. 1, 2, 3 and 4), their SFG values were (2-2-1) or (2-0-0) before the L-4 administration, and those values changed dramatically down to the level of (0-2-2) or (0-1-2) at the end of 5 to 9 months treatment with L-4. Similarly, SFG values of patients No. 4117 and 4045 (Fig. 5 and 6) whose SFG values were (1-2-1) before L-4 administration became (0-2-2) respectively at the end of 2 months and 5 months treatment with L-4. Those drastic changes of SFG values strongly indicated that there occurred so rapid damage and destruction of Mycobacterium leprae by L-4 administration that the bacteriological examinations of the skin smears of the patients hardly revealed the presence of so-called solid-staining bacilli at the end of such relatively short periods of L-4 treatment.

However, in some cases such as shown

Fig. 2. Changes of Bacterial Index and SFG value by L-4 administration (Pt. No. 4010).

Fig. 3. Changes of Bacterial Index and SFG value by L-4 administration (Pt. No. 4139).

Fig. 4. Changes of Bacterial Index and SFG value by L-4 administration (Pt. No. 4098).
Fig. 5. Changes of Bacterial Index and SFG value by L-4 administration (Pt. No. 4117).

Fig. 6. Changes of Bacterial Index and SFG value by L-4 administration (Pt. No. 4045).

Fig. 7. Changes of Bacterial Index and SFG value by L-4 administration (Pt. No. 3672).

Fig. 8. Changes of Bacterial Index and SFG value after L-4 administration and combined therapy with L-4 and DDS (Pt. No. 3518).

Fig. 9. Changes of Bacterial Index and SFG value after L-4 administration and combined therapy with L-4 and DDS (Pt. No. 3358).

Fig. 10. Changes of Bacterial Index and SFG value by DDS administration (Pt. No. 3938).
in Fig. 7, 8 and 9, practically no decrease in Bacterial Indices in patients No. 3672, 3518 and 3358 was observed though they had been treated with L-4 for more than a year. Of course, there were clear signs of clinical improvement in those patients. Therefore, as a pilot trial, combined therapy of L-4 and DDS was initiated at the end of 16 and 20 months of L-4 treatment in patients No. 3518 and 3358. Following combined therapy, rapid decreases in Bacterial Indices and significant changes of SFG values were observed as shown in Fig. 8 and 9, particularly in patient No. 3518. These observations were interpreted as suggesting the possible effective treatment of leprosy with combined therapy of L-4 and DDS.


As shown in Fig. 10, 11, 12, and 13, the changes of Bacterial Indices in patients given DDS medication were rather insignificant, such as (6+) to (5+) in 1 case, (5+) to (4+) 1 case, and (5+) to (3+) 2 cases. Meanwhile, in patients (No. 3938 and 3914) whose SFG values were (2-1-0) before DDS administration, the SFG values became (0-2-2) or lower after 6 to 8 months of DDS treatment (Fig. 10 and 11). However, the SFG values of the patients (No. 4033 and 3962), whose SFG values before DDS treatment were (2-1-0), were still at the levels of (1-2-2) and (1-1-2) after 7 to 9 months of DDS treatment (Fig. 12 and 13). In general, there was a tendency to parallel changes of Bacterial Indices and of SFG values in DDS given control group.

C. Side reactions and toxicity of L-4

Out of a total of 62 patients included for clinical trial of L-4, side reactions were observed in 6 cases: 1 case of neuritic symptom, 2 cases of gastrointestinal irritation such as nausea and vomiting, and 3 cases of pos-
sible toxic jaundice. The appearance of jaundice in such cases was preceded by the signs of gastrointestinal upsets such as anorexia, nausea and vomiting. These jaundice conditions were easily controlled by the withdrawal of L-4 administration, bed rest and fluid therapy. The development of jaundice conditions was assumed to be due to the residual benzidine that was not completely removed through the processes of L-4 synthesis during the early phase of this study.

**DISCUSSION**

Though DDS was originally synthesized by Fromm and Whittmann in 1908, the recognition of its antileprosy activity followed the clinical studies conducted by Cochrane et al. (1949), Molesworth and Narayawami (1949), Muir (1950) and Lowe (1950). Particularly, Lowe’s work (1950) on the oral administration of DDS retains high credit and the oral route has become the method of choice for widespread sulphone therapy. Eventually, the introduction of DDS as an antileprosy drug has really brought the promise that ‘leprosy is curable’ and drastic changes have taken place in the epidemiology of leprosy today in the world.

Through the experiences of clinical use of DDS in the treatment of leprosy, not only the virtues of DDS but also its limitations have been recognized as have been reviewed by Davey (1964). Therefore, efforts have been made to develop compounds of lesser toxicity than DDS and of better antileprosy activity in order to replace DDS, and these were the very beginning of numerous studies involved in the development of new antileprosy drugs.

Recently, Choi and Lew (1965) synthesized a series of thio-carbanilide derivatives in the hope of developing new compounds of antituberculosis and antileprosy activity. Their studies showed that 1) two of synthesized thio-carbanilide derivatives, i.e., L-1 and L-4, possessed remarkable growth inhibiting activity against Mycobacterium tuberculosis in in-vitro experiment and 2) L-4 exerted significant suppressive effect on the development of leprosy in murine leprosy. More recently, Kim and Lew (1967) reported that both L-1 and L-4 showed remarkable suppressive effect on most of the superficial mycoses in in-vitro experiment, and Chang and Lew (1967), based on the data of nonspecific and insignificant antibacterial activities of antileprosy, antituberculosis and synthesized thio-carbanilides L-1 and L-4, concluded that potent antileprosy, antituberculosis and antifungal activities possessed by them were specific and selective ones. Furthermore, according to the calculations made by Choi and Lew (1965), LDF of L-1 was 1,354 mg/kg and of L-4 was 1,028 mg/kg of body weight in mouse. These data on L-4 clearly indicated the possible clinical trial of L-4 in the treatment of human leprosy, and clinical and bacteriological assessment of L-4 administration in the treatment of leprosy were undertaken in this study.

In the first experiment of this study, L-4 treatment of 16 patients, including 15 lepromatous and 1 tuberculoid, for a period of 4 to 14 months were quite impressive. Responses of 16 patients to L-4 medication could be graded, according to the criteria of evaluation (Table 3), as follows; 6 cases of Excellent, 6 Good, and 1 Stationary (Table 4, 5 and 6). The gradings used in the evaluation of L-4 treatment, i.e., Excellent, Better, Good, Stationary and Worse (Table 3) appears to be very much similar to Waters’ (1963) classification of clinical improvement in drug trial, i.e., Marked, Moderate and Slight improvement, No change and Deterioration. Clinical improvement observed in lepromatous type patients having leprosy reaction or sulfone allergy (Table 5 and 6) were the most significant ones.

The importance of the selection of patients in clinical trial of new antileprosy compounds has
been emphasized, and Davey (1960) suggested that in such a trial only pure lepromatous cases should be included, and that the patients should be in an active, progressing condition, untreated by previous chemotherapy.

Waters et al. (1967) also suggested that a patient whose MI (Morphologic Index, Waters and Rees 1962) is less than 25 is unsuitable for inclusion in a standard trial of antileprosy drug. The results of the first experiment of this study clearly showed that the oral administration of L-4 was quite acceptable to and well tolerated by patients, and the clinical improvements which followed L-4 administration were highly impressive. Therefore, in the second experiment of this study it was attempted to carry out a follow-up study of bacteriological changes, i.e., decreases in Bacterial Indices and changes of SFG values in patients whose bacteriology of skin smears could fulfill the requirement suggested by Waters et al. (1967).

By L-4 administration, the changes of SFG values were speedier and much more significant than the decreases in Bacterial Indices. As shown in Fig. 1, 2, 3, 4, 5 and 6, SFG values of the patients (No. 4067, 4010, 4139 and 4098) whose SFG values were (2-2-1) or (2-0-0) prior to L-4 administration have been changed to (0-2-2) or (0-1-2) at the end of relatively short periods of treatment, ranging from 5 months to 9 months (Fig. 1, 2, 3 and 4). Similarly, original SFG values of (1-2-1) of the patients (No. 4117 and 4045) have been changed to (0-2-2) at the end of 2 to 5 months of L-4 administration. In comparison with, the changes of SFG values observed in L-4 treated patients appeared to be much more significant than observed in DDS given patients (Fig. 10, 11, 12 and 13).

Though the SFG values instead of MI were followed in the second experiment of this study, the estimated MI of the patients (No. 4067, 4010, 4139 and 4098) appeared to be, at least, over 25% (Fig. 1, 2, 3 and 4).

Through the first and second experiment, it was assumed that the remarkable clinical improvement which followed L-4 administration were in accordance with the changes of SFG values rather than with the decreases in Bacterial Indices of the patients.

In some instances such as seen in patients (No. 3672, 3518 and 3358) (Fig. 7, 8 and 9), L-4 administration resulted in rather insignificant changes of bacteriology of the patients without any indication of correlation to clinical improvements of the patients. As shown in Fig. 8 and 9, administration of DDS in addition to L-4 did induce remarkable bacteriological changes in them, and the results are highly suggestive of combined effective therapy of leprosy with L-4 and DDS.

Finally, out of a total of 62 patients included in this study, 6 cases of incompatibility due to side effects and toxicity of L-4 have been encountered. The cause of 3 incidences of jaundice appeared to be due to incomplete removal of residual benzidine in the processes of L-4 synthesis during the early phase of this study. Efforts were made to achieve complete removal of residual benzidine from L-4 preparation and this precaution worked out effectively.

REFERENCES


Buu-Hoi, N. P., Nguyen-Ba-Khu yen and Nguyen-Dat-

Fig. 14. Before L-4 treatment (lepromatous. Pt. No. 418).

Fig. 15. After 11 months of L-4 treatment.

Fig. 16. Before L-4 treatment (lepromatous. Pt. No. 2428).

Fig. 17. After 1 year of L-4 treatment.

Fig. 18. Before L-4 treatment (Reactional tuberculoid Pt. No. 3811).

Fig. 19. After 1 year of L-4 treatment.
APPENDIX

Table 7. Bacterial index (Ridley 1964)

<table>
<thead>
<tr>
<th>The Bacterial Index</th>
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<tbody>
<tr>
<td>6+: Many clumps of bacilli in an average microscopic field (over 1000 bacilli).</td>
</tr>
<tr>
<td>5+: 100–1000 bacilli in an average microscopic field.</td>
</tr>
<tr>
<td>4+: 10–100 bacilli in an average microscopic field.</td>
</tr>
<tr>
<td>3+: 1–10 bacilli in an average microscopic field.</td>
</tr>
<tr>
<td>2+: 1–10 bacilli on average in 10 microscopic fields.</td>
</tr>
<tr>
<td>1+: 1–10 bacilli on average in 100 microscopic fields.</td>
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</tbody>
</table>

Table 8. SFG value and Granularity Index (Ridley 1964)

<table>
<thead>
<tr>
<th>Calculation of Granularity Index</th>
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</thead>
<tbody>
<tr>
<td>S.F.G.*</td>
</tr>
<tr>
<td>Value</td>
</tr>
<tr>
<td>2–0–0**</td>
</tr>
<tr>
<td>2–1–0</td>
</tr>
<tr>
<td>2–2–0</td>
</tr>
<tr>
<td>2–1–2(=1–2–0)</td>
</tr>
<tr>
<td>2–2–1</td>
</tr>
<tr>
<td>1–2–1(=2–2–2)</td>
</tr>
<tr>
<td>1–2–2</td>
</tr>
<tr>
<td>1–1–2(=0–2–1)</td>
</tr>
<tr>
<td>0–2–2</td>
</tr>
<tr>
<td>0–1–2</td>
</tr>
<tr>
<td>0–0–2</td>
</tr>
</tbody>
</table>

*: S = "Solid" - solid-staining unbroken rods.
F = "Fragmented" - bacilli in which the acid-fast substance is interrupted at one or more points.
G = "Granular" - round granules either in line or clumps.

**: 2 = numerous (over 25% of all bacilli)
1 = few (1–25%)
0 = less than 1%