

The Review of Chemotherapeutic Trials on Leprosy and its Present States in Korea

Joon Lew*

*Presented at International Symposium on Leprosy and Joint Chemotherapy
Trial meeting. May 30~June 4, 1978*

Seoul, Korea

A rather definitive description of leprosy in Korean history appears in 13 AD (Lew, J. 1960 and Hyangyakjipseongbang, 1433)

The treatment of leprosy in those early times was mainly herb-medicine to help digestion and a tonic such as sanke-wine, soup, etc. (Hyangyakjipseongbang, 1433)

The use of chaulmoogra (Mikis, 1962) appears in Tong-I-Bogam, a medical text book by Dr. Joon HUH in 1613.

Chaulmoogra with herbs as digestive aids and tonics of some specific species of snake have long been the standard treatment of leprosy in Korea through her past history.

Chaulmoogra and other various types of chemotherapeutic trials were attempted without much success from 1910~1950.

Promin, the first effective sulfone derivative was brought to Korea as a trial sample in considerable quantity by Dr. A.G. Fletcher in 1947 who was one of the pioneer workers in leprosy service in Korea.

Some considerable beneficial results were observed in the promin trial at Sorok Island Leprosarium and other leprosy institutes. However these trials were all stopped without

any assessment of data due to the Korean War in 1950.

DDS(Dapsoné) was introduced by Dr. R.G. Cochrane, a civil assistance command consultant, in 1955. (Cochrane RG, 1955)

The amount of Dapsone brought to the country was sufficient enough to cover all cases of leprosy who wanted to receive treatment, but without being informed with sufficient education about the use or side effects of the drug. There were countless incidents of Dapsone intoxication, acute dermatitis or iridocyclitis

A study (Lew, J & Chung, M) was therefore conducted to confirm the optimum dosage of DDS for patients. Doses of 300~400mg/week of DDS were recommended, with much attention to the eyes and its side reactions.

These measures of approach diminished the problems of DDS complication to almost negligible status.

A study (Lew J. & Kim YS 1966, Lew J. & Kim YS 1969) of chemoprophylaxis of leprosy contacts with DDS was carried out with considerably encouraging results.

The effectiveness of DDS administration as a prophylactic measure to the children of leprosy patients and leprosy contacts has been evaluated through two separate field experiments.

* Received March 6, 1979

*** Professor of Microbiology, Yonsei University, College of Medicine, Director, World Vision Special Skin Clinic and Leprosy Research Institute, Seoul, Korea

Experiment I:

A total of 760 children whose parents had leprosy, living at various preventoria throughout the nation, were divided into two groups of 435 children. DDS, in a dosage of 50 mg to 300 mg per week, was given to the children of these experimental groups.

Throughout the observation period of 2~7 years, only two children among the DDS medicated group developed leprosy while 31 children (7.1%) out of 435 children in the control group developed leprosy or suspicious leprosy.

Experiment II:

A total of 1,527 leprosy contacts was included in this study. The first group consisted of 778 household contacts who were exposed to 156 bacteriologically positive leprosy patients, and the contacts who were exposed to 160 leprosy patients, and a control group of 749 individuals was household contacts of 160 leprosy patients of various types in Kangwondo province.

Throughout the observation period of 3 to 10 years, only one case of indeterminate leprosy was observed in the DDS-medicated group, while 13 cases of leprosy (1.7%) developed among those in the control group.

In an attempt (Choi, TK & Lew, J, 1965) to develop a new chemotherapeutic agent effective for the treatment of leprosy, a series of thiocarbanilide compounds was synthesized and one compound, namely "L-4", was selected.

Through *in vitro* and *in vivo* basic screening systems, L-4 was highly evaluated as a possible agent for chemotherapeutic trials.

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 therapeutic effectiveness of L-4 administration for leprosy was evaluated on the basis of clinical and bacteriological improvements.

Following are the summarized results and conclusions derived from the experiment.

1. L-4 prepared in gelatin capsule can be safely administered to patients to maintain therapeutic maintenance levels of 200 mg to 300 mg daily by increasing the initial dosage of 50 mg by 50 mg successively periods of time.
2. L-4 administration brought an apparent and remarkable improvement in clinical symptoms of the patients after a relatively short period of medication, compared with that of DDS administration.
3. The speed of changes in SFG values induced by L-4 was faster than (or at least, equivalent to) those induced by DDS. The changes of SFG values were, in general, synchronized fairly well with clinical improvement of the patients.
4. Lepromatous cases, who showed a leprosy reaction of sulfone allergy, responded well to L-4 medication, with remarkable clinical improvement, and prolonged administration of L-4 did not provoke such a precipitating reaction as the leprosy reaction seen in DDS treatment.

Lamprene (clofazimine) also has been used for leprosy treatment. However, colorization due to the drug made it very difficult, especially at an ambulatory clinic, to continue the treatment.

Thiambutosine (Ciba 1906) and TBI were also tried in various leprosy clinics and institutions without conclusive results.

Among these therapeutics, Rifampicin is a drug which has been extensively used in many clinics for leprosy patients particularly

for patients who are clinically resistant to DDS and/or for relapsed cases.

At the World Vision Skin Clinic, 96 cases of leprosy were treated with Rifampicin to evaluate its efficacy.

Dose response and effectiveness of a combination of the drug with DDS in various periods of treatment time, ranging from 12 months to 36 months, were carefully analyzed. The combined treatment with DDS appeared to be superior to that with DDS or Rifampicin alone.

Through the above experiments, it was well recognized that a good animal model system is definitely necessary for the precise evaluation of chemotherapy, as well as for bacteriological research.

Various species of animals had been investigated for the purpose without any positive results.

In search for a better animal host in the study of human leprosy, since 1967 we have been working on the experimental infection of the Korean Chipmunk (*Eutamias sibiricus asiaticus*, Gmelin) with *M. leprae*.

Utilization (Lew J, Yang YT & Pyun WS, 1974) Korean chipmunks as experimental animals for the growth of *M. leprae* is based on the fact that: 1) the chipmunks are readily available in large numbers and they can be easily maintained in the laboratory for experimental purposes, 2) the average life span of the chipmunks is known to be approximately three years which is longer than that of mice, and 3) the chipmunks proved to be highly sensitive to experimental infection with several Mycobacterial species.

The experimental results from the Korean chipmunks are summarized as follows;

I) *M. leprae* in chipmunks

1. *M. leprae*, obtained from lepromatous nod-

ules, either by conventional grinding or trypsin purification methods, multiplied in both foot pads and ears of the Korean chipmunks through the first and the second passage experiments. Growth of *M. leprae* in these inoculated tissues became evident after a lag phase of approximately seven months post-inoculation.

2. Characteristic leprotic changes were observed in the foot pads of the chipmunks inoculated with trypsin-purified *M. leprae* 13 and 16 months previously, and these changes included extensive leproma formation, the presence of massive numbers of acid-fast bacilli in the foam cells and the involvement of dermal nerve fibers by acid-fast bacilli.
3. Among the chipmunks inoculated with trypsin-purified *M. leprae* for the preparation of the chipmunk lepromin antigen, apparent swelling of the inoculated tissues was observed in a considerable number of the chipmunks ten months after inoculation. Two such swollen foot pads contained 2.0×10^{10} acid-fast bacilli each.
4. The results of skin tests in a series of leprosy patients with the chipmunk lepromin antigen, prepared with acid-fast bacilli harvested from swollen infected foot pads, were identical with those of standard lepromin antigen prepared from biopsied lepromatous nodules.

II) Other Mycobacteria in chipmunks

(Lew Joon, Kang W.S, 1976.)

1. *M. scrofulaceum*, (BCG) and *M. phlei*, which were previously known as nonpathogenic to any animal host, showed a high degree of pathogenic susceptibility in the Korean chipmunks (*Eutamias sibiricus asiaticus*)
2. The chipmunks showed pathogenic susceptibility to *M. leprae*, *M. tuberculosis*, *M.*

- bovis*, *M. avium*, *M. marinum*, *M. balnei*,
M. scrofulaceum, *M. intracellulare*,
M. ulcerans and *M. phlei*.
3. *M. kansasii* and *M. fortuitum* which are known to produce progressive disease in hamsters and mice did not produce progressive infection in the Korean chipmunks. From the above results it is suggested that the Korean chipmunk (*Eutamias sibiricus asiaticus*) is very susceptible to various mycobacteria and can be used as a suitable experimental animal model in various mycobacterial researches.

REFERENCES

- Choi TK, Lew J: *Studies on the Newly Synthesized Thiocarbanilides for chemotherapeutic activity against Mycobacterium tuberculosis and Mycobacterium lepraemurium*. Korean Centr. J. Med. 8:16, 1975
- Cochrane RG: *Leprosy in Korea Official Report of Korean civil assistance command (Mimeographe)*, 1955
- Hyangyakjipseongbang: *Classic Medical Text book*, Co. 3:22, 1433 (Reprinted by Hyang-Rim publishing Co. Seoul, in 1942)
- Lew J: *Leprosy in Korea*. Yonsei Med J 1:1, 1960
- Lew J, Chang CH, Choi TK: *Chemotherapy of leprosy with Newly Synthesized Thiocarbanilides*. Yonsei Med J 7:52, 1966
- Lew J, Chang CH, Choi TK: *Studies on the treatment of leprosy with a Synthesized Thiocarbanilides derivative L-4*, Yonsei Med J 9:24, 1968
- Lew J, Chung M: *Observation on optimum dosage of DDS in the treatment of leprosy in Korea VIIIth Int Cong Lep (Tokyo)*, Abstracts p142
- Lew J, Kang WS: *The pathogenecity of various Mycobacteria on Korean chipmunk (Eutamias sibiricus asiaticus)*, Kor Leprosy Bull 11:63, 1976
- Lew J, Kim YS: *Chemoprophylaxis of leprosy contacts with DDS*, Yonsei Med J 7:49, 1966
- Lew J, Kim YS: *Chemoprophylaxis of leprosy contacts with DDS*, IXth Int Nat Lep Cong (London) Abstracts 1969
- Lew J, Yang YT, Pyun WS: *Experimental infection of the Korean chipmunk (Tamias sibiricus asiaticus, Gmelin) with M. leprae*. Int J Leprosy 42:193, 1974
- Miki S: *History of Korean Medicine and of diseases of Korea*, OSAKA (SAKAI CITY), JAPAN p112, 1962