INTERNATIONAL JOURNAL OF LEPROSY

VOL. 9 JANUARY-MARCH, 1941 NO. 1

THE USE OF DIPHTHERIA TOXOID IN THE TREATMENT OF LEPROSY

SECOND REPORT

BY D. R. COLLIER, M.D., F.A.C.S.
Chiengmai Leper Asylum
Chiengmai, Thailand

INTRODUCTION

In the *Thai Science Bulletin*, April, 1939, I reported on the results obtained from the use of diphtheria antitoxin and toxoid in the treatment of leprosy during a limited period of a few months. The present report is made after ten months' use of toxoid, twenty-one months after the use of antitoxin was begun. In a disease of the chronicity of leprosy, observations of new methods of treatment must of necessity cover a considerable period of time. This is particularly so with leprosy itself, which is noted for its long periods of exacerbation and quiescence. The results observed in the beginning were striking, and it was hoped that further experience would prove consistent with them. At the time of the former article 128 patients were under treatment. The number has been increased to slightly over 600.

The reasons for attempting to use diphtheria antitoxin in our institution may be restated as follows: Oberdoerffer had advanced the theory that adrenal insufficiency predisposes an individual to leprosy. This insufficiency may be caused by the sapotoxins in certain food plants, as well as by other causes of glandular hypofunction. Oberdoerffer, who at that time was a member of the staff of the Chiengmai asylum, and I thought that there might be something more than an analogy between

the well-proven attempts of the body to form antibodies against a toxin such as that of diphtheria, which essentially damages the adrenals, and the lack of such an attempt in leprosy. We did not expect that diphtheria antitoxin would cure leprosy, but we did think that perhaps it would neutralize leprosy toxin in the toxemic syndrome of the disease, namely, lepra reaction. As far as we could determine the only reference in the literature on this subject is that Babes treated two cases with this serum, but did not follow up the work.

Since the results following the use of antitoxin were encouraging, it was decided to try diphtheria toxoid. The patients who have been given that treatment are considered in this report.

METHOD OF TREATMENT

The method of administering the toxoid first used in this work has been found satisfactory and is still being followed. Briefly, 1 cc. of plain formol toxoid is given hypodermically as an initial dose. Injections are repeated every two weeks, increasing by 0.5 cc. each time until a maximum of 3 cc. is reached. In some of the outpatients the interval has been four weeks instead of two. So far, no definite preference for one interval over the other has been formed. While a number of patients have had ten to twelve injections, it seems that in many cases the maximum benefit is obtained after five or six. One reason for continuing the injections after the sixth dose has been to encourage the patients, particularly the nonresidents, to return at regular intervals for inspection. When this has been the primary object the dose has been decreased to 1 cc.

RESULTS OF TREATMENT

In total, over 600 patients, representing all types of the disease, have been treated with toxoid or antitoxin or both. In the detailed analysis to follow, only the 193 cases in the asylum which have received toxoid for periods of from 7 to 10 months will be considered.

Evaluation of results.—In evaluating the results of the ten-months' treatment with toxoid the following procedures have been employed:

1. Bacteriological examination of skin, ear lobes and nasal mucous membrane.
2. Determination of the erythrocyte sedimentation rate.

3. Recording of weight.
4. Urinalysis, stool examination.
5. Charting of skin lesions and of areas of anesthesia.
6. Examinations for nerve enlargement (ulnar, median, posterior auriculars and peroneal nerves).
7. Record of lepra reactions during the period under observation and comparison with the previous similar period.
8. Photographs. (More than 300 photographs were taken during this period.)

GENERAL OBSERVATIONS

The rate of response to toxoid treatment has not been uniform. Some individuals respond within a few days, while others do not seem to undergo any appreciable change for some weeks, and then they may improve rapidly. Other patients improve to a point after which they seem to remain stationary, subsequent injections of toxoid having little effect, but this group is a small part of the total. As is shown in Table 1, the best results were obtained in the early cases; that is, in subtypes N1, N2 and L1, and also in what might be called "preinstitutional" or very early cases seen in the outpatient department. Patients in the N3 group often insist that they have derived considerable relief of pain following toxoid, and general improvement, though naturally there may be little external evidence of that. In general, the longer the leprous lesions have existed the longer the period of time required to clear them up, particularly in the lepromatous type with marked nodules and plaques.

Dealing more specifically with the various symptoms of leprosy and the effect of toxoid, the following observations have been made:

Bacteriology.—There is prompt fragmentation and granulation of the bacilli, which are found so consistently in all lepromatous cases. In those neural cases in which bacilli are found the same thing may be expected. In some of the slides taken from areas in L2 cases that were formerly rich in bacilli, none may be found; instead, there are seen large masses of acid-fast granules, often surrounded by a transparent zone. Occasionally slides are found which look as though they had been sprinkled with red pepper. While granulation is occasionally seen under ordinary circumstances in lepromatous cases which are showing steady improvement and are apparently on the way to recovery, after toxoid treatment it is found in a very large major-

ity, and to a far greater extent than I had ever seen it before beginning to use toxoid. In one or two cases which did not show clinical improvement after toxoid, there was no granulation or fragmentation of bacilli.

These are the first changes seen. The final data (see Table 1) show a very marked reduction both in the number of cases in which bacilli are present, and in the numbers and locations in which they were found. Among the early cases treated for eight months or more, more than one-half of those that were positive at first became negative. Of all the cases examined, 95 percent showed improvement at one or more points.

Skin lesions.—The majority of cases show, within a few days, reduction of leprous infiltrations, nodules, plaques, or tuberculoid lesions. Photographs are reproduced to show some of the more striking examples. In general, following treatment the raised red edges of tuberculoid leprids, or the red plaques and nodules, tend to shrink, showing fine lines or wrinkles. Over the larger areas of leprous infiltration there is frequently a fine, branny desquamation. At the same time there is usually a change in color, the bright red areas turning dark brown, then gradually fading out, accompanied by flattening of the lesion until it finally disappears. In some cases in which there was previously a generalized bronzing or dark brown pigmentation, there has been a gradual return to normal pigmentation. In early cases in which depigmentation is the only symptom, there may be complete return to normal, or the skin may remain more or less depigmented.

Nerve manifestations.—Improvement in nerve manifestations is found in several respects. Painful enlarged nerves, particularly the ulnars, sometimes respond over night, with relief of pain and gradually diminution of size. This response has been met in practically all such cases treated. In a fair percentage of cases there is a return, partial or complete, of sensation in previously anesthetic areas. This, however, is perhaps the least constant of all the varied responses to treatment. In some cases there is a temporary increase in anesthesia, followed later by its disappearance. In other cases the patient may complain temporarily of burning, or prickling, or itching of previously anesthetic areas. This I interpret as the first stage of returning sensation. In a few of the early cases a small area of anesthesia to light touch is the only suggestion of leprosy that remains.

Occasionally an increase of the strength and grip of the hands, and increased use of the fingers, have been observed. Previously in this asylum we operated for the relief of nerve pain, particularly of the ulnars, in an effort to relieve the pressure caused by the unyielding capsule on the swollen nerve. As discussed in a former paper, we believe that nerve compression resulting in partial paralysis of the muscles of the digits and stagnation of the circulation is the principal cause of bone absorption of the digits. Since the use of toxoid was begun it has not been found necessary or advisable to operate on a single case.

Eye symptoms.—A number of patients with iritis have received toxoid treatment, and for the most part have derived decided benefit. Here again the response has not been uniform. It is possible that, in those cases in which little relief has been obtained, the causative factor was something other than leprosy.

STATISTICS OF RESULTS

Detailed data are given in Table 1 of the results of toxoid treatment of 193 cases which have been treated in the asylum for from 7 to 10 months, most of them for the full period. Comparison is made of the condition of the patients between November, 1939, just prior to the beginning of the new treatment, and September 15, 1940.

In the tabulation the standard terminology with regard to the type of the disease is followed; that is, "N" refers to neural cases, including all of the tuberculoid variety; "L" refers to lepromatous ("cutaneous") leprosy. The degree of each is given as "1" for early, "2" for moderately advanced, and "3" for well advanced or severe cases.

Comment.—The total number of patients approved for discharge, together with the number already discharged during the first seven months of 1940, was 98. The number discharged during the preceding five years was 35, or an average of 7 per year. In our institution a patient is discharged only after he has been bacteriologically negative in nose, skin and ears, and otherwise symptom free for two consecutive routine examinations made at intervals of six months. It will be readily seen that the number of patients approved for discharge is considerably less than the total number found bacteriologically negative on the last examination. In the N3 group there were 28 negatives, but only 4 were approved for discharge. The reason for this is that in this group there are many of the old "burned-out" cases whose serious deformities of hands and feet make

them dependent on some form of charity for the rest of their lives; they are no longer active lepers in the sense that they are infective, but they need institutional case.

TABLE 1.—*Results of toxoid treatment of 193 patients in the Chiengmai Leper Asylum, according to the type of the disease.*

Changes	Type of the disease						Total
	N1	N2	N3	L1	L2	L3	
Cases treated	14	13	30	37	40	59	193
Bacteriology							
Negative throughout	9	6	17	3	—	—	35
Positive to negative	4	6	11	21	4	4	50
Negative to positive	—	—	—	—	1	—	1
Skin lesions							
Improved	14	13	14	35	40	57	173
Unchanged	—	—	16	2	—	1	19
Worse	—	—	—	—	—	1	1
Anesthesia							
Improved	10	10	10	18	16	14	78
Unchanged	4	3	18	14	17	32	88
Worse	—	—	2	5	7	13	27
Lepra Reactions[a]							
Ceased	1	2	2	11	11	15	42
Diminished	—	—	—	1	9	11	21
Increased	—	—	—	—	2	1	3
None throughout	13	11	28	25	18	32	127
Approved for discharge after treatment with:[b]							
Toxoid	12	7	4	15	1	—	39
Diathermy	2	1	2	5	4	1	15
Chaulmoogra only	—	2	7	2	2	—	13

[a] Comparison of events during the treatment period with those of an equal period previous to treatment.

[b] Only the toxoid-treated patients are of the cases dealt with in the preceding part of this table. The numbers shown do not include 40 cases already discharged, between January 1 and August 1, 1940.

The highest percentages of cases approved for discharge following treatment are in the N1, N2 and the L1 groups. This would be expected, of course, since the N cases have a relatively high natural immunity, and in the L1 group the road to recovery is shorter than in the more severe cases of that type. In the groups mentioned, 34 out of 64 cases are approved for discharge, or 53 percent. An additional 15 cases were free from bacilli at the time of examination, so that we may expect an additional group to be ready for discharge at the time of the next examination, six months later. Stated in another way,

70 percent of these early groups were positive at the beginning of the treatment, and only 25 percent after 10 months. It will be noted that the entire group improved as regards the condition of the skin lesions. Furthermore, while 15 cases of these groups had lepra reactions during the year before toxoid treatment was begun, only one of them showed that condition afterward, and that of diminished severity.

Attention is directed especially to the results obtained in the lepromatous groups. Our experience heretofore, in accordance with the generally accepted belief, is that in cases of these classes the prognosis is extremely bad. In the series here reported, 21 out of 37 L1 cases became bacteriologically negative. Fifteen of this group, or 41 percent, were recommended for discharge after the period of treatment. Only one patient did not show improvement bacteriologically. The improvement with respect to lepra reactions has been mentioned.

In the L2 group definite improvement has been seen, with respect to diminished numbers of bacilli found, improvement of skin lesions, and in the number and severity of reactions. Whether or not they will continue to improve to the point where they, too, can be discharged remains to be seen.

TREATMENT OF OUTPATIENTS

Experience in the treatment of outpatients with toxoid parallels that of the asylum cases. Details regarding the Chomtong outpatient clinic will be reported elsewhere, but are summarized briefly here. The total enrollment of the clinic is now 205, most of the cases being mild neural ones. Monthly visits have been made for the past ten months, at which time injections of toxoid have been given.

Fifty-four nonlepers living in contact with lepers, most of them children living with leper parents, were also injected with toxoid in the hope that this would confer some measure of protection against the disease. Of this number some did not return, and with others the interval between the time of injection and the last examination was less than six months. Twenty-six such persons, whose periods of observation were eight months or more, were closely examined without finding any sign or symptom of the disease.

Of 129 patients whom we were able to observe for a considerable part of the ten-month period, and whose records were satisfactory for evaluation, there were 16 who seemed inactive

at the beginning, they being for the most part burned-out N3 cases. Of the remaining 113 patients, in whom the disease was more or less active at the start, only 15 showed clinical activity on October 1, 1940, the date of the last examination. Thus it appears that 85 percent of the active cases became inactive under treatment. Bacteriological examinations were made in a few cases, but facilities for routine laboratory examinations were not available and the cases were judged on their clinical appearance. Doubtless most of those regarded as inactive would also be symptom-free according to accepted standards had the regular bacteriological examinations been made.

Mr. J. H. McKean, the superintendent of the Chiengmai asylum, who took part in the experiment, agrees with me that in many of the cases the improvement obtained was as much as would have been expected had the patients received toxoid treatment as inpatients in the asylum. It should be added that possibly one-half of the patients enrolled received biweekly injections of chaulmoogra oil during this period, administered by one of their number, together with a few simple medicines such as quinine, aspirin, salts, etc. The dosages of oil given in this way were small, usually less than 5 cc. per person.

CAUSE OF THE BENEFICIAL RESULTS OBTAINED

Before the beneficial effects obtained through the use of diphtheria toxoid and antitoxin can be explained, more must be known about the mechanism invoked by such injections. It has been suggested that antitoxin may have effective antibacterial antibodies, or that toxoid may produce an antibody that causes some sort of allergic reaction. A further possibility is that there may be some antigenic factor common to both the diphtheria and leprosy bacilli since these organisms are more closely related to each other than to the common bacteria.

With that possibility in mind, the entire group of patients in the asylum was given the Schick test. Most of the group had already received one or more doses of toxoid or antitoxin; not surprisingly they were all Schick negative. Of the 120 who had not had either toxoid or antitoxin, only one was Schick positive. To check these results a group of 100 nonlepers in an adjacent community were tested. Of 51 persons between the ages of six and twenty-five, 20 percent were positive, while of the 49 between the ages of twenty-six and sixty, 12 percent were positives. In a leper community some distance from the

asylum, where no toxoid or antitoxin had been given, there was one positive Schick reaction in 40 patients; and among nonlepers, 6 out of 50. A third distant leper group who had not had toxoid or antitoxin showed 2 positives out of 69 patients. In total, the 229 untreated lepers thus tested yielded only 1.7 percent of positive reactors, while the 150 nonlepers gave 14.7 percent. However, it is to be said that a similar test performed by Dr. M. Volupillay of the Leper Settlement at Sungei Buloh, in Malaya, on 100 leprosy patients revealed 9 percent of positives.

A third possibility of the cause of beneficial results might be a stimulating effect on the adrenals. Consistently good results have been obtained in this institution in the use of diathermy over the adrenal areas. These results have been checked eight months after the treatment was stopped, and the improvement has been maintained and even enhanced since that time. Since excessive doses of toxoid or toxin cause hemorrhagic degeneration of the adrenals, it may be that smaller doses cause a stimulation of them. Temporary improvement in cases of lepra reaction, and general improvement in ordinary active cases, has been noted in our asylum from the use of injections of a synthetic adrenal hormone, desoxycorticosterone acetate. A more prolonged study of this method of treatment is indicated.

Another method of adrenal stimulation which has been tried on 48 patients here is the implantation of adrenal glands taken from pigs and inserted under the skin of the upper abdomen. In many cases the gland sloughed out, but in others it did not. Some beneficial response has been obtained. Whether this response is due to the adrenal secretions absorbed, or to the presence of a fixation abscess, cannot as yet be said; it is expected that this subject will be studied more fully. A recent communication from the Mayo Foundation suggests that other substances isolated from the adrenals might be tried, in addition to the desoxycorticosterone acetate mentioned.

SUMMARY

Treatment of over 600 leprosy patients with diphtheria toxoid or antitoxin, over periods varying from a few weeks to 10 months, has given results which far exceed any obtained by me with any other method or combination of methods. Fifty percent of all early cases treated for six months or more have become symptom-free as judged from the bacteriological examination, the condition of skin lesions and of areas of anesthesia, and a

general appraisal of the patients' physical condition. The more advanced cases show definite improvement in a high percentage of cases according to the same standards.

Other methods of treatment which have brought encouraging results to a selected group of patients are mentioned.

ACKNOWLEDGMENTS

The Chiengmai Leper Asylum wishes to acknowledge the continued support of the American Mission to Lepers and of the Thailand government, which support has made this research work possible. We wish to take this occasion to thank the Lederle Laboratories who have supplied gratis a large part of the toxoid used in the work, and Eli Lilly and Co. for a further generous supply of toxoid.

DESCRIPTION OF PLATE

PLATE 1

FIGS. 1 and 2. Patient with extensive and marked lepromatous lesions of the face, confluent but not diffusing, showing improvement that occurred between April 10 and August 30, 1940.

FIGS. 3 and 4. Patient with marked nodular and plaque-like lesions of the face, in part confluent, with less affection of the body, showing the improvement that occurred between August 11, 1939, and September 16, 1940.

FIGS. 5 and 6. Extensive tuberculoid plaque of the abdomen and loin, as seen on November 1, 1939, and the residual condition that remained on September 25, 1940.

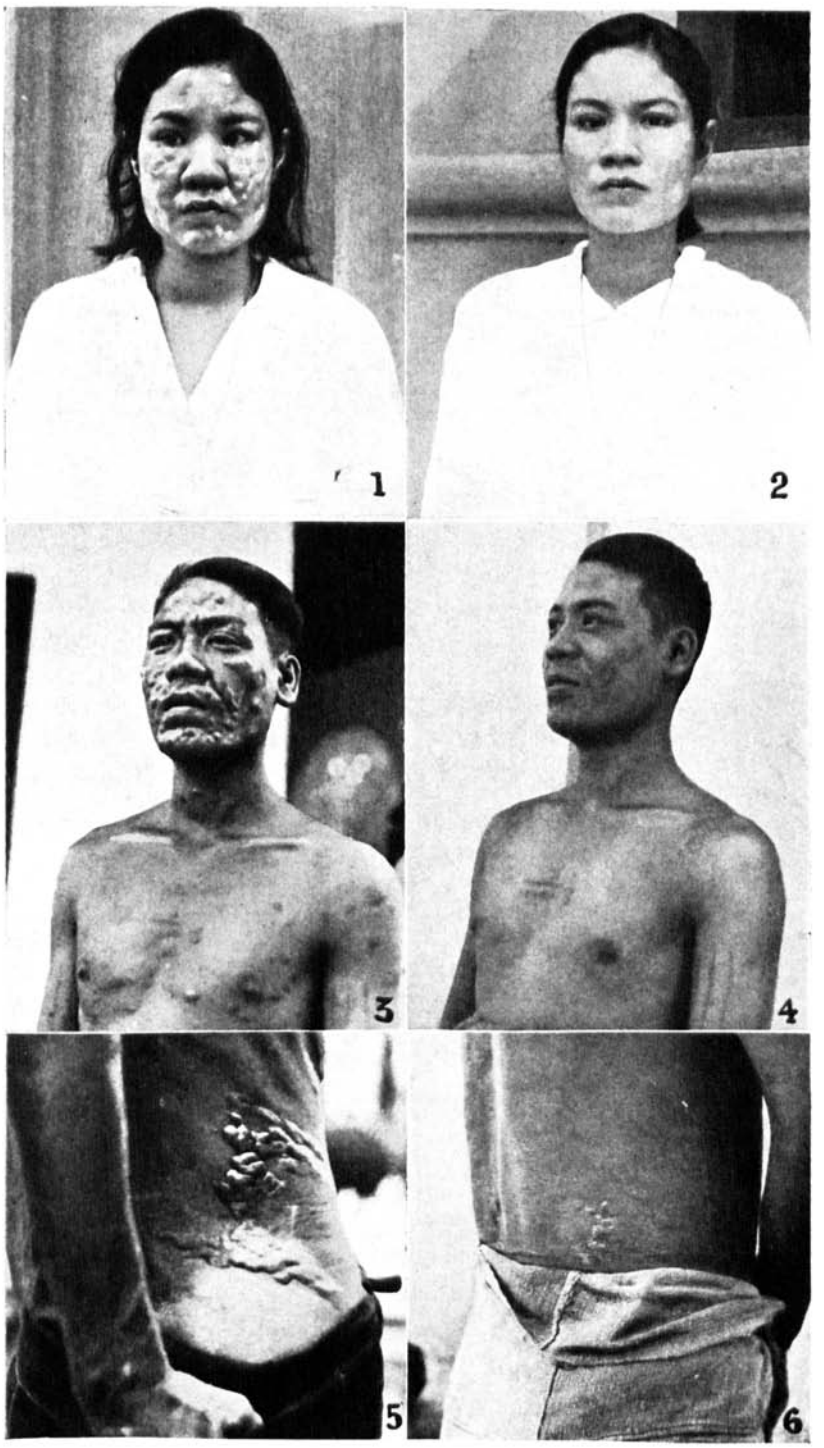

PLATE 1