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## LIMITATIONS OF THE DIPHTHERIA TOXOID TREATMENT OF LEPROSY

By J. HUGH MCKEAN  
*Chiengmai Leper Asylum*  
*Chiengmai, Thailand*

Three articles on the treatment of leprosy with diphtheria toxoid have been published from the Chiengmai Leper Asylum, Chiengmai, Thailand. The first one, by Collier and McKean (4), was a preliminary report dealing primarily with the use of diphtheria antitoxin; toxoid had been used for only two months, in 60 cases. The second, by Collier (1), was on the latter treatment alone, written after some 450 cases had been subjected to it. The third report, also by Collier (2), was far more comprehensive than the others and covered a period of observation of more than ten months. In it mention was made of the fact that the response to treatment was not uniform, but no specific information was given. It is the purpose of the present article to discuss certain of the inequalities and limitations of this method of treatment as observed over a period of eighteen months, from October, 1939 to May, 1941.

That the diphtheria toxoid treatment of leprosy has its limitations was evident from the very beginning. Not only did the response in cases of the same classification vary greatly, but conditions that in some cases were apparently benefited or cured by the treatment would develop in others already receiving it. For example, during the first few months of experimentation patients with swollen and painful ulnar and median nerves were given injections of toxoid with considerable success (3). On the other hand, a number of patients under routine toxoid treatment developed these same symptoms. This brought to mind a similar experience some years ago in the use of dyes. Injections of fluorescein gave fairly good results in cases of lepra reaction, but did not prevent the occurrence of reactions in some 30 patients out of a total of 75 who were being given semiweekly injections of this dye. The recollection of this experience fostered the suspicion that the toxoid treatment might also fail to live up to expectations.

This statement does not mean that the toxoid treatment is of no value. Injections of this material are being made more or less routinely in this institution, and more than 600 patients have received this form of treatment. It has been beneficial in many cases, and in some instances the results have been remarkably good. However, we know very little about its action. We do not know if in some way it acts directly and injuriously on the bacilli, or if the response to its introduction into the body results in neutralization of some toxic element produced by the infection, or if that response serves in a non-specific manner to increase the resistance of the patient. It is for this reason that we need to study all facts regarding its action, and its limitations are a vital feature which cannot be overlooked in any attempt to evaluate its worth.

#### EFFECTS IN LEPROMATOUS CASES

Lepromatous cases, in our experience, are the most difficult to treat and their response is the least predictable. This is especially true of advanced (L3) ones, which show a wide variation in results. Some react favorably at once, some show little if any improvement, while in others the treatment must be stopped because of adverse effects. Cases of moderate degree (L2) follow very much the same pattern. There is a possible explanation for this, and it is given for what it is worth.

The L3 stage of leprosy covers a fairly long period. In those cases in which the peak of infection has been passed and the patient, with increased resistance, is already making good progress in eliminating the bacilli, a considerable degree of improvement may be expected. Conversely, cases that are progressively active will tend to respond less favorably. In L2 cases, again, the results will depend on whether or not the patient is approaching the peak of infection or making a successful fight against the disease. Little if any improvement will be seen in the former instance, but in the latter a fair response may be anticipated. It is to be understood that the cases mentioned as having passed the peak of infection and undergoing improvement are still frankly of the L3 and L2 stages, bacteriologically and clinically.

The earlier (L1) cases have done well in many instances, though it remains to be seen whether the improvement in their condition will be maintained. Periods of activity and quiescence are so usual and typical in leprosy that a longer period of obser-

vation is necessary if this phenomenon is to be completely ruled out. Three of 21 cases which became negative under the treatment have again become positive and have been readmitted.

Lepromatous cases that show many widespread papules have proven to be exceedingly resistant. There are only four patients with such lesions in the institution at present. All have been under treatment with toxoid for periods varying from ten to eighteen months. Not one of them has shown beneficial results, and the trial has been abandoned.

#### EFFECTS IN NEURAL CASES

For the purpose of this discussion the major tuberculoid cases are divided into: (a) those which are bacteriologically negative, and (b) those in which more or less numerous bacilli are found. The response of the first group has been, on the whole, good. The usual course is a gradual fading of color and flattening of the lesion. These changes are noticed early, generally after the first or second injection, and the improvement continues until the lesion loses its characteristic contours.

As this is being written, however, a patient, a young Chinese boy eight years of age, originally with one bacteriologically negative major tuberculoid lesion on the right buttock, has been reexamined. Since he is an outpatient and comes only once in fourteen days, his progress has not been followed closely. After nine injections of the toxoid the lesion is still active and another, new one has appeared on his right shoulder. His physical condition reveals no apparent reason for this new activity, there being no evidence of any concurrent disease such as malaria, intestinal parasites, etc.

The second group, the major tuberculoid cases with numerous bacilli, are seldom seen here. During the past eighteen months only two recognized cases have been treated. Both of them became progressively worse under the toxoid injections and the trial was given up in favor of large doses of chaulmoogra oil.

Minor tuberculoid cases respond in much the same manner as those of the major variety. Those macules which have the appearance of being highly active, even though no bacilli are found, are refractory to treatment.

The simple macular and the anesthetic or nonmacular types (early Ns and Na) have shown good results. Depigmentation disappears as a rule, and return of sensation may follow. In such cases, however, in which progress is judged by clinical signs only, it is most important that all macules and anesthetic areas be carefully and exactly plotted in order to avoid errors in judgment.

## GENERAL OBSERVATIONS

It was stated at the beginning of this note that, though some cases with painful and swollen ulnar and median nerves have responded favorably to injections of toxoid, others undergoing routine treatment had developed these same symptoms. As time goes on an increasingly large number of such cases fail to be helped by the treatment, and such symptoms persistently develop in many instances in which the patient has been under treatment for months. Relief of pain is often temporary, lasting only a few days and appearing again before the next injection two weeks later. Three operations for the relief of ulnar pain have been performed in recent months, in cases that were under toxoid treatment at the time the symptoms appeared.

One of these patients had shown remarkable improvement with diphtheria antitoxin more than two years ago, and was one of the original group to take toxoid injections. This case is particularly interesting because of the excellent response made under both treatments. However, after a period of rest of some four months he developed severe ulnar nerve pains. Toxoid injections were resumed at once, a total of four being given at fourteen-day intervals, and diathermy was also employed. This treatment failed to give relief, and he was finally operated on at his own request.

Toxoid injections had not only failed to give relief, but following the operation he had such severe lepra reactions that he was hospitalized for ten weeks. His appearance before the operation was that of a man well on the road to recovery. His extremely severe and uncontrollable reactions came as a complete surprise, for the operation is quite simple and in more than one hundred previous cases no instance of reaction of such severity had been seen. This patient received malaria treatment prior to and following the operation, which is our usual procedure in such cases.

In spite of all outward appearances the actual improvement in this instance seems open to doubt. The case is most unusual and if taken alone would not have much weight, but the failure of toxoid in so many others has made it evident that its action is hardly more uniform than that of other forms of treatment used to control acute leprous neuritis.

Cases which have received the maximum benefit from the toxoid treatment show improvement early, usually after from the first to the third injections. The sooner the improvement becomes evident, the greater is that improvement. When there is no response by the third or fourth injection, subsequent treatment is of little promise. Whether there is early improvement or not, however, treatment is generally continued to the tenth or twelfth

injection. Patients are then advised to stop for several months, and unless reactions occur in this group this period of rest is prolonged indefinitely.

Should treatment be resumed because of lepra reactions, its effectiveness seems to be largely lost and the benefits tend to be temporary. Reactions in such cases are generally mild. Toxoid injections, when effective in them, usually bring about a gradual subsidence of the active lesions, but at the same time there is commonly to be seen new activity in some other part of the body. This happens not once, but many times in the same patient. Our records show that in the past few months twelve cases of this kind have followed the course described for seven successive injections—i.e., subsidence of activity in one part of the body and simultaneous appearance of new lesions elsewhere.

Ill effects from overdosage may occur and in some cases may be very severe. They can be avoided, and they have been avoided by us except for four cases which received large injections early in the experiment, before the maximum dosage had been established empirically at 3 cc. Since then such accidents have not occurred.

Three of these four cases were lepromatous, with many nodules. Overdosage resulted in a reactivation of these nodules, which ulcerated and exuded purulent masses of degenerated tissue, with abundant bacilli. This development was accompanied by general involvement of the lymph nodes. The fourth case was a mixed one, predominantly neural, in which the excessive dosage caused a swelling of the face so severe that both eyes were completely shut. The patient recovered from this in about 10 days. One of the nodular cases was not so fortunate and was hospitalized for 57 days. Subsequent doses of from 1 to 3 cc. have been well tolerated by these patients, though there has been little appreciable improvement in their condition. In fact, after fifteen months treatment with toxoid they are still highly active. The mixed case is now being given toxoid injections for persistent and recurring reactions, without success.

With regard to unusually marked fragmentation of bacilli after injections of toxoid mentioned in the preliminary report by Collier and McKean, further studies have been made. During the months of March and April, 1941, 367 patients were examined and smears were taken from skin, ear and nose in each instance. Of this number, 286 had been under treatment with toxoid. Unusual fragmentation was found in the slides from 38 patients; the others showed this feature in ordinary degrees. All of these examinations were done by the writer, and special attention was paid to the degree of fragmentation as well as to the number of bacilli.

## SUMMARY

One of the first things noted when diphtheria toxoid was first used in the treatment of leprosy at Chiangmai was the wide variation in the response to this treatment in cases of the same classification. This has been especially true of lepromatous cases of moderate and marked degrees of advancement (L2 and L3).

The best results were seen in major tuberculoid cases which were bacteriologically negative, and in early neural cases of anesthetic and simple macular types. The earlier lepromatous (L1) cases also showed excellent results, but the relapse of three of 21 cases rendered negative suggests that further observation is needed with regard to the permanence of such improvement.

The treatment has been of no value in major tuberculoid cases with numerous bacilli, or in the papular type of lepromatous cases. Minor tuberculoid cases in which lesions appear to be active, though bacteriologically negative, have also failed to respond.

Those cases in which favorable results appear early—i.e., after one or two injections of toxoid, given at two-week intervals—derive the maximum benefit from the treatment.

There is a tendency to relapse, and in such cases the benefits of further treatment are generally temporary, as regards the relief of nerve pain and the control of lepra reactions. In such cases, too, the gradual subsidence of active lesions after an injection of toxoid is commonly accompanied by the development of new activity in another part of the body.

The maximum dose has been empirically set at 3 cc. Accidents have been avoided by never exceeding that amount.

Bacteriological examinations revealed that 38 of 286 patients under toxoid treatment showed unusually marked fragmentation of bacilli.

## REFERENCES

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