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## EDITORIALS

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### DIPHTHERIA TOXOID IN TREATMENT AND THE ADRENAL INJURY THEORY



Not since the time several years ago, when for a while aniline dyes were hopefully tried out in leprosy treatment, has so much been claimed for a therapeutic innovation as has been indicated in reports on the experimental use of diphtheria antitoxin and toxoid which have recently appeared from the Chiengmai Leper Asylum, in Thailand. The work was started with antitoxin by Oberdoerffer when he was temporarily connected with the institution in 1939, based—some what vaguely, it would seem, —on his very special theory concerning the etiology of the disease. Collier, who collaborated in this earlier experiment and carried on with the toxoid treatment later, as also with certain other experiments to be mentioned, published with J. H. McKean a highly optimistic preliminary report;[1] and Oberdoerffer has also published briefly in similar vein.[2] In the meantime the matter has been written up in news dispatches and otherwise by certain visitors to Chiengmai and others who have been in-

[1] COLLIER, D. R. AND MCKEAN, J. H. The use of diphtheria antitoxin and toxin in leprosy; preliminary report. *Thai Sci. Bull.* **2** (1940) 117-125; reprinted in *Lep. Rev.* **11** (1940) 140-146.

[2] OBERDOERFFER, M. Vorläufige Mitteilung zur Leprabehandlung mit Formoltoxoiden, Diphtherieantitoxin und Nebennierenbestrahlung mit Kurzwellen. *Arch. Schiffs- u. Trop.-Hyg.* **44** (1940) 180-181.

fected with Collier's obvious enthusiasm. As a result, much interest has been aroused in the matter, and many people have received the impression that the main problem of leprosy has at last been solved. Naturally, too, high hopes have been aroused on the part of many of the victims of the disease—hopes that, if not fulfilled, will turn to cruel disappointment.

The latest report by Collier,[3] prepared 10 months after the use of toxoid was begun—21 months after the work was started with antitoxin—states that over 600 patients had been treated with toxoid for from a few weeks to 10 months, and that exceptional results had been obtained; that 50 percent of all early cases treated for six months or more had become symptom free, and that among the more advanced cases high percentages showed definite improvement. It is stated, but not stressed, that in many cases the maximum effect is obtained after five or six doses (usually given one every two weeks); but it is also said that those patients who improve only to a point and become stationary are only a small part of the total. Bacilli are described as promptly becoming fragmented and diminishing. Skin lesions soon show improvement; "the majority of cases show, within a few days, reduction of leprous infiltrations, nodules, plaques, or tuberculoid lesions"; and in the original report[1] it was said that in many instances nodules and plaques had become flat within six weeks. Nerve manifestations, and also iritis, are markedly benefited. Another report, which appears in the present issue of THE JOURNAL, deals with toxoid treatment of acute nerve pain; it is said that whereas operations for relief of that condition were previously fairly numerous, they have not been necessary since the use of toxoid was begun. When to such claims is added the intimation that it is hoped to immunize the children and associates of lepers, "and so in time to eradicate the disease," it is clear that the development is regarded as epoch-making.

The avowed basis of this method of treatment being Oberdoerffer's theory that adrenal damage plays an important role in the etiology of leprosy, that idea should be examined. Observing first[4] a seasonal variation in cases in Southern Nigeria, with respect especially to positive bacteriological findings in macular

[3]COLLIER, D. R. The use of diphtheria toxoid in the treatment of leprosy; second report. *Internat. Jour. Lep.* **9** (1941) 1-10; also *Leper Quart.* **15** (1941) 21-28.

[4]OBERDOERFFER, M. Untersuchungen über den Leprabefall in Südost-Nigeria. *Arch. Schiffs- u. Trop.-Hyg.* **42** (1938) 310-321.

lesions, Oberdoerffer soon[5] explained the periods of activity and relative quiescence of the disease primarily and chiefly on the grounds of toxicity of a vegetable, *Colocasia antiquorum*, known throughout the tropics as *taro, gabi* and by a host of other vernacular names. The curve of activity of leprosy is highest in certain months when this vegetable is eaten and has its maximum poison content; the disease is least active in those months when no colocasia is eaten. This theory was soon extended in explanation of regional or racial variations in leprosy in different parts of the world.[6,7] The essential idea is that vegetables of this class—aroid tuberous plants including *Colocasia, Alocasia* and *Xanthosoma*—contain a sapotoxin, the concentration of which varies with the season; that this toxin damages the adrenal cortex (at least, according to later statements,[8] "in individuals with constitutionally weak adrenals"); that such injury of that organ, of whatever cause, constitutes an important factor in leprosy. In the first place it predisposes to infection, while in infected persons it affects the course of the disease unfavorably.

Adrenal disturbance, Oberdoerffer asserts, may be due to (*a*) insufficient development in childhood, particularly in status thymolymphaticus; (*b*) lack of climatic stimulation (Mills); and (*c*) the sapotoxin-containing foods mentioned—and, he suspects, *Agrostemma githago*, the "common corncockle" of Europe. He cites Clark[9] as ascribing "general debility" and a high incidence of nephritis in taro-fed populations to the toxic properties of these tubers. Regarding seasonal variations in leprosy, he sees them in connection with onset of the disease, as well as in activity in cases; in the latter connection sapotoxin injury is likely to induce transition of the tuberculoid to the lepromatous tissue reaction. Regarding regional variations—and this is an example of his epidemiological data—he compares Nigeria west of the Niger (Yorubaland), where colocasia is not eaten and there is

[5] OBERDOERFFER, M. Untersuchungen über die prädisponierenden Faktoren der Lepra in Süd-Nigeria. *Arch. Schiffs- u. Trop.-Hyg.* **42** (1938) 367-372.

[6] OBERDOERFFER, M. Introduction to an investigation of racial differences in the clinical picture of leprosy. *Lep. Rev.* **10** (1939) 112-114.

[7] OBERDOERFFER, M. J. Regional variation of clinical types in leprosy, seasonal variation of bacteriological findings in tuberculoid leprosy, and their possible causation by sapotoxins in certain foodplants. *Compt. rend. Far Eastern Assoc. Trop. Med.*, 10th Congress, Hanoi, 1938; Hanoi, 1940, pp. 141-152.

[8] OBERDOERFFER, M. J. Uebertragung von Lepra auf sapotoxingefuetterte Affem. *Dermat. Wschr.* **109** (1939) 1407-1411.

[9] CLARK, A. *Trans. Roy. Soc. Trop. Med.* **26** (1932) 301; CLARK, A. and WATERS, R. B. *Biochem. Jour.* **28** (1934) 1131.

little leprosy, with the portion east of the Niger, where the opposite conditions obtain. He finds an explanation for the lesser incidence of the disease in women; they are partially protected by repeated stimulation of the adrenals during the menstrual cycle!

Oberdoerffer claims to have found confirmation of his views in India and elsewhere; but whereas Lowe and Chatterji[10] agree that there is an interesting seasonal variation in certain features of the disease, they cannot ascribe it to the factor claimed by Oberdoerffer. Read[11] says flatly that this theory cannot be considered seriously because many lepers never eat taro. Rodriguez, in a newspaper interview resulting from the present excitement, stated that the intensive epidemiological investigations that have been carried on in Cebu have not shown any correlation between the eating of gabi and leprosy. One is unavoidably reminded strongly of Sir Jonathan Hutchinson's effort to elucidate the etiology of the disease.

One attempt has been made to support the adrenal injury hypothesis experimentally. As reported separately by Oberdoerffer[8] and by Collier,[12] monkeys were inoculated and given large amounts of colocasia in their diet, with the development of primary and secondary manifestations that are said to have been lacking in control animals. It was believed that leprous infection had been established.

Since Oberdoerffer's return to Germany, his theory has been applied in an unusual series of arm-chair studies by Gehr. First[13] he discussed the disappearance of leprosy from most of Europe in the Middle Ages, and found for mediaeval Germany that that event coincided with the cleansing of bread-grain from the seeds of corn-cockle (*Agrostemma githago*). This author[14] also ascribes the rise and subsidence of the well-known little Memel epidemic to this factor: late in the 19th century the bread-grain of West Prussia contained up to 10 percent of corn-cockle; since 1910 this condition has improved, and coincidentally this leprosy

[10]Lowe, J. and Chatterjee, M. B. Seasonal variations in leprosy in Calcutta. *Internat. Jour. Lep.* **7** (1939) 137-148.

[11]Read, B. E. The cause and transmission of leprosy. *Lep. Quart.* **14** (1940) 117-123.

[12]Collier, D. R. Inoculation of monkeys with leprosy, following a diet of puak (Colocasia). *Thai Sci. Bull.* **2** (1940) 101-108; reprinted in *Lep. Rev.* **11** (1940) 135-140; also *Chinese Med. Jour.* **58** (1940) 213-217.

[13]Gehr, E. Ist die Reinigung des Brotgetreides von Kornradesamen mitbeteiligt am Erlöschen der mittelalterlichen Lepra? *Ztschr. f. Hyg. u. Infektionskr.* **122** (1939) 238.

[14]Gehr, E. Die Lepra im Kreise Memel. *Deutsch. med. Wchnschr.* **66** (1940) 715-720.

focus has become virtually extinct. Much farther afield,[15] he discusses the disappearance of leprosy from New Zealand, where—in complete divergence from all standard authorities, none of whom holds that that terrain has ever been invaded—he says the disease "must have been endemic for many centuries, disappearing within three generations from the time of 1830"; in that period, he asserts, taro disappeared from the dietary of the Maori, replaced by the potato. Finally, Oberdoerffer and Gehr[16] have summarized and supplemented these observations and opinions.

Difficult to accept as this theory may be, and as little accepted as it has been as yet, it is the background of the therapeutic innovation under discussion. Collier[3] states that he and Oberdoerffer "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" [i.e., to produce antibodies] "in leprosy." This statement is not explained, but it is added that they thought that diphtheria antitoxin would "neutralize leprosy toxin in the toxemic syndrome" of the disease, lepra reaction. The results obtained with that serum were soon found encouraging—those with antitetanus serum and antivenin were quite negative, it is said—and (for reasons not made clear) it was decided to try diphtheria toxoid. There has followed an apparent shift in the point of view, for, among the several possibilities suggested to explain the results reported, one is stimulation of the adrenals. Collier has said[17] that diathermy applied over the adrenal areas has given consistently good results that have persisted. Surgical implantation of adrenal glands from pigs has even been tried, on no fewer than 48 patients, with benefit claimed.

Whatever may be one's opinion of the adrenal injury theory in relation to the etiology and progression of leprosy, or of the line of reasoning that led to the application in treatment of the substances under discussion, there remains an immediate, practical question, namely, whether or not the chain of events in the patient's economy which results from that procedure does actually

[15]Gehr, E. Lepra und Ernährung auf Neuseeland. *Arch. f. Schiffs- u. Trop.-Hyg.* **44** (1940) 73-78.

[16]Oberdoerffer, M. and Gehr, E. Die Zusammenhänge zwischen sapotoxinhaltigen Nahrungspflanzen und der Lepra. *Zeitschr. f. Hyg. u. Infekt.* **122** (1940) 472-502.

[17]Collier, D. R. The use of diathermy in leprosy; a preliminary report. *Thai Sci. Bull.* **2** (1940) 109-116; also personal communication.

lead to beneficial effects that cannot be obtained by more familiar means. It is no reflection on the experimenters in question to insist that, pending ample confirmation, the question should be regarded strictly as an open one. Leprosy being what it is, much time, perhaps several years, must elapse before the real value of this treatment can be established. Collier has given some evidence of recognition of this point of view. He has also expressed a desire that workers expert in the field of leprosy should visit Chiengmai to examine his cases. That has been done by Dr. G. A. Ryrie, of the Sungei Buloh Settlements, F.M.S. The main points of his observations may be stated as follows:

From the scientific point of view, the work has been carried on under the handicaps common in most leprosy asylums, where duties are heavy and assistance inadequate, this affecting the examinations and records, though a large number of illustrative photographs has been taken. Due to overlapping of experiments, they are not in "pure culture," different methods of treatment being applied at different times to the same cases. There would also seem to be some difficulty in connection with classification, at least with respect to recognition of the more marked and least clear-cut cases of the tuberculoid form. Despite these facts, however, the impression was gained very definitely that in many of the cases there had been obtained results more favorable than would have been expected from ordinary methods of treatment. Whatever the explanation of its effects, he has written us, diphtheria toxoid merits serious attention.

Two or three references have been seen in published material to trials under way in other institutions, but nothing definite or noteworthy—or, it may be added, particularly enthusiastic—with regard to effects observed. Mention may be made of a statement received from an investigator who has been treating 40 cases for four months, and who prefers not to be cited. He gives his present impressions as follows: (*a*) that no real benefit has been seen in lepromatous cases, but harm in some when the treatment has been continued too long; (*b*) that recent tuberculoid cases, on the other hand, often—though not always—do well, as apparently do incipient cases generally; (*c*) that many—though not all—reaction cases do well, and those with nerve pain are usually relieved. It has been necessary to hospitalize a few cases with acute arthritis, low fever and edema, lasting for about a week. On the whole, our correspondent feels that the drug is not one to be used carelessly or indiscriminately, but that it is worthy of further study.

Accepting the evidence so far presented that diphtheria toxoid has some effect in at least certain forms and cases of leprosy, it may very well be that not all workers will obtain, in their cases, results as hopeful as those reported from Thailand. Indeed, it may be that the proper rôle of this drug will be found to be that of an adjuvant, for use in a limited variety of selected cases. Even so, its introduction may very well prove to be a material step forward in the discouraging field of leprosy therapy, but it would be premature, to say the least, to hold out the hope that this problem has been solved. As yet, indeed, there can be seen no justification for employing this treatment on any other than an experimental basis.

—H. W. W.

ADDENDUM

After the draft of the foregoing note had been sent to press, there came to our attention an article entitled "New Hope for the Leper," in the April 12, 1941, issue of the popular American weekly magazine *Collier's*. Illustrated by a posed photograph of Doctor Collier, and by "before-and-after" photographs of a patient (obviously a major tuberculoid case, in a state of reaction in the first photograph), the article describes this work, its initiation, and the results that have been reported.

"And, best of all," it is stated toward the end, "the resistance to infection among the children of lepers, and their other intimate associates, seems to be increased. This, Dr. Collier feels, is the most hopeful sign of all. He summarizes, with scientific caution [*sic*]:

" 'Just what the final results will be, I cannot say. . . . It would appear, however, that in the use of toxoid and antitoxin, we have a treatment which far surpasses any other method yet known. . . . Looking into the future, we cannot escape the thought that we may have opened the way to a possible means to protect the intimate associates of lepers and the general population. We know that in diphtheria, toxoid protects for life. If such is the case in leprosy, then it is conceivable that the terrible scourge will eventually be eliminated from the earth . . . At last there are rays of hope shining down the dark and lonely road of that miserable, forlorn creature—the leper! Relief is in sight!' "

The only data to be found which might conceivably be regarded as giving support to such a conclusion is contained in the following paragraph:[3] "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." The italics are ours. Comment would be superfluous.