

## THE TREATMENT OF LEPROSY WITH CONTEBEN

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The almost identical morphological and staining properties of tubercle and leprosy bacilli permit the assumption of a close biological relationship of these acid-fast microorganisms. In addition, there is the fact that the development of leprosy and of tuberculosis is based upon an obviously similar combination of constitutional factors. The frequent cause of death in leprosy is not leprosy itself but tuberculosis, since the Koch bacillus is by far the more pathogenic microbe for man. Since leprosy would seem to be by far the older of these two diseases of man caused by acid-fast bacilli, there has existed a much longer period for adaptation of the human organism to the Hansen bacillus than to that of Koch.

The relationship of these microorganisms and the similarities of the constitutional factors involved in the two infections result in numerous common features in both the pathological-anatomic characteristics and the clinical pictures of these diseases. It is natural, therefore, that experiences gained in the treatment of tuberculosis should be made use of in the therapy of leprosy. Thus, for example, the well-known hygienic-dietetic treatment, especially with food with a low salt content, which has proved effective in cutaneous tuberculosis has also proved effective in leprosy. Long before sulfone preparations were used in the chemotherapy of leprosy, an attempt had been made to use them in the treatment of tuberculosis.

The chemotherapy of tuberculosis has received a tremendous stimulus in recent years through the discovery by Domagk and co-workers (3) of the tuberculostatic action of the thiosemicarbazones, especially of conteben (sometimes called TB-1, or tibione). The favorable experiences with this new drug over a period of several years, reported in more than 375 papers to date, led to the expectation that leprologists would soon take it up. The experiences in leprosy recorded so far, although neither extensive nor prolonged, are most promising. It is all the more remarkable that this drug appears to be particularly effective in lepromatous leprosy, which—at least before the introduction of the sulfones—was regarded as practically re-

fractory to therapy and therefore of the worst prognosis, and which represents epidemiologically the most important form of the disease because of the massive dissemination of the bacilli.

Since autochthonous leprosy no longer occurs in Germany, the first observations of the effect of conteben in this disease could be made only in single cases. The patients have been people returned from leprosy countries.

In the first case of leprosy treated with this drug, Hohenner (5) described "retrogression of the lepromas, which follows such a rapid course that after a few days they could hardly be detected at all by palpation."

This excellent effect, especially on the lepromatous manifestations, was soon confirmed by Grosch and Kaliebe (4). In the course of conteben treatment of their case the lepromas and the acrocyanosis vanished rapidly, the ulcers healed, and the disease changed from the lepromatous course to the prognostically favorable tuberculoid course. After six months of treatment degenerative changes in the bacilli were observed. "In the previously extremely positive nasal and wound smears, it was possible to find only acid-fast residual forms and granulations." These retrogressive changes in the lesions and bacilli permit the assumption of a direct, specific action by conteben on the leprosy bacillus and the leprous tissues. The relatively slow decomposition of the bacilli under the influence of conteben may be attributed to their special structure and the slow metabolic process of the acid-fast bacilli.

Walter (15), who reported on the same case as Grosch and Kaliebe, particularly emphasized the rapid and marked effect of conteben on the lesions of the mucous membranes. There had been extensive ulcerous lesions of the larynx, throat and mouth, changes which are frequent in advanced lepromatous leprosy and hitherto overcome only with the greatest difficulty. The conteben treatment led to rapid normalization of the voice, complete relief from the pain usually associated with swallowing, which hinders the taking of food, and retrogression of the lepromas and vanishing of the leprous infiltrates. Walter described conteben as the sovereign remedy for the leprous affections of the mucous membrane.

The action of conteben on the leprous affections of the mucosa of the nose, throat and larynx has made a deep impression on all who have had an opportunity of observing it. Obviously in conditions where, because of good penetration by the blood stream, conteben reaches the disease focus in adequate

quantities—for example, in fresh leukocytic inflammatory (i.e., reactional) processes—it has a rapid and prolonged effect. Fresh ulcerous processes respond better to conteben than the old granulomatous ulcers, which have little tendency to reaction.

Vegas and associates (14), who have treated 42 lepromatous cases with conteben, reported the retrogression of the erythematous infiltrative and nodular lesions in the skin, clearly evident from the second month of treatment. At the end of the fourth month the erythematous patches had vanished in all cases, and in the majority of patients the lepromas had also subsided. The infiltrates retrogressed in an impressive manner, and the lesions of mucous membranes improved considerably.

Ryrie (10) recorded results with conteben such as he had never achieved by other means, in 10 cases—8 lepromatous and 2 chronic tuberculoid—treated for four months. He found it effective even in advanced and old lepromatous cases, and cases of that type which had failed to respond to treatment with sulfone compounds or paraaminosalicylic acid, or had deteriorated under it.

A similar report has been made by Schneider and co-workers (11) who, after observing a good response in a case in Paris which had not responded to any other therapy, treated 13 others in Africa with good results and no notable evidence of intolerance. Ceccarini (2) also obtained good results in a refractory case of lepromatous leprosy which had not responded to sulfone, PAS, streptomycin or vitamin D<sub>2</sub>. Johansen and Erickson (6), from the leprosy hospital at Carville, Louisiana, have said that they regard conteben as one of the most promising drugs outside of the sulfone series for further clinical testing.

All of the reports as yet available point to the conclusion that conteben is capable of causing reduction of the leprosy infection. Naturally, the drug is unable to overcome the disposition which first imparts the malignant character to the infection in lepromatous cases. If that disposition is maintained, every leprosy focus which is overcome is liable to be reinfected, either exogenically or endogenically; but the disposition factors can be influenced by general hygienic and dietetic treatment. This includes above all roborant treatment, and a diet which is poor in salt and with restricted carbohydrates but rich in albumin and, above all, vitamins and fat. A further condition for the permanent success of conteben treatment is the overcoming of any other concomitant infections which may be present.

As can be seen from the extensive literature of recent years,

particularly of Anglo-American origin, the sulfone compounds have similarly proved effective for the treatment of the lepromatous form of leprosy, but the more recent papers now available suggest that conteben has a considerably greater effect in a much shorter period. Whereas the success of the sulfone treatment in advanced lepromatous cases often does not become manifest until after a year, the effect on the lepra bacilli appearing even later, the effect of conteben treatment can be generally observed within four months, evident in the improvement of the general condition and the clinical findings (10, 14).

Sulfone preparations are cheaper than conteben—a point which plays an important part in leprosy countries, which are often economically underdeveloped. That difficulty will be compensated if it proves true that with the correct conteben treatment the same therapeutic effect can be achieved in a materially shorter time.

It is hardly to be expected that the results of treatment can be improved by a combination of conteben with a sulfone preparation. Both are sulfur-containing compounds, and their effects are probably gained by a similar mechanism.

A further advantage of conteben for the treatment of leprosy is that it is better tolerated than the sulfone preparations. Unlike them, it causes practically no serious by-effects. Accurate control is, however, advisable with patients who are disposed to allergic diseases, such as asthma, urticaria, eczema or acute polyarthritis, in order to permit timely recognition of the effects on the hematopoietic system which occur in very rare cases. However, the experience of Ryrie indicates that it is not necessary to control the blood as strictly as is required during the application of the sulfones.

Vegas and associates also emphasize the excellent tolerance of their patients for conteben. In their cases they observed neither changes of the blood nor of the liver function, or any other damage. Schneider and co-workers emphasize that in their nine months of experience no by-effects occurred which required interruption of the treatment. There had been no detectable damage to the hematopoietic system, and the liver function had been uninfluenced. The low effective toxicity of the leprosy bacillus probably contributes to the particularly good tolerance of conteben.

The by-effects occasionally observed during conteben treatment include anorexia, stomach pains and nausea, and resultant initial loss in weight, particularly after overdosage. As a rule,

however, the patients get accustomed to the remedy in the further course of treatment.

The observations of Stuehmer (13), Brandner (1) and others, who have reported the frequent occurrence of allergic symptoms in patients suffering from cutaneous tuberculosis who had eaten salted fish during conteben treatment, are of interest. Brandner considers the cause to be a dietetic allergy which is connected with the conteben effect. He assumes that conteben acts as a hapten, and that with certain protein substances in the diet a compound can result which forms a full antigen. His observation that these reactions can be weakened or completely suppressed by antihistamines supports the view that they are of allergic nature. If these patients are given milk in some form before taking conteben, these allergic symptoms can apparently be suppressed (calcium effect?). Protein decomposition products formed by decay in old cheese or stale meat are also reputed to be able to give rise to these allergic symptoms. If conteben is able to give rise to certain allergies in combination with nutritional proteins, it is certainly not due to the conteben molecule itself, but to the formation of a drug-protein complex and its action as a whole.

In the leprosy literature, since more than 500 years ago, reports have appeared to the effect that the eating of dried and salted fish exercises an unfavorable influence on the course of leprosy (7). Klingmüller, in his well-known treatise (8), enumerates 42 papers which deal with this question. Although there are no reports available on the setting up of allergic reactions after leprosy patients have eaten salted fish during conteben treatment, this aspect would appear worth consideration.

As Domagk has proved, conteben exerts a bacteriostatic influence on tubercle bacilli, and it may be assumed that this is also valid for the leprosy bacillus. The success of conteben treatment does, however, certainly depend upon the cooperation of the organism. Besides the bacteriostasis, a nonspecific tissue action which is connected with antiallergically effective factors is also of decisive importance for therapeutic success. Leprosy is a complex condition which comprises the results of the pathogenic action of the bacilli and the reaction of the organism to their presence. The connection between chemical and neurological allergic processes is generally recognized today (9, 12), and its cooperation with humoral, infectious and toxic factors is indispensable for the understanding of the leprosy syndrome. As a hypothesis, it may be assumed that conteben intervenes in



allergic reactions of the leprous organism by altering the susceptibility to such reactions. A pronounced antiexudative effect stands in the foreground of the action of conteben. The best successes of conteben treatment are, therefore, to be observed in the acute form of leprosy; and, indeed, the action is the more striking the more severe the defense struggle or the more sensitized the organism. For this reason conteben is particularly effective when the multiplication of the bacillus is predominant, i.e., in the lepromatous condition.

The observation has been made that the rapid retrogression of the lepromatous lesions during conteben treatment, especially fresh inflammatory reactional foci, is by no means paralleled by the decomposition and reduction in the numbers of bacilli; only after a number of months is a slow but persistent reduction in their numbers to be observed. The impression has been given that, despite almost complete retrogression of the lesions, the bacilli in the tissue had actually increased in numbers. It may be assumed with certainty that no actual increase in their numbers takes place in the earlier months of treatment, but that because of reduction of the lesion mass, without correspondingly rapid destruction of the bacilli originally present in it, there is created a false impression of an increase.

As regards the dosage of conteben in leprosy, on summarizing the experiences available it appears that small doses have proved most effective at the beginning of the treatment. A dose of 25 to 50 mgm. ( $\frac{1}{2}$ -1 tablet of 0.05 gm.) per day has been recommended for the initial dose. The daily dose is then raised to 100 mgm. or a maximum of 150 mgm., according to the form and stage of the disease and the tolerance of the patient. It would seem that a daily dose of 150 mgm. should not be exceeded, even with good tolerance. The disadvantages of over-dosage are more serious than those of inadequate dosage. The action of conteben depends not only on the blood level attained, but also on the reaction of the organism; and the latter is the more decisive for the development of the therapeutic regimen in leprosy. With over-dosage very undesirable reactional conditions may easily develop, resulting in aggravation of the lesions and new hematogenous dissemination of the bacilli. As in chemotherapy as a whole, so also in the treatment of leprosy with conteben, the success of the treatment depends to a great extent on an optimum dosage. In the labile and sensitive lepromatous form of leprosy particular consideration must be given to the adjustment of the dosage to the individual, and advance to

the optimum level should be made carefully and with consideration of all the clinical data.

Despite large expenditures of money, few leprosy countries have as yet succeeded in limiting the spreading of the disease. Failure has been due primarily to the fact that with the methods of treatment hitherto available it was completely impossible to influence therapeutically and render negative the lepromatous cases, which are to be regarded as the primary sources of infection. Attempts at thorough compulsory isolation of all cases of leprosy has proved unsuccessful, for the affected individuals stay under cover as long as possible and serve as disseminators of the infection. When it becomes known that it is possible to stop the deterioration of their condition and to render them negative and thus noninfectious within a limited period, then they will report voluntarily and in good time for treatment. With the period of isolation and treatment reduced to within reasonable limits, and with early discharge to subsequent outpatient care, the treatment and control of leprosy will not only become more humane, but it will also be much less expensive and considerably more successful epidemiologically than hitherto.

*Addendum.*—To complete this review as known to the time of going to press, note should be made of a preliminary report by J. Gómez Orbaneja, M. Such and A. García Pérez, entitled *Resultados del tratamiento de la lepra con tiosemicarbazona* [Rev. IBYS 9 (1951) 7-13]. They had used it in eight cases, one treated for 11 months, the others for 4 months, with such good results that they had started more cases on this drug. In seven cases the nasal mucus had been bacteriologically positive, and in five it had become negative. They, as others, saw improvement in cases which had to a certain degree been resistant to the sulfones.—EDITOR.

#### ABSTRACTO

Debido a las semejanzas entre los agentes etiológicos de la tuberculosis y la lepra, y las características clínicas que ambos producen, es lógico pensar que una droga de valor en una de éstas enfermedades lo sea también en la otra. El "tiosemicarbazono" de Domagk y colaboradores, llamado "conteben" en Alemania que es de valor probado en la tuberculosis, ha demostrado promesa en el tratamiento de la lepra a aquellos que lo han usado.

En Alemania, dos casos han sido tratados, con resultados excelentes. Reportes de otros sitios, Vegas et al de Venezuela, Ryrie de Inglaterra, Schneider et al de Africa, Ceccarini de Italia, y Johansen y Erickson en los Estados Unidos, todos son favorables.

Se opina que el conteben demuestra efectos benéficos más rápidamente que las sulfonas, aunque cuesta más que éstas, pero también es mejor

tolerado. Sus efectos no solo son bacteriostáticos, sino que actúa como agente antialérgico, aunque en ciertas condiciones la droga en sí puede ser la causa de alergia. La dosis óptima y no la máxima debe ser usada.

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