

## Progress in the Chemotherapy of Leprosy as Reflected in the International Congresses

In the forthcoming International Leprosy Congress in London in September of this year the chemotherapy of leprosy will receive renewed consideration. It has been a major subject of discussion ever since the first congress after the founding of the International Leprosy Association. Papers will be presented on its experimental and clinical aspects, and distinguished chairmen have been selected to preside over the sessions devoted to these subjects.

It seems appropriate at this time to review the development of chemotherapy in leprosy as reflected in the reports of previous international leprosy congresses. At the Cairo congress, in 1938, the first of the international leprosy congresses in which the International Leprosy Association was a primary organizing element, papers were submitted on the distribution of leprosy, its epidemiology and control, its clinical aspects, and its therapy, with a somewhat smaller number on its bacteriology, immunology, and chemistry. The papers that were devoted to therapy are of special interest now because they represented what proved to be the end of an era, that of dependence on chaulmoogra oil in the treatment of leprosy. The Sub-Committee on Treatment,<sup>1</sup> under the chairmanship of

Dr. G.A. Ryrie of the Sungei Buloh Settlement, in summarizing current views on therapy, stated that as far as current knowledge went, hydnocarpus oil and its esters, administered intramuscularly, subcutaneously, and intradermally, remained the most efficacious drugs for the special treatment of leprosy.

Attention was devoted in the subcommittee's report to such practical factors as methods of administration, dosage, and toxicity. There was virtually no foreshadowing, however, of the specific antimicrobial therapy to come. Treatment by certain aniline dyes, and potassium iodide, was mentioned briefly, but with disapprobation, and in conclusion the subcommittee agreed that no form of treatment was wholly satisfactory and urged vigorous prosecution of therapeutic research.

In passing we may note that a huge literature had accumulated on the action of chaulmoogra oil in leprosy, a medicament that had been used in leprosy to some extent for centuries, but studied scientifically chiefly after fresh interest had been focused on it by Leonard Rogers in 1916. The supposed effectiveness of the drug was attributed in later years, and rather vaguely at the best, to the oleolytic properties of the oil and its derivatives, and their surface effect on the lipid-rich mycobacteria. By 1938, however, in spite of official pronouncements, a mounting dissatisfaction

<sup>1</sup> [CONGRESS, CAIRO] The treatment of leprosy. Report of the Subcommittee on Treatment. The Cairo Congress, March 1938. *Internat. J. Leprosy* 6 (1938) 397-400.

with the drug was evident, and the time was indeed ripe for its replacement.

The next international leprosy congress was ten years later, the projected Paris meeting for 1943 having been cancelled inevitably by World War II. It is interesting to speculate on what might have been discussed in the field of chemotherapy had the Paris meeting been held. Encouraging results with the drug Promin were reported in that year, but few investigators as yet had had experience with it. As late as the preceding year the eminent authority Leonard Rogers<sup>2</sup> had written "The great progress made during the last two decades in the control of leprosy is essentially based on the discovery of more efficient treatment by injection of suitable preparations of chaulmoogra and hydnocarpus oils, and on studies of the epidemiology of the disease, by means of which the whole outlook of the unfortunate sufferers from leprosy has been immeasurably improved."

By the time of the Havana meeting in 1948, however, the break from chaulmoogra and hydnocarpus oils had been made. But these long-used therapeutic agents were not yet wholly discarded. The Committee on Therapy,<sup>3</sup> under the chairmanship of Dr. L. Souza-Lima of São Paulo, noted that much progress had been made since the Cairo Congress, calling attention to the introduction of the sulfone drugs, notably Promin, Diasone and Sulphetrone, but adding that there had been progress also in the employment of hydnocarpus (chaulmoogra) oil, particularly through the use of larger doses than had been employed hitherto. The Committee pointed out that the new synthetic derivatives of diaminodiphenyl sulfone satisfied what it considered minimal therapeutic requirements to be established by clinical research, viz., (1) direct or indirect evidence of antibacterial action against mycobacterial diseases, (2) effective use without evi-

dence of toxicity or irreversible physiologic change, and (3) freedom from undue discomfort of the patient on administration of the drug. Of the proffered papers for the meeting more than forty represented experience with one or more of the sulfone drugs, while only half a dozen dealt specifically with chaulmoogra oil, and some of these with combinations of the oil and a sulfone drug.

The Havana committee discussed dosage, toxicity, and drug sensitivity and resistance. A review of the papers read at the Congress indicates that the results reported were largely empirical. Satisfactory studies of the nature of action of the drug were not to come for some years.

In 1953, at Madrid, the favorable results of current sulfone therapy were stressed by the Committee on Treatment,<sup>4</sup> under the chairmanship of Dr. Jose N. Rodriguez of Manila, but emphasis was placed on its frequent inadequacy, and the need for other measures, and the discovery of new antimicrobial drugs, for ultimate success in leprosy therapy. The discussion covered the mono- and disubstituted sulfone preparations available, their dosage, and their toxicity. It was noted, in what seems to have been an early pronouncement on the nature of their effect, that their mode of action in leprosy was not clear; the most, apparently, that could be said with any confidence was that they were apparently not bactericidal, but might be bacteriostatic.

In the period since the preceding congress several new drugs had been investigated. These included a number that had proven of more or less value in tuberculosis. Prominent among them were streptomycin, the thiosemicarbazone designated TB-1, isonicotinic acid hydrazide (isoniazid, INH), para-aminosalicylic acid (PAS) and the hormones ACTH and cortisone. For most of these, striking results were not recorded, although virtue was apparent in special situations, as in the case of cortisone in acute lepra reaction. It was noted, not

<sup>2</sup> ROGERS, L. Progress in the control of leprosy in the British Empire. *Internat. J. Leprosy* **10** (1942) 87-95.

<sup>3</sup> [CONGRESS, HAVANA] Therapy. Report of the Committee on Therapy. Vth International Leprosy Congress, Havana, April 1948. *Internat. J. Leprosy* **16** (1948) 209-221.

<sup>4</sup> [CONGRESS, MADRID] Treatment. Report of the Committee on Therapy. Vth International Leprosy Congress, Madrid, October 1953. *Internat. J. Leprosy* **21** (1953) 516-526.

surprisingly, that "nearly all workers had abandoned the use of chaulmoogra oil in favor of sulfone treatment."

Five years later, in 1958, at Tokyo, the Committee on Therapy,<sup>5</sup> again under the chairmanship of Dr. Rodriguez, cited 4,4'-diaminodiphenyl sulfone (DDS) as the drug most widely used. The dosage was noted as variable, according to circumstances, ranging from 600 to 1,200 mgm. per week. Somewhat more emphasis than previously was accorded to the toxic episodes occurring during DDS treatment, particularly erythema nodosum leprosum, a complication, incidentally, for which treatment with corticosteroids had been found efficacious. Special attention, too, was devoted to the phenomenon of relapse.

Reports had accumulated since 1953 on all the drugs to which attention was devoted at the Madrid congress, but a few new ones were now under scrutiny, particularly certain thioureas, including thiambutosine (DPT, Ciba 1906), which had been studied in several centers and found therapeutically active and essentially devoid of toxicity. Other drugs to which attention was called included a chemical relative of DDS, diaminodiphenyl sulfoxide (DDSO), and the tuberculostatic antibiotic cycloserine. In the case of several of these drugs high cost was noted as an element limiting their use.

The last conference held, that of Rio de Janeiro in 1963, is presumably still fresh in the minds of readers of THE JOURNAL. The committee on Therapy,<sup>6</sup> under the chairmanship of Dr. S. G. Browne, then of Uzuakoli, Nigeria, reviewed a lengthy list of drugs, some of them of long standing as antileprosy drugs, and others that were not new but had come into special prominence in more recent years. The latter group included compounds capable of releasing ethyl mercaptan, a substance of known

antimycobacterial activity *in vivo*; prominent among them was diethyldithiolisophthalate (Etisul, ETIP), which has figured in numerous studies since then.

Special attention was given to the long-acting sulfonamides, which appeared advantageous in that administration, while oral, was necessary only once a week. The group included sulfamethoxypyrazine, its acetyl derivative (Kelfizine, or 11,589 R.P.), and the drug known as Ro 4-4393.

Other newly conspicuous drugs to which the committee gave attention included B.663, a "rimino" phenazine derivative of analinoaposafranine, and a series of antibiotics that had given favorable results in tuberculosis. The committee redefined, and more closely than hitherto, the requirements that must be fulfilled in good chemotherapy, and stressed the need for more effective drugs in the treatment of long-standing lepromatous leprosy, and the reactional tuberculoid forms. A new emphasis was set forth on the desirability of recording changes in the bacterial index, and particularly on the morphologic index in terms of the percentages of solid- and non-solid-staining forms of *M. leprae*, in assessing changes in leprotic lesions under treatment.

In effect a steadily growing emphasis is evident, in this long series of deliberations by successive committees on therapy of the International Leprosy Association, on precision and control in determining the success or failure of a tested drug. There is a constant but restrained expression of commendation for DDS in the treatment of the various manifestations of leprosy, marked, however, by an undercurrent of something less than satisfaction in its not infrequent inadequacy in individual circumstances and the long period of administration required for good results. Clearly a more steadily effective drug appears desirable, with such elements in mind as drug resistance, toxicity, reactive episodes, relapse after treatment and other untoward circumstances. The search obviously continues, and the periodic reports of the committees on therapy show that the tempo of exploration is increasing. It will be interesting to see what develops at the forthcoming ninth congress.—E.R.L.

<sup>5</sup>[CONGRESS, TOKYO] Therapy. Report of the Committee on Therapy. VIIth International Congress of Leprosy, Tokyo, November 1958. *Internat. J. Leprosy* **26** (1958) 389-394.

<sup>6</sup>[CONGRESS, RIO DE JANEIRO] Report of the Panel on Therapy. VIIIth International Congress of Leprosy, Rio de Janeiro, September 1963. *Internat. J. Leprosy* **31** (1963) 483-485.