

# Approaches to Clinical Research

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The efficacy of the sulfones in the treatment of leprosy was proven in a controlled study by Doull *et al.* (<sup>5</sup>), but, because it takes several years to arrest the disease in a case of leprosy and make it bacteriologically negative, search for more effective drugs has continued to the present time.

Several drugs found effective in human leprosy have been evaluated by Doull (<sup>5</sup>) and Doull *et al.* (<sup>6,7</sup>) in controlled studies. Only dihydrostreptomycin was found equal to the sulfones, and it was not superior. Para-aminosalicylic acid, isoniazid, Ciba 1906, cycloserine, and pyrazinamide were all found less effective than DDS as antileprosy drugs. The sulfones were originally proven ineffective in human tuberculosis, but later found effective in leprosy. Perhaps many similar drugs are active against acid-fast infections *in vitro* and in laboratory animals, and should be tried and evaluated in leprosy also.

The literature furnishes records of several drugs that have been tried in human leprosy in uncontrolled pilot studies. Those who tried them recommend more intensive trials in a larger number of patients and for longer periods of observation.

## CONTINUED SEARCH FOR ANTILEPROSY DRUGS MORE EFFECTIVE THAN DDS

Since it takes two years or more to bring about clinical arrest in a mild case and cause it to become bacteriologically negative, and from five to ten or more years to

attain similar results in a moderately advanced or advanced case, the first approach to clinical research is to continue more intensive search for better drugs than DDS. The following may be suggested:

1. Ro. 4-4393, a long acting sulfonamide tested in uncontrolled trials in a few cases by Lopes and Diniz (<sup>10</sup>) with encouraging results.

2. Capreomycin, reported by Shepard (<sup>13</sup>) to be active against *M. leprae*, and of low toxicity for man. He suggests a controlled therapeutic trial in human leprosy.

3. B.283, a dye derivative of phenylphenazine, claimed by Lane (<sup>8</sup>) to be effective in urinary tract tuberculosis in man, and found by Allday and Barnes <sup>8</sup> to bring about bacteriologic negativity in three out of ten lepromatous patients treated with this drug.

4. B.663. In a previous study Chang (<sup>3</sup>) found complete resistance to isoniazid alone for 407 days. In a later study, it appeared that combined therapy had prevented the acquisition of resistance against isoniazid in a period of 27 months. A trial of combined treatment of leprosy with B. 663 and isoniazid is suggested by Chang.

5. Ethionamide. Schwartz (<sup>12</sup>) found that ethionamide and isoniazid, when combined with streptomycin, are of approximately equal therapeutic efficacy in tuberculosis as measured by x-ray change and conversion of sputum. Although approximately equally effective in tuberculosis, ethionamide may prove more effective than isoniazid in leprosy.

Since the clinical researches by the Leonard Wood Memorial from 1952 on have been limited almost exclusively to the clinical evaluation of antileprosy drugs,

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it is now time to look for other lines to investigate. The following subjects may be interesting for clinical research.

#### MULTIPLE DRUG THERAPY GIVEN ALTERNATELY INSTEAD OF IN COMBINATION

Claims to the contrary notwithstanding, observations in five clinical evaluation series conducted by Doull<sup>(5)</sup>, and Doull *et al.*<sup>(6,7)</sup> with eleven combinations of two drugs, showed that dihydrostreptomycin (DHSM), isoniazid (INH), pyrazinamide, nicotinamide, antigen marianum, and Etisul, when combined with Diasone, or in the case of DHSM with INH or PAS, and in the case of INH with either Tibione, nicotinamide or Diamidin, gave no better results than each component drug administered singly. The explanation may be the development of resistance of *M. leprae* to the two component drugs simultaneously. Double-drug and triple-drug therapy have been tried also by Aguilar Filho and associates<sup>(1)</sup> in tuberculosis, without apparent advantage over the single drug. This unfavorable finding may be remedied by giving the two or more drugs alternately for short terms of two or three months each, in order to allow no time for the microorganisms to develop resistance before therapy is shifted to another drug.

Drug resistance is observed in many patients who improve at the beginning of treatment and then remain stationary for a long time. A change in chemotherapy often causes these cases to improve further. Some patients, however, cease to improve after some time with new drugs. Hence alternate administration of drugs in short terms in resistant cases is worth trying.

#### SEARCH FOR A NEW METHOD OF ASSESSING EFFICACY OF ANTILEPROSY DRUGS

In the chaulmoogra era many leprosy workers observed that intradermal injection of iodized ethyl esters of *Hydnocarpus wightiana* was far superior to injection by the intramuscular route in effecting resolution of leprotic lesions. In cases alternately improving and worsening, Cochrane<sup>(4)</sup> advocated combination of intradermal injection

of these ethyl esters and sulfone treatment, which he believes is the most logical treatment of leprosy, claiming that it is the only method through which persistently positive cases can be rendered negative in a reasonable period of time. These clinical observations have been confirmed by Nolasco<sup>(11)</sup> in histopathologic studies of tissues of patients treated by the same method.

It would be interesting, therefore, to learn if intradermal infiltration is not superior to the other modes of administration of antileprosy drugs other than chaulmoogra compounds, and at the same time a quicker means of assessing the value of a new drug.

#### DETERMINATION OF THE LOWEST EFFECTIVE DOSE OF DDS

The first recommended dose of DDS was 200 mgm. daily, or 1,200 mgm. a week. In 1957 a lower dose, of approximately 100 mgm. a day, or 600 mgm. a week, was evaluated in Leonard Wood Memorial clinical studies and found to be just as effective as the higher dose. At the VIth Conference of the Association of Indian Leprologists in January 1965, a report was read by Browne<sup>(2)</sup> on studies in which doses of 100 mgm. and 50 mgm. of DDS given twice a week were found to result in clinical and bacteriologic improvements comparable to those noted with much higher doses. The question arises if the dose cannot be reduced still further and still be effective, and if so what would be the lowest effective dose of DDS? The minimum dose may not necessarily be the optimum dose, but still it is of interest to know how much the minimum dose would be.

#### THE ROLE OF THE THYROID GLAND IN LEPROSY

Hypothyroidism may manifest itself in advanced cases of myxedema, characterized, among other features, by nonpitting edema of the face, hands, and feet; dryness of the skin, and absence of perspiration; dryness and loss of hair; brittleness and atrophy of the nails; paresthesia; anemia; and change in the plasma protein levels—all of which are also present in leprosy. It would be of

interest to learn if the thyroid gland plays a role in the production of these signs and symptoms in leprosy. As far as known, this point has not yet been investigated.

#### **EFFECT OF LEPROMIN TESTING ON IMPROVEMENT OF LEPROSY WITH VARIOUS ANTILEPROSY DRUGS**

Before the start of the clinical evaluation studies in the Eversley Childs Sanitarium in 1952, only a few cases under special study were lepromin-tested, because the patients, in general, refused to submit to this test in the false belief that they would become worse. In order to combat this refusal, newly admitted patients, who were ignorant of this erroneous belief and, hence, still cooperative, have been lepromin-tested on admission since 1953. The number of patients whose leprosy became arrested by treatment and who were discharged went up from an average of 2.5 per cent in five years before the general lepromin-testing of patients in 1952 to an unprecedented average of 15.2 per cent in the subsequent 10 years. In the Central Luzon Sanitarium, where routine lepromin-testing was not done, the percentage of paroled patients for the same period was only 9.1 per cent. It is of course unjustified at this stage to conclude that the testing was responsible for the rise in percentage of discharged patients in the Eversley Childs Sanitarium in the 10 years subsequent to the testing, because the conditions of the patients may have been quite different before and after the start of the lepromin testing of newly admitted patients, and also may be different in the two leprosaria. It would be interesting, however, to find out what role, if any, lepromin testing plays in the improvement of cases under therapy.

#### **INCIDENCE OF LEPROSY AMONG CHILDREN OF LEPROUS PARENTAGE AND SPONTANEOUS HEALING OF THEIR DISEASE**

Lara and Nolasco<sup>(9)</sup> found that many of the children of leprosy patients born in the Cullion Leprosarium and observed for 24 years have developed unquestionable leprotic lesions. The disease in approximately

three-fourths of these infected cases healed spontaneously, in spite of their continued residence in the infected environment. The morphology of the initial lesions was described as papulo-nodular, scar-like, indurated lichenoid (pebbled), wheal-like, raised macular, and flat macular. The initial lesion is now considered to be the indeterminate form of leprosy. This form was described by the Committee on Classification of the International Congress of Leprology in Madrid in 1953 as flat skin lesions, which may be hypopigmented or erythematous, and as essentially of the "simple macular" type. Probably Lara and Nolasco are, thus far, the only ones who have reported findings on the spontaneous healing and morphology of the initial lesions in children.

#### **CONTROLLED STUDY OF SULFONES IN TUBERCULOID LEPROSY**

In nonlepromatous leprosy, the course is characterized by a tendency to spontaneous remission, which is very slightly evident, if it exists at all, in the more stable lepromatous type of the disease. For this reason, and in order to minimize as much as possible the role played by improvement due to the natural remissions of the disease, only patients in whom the disease has been diagnosed as lepromatous, and who are positive bacteriologically and negative to lepromin, have been used in the clinical evaluation studies of antileprosy drugs. As a result the activities of antileprosy drugs are known mainly as they affect the lepromatous type, and little, if anything, is known as to their effect also on the tuberculoid and other nonlepromatous forms. It is timely, therefore, to assess antileprosy drugs also in the tuberculoid and other nonlepromatous cases.

#### **DRUGS IN THE PREVENTION AND TREATMENT OF LEPRO REACTIONS**

The only drugs that can control lepra reactions effectively, especially erythema nodosum leprosum, are the corticosteroid hormones and ACTH, but the reaction recurs soon after the drugs are discontinued. For this reason, they cannot be considered as really effective drugs for reactions.

Search for drugs that produce more permanent improvement, or can suppress the reaction permanently, should be intensified.

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**Dr. Skinsnes.** Thank you, Dr. Tolentino. I suggest that we proceed with the other two papers, which are related to the one Dr. Tolentino just gave, and recapture a little discussion time thereafter. So from the Chief of Clinical Research of the Leonard Wood Memorial in Cebu, on the other side of the world, we will move to a

paper by Dr. Vernon Knight, who is Chief of Laboratory Clinical Investigation at the National Institute of Allergy and Infectious Diseases of the National Institutes of Health in Bethesda. In order to conserve time Dr. Knight will introduce his colleague Dr. Williams immediately after his own talk.