TREATMENT [1]

General

In the report of the Fifth International Leprosy Congress, held in Havana in 1948, sulphone treatment of leprosy was discussed and very favourable results were recorded. In the five years that have passed since then the use of the earlier forms of sulphone treatment have been continued and extended, new forms of sulphone treatment have been developed and very widely applied, and much more information is now available. In general, the value of the sulphones in the treatment of all forms of leprosy has been confirmed, but at the same time certain limitations of the treatment have become more apparent. In the present report an attempt is made to assess the present position.

During these five years, new chemotherapeutic agents and antibiotics originally developed for use in tuberculosis have been used in leprosy. The results of such trials are here considered, and a preliminary assessment of them is attempted.

Sulphone Treatment

The Committee is agreed that the sulphone drugs have been proved by twelve years of clinical trials to be more effective than any treatment previously used. At present they must be considered the basic treatment of all forms of leprosy.

Forms of sulphone treatment.—A variety of mono- and di-substituted forms of sulphone drugs have been prepared and tried clinically since 1941, but there is no clear indication that any one compound is more effective than any other. The parent drug, 4,4'-diaminodiphenyl sulphone (DDS), once found too toxic for use in man, has been used extensively since 1948 in a much reduced dosage, and is safe and as effective as the substituted compounds. The smallness of the dose of D.D.S. makes it much less expensive to use than the compounds.

The tolerance of different people and different races to sulphones appears to vary. The standard dose of D.D.S. for adults should not be less than 300 mg a week, and not more than 1,200 mg. a

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1 The Committee on Treatment was composed as follows: Dr. José N. Rodriguez, *chairman*, Dr. Lauro de Souza Lima, *vice-chairman*, Dr. José Gómez Orbaneja, *secretary*, and Drs. A. R. Davison, H. Floch, John Lowe, Salomón Schujman, M. Santos Silva, and Rolla R. Walcott, *members*.

week. The drug can be given daily, on alternate days, twice weekly, or weekly. It can be given by mouth or by intramuscular injection. The very large number of complex sulphones now in use makes it impossible to give here details of dosages. The dosages of some of them are detailed in the proceedings of the Havana Congress.

Induction and maintenance.—Gradual induction of sulphone treatment is of paramount importance. Even in robust patients the initial dose should be about one-fourth of the standard, and the gradual increase to the standard should take six to eight weeks. In debilitated patients the initial dose should be lower and the increase slower. Regular treatment must be maintained, but some workers find brief rest periods desirable. Increase of the dosage above those generally accepted may increase toxicity and does not improve results. Attempts to improve treatment by giving sulphones in combination with other therapeutic agents have been made, without conclusive results.

Toxicity and complications.—The following toxic effects of sulphone therapy have been recorded: allergic dermatitis, psychosis, hepatitis, anaemia and anorexia. Of these, dermatitis and psychosis are the most serious. The frequency and severity of these conditions vary widely in different parts of the world.

Various complications may arise during sulphone treatment, among which are erythema nodosum leprosum, neuritis, eye complications and other sub-acute manifestations.

The above toxic effects and complications necessitate careful regulation of the treatment to the individual patient, stoppage of treatment for a period, or occasionally a change to another form of treatment.

Mode of action.—The mode of action of sulphone drugs in leprosy is not clear. They are apparently not bacteriological; they may be bacteriostatic.

Results.—The *early results* of sulphone treatment as described below are recorded by almost all workers. Most patients show decided clinical improvement within a period of months after the treatment is begun. There is usually an improvement of general health with increased appetite, body weight and strength, which is accompanied by a decrease of distressing symptoms due to the disease. Specific lesions usually recede. Bacteriological improvement is slower than symptomatic and clinical improvement.

Experience of the *later phases* and *end results* of treatment varies widely. In some centres, after prolonged treatment, clinical and bacteriological arrest of the disease has been attained in a high

proportion of cases, and has been maintained over a period of years. In other centres, arrest has occurred in only a relatively small proportion of cases, and relapse has not been uncommon; such findings have led to the suggestion, that after long treatment, sulphone resistance may develop in the bacilli. There is no strong evidence for or against this idea.

The type and the duration of the disease before the institution of treatment vary widely in different centres, and this has an influence on the duration of treatment needed to arrest the disease, and on the end results of treatment.

Further, it is generally accepted that the severity of leprosy differs in different races, and it seems likely that the response to treatment will vary correspondingly.

These two factors may help to explain the disparity of results recorded in different centres.

Management of "arrested" cases.—Various observations indicate that arrested cases are not completely freed of leprosy bacilli, and that reactivation of the disease is therefore not unlikely. Continuing observation is indicated in all "arrested" cases in order that any reactivation may be detected as soon as possible.

The after-treatment of "arrested" cases may reduce the relapse rate, and, with oral administration of the drug after-treatment can be very simple. It is a recommended procedure in those areas where it is practicable.

OTHER THERAPEUTIC AGENTS

(a) Chaulmoogra oil and derivatives.—Nearly all workers have abandoned the use of chaulmoogra oil in favour of sulphone treatment. A few experienced workers continue to use chaulmoogra oil as well as sulphones.

(b) Thiosemicarbazones.—Para-acetamidobenzaldehyde thiosemicarbazone (TB-1) is the only one of these drugs which has been widely used. Reports of its value in leprosy vary greatly. A few workers have found it equal to sulphones; most find it less effective.

Serious toxic effects may be seen, especially in the first few weeks of treatment, agranulocytosis, hepatitis, and severe anaemia being the most important.

We consider that the dose should not exceed 300 mg. a day in the adult. Some workers find even this dose too high, and use a maximum of 150 or 200 mg.

At present, thiosemicarbazone is recommended only as a *useful alternative treatment* for those patients who do not tolerate sulphones, or who fail to respond to sulphones. Further work is

needed before a definite appraisal of this drug in leprosy can be made.

(c) Isonicotinyl hydrazide (INH).—Nearly all workers feel that INH has little beneficial action in human leprosy. Its use in combination with other agents may be worth study.

(d) ACTH and cortisone.—There is wide agreement that intramuscular injections of these hormones have a striking effect in relieving the acute and sub-acute manifestations of leprosy, and that small doses may be effective. There is, however, a wide difference of opinion regarding the late results of this hormone treatment in leprosy. Some workers find that the cessation of hormone treatment is frequently followed by the recurrence of the acute manifestations, and by an increase in the underlying disease; they think that the use of these hormones should if possible be avoided in the presence of leprous or any other infection. Other workers have not encountered this difficulty and do not share this view.

The local use of cortisone for eye complications by eye-drops or by subconjunctival injection is not open to this objection, and is often of great value.

Short courses of injections of ACTH or cortisone have been reported to be of great value in the treatment of serious toxic and allergic reactions to drugs, e.g. sulphones and thiosemicarbazone.

(e) Streptomycin.—Trials of this antibiotic have been made and are in progress. As yet no striking results have been recorded.

Because of its lower toxicity dihydrostreptomycin has been found preferable to ordinary streptomycin. The early response of the disease to streptomycin has tended to be slower than to sulphones. Later, after nearly one year, the difference has been slight.

The dose recommended, 1 gramme three times a week, has been given for one year without measurable damage to the eighth cranial nerve.

Some workers have found streptomycin to be of some value in the relief of the acute manifestations of leprosy.

The use of streptomycin in leprosy must still be regarded as experimental.

(f) P.A.S.—This drug has been tried in leprosy, alone and in combination with other agents. No striking results have been observed.

PHYSICAL THERAPY AND SURGERY

While chemotherapy has greatly improved the general outlook in the treatment of leprosy, its action on trophic lesions produced

by nerve involvement or nerve destruction is often slight. In dealing with these conditions affecting the hands, the feet, and sometimes the face, physiotherapy, surgery and orthopaedics have a place, which however has not yet been fully defined. A more thorough study of these matters is urgently needed.

Physiotherapy may ameliorate some of the symptoms caused by peripheral neuritis, and may be a valuable aid in the post-operative care of patients undergoing surgical treatment.

Reconstructive surgery is most beneficial in patients whose disease is clinically quiescent or arrested. Tendon transplantations, arthrodeses, and other surgical procedures may improve the function of contracted hands. Amputations may be needed, particularly in the feet. Successful surgery of this nature may contribute much to the rehabilitation of patients in whom the disease has become arrested.

THERAPY RESEARCH

The favourable results of the present methods of chemotherapy of leprosy should not be allowed to obscure the great need for new chemotherapeutic agents acting with greater speed and efficacy, or to handicap research directed towards the establishment of more effective treatment.

There is urgent need for large scale, carefully planned and accurately conducted therapeutic trials of certain agents already available, and of new agents as they become available. Such trails should include studies of possible therapeutic agents given singly and in combination. In view of the rather wide differences of results of chemotherapy in people of different races, therapeutic trials should be made in different centres and in different countries.

The response of a suitable group of cases of leprosy to the well-established sulphone drugs may be used as the control in experiments designed to assess the value of newer drugs.

ADDENDUM

DR. SCHUJMAN holds that some authors who have studied comparatively the effects of both chaulmoogra and the sulphones maintain that chaulmoogra oil, if given in sufficient doses (15 to 25 c.c. weekly) is sufficiently active in all forms of leprosy to justify its retention in the therapeutic armamentarium.