A COMPARISON OF SULPHONE AND HYDNOCARPUS THERAPY OF LEPROSY

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In view of the fact that hydnocarpus (chaulmoogra) oil has been the basic treatment of leprosy for a great many years—it was an ancient folk remedy in India when Mouat (3) made the first report of it—it appears to me important that some comparison should be made between the older methods of treatment and the newer sulphone therapy before the former is altogether discarded, as has been suggested by some workers. The purpose of this paper, then, is to compare briefly the present hydnocarpus therapy and that of the newer sulphone drugs.

In order to arrive at a true appraisal of the value of these drugs I shall not include in this discussion any neural cases, either pure neural, tuberculoid, or atypical. The reasons for this are:

(1) In the neuro-macular or neuro-anesthetic case there is no yardstick by which to assess the results of the treatment, as there is in lepromatous cases, where one can follow improvement by the progressive disappearance of bacilli from the skin lesions. Further, it is quite impossible to say whether the nerve change, anesthesia or deformity is due to the presence of the bacilli or to damage resulting from pathological changes in the nerves secondary to tissue reaction.

(2) In the tuberculoid case, and for that matter in the large atypical (intermediate) or borderline group of cases, the tendency to spontaneous healing is so great that it is not justifiable to attribute the clearing up of any lesion to the efficacy of the drug. Estimates of efficacy can be obtained only from large groups of cases treated with adequate controls.

If the claim that the sulphones have now replaced hydnocarpus oil and its derivatives is to be sustained, therefore, comparison must alone be made in the lepromatous case. Schujman (6) has recently emphasized that the success of hydnocarpus therapy is largely dependent on the dosage and method of ad-

ministration. He states that any method used which does not include intradermal injections, or in which the patient receives a total of less than 400 cc. in a year, is liable to bring these drugs into disrepute. In this opinion I heartily concur.

RESULTS WITH HYDNOCARPUS OIL

During the past six years experiments have been undertaken at the Lady Willingdon Leprosy Sanatorium on the optimum method of employing hydnocarpus oil. The first series had reference to the dosage, the second to the method of administration. Table 1 gives the summary of the results of our experience with regard to dosage.

TABLE 1.—*Dosage and results, hydnocarpus oil therapy.*

Dosage, per week	Cases negative
15-25 cc.	18%
10-15 cc.	33%
1-10 cc.	24%

The number of cases and the distribution as regards the various grades of the lepromatous involvement in each group were as similar as possible. At the time it was our considered opinion that dosages above 15 cc. per week tended, after a preliminary period of improvement, to set up a state in which the patient went into a series of lepra reactions which were difficult to control. Teichmann, of Purulia, has recently told the author that, although the number of negative cases resulting over a long period with high dosages may not be striking, lepromatous deformities appear to be less in those who received above 20 cc. per week. Schujman definitely recommends relatively higher dosages. Ryrie (5) has for many years recommended a dosage of 1 cc. of hydnocarpus oil for every 10 pounds of body weight, particularly in the kind of ulcerating tuberculoid case which is seen in Malaya.

In order to test the efficacy of the various methods of administration an equal number of cases were chosen, one-half of which received 15 cc. per week subcutaneously while one-half received this dose divided equally between the subcutaneous and intradermal routes. The results at the end of two years are shown in Table 2.

TABLE 2.—*Comparison of routes, hydnocarpus oil therapy.*

Route	Negative	Improved	Stationary	Worse
Subcutaneous only	12.3%	34.2%	45.2%	8.3%
Subcutaneous and intradermal	17.5%	40.2%	35.7%	6.6%

From these figures it was concluded that the optimum dose and method of administration of the hydnocarpus preparation in lepromatous cases—in Madras—was 15 cc. per week, equally divided between the subcutaneous and intradermal routes.

Further, the early lepromatous cases (L_1) admitted into the Lady Willingdon Leprosy Sanatorium during the last two or three years and given adequate dosage of hydnocarpus oil both subcutaneously and intradermally were analysed, and the following results were obtained:

Number of cases treated.....	167
Number of cases negative.....	84
Percentage negative	50.3
Average period of treatment, weeks.....	94

RESULTS WITH SULPHONE DRUGS

We have been using drugs of the sulphone group for the past two years, and while we have to a large extent confirmed the observation of Faget and associates (1), of Muir (4), and of Wharton (7), we have not as yet seen a single case become completely negative. Our general conclusions with regard to the sulphone preparations are that they are effective in lepromatous leprosy, but that the period of time it takes to render even early lepromatous cases negative is still too long. Of the various preparations at present available, or about to be made available, promin appears to be the least satisfactory. It is too toxic for the average Indian patient, and too tedious to administer when large numbers of patients are receiving injections. Diasone tends to precipitate reactions in about 25 per cent of cases, and these reactions may be so severe as to necessitate the withdrawal of the drug. Apart from the inconvenience of having to take large doses, sulphetrone appears to be the drug of choice. Although the number of our cases receiving this drug is small, we have observed that it has a markedly less tendency than the others to precipitate lepra reaction, and the results appear to be more rapid with little or no danger of toxic signs developing.

We have not followed the practice of other workers in the matter of dosage with the sulphones. If, as is generally be-

lieved, these drugs act by virtue of their chemotherapeutic effect, then it would seem to be a sound policy to commence with high dosages and increase them up to what we at present consider a safe limit. In the case of diasone, our commencing dose for adults is three tablets a day, increasing by one tablet daily each month till six a day are given; in children we have never exceeded four tablets a day. With regard to sulphetrone, we aim at reaching the maximum dose of twelve tablets a day as rapidly as possible; the commencing dose is four tablets in 24 hours, increasing by two every second day until a daily total of twelve is reached. We do not believe that there should be any rest period except where there is a definite indication of secondary anemia; i.e., if the red-cell count drops below 3 million and the hemoglobin below 10 grams per cent (or 45%). In such instances the drug should be stopped altogether until the red-cell count has reached 4 millions and the hemoglobin 12 grams per cent (or 75%). Adequate doses of yeast and iron should be administered along with the sulphones. Especially in the case of sulphetrone, great care must be taken to keep the bowels free; constipation may result in serious consequences.

DISADVANTAGES OF SULPHONE THERAPY

In the sulphone drugs we have a new and powerful remedy for advanced lepromatous leprosy, but there is a tendency to treat lightly, or ignore, certain very definite disadvantages in this new therapy. These drawbacks, I believe, are important, and until overcome they will prevent the use of the sulphones for mass treatment such as is necessary in India, Africa or China. The disadvantages are as follows:

(1) The method of administration is not suitable for masses of people who are not used to taking large numbers of tablets every day. It is quite impossible to expect success with sulphone therapy by mouth unless the patients are closely supervised.

(2) The cost of these remedies is at present prohibitive, and therefore they are out of the question for general use.

EXPERIMENTATION

In order to overcome these difficulties we have been using for clinical trials (1) a 25 per cent suspension of diaminodiphenyl sulphone in arachis oil, and (2) a 25 per cent emulsion of sulphetrone in arachis oil with 0.5 per cent beeswax. The latter preparation has been employed only recently, and there-

fore it is too soon to make any special comments about it. It may be said, however, that with both preparations blood levels of 1 to 3 mgm. per cent can be maintained. Furthermore, what appears to be more significant, by this method as well as by the usual oral route the concentration of the drug in the skin (varying between 5 to 14 mgm. per gram of skin tissue) can also be maintained.

The great advantage of injectable forms of the sulphones is seen in the relatively small dosages which are needed for comparable clinical results. For instance, in two cases in which the stage of the disease was similar as shown by the bacteriological index, one receiving sulphetrone by mouth took 2,471.5 gm. in a period of sixteen months, whereas the other receiving the 25 per cent suspension of diamino-diphenyl sulphone was given only 70 gm. in eleven months. In the former case the bacteriological index changed relatively little, indicating only slight improvement, whereas in the latter case the change was great, indicating a very marked improvement.

BACTERIOLOGICAL INDEX

The usual way in which improvement of a case is determined is by clinical observation, perhaps supported by photographs, and the more or less casual examination of bacteriological smears made from time to time; some workers are so situated that they can also make periodical histological examinations of biopsy specimens. We feel that it is advantageous to have a method by which the efficacy of any method of treatment can be assessed and expressed numerically from time to time, and therefore we use a bacteriological index.[1]

A minimum of sixteen smears is made from each patient, the sites including the areas where lepromatous infiltration is most common, namely, the earlobes, cheeks, chin, forehead, back, buttocks, and outer aspects of the extremities. Each smear is graded on a 0 to 6-plus scale, and the bacteriological index calculated as follows: Add the plus-values of all smears and divide by the number of smears. For example: if in a case 6 smears were 4-plus ($6 \times 4 = 24$), 6 smears 2-plus ($6 \times 2 = 12$), and four smears negative (0), the index would be ($36 \div 16 =$) 2.25 —the average degree of positivity of the entire lot. The maxi-

[1] After trial of another method of calculating an index, we have adopted the one described here, first suggested to us by Dr. K. Romanujam, and later by Dr. H. W. Wade who has used it in calculating the responsiveness of different groups of cases to lepromin.

mum possible would of course be 6.0; in a case become entirely negative the index would be 0.0.

CONCLUSIONS

Our conclusions are that, so far as the Indian race is concerned, the sulphone remedies are at present indicated only in the following types of cases:

(1) Advanced lepromatous cases, especially those with nasal and laryngeal symptoms.

(2) Cases which have not responded to properly administered hydnocarpus therapy.

(3) Cases which have relapsed.

Our better results with hydnocarpus remedies are explained on two grounds. First, the Indian racial group with which we usually work responds better to the hydnocarpus therapy than Europeans. This is demonstrated in our generally poor results with hydnocarpus in the Anglo-Indian (Eurasian) group. Second, our insistence on intensive intradermal medication.

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