CORRESPONDENCE

This department is for the publication of informal communications that are of interest because they are informative and stimulating, and for the discussion of controversial matters. The mandate of this JOURNAL is to disseminate information relating to leprosy in particular and also other mycobacterial diseases. Dissident comment or interpretation on published research is of course valid, but personality attacks on individuals would seem unnecessary. Political comments, valid or not, also are unwelcome. They might result in interference with the distribution of the JOURNAL and thus interfere with its prime purpose.

Treatment of Leprosy Using Combination Therapy—But How?

TO THE EDITOR:

During the last decade, a great number of therapy recommendations have been made, most of which had only a short life, were never confirmed in practice, and had been formulated almost entirely on the basis of theoretical considerations. They characterize the thorny way from an often dogmatically advocated monotherapy with dapsone (DDS) to combination therapy. The latter is slowly being accepted. However, up to this date there is much uncertainty as to what kind of combinations accomplish the minimum conditions made today on a leprosy therapy resulting, in a relatively short time, in final cure and preventing the emergence of resistance and relapses.

On the background of these requirements only a therapy which

- can be administered orally,
- is well tolerated,
- can be given at any time of day (without interruption of the course of the day or work),
- can be taken inconspicuously and without special circumstances (since otherwise compliance of the patient will be affected),
- is applicable under out-patient conditions (self medication included),
- is highly effective in a daily dose of not more than 1500 mg (a higher dose would affect compliance of the patient)

can be considered suitable.

Taken together, these criteria form a kind of screen through which a lot of effective substances fall—not because they are of no value, but because they are not suitable for the special purpose of an ambulatory field therapy. Out of the small number of remaining substances and based on *in vitro* results, animal experiments, and clinical work, we are using mainly

Rifampin	(RMP)	10 mg/kg daily
Isoniazid	(INH)	5 mg/kg daily
Prothionamide	(PTH)	5 mg/kg daily
Dapsone	(DDS)	1.2 mg/kg daily

because they can be combined and develop synergistic effects when used in combination. They need not be administered in large daily doses, are well tolerated in the doses administered, and their combined action covers the differing sensitivities of most of the various mycobacterial strains virulent for man, including *Mycobacterium leprae.*

INH is often underrated for the treatment of leprosy. Indeed this drug shows little activity when tested in the mouse foot pad, but this method is not a reliable one for testing combinations of synergistically active substances. More specific methods show that INH (when used in combination with other suitable substances) develops synergistic effects against the mycobacterial species we are using as substitutes for *M. leprae.* Highly experienced leprologists have noted the effectiveness of INH clinically (e.g., Dr. Dharmendra). PTH meanwhile is recognized by most doctors as a valuable drug, well tolerated in the small dose (5 mg/kg) used by us. RMP is known to be the most effective antimycobacterial substance available today.

Therapeutic practice

In order a) to fully exploit the synergistic effect of drug combinations, b) to ensure the safe and simple intake of the drugs, and c) to make sure that the substances are taken in the correct dose proportions, INH, PTH and DDS were incorporated in a single tablet, available under the trade name Isoprodian® (IPD). Its antimycobacterial activity is as high as that of rifampin, but it offers the advantage of being a triple combination which can be given alone. RMP should never be given alone. Both forms of therapy (IPD alone and IPD + RMP) are suitable for self medication, for use under out-patient conditions, and are also effective in dapsone-resistant leprosy cases.

To make treatment as inexpensive and as efficient as possible, we recommend to begin with rifampin + Isoprodian daily for a minimum of eight weeks. Dependent on the patient's state, it is subsequently decided whether a) treatment is to be continued with rifampin + Isoprodian, b) treatment is to be continued with Isoprodian alone, or c) treatment is to be discontinued.

If rifampin is not available, we recommend an initial treatment with Isoprodian alone for a minimum of eight months. Dependent on the patient's state, it is subsequently decided whether a) treatment is to be continued or b) treatment is to be discontinued.

All patients (also the initially bacteriologically negative cases) are checked monthly, both clinically and bacteriologically. The therapeutic effect obtained in bacteriologically positive cases can be judged by smears with certainty. In bacteriologically negative cases and in cases having become negative through treatment, the doctor's experience is challenged by the necessity to decide if treatment is to be continued or not. The duration of treatment is indeed a crucial point. As in all other infectious diseases, discontinuation of treatment in leprosy should also be made dependent upon the result of therapy obtained in the individual patient. Generally, the smaller the number of bacteria, the shorter the duration of treatment, and vice versa. But this is not true for all cases. A standard duration of treatment (e.g., two years) implies the danger that many patients are treated for too long a time, while (even worse) others are not treated long enough and thus remain infectious. They continue to be carriers of the disease and disseminate bacteria into their environment. All efforts to cure the patients and to eliminate the epidemic will be brought to nothing if such recommendations are followed. After withdrawal of therapy, the patients should be followed up by monthly clinical and bacteriological examinations to ascertain the absence of relapses.

A leprosy therapy should be applied on a large scale only when it has been clearly proved that no relapse occurs after its withdrawal. This capacity determines the value of an antibacterial therapy.

Recommendations become dangerous when they are associated with daily DDS therapy, supplemented once a month by a single dose of RMP or clofazimine (Lamprene®), or both. This is not true combination therapy, but remains basically DDS monotherapy. Dapsone resistance will continue to occur and resistance to RMP can be anticipated. In addition, the treatment of tuberculosis, which might be required, is rendered ineffective in advance.

The patient's compliance is limited, as is generally known from numerous investigations and daily medical experience. The patient's tendency not to take medication (be it intentionally or from carelessness) is favored by certain external factors, e.g., too large a daily dose, poor tolerance, bad taste, etc. Drug compliance can be enhanced by understanding psychological guidance of the patient and by consciously avoiding compliance-reducing factors. The surest way to ensure a high degree of compliance is to keep the period of treatment as short as possible.

Until now, the combination RMP + IPD is the most effective we have, the results of therapy with which have been thoroughly scrutinized by two W.H.O. consultants (D. L. Leiker, Amsterdam, and W. Jopling with M. Ridley, London) at different times. But we need alternatives, and we (Freerksen, Rosenfeld, Seydel) are working in this field.

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