ISONICOTINIC HYDRAZIDE IN THE TREATMENT OF LEPROSY

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The premature publicity given to isonicotinic hydrazide for the treatment of tuberculosis in the lay press, early in 1952, brought this drug forcibly to the attention of workers in the leprosy field (6). Experiments with murine leprosy showed that it was extremely successful in inhibiting the multiplication of *Mycobacterium leprae murium* (1, 7, 9).

In order to assess the efficacy of this compound (INH) in human leprosy a clinical trial was undertaken at the Sungei Buloh Settlement, with adequate laboratory control, and the findings are reported in this communication. During the completion of this program a report by Lowe suggested that this drug gave very poor results in human leprosy (11). Other reports have appeared since then, especially as papers presented at the Madrid Congress.

METHODS

Selection and classification of cases.—The first 100 new cases presenting for inpatient treatment after the plan was adopted were put under treatment with isonicotinic hydrazide. Naturally, this meant that most of them were of the lepromatous and atypical forms, neural cases being usually put under outpatient treatment because of the great demand for places in the settlement. Before treatment all cases were examined and classified as either tuberculoid, lepromatous or atypical. The following criteria were employed:

Tuberculoid: Must be typical clinically; a skin biopsy should show a tuberculoid lesion; the lepromin reaction must be strongly positive. Lepromin testing was done with the Dharmendra antigen (5).

Lepromatous: Clinically typical; a skin biopsy should show a lepromatous lesion, with a marked infiltration of lepra cells; and the lepromin reaction must be negative.

Atypical: Cases which did not fit either of the above categories were assigned to this group. It was found that a very large proportion of Malayan cases are of this type, which is more or less of the order of what is called "borderline" by some workers.

Skin biopsies of the atypical cases showed lesions which varied considerably, ranging from those closely simulating tuberculoid to some which were almost lepromatous. The lepromin reaction in these cases might be positive or negative. In Malaya there appears to be a wide spectrum, and cases without treatment pass through the atypical phase to frank lepromatous.

Dosage.—Cases were started with a dose of 25 mgm. daily, and were increased gradually to 150 mgm. daily. This was found to be the maximum dose tolerated; the majority could take only 100 mgm. daily.

Iron and multivitamin tablets were given to all patients as a routine measure.

Method of assessing progress.—Clinical: The clinical status of each case was assessed by each member of the team after three, six and nine months. A photograph

of each patient taken before treatment to show the major lesions was of great assistance in the later assessments.

Pathological: A suitable skin lesion was biopsied before treatment was commenced. Six months later a second biopsy was performed, the specimen being taken as close to the first site as possible; in fact, it was quite often through the stitch scars of the previous operation. The specimens were fixed for four hours in Zenker's fluid, and washed and embedded in paraffin wax as usual, cedar oil being used for clearing before the paraffin bath. Sections were stained by hematoxylin-eosin, by Lillie's modification of the trichrome stain ([10]), and by a modified Fite-Faraco method ([10]) to demonstrate acid-fast bacilli.

Bacteriological: Smears were made from snippets of skin from the earlobes, and also from the biopsy sites whenever skin specimens were obtained. Ear smears were taken before treatment and every three months during treatment. The numbers of bacilli in the smears were estimated roughly as follows:

3 + = Many bacilli in every field, globi present.
2 + = At least 10 bacilli in very field.
1 + = A few bacilli in all fields.
± = Bacilli present, but not in every field examined.

RESULTS

Initially it was intended to maintain this group on INH therapy for twelve months, but the patients became so restive that the experiment had to be discontinued after only eight months. This attitude of the patients was due to their witnessing the greater clinical improvement made by their fellows receiving sulfones. Despite this apparently obvious failure of the drug, analysis of the series showed that certain changes had been induced in the group.

Within a few weeks of commencing therapy the patients put on weight, and their appetites improved. This has also been reported in INH treatment of patients with pulmonary tuberculosis ([12]). In the present instance it is difficult to ascribe the weight increase entirely to the effects of the drug. The majority of the patients came from kampongs in rural areas where life is hard, and their lot is often made harder as they are liable to be shunned and neglected by the rest of the people. In such circumstances malnutrition is invariably present. Life in the settlement means freedom from anxiety and a far better diet than they previously had. It is therefore not surprising that they put on weight; in fact, it is a general finding with all patients admitted to the settlement. It was felt, however, that the INH group showed greater weight increase, and that their general feeling of well being was more marked, than the rest of the patients on other types of therapy. (Cf Figs. 5 and 6.)

An assessment of progress made after eight months of treatment gave the results shown in Table 1. Although we started with 100 cases, only 83 completed the eight-month period. Four cases had to be dropped from treatment for reasons that will be discussed later. Others were discharged, and some absconded from the settlement completely or for periods sufficiently long to have interfered with treatment.

One of the 5 tuberculoid cases improved clinically; the second biopsy showed a change from the initial reacting tuberculoid to an indeterminate type of lesion; and the ear smears changed from ± to negative.

TABLE 1.—*Status after therapy of the 83 patients who completed 8 months of treatment.*

Type	Number of cases	Improved	Stationary	Worse
Tuberculoid	5	1	4	0
Atypical	38	18	12	8
Lepromatous	40	7	21	12
Total	83	26	37	20

The improved atypical cases—18 of 38, or 47.5 per cent—can be broken down as in the first part of Table 2. Plate 1 illustrates the type of improvement encountered in this group. The analysis of the improved lep-

TABLE 2.—*Analysis of the improvement seen in 18 of the atypical cases, and 7 of the lepromatous cases.*

Number of cases	Assessment		
	Clinical	Pathological	Bacteriological
Atypical (18 of 38)			
3	Improved	Improved	Improved
1	Improved	Improved	Stationary
3	Improved	Stationary	Improved
3	Improved	Stationary	Stationary
5	Stationary	Improved	Improved
3	Stationary	Stationary	Improved
Lepromatous (7 of 40)			
1	Improved	Improved	Improved
1	Improved	Stationary	Improved
1	Improved	Stationary	Stationary
1	Stationary	Improved	Improved
1	Stationary	Improved	Stationary
2	Stationary	Stationary	Improved

romatous cases—7 of 40, or 17.5 per cent—is given in the second part of Table 2. Plate 2 shows a representative case from this group.

The 37 cases of Table 1 which had remained stationary showed no change clinically, pathologically or bacteriologically. Of the atypical cases which deteriorated, 6 were worse from the clinical aspect with no change in pathology or bacteriology; 1 had deteriorated in all three respects; and 2 of them had worsened pathologically, 1 showing increased numbers of bacilli in smears. In the lepromatous series, 8 cases deteriorated clinically; 1 clinically and pathologically; 1 clinically and bacteriologically; and 2 in all respects.

Complications.—On the whole, tolerance was good up to 100 mgm. daily; some patients tolerated 150 mgm. In general they felt better, but most of them passed through a short phase of nausea and giddiness. Gastritis occurred in a few cases, and in one it was of sufficient severity to cause withdrawal of the treatment. Edema of the hands and feet appeared in two cases, and jaundice in one.

Erythema nodosum occurred in many lepromatous and atypical cases, especially if dosage was pushed to 150 mgm. or beyond. In three tuberculoid cases there was an unusual form of reaction we have not seen before. In this condition the lesions became intensely congested and stood out in the most startling manner, dark against the surrounding skin. In one of these, the reaction was so intense that the lesions ulcerated. The treatment was discontinued in these three cases.

DISCUSSION

Of the 83 patients who underwent treatment for eight months, 26 showed some form of improvement, but it must be noted that 18 of these were in the atypical group. This group in our experience is one in which there is a good deal of flux, and although over a prolonged period the tendency is always toward a downhill progression to the lepromatous condition, they do often show spontaneous clinical and pathological improvement. It is therefore difficult to decide whether the changes in these improved cases were induced by the isonicotinic hydrazide, or were spontaneous.

An outstanding finding is that, of 40 lepromatous cases, only 12 showed progression of the disease during the 8-month period of treatment, while 17.5 per cent improved and over 50 per cent remained stationary. Our experience has been that, without treatment, lepromatous cases in this country show marked and rapid progression. We therefore feel that isonicotinic hydrazide must exert some effect upon leprosy. The number of lepra reactions that occurred in the early stages of the treatment probably indicates an interference with the metabolism of the bacillus by the drug, and disintegration of large numbers of bacilli.

As a therapeutic agent, isonicotinic hydrazide is not comparable in efficiency to the sulfones, as demonstrated by Molesworth *et al.* (13) and

many others. It may well be that the comparatively poor results obtained with INH, despite its efficacy against the rat leprosy bacillus, represents rapidly developing drug resistance of the Hansen bacillus. *M. leprae murium* very quickly develops resistance to INH (3). This is also thought to be true in the case of the tubercle bacillus, although there are certain difficulties about *in vitro* testing for resistance to this drug (4). It has been stated (8) that INH alone has no place in the treatment of pulmonary tuberculosis, because initial improvement is always followed by relapse. It appears to be equally true that INH alone has no place in the treatment of leprosy.

If the premise is correct that failure in treatment is due to developing drug resistance, it may be worth while combining INH with other therapeutic agents. Such a combination might suppress the appearance of INH-resistant strains and give better therapeutic results than would either drug when used alone. We are at present trying out various combinations of INH and sulfones.

SUMMARY

1. A trial of isonicotinic hydrazide treatment of leprosy in Malaya is reported.

2. Only 26 patients out of a total of 83 showed any improvement at the end of an eight-month period.

3. Eighteen of the patients showing improvement were from the group classified as atypical. Since spontaneous changes take place frequently in cases of this group, it is difficult to assess the effect of the drug.

4. Because only 24 per cent of the whole series became progressively worse while under the treatment, we believe that the drug is not without some limited therapeutic effect. It is not, however, comparable in efficiency to the sulfones.

RESÚMEN

1. Se reporta un ensayo sobre el tratamiento de la lepra en Malaya con "isonicotinic hydrazide."

2. Salo 26 pacientes de un total de 83 desmostraron mejoría al terminar un período de 8 meses.

3. 18 de los pacientes que mejoraron pertenecían al grupo en que se observan cambios espontáneos frecuentemente. En éste grupo es difícil valorar el efecto de la droga.

4. Debido a que solo el 24% de la serie empeoró durante el tratamiento, creemos que la droga tiene efecto terapéutico limitado. Sinembargo, no se compara con la eficiencia de las sulfonas.

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DESCRIPTION OF PLATES

PLATE (21)

FIG. 1. Case 11,453 (P. 59). Clinical photomicrograph, before treatment, of a patient with atypical leprosy who showed improvement while under treatment. Smears from the ear were 3+ before treatment, 2+ after 3 months, and 1+ after 6 months. The lepromin reaction was positive.

FIG. 2. The same patient after 8 months of treatment with INH.

FIG. 3. Photomicrograph of a lesion before treatment. The condition was diagnosed as "atypical lepromatous." A smear from the site of the specimen was 1+, as were sections stained for acid-fasts.

FIG. 4. Photomicrograph of a lesion after treatment, diagnosed as "atypical tuberculoid." Site smears and sections were negative for acid-fasts.

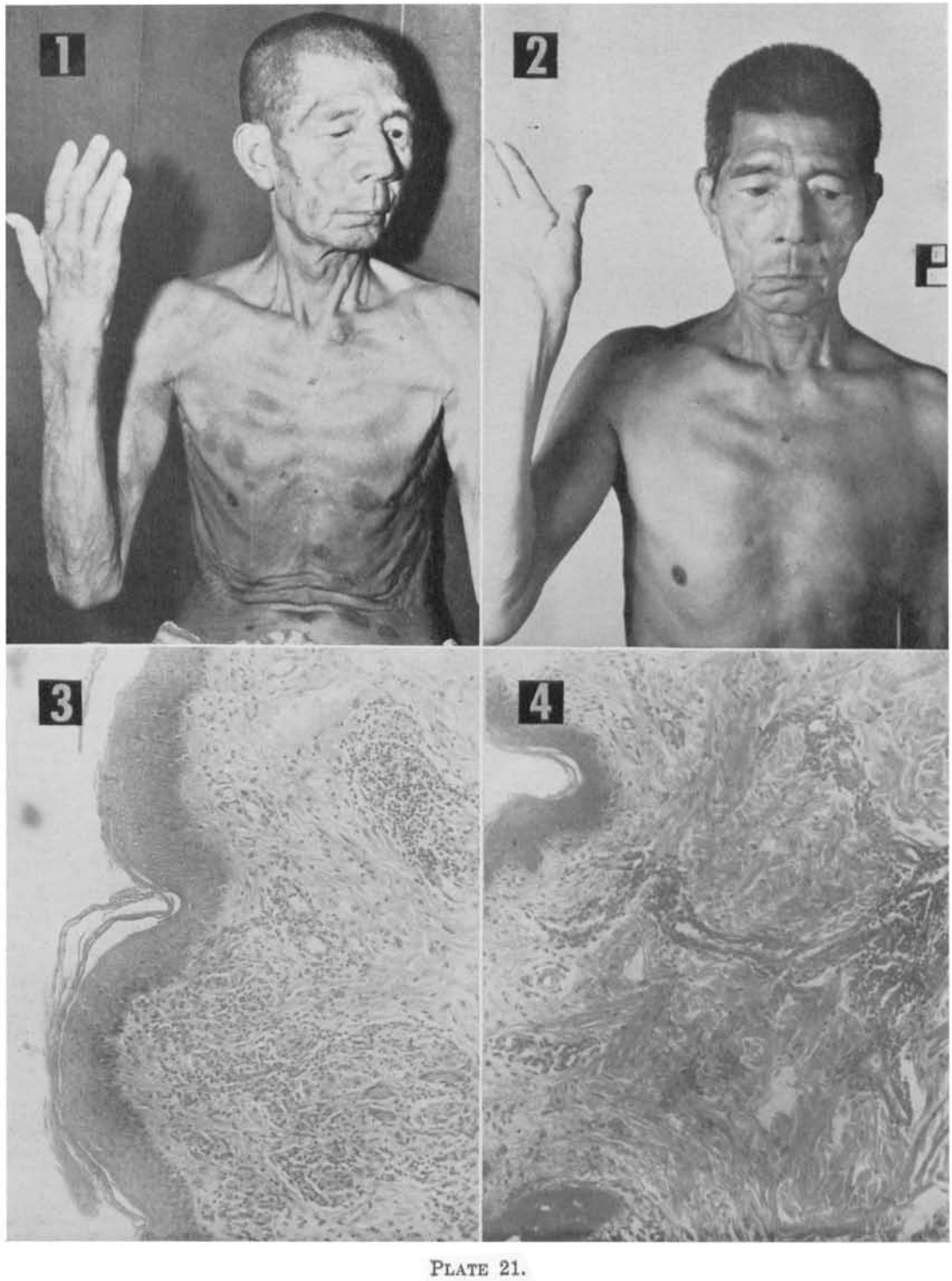

PLATE 21.

PLATE (22)

FIG. 5. Case 11,440 (P. 19). Clinical photograph, before treatment, of a patient with lepromatous leprosy who showed improvement under treatment. Smears from the ear were 3+ before treatment, 2+ after 3 months, and 1+ after 6 months. The lepromin reaction was negative.

FIG. 6. The same patient after 8 months of treatment with INH.

FIG. 7. Photomicrograph of a lesion before treatment. The condition was diagnosed as "atypical lepromatous." The smear from the specimen site was graded ± for bacilli; the sections were negative.

FIG. 8. Photomicrograph of a lesion after treatment. The condition was diagnosed as "indeterminate." The smear and sections were negative for bacilli.

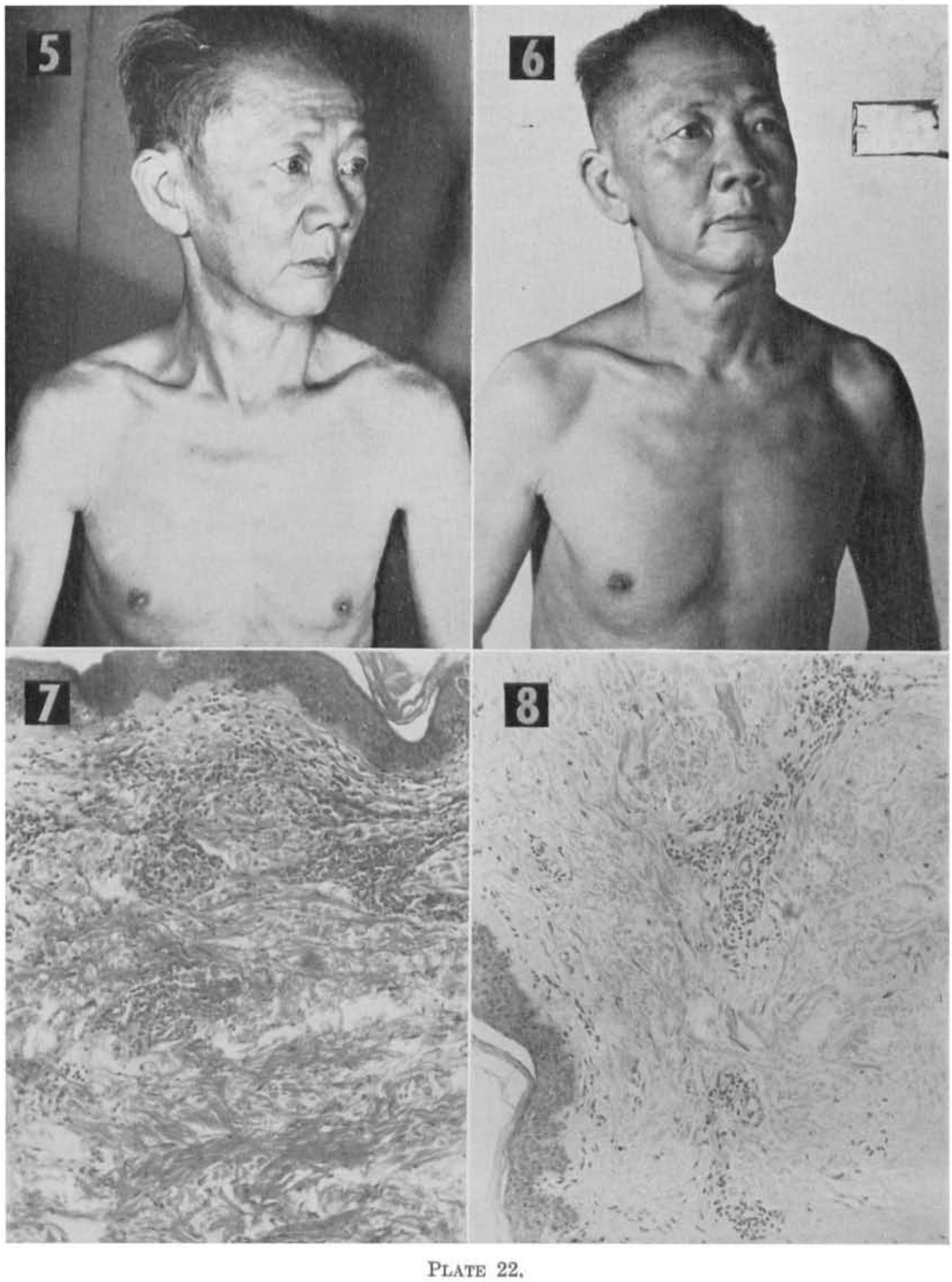

PLATE 22.