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Viability of *Myco. leprae* in the Skin and Bone Marrow of Patients with Lepromatous Leprosy While on Dapsone or Lamprene

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The pattern of killing of *Myco. leprae* in the skin and bone marrow of untreated lepromatous leprosy patients was studied after initiation of specific treatment with dapsone 100 mg daily (5 patients) as compared with clofazimine 100 mg daily (5 patients). It was found that while both clofazimine and dapsone appear to be equally effective in killing *Myco. leprae* in the skin, bacilli remained viable in the bone marrow long after they ceased to be viable in the skin, in 4 patients (2 on dapsone and 2 on clofazimine) after 720 days. The implications of this in relation to relapse/recrudescence are discussed, and the usefulness of the mouse model in providing information of value to the clinician is emphasized.

Introduction

It has been fairly widely accepted that *Myco. leprae* multiply better in the cooler parts of the body. The persistence of *Myco. leprae* in the reticulo-endothelial system (e.g. liver and bone marrow) after their disappearance from the skin casts some doubts on this hypothesis (Karat, 1966; Karat *et al.*, 1971). It was further demonstrated that *Myco. leprae* in the liver and bone marrow were not effete organisms but viable and able to multiply in the footpads of mice.

A prospective study was therefore undertaken to determine the pattern of killing of *Myco. leprae* in the skin and bone marrow of untreated lepromatous leprosy patients after initiation of specific treatment with dapsone 100 mg daily and compare it with patients on Lamprene 100 mg daily.

Materials and Methods

Consecutive patients with untreated lepromatous leprosy and B.I. more than 3+ (Ridley, 1964) were randomly allocated to 2 therapy groups:

I To receive 100 mg dapsone daily orally
II To receive 100 mg Lamprene daily orally.

Skin biopsy and bone marrow aspiration were obtained on day "0" and every 90 days thereafter for two years. The skin biopsy and bone marrow aspirate were homogenized in the usual way to obtain *Myco. leprae* in suspension and 5000 *Myco. leprae* were innoculated into the hind footpads of thymectomized C.B.A.

mice. These mice were harvested at regular intervals and harvest counts of *Myco. leprae* were obtained.

Of the 15 patients who entered the study 5 dropped out and results presented here in relation to the remaining 10 patients (5 on dapsone and 5 on Lamprene).

Results

Dapsone treated patients

The viability of *Myco. leprae* in the skin and bone marrow aspirate of dapsone treated patients is shown in Table 1.

TABLE 1

Viability of Myco. leprae *in skin and bone marrow of dapsone treated patients*

No. of days	I		II		III		IV		V	
	S[a]	BM[b]	S	BM	S	BM	S	BM	S	BM
0	+	+	+	+	+	+	+	+	+	+
90	–	+	+	+	+	+	+	+	–	+
180	–	+	–	+	+	+	–	+	–	+
270	–	–	–	+	–	+	–	+	–	+
360	–	–	–	+	–	+	–	+	–	+
450	–	–	–	–	–	+	–	+	–	+
540	–	–	–	–	–	+	–	+	–	+
630	–	–	–	–	–	+	–	–	–	+
720	–	–	–	–	–	+	–	–	–	+

[a] S = skin.
[b] BM = bone marrow.

Between 90 and 270 days (3 to 9 months) *Myco. leprae* in the skin were non-viable in the footpads of mice. The *Myco. leprae* from bone marrow remained viable in 2 cases at the end of 2 years; in one they were non-viable at 9 months, in another at 15 months and in the third at 21 months.

Lamprene treated patients

The viability of *Myco. leprae* in the skin and bone marrow aspirate of Lamprene treated patients is shown in Table 2.

Myco. leprae in the skin became non-viable in 180 to 360 days (6 to 12 months) and those in the bone marrow aspirate in 3 cases at 360, 450 and 540 days (12, 15 and 18 months) respectively. In 2 cases they remained viable at the end of 2 years.

Comments

Both Lamprene and dapsone appear to be equally effective in killing *Myco. leprae* in the skin of lepromatous leprosy patients when administered orally in a

TABLE 2

Viability of Myco. leprae *in skin and bone marrow of Lamprene treated patients*

No. of days	I		II		III		IV		V	
	S	BM	S	BM	S	BM	S	BM	S	BM
0	+	+	+	+	+	+	+	+	+	+
90	+	+	+	+	+	+	+	+	+	+
180	–	+	–	+	+	+	+	+	–	+
270	–	+	–	+	+	+	–	+	–	+
360	–	+	–	+	–	+	–	–	–	+
450	–	–	–	+	–	+	–	–	–	+
540	–	–	–	–	–	+	–	–	–	+
630	–	–	–	–	–	+	–	–	–	+
720	–	–	–	–	–	+	–	–	–	+

dose of 100 mg daily. The leprosy bacilli in the skin of lepromatous leprosy patients appear to be very sensitive to orally administered dapsone and Lamprene.

By contrast *Myco. leprae* in human bone marrow appear to be relatively refractory to orally administered dapsone and Lamprene, remaining viable in the bone marrow long after they have ceased to be viable in the skin. This could be either due to the inaccessibility of *Myco. leprae* in the bone marrow to the action of these drugs or because the drugs do not attain the required lethal level of concentration in the bone marrow. The latter is not the case as far as dapsone is concerned since the blood level of dapsone and the level of dapsone in the bone marrow aspirate were comparable in these patients. On the other hand it is conceivable that the environment of the bone marrow may be more conducive for the multiplication of *Myco. leprae* despite the known higher temperature of the bone marrow in man.

If in fact *Myco. leprae* not only persist in the bone marrow longer than in the skin but also remain viable in the bone marrow longer than in the skin, this has far-reaching therapeutic and clinical significance. These "persisters" among *Myco. leprae* in man could explain the rather high rate of relapse/recrudescence of leprosy among bacillated types of leprosy patients following premature cessation of specific therapy. Thus prolonged uninterrupted specific therapy becomes mandatory in bacillated types of leprosy in order to reduce the possibility of relapse/recrudescence of leprosy. The problem of persisters also raises a query as to the merits of monotherapy and polytherapy of leprosy with 2 or more drugs given simultaneously. Further longitudinal studies along these lines are indicated.

Once again the footpads of mice have provided very valuable information regarding the behaviour of *Myco. leprae* in man, which enables the clinician to make rational therapeutic desisions.

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References

Ridley, D. S. (1964). Leprosy in Theory and Practice 2nd ed. (Eds. R. G. Cochrane and T. F. Davey) p. 620. Bristol: John Wright & Sons Ltd.
Karat, A. B. A., Job, C. K., Rao, P. S. S. (1971). *Brit. med. J.* **1**, 307.
Karat, A. B. A. (1966). *Int. J. Lepr.* **34**, 415.