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Secondary dapsone-resistant leprosy in Shanghai Municipality

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Summary A formal survey of the prevalence of secondary dapsone-resistant leprosy, conducted in Shanghai Municipality according to the THELEP Protocol, has revealed an estimated prevalence of from 5·66 to 8·62 per 100 patients at risk.

Secondary resistance to dapsone has been detected with increasing frequency among patients with multibacillary (LL, LI and BL) leprosy in many countries.[4] In order to assess the severity of the problem in the Shanghai area and measure the magnitude of the threat to leprosy control activities, we undertook a survey of the prevalence of secondary dapsone resistance in Shanghai Municipality according to the THELEP Protocol for Surveys of Dapsone Resistance.[1]

In Shanghai Municipality, which includes a total population of about 11·5 million in an area of 6185 km^2, a leprosy control programme has been active since 1956. At the end of 1979, 5326 patients of all types were registered, of whom 1195 (22·4%) had been classified lepromatous according to the Madrid classification.[6] Patients with multibacillary leprosy are usually hospitalized until smears become negative, after which treatment is continued on an out-patient basis. Case records have been maintained with reasonable accuracy since 1956.

Sulphone therapy was introduced into this area in the early 1950s. Dapsone, which soon became the sulphone of choice, is routinely administered to leprosy patients in a daily dosage of 100 mg. Thiacetazone, 100–200 mg daily for 0·5–4 years, and thiambutosine, 2–3 g daily for 1–2 years, have been administered to some lepromatous patients, usually in combination with dapsone. In addition, some patients, the majority of whom had relapsed, were treated with other 'first-line' drugs, among them clofazimine, B628, rifampicin, AF-MO (the methyloxime of 3-formylrifamycin SV), *iso*butylpiperazinylrifamycin, ethionamide and prothionamide, for 0·5–2 years.

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Materials and methods

A team of 8 physicians, nurses and laboratory technicians was organized for this survey. Analysis of the records of all registered patients revealed that 795 lepromatous patients—573 males and 222 females—who had been treated with dapsone for at least 5 years were still living. Of these, 777 (97·7%)—560 males and 217 females—were found by the team and assessed clinically and by skin smears. These 777 patients comprise the denominator—the patients at risk of dapsone resistance. Ninety-two (11·8%) of the patients yielded positive smears of whom 67 (8·62% of the total) were found to have a bacterial index (BI) $\geqslant 3$ in at least 1 skin lesion, and were therefore suspected of harbouring dapsone-resistant *Mycobacterium leprae*. All but 6 of these patients were subjected to skin biopsy and measurement of the susceptibility of their *M. leprae* to dapsone.

The susceptibility of *M. leprae* to dapsone was measured by published methods.[5] Briefly, 10^4 *M. leprae* were inoculated into each hind foot-pad of a number of locally bred Swiss mice. One group of 14–20 mice served as untreated controls, and groups of 7–14 mice were administered dapsone incorporated into the mouse diet in a concentration of 0·0001, 0·001 or 0·01 g dapsone per 100 g diet. Harvests of *M. leprae* were performed from both hind foot-pads of 2 to 4 untreated, control mice at intervals of 45–60 days, beginning 8–10 months after inoculation, until evidence of multiplication (an average yield of at least $10^{5·7}$ *M. leprae* per foot-pad) was observed. At this time, the remaining control mice and all of the treated mice were harvested individually. If, by the end of 14 months, control harvests had yielded an average of less than $10^{5·7}$ but at least $10^{5·0}$ organisms per foot-pad, harvests of *M. leprae* from the dapsone-treated mice were carried out at that time. However, if the yield of *M. leprae* after 14 months was fewer than $10^{5·0}$ organisms per foot-pad, no further harvests were carried out, and the patient's *M. leprae* were considered to have been non-infective for the mouse foot-pad. A strain of *M. leprae* was considered resistant to a given concentration of dapsone if more than half of the mice treated with dapsone in that concentration yielded at least $10^{5·0}$ organisms per foot-pad.

Results and interpretation

RESULTS OF SCREENING

The results of screening the 777 patients at risk are summarized in Table 1, in which the patients are divided between 2 groups. The patients in Group I had received no treatment other than dapsone, or had received additional treatment with thiacetazone or thiambutosine, both weak, bacteriostatic drugs. The patients of Group II, most of whom had exhibited clinical evidence of relapse or deterioration after a period of dapsone as monotherapy, had all received

Table 1. Results of screening

Group	Treatment	Number of patients	Relapse or deterioration	BI 0	BI 1–2	BI ⩾3
I	Dapsone + bacteriostatic drugs	718	48	665	12	41 (5·71%)
II	Dapsone + other first-line drugs	59	52	20	13	26 (44·1%)

additional treatment with first-line drugs. Fewer than 6% of the patients of Group I were suspected of harbouring dapsone-resistant *M. leprae*, whereas 44% of the patients of Group II met the criteria for biopsy and mouse inoculation. On the other hand, it is clear that some of the Group II patients had responded to therapy with first-line drugs in addition to dapsone; most of them had been found to have BI ⩾ 3 at the time that the additional treatment had been instituted.

RESULTS OF MOUSE FOOT-PAD INOCULATION

The results of the measurements of susceptibility to dapsone of 61 strains of *M. leprae* are summarized in Table 2. The organisms of 15 strains failed to infect mice. Seven of these strains, representing patients of Group I, may be concluded to have been fully susceptible to dapsone, which was being administered as monotherapy to these 7 patients at the time of the survey. Presumably, the *M. leprae* had been killed in the patient, but the BI had not yet decreased to < 3. The

Table 2. Results of dapsone-susceptibility testing

Group	Number of specimens: Number tested	Not infective	Fully susceptible	Resistant to dapsone (g%): 0·0001	0·001	0·01	Uncertain
I Relapse	26	2	2	2	5	14	1
No relapse	13	5	6	1	0	1	0
Not biopsied	2*	—	—	—	—	—	—
II Relapse	22	8	4	0	0	10	0
No relapse	0	0	0	0	0	0	0
Not biopsied	4*	—	—	—	—	—	—

* Refused biopsy.

patients among 777 at risk, for a prevalence of 8·62 per 100; the 95% confidence limits are 6·79 and 10·88 per 100.

Discussion

Although cases of secondary resistance to dapsone had been previously reported from China,[3] no estimate of prevalence was available. Prevalence surveys among leprosarium patients may well result in biased estimates, because patients who do not do well on treatment are likely to remain longer in and around treatment centres, whereas those who have responded to treatment are more likely to return to their homes. Therefore, in order to obtain an unbiased estimate of the prevalence of secondary dapsone resistance, it is necessary to examine all of the patients at risk; this is the basis of the THELEP protocol.[1] Such a prevalence survey was possible in Shanghai Municipality.

This first survey of the prevalence of secondary dapsone resistance in China has yielded evidence that secondary resistance to dapsone may already be an important problem in Shanghai, affecting as many as 10% of the patients at risk. Because one consequence may be the transmission of dapsone-resistant *M. leprae* in the community, an on-going survey of primary dapsone-resistant leprosy has recently been initiated. In addition, it may appear reasonable to treat all of the patients who remain at risk of secondary resistance with a combination of two first-line drugs in addition to dapsone; such a programme is now being actively considered.

It is interesting to note that, of the 34 strains of dapsone-resistant *M. leprae* isolated, all but 4 were of intermediate and high degrees of resistance. This testifies to the excellence of the leprosy control programme in Shanghai Municipality in the past,[5] and serves warning that an intensive programme of leprosy control based on dapsone monotherapy will not protect a community against secondary resistance to dapsone.

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