counted for 2.8 per cent of the tuberculosis cases counted nationally in 1979 and 7.8 per cent in 1980 (5.3 per cent over the two-year period). The leveling off of the total number of reported tuberculosis cases observed in the United States over the past two and a half years is accounted for by refugee cases being added to the slowly declining number of indigenous cases.

Before entering the United States, Indochinese refugees are screened overseas for tuberculosis and categorized in one of three ways: active or suspected active disease (Class A-TB), disease not considered active (Class B-TB), and no evidence of tuberculous disease. Refugees with Class A-TB may travel only if their disease is non-contagious (i.e., two consecutive negative sputum smears taken on separate days). On arrival in the United States, all refugees with Class A-TB and Class B-TB are referred to a local health department for medical evaluation. Refugees certified as having Class A-TB accounted for about 2 per cent of all entering refugees and 57 per cent of the tuberculosis cases among refugees; refugees certified as having Class B-TB accounted for about 2 per cent of all entering refugees and 20 per cent of the cases among refugees; the remaining refugees accounted for 23 per cent of the reported cases.

The three-fold decrease in incidence from 1979 to 1980 for refugees who entered in 1979 probably reflects a combination of the natural decrease in risk of disease for those infected before arrival and successful efforts to reduce transmission of tuberculosis after arrival. Reduced transmission is the result of several factors: treatment of refugees with infectious tuberculosis (positive smear) is started in Asia; most refugees with Class A-TB have been evaluated promptly after arrival and, if necessary, are continued or started on treatment; over 46,000 refugees (about 18 per cent of the total) have been given preventive treatment; and, presumably, a high level of suspicion in the medical community has led to the prompt evaluation and treatment of refugees with symptoms compatible with tuberculosis. Because of the reduced transmission, tuberculosis case rates among refugees are expected to continue to fall. Nevertheless, they will remain higher than the rates of other persons in the United States for years to come because so many have been infected before arrival.


Drug Resistance in the Treatment of Leprosy

Leprosy control programs have used dapsone (diamino-diphenylsulfone), which probably acts as an antimetabolite, as a specific treatment because of its proven effectiveness, low cost, and reduced toxic effects. Rifampicin, clofazimine, ethionamide, and prothionamide also have a demonstrated bactericidal effect against Mycobacterium leprae. Other medications such as thiacetazone, sulfometoxypyridazine, and thiambutazine have only a bacteriostatic effect.

Outpatient monotherapy of leprosy, usually with dapsone (at a dose of 6-10 mg/kg of body weight per week), revolutionized the control of the disease from the operational standpoint. However, new knowledge of primary and secondary drug resistance in the treatment of leprosy indicates an urgent need to establish therapeutic regimens that combine two or three drugs. Large-scale application of this type of treatment requires sufficient resources and operational experience in order to select strategies that will permit more effective control of the disease.

Resistance to dapsone was first verified in 1964, by means of inoculations of mouse footpads. Table 1 summarizes some of the studies made subsequently, which have reinforced the findings of secondary dapsone resistance of M. leprae.

The finding of bacterial resistance to dapsone is based on the fact that until 1970 nearly all isolated strains of M. leprae (both in mice and in untreated patients) were inhibited when the drug was administered in the diet at a con-
concentration of 0.0001 per cent. The following are the accepted definitions of levels of dapsone resistance of *M. leprae*:

**Susceptible:** strains inhibited by a concentration of 0.0001 per cent.

**Resistant:**
- Low-grade resistance: strains capable of multiplying with 0.0001 per cent, inhibited by concentrations of 0.001 per cent.
- Medium-grade resistance: strains capable of multiplying with 0.001 per cent, inhibited by concentrations of 0.01 per cent.
- Complete resistance: strains capable of multiplying with concentrations of 0.01 per cent in the diet of mice.

The concentration of 0.01 per cent produces dapsone levels in plasma of 1 mg/ml similar to that obtained by administering 100 mg of dapsone to humans.

From the bacteriological standpoint it is impossible to differentiate primary from secondary resistance, and it is clinically difficult to ensure that a patient has not been treated previously with sulfones. In theory, it is possible for a patient with lepromatous or dimorphous leprosy who shows secondary resistance, to infect a contact who in turn develops leprosy with primary resistance. Because the incubation period of tuberculoid forms is shorter than that of lepromatous forms, the prevalence of primary dapsone resistance is probably higher in the former. There has also been verification of secondary resistance to monotherapy with rifampicin and ethionamide, and in the latter cases, cross-resistance to prothionamide.

It is important to use the experience acquired in studies of drug resistance in the treatment of tuberculosis, which demonstrate the success of multiple drug regimens and the failure of monotherapy. The latter results in the survival and proliferation of drug-resistant mutant bacilli which are increasingly less sensitive. The bacilli remaining—in a state of metabolic quiescence—survive concentrations of bactericidal drugs in the blood even though they are sensitive to them. Personnel of leprosy control agencies should keep themselves informed about the problem of possible resistance to the monotherapy employed and, insofar as possible, should adopt combined treatment regimens.

In 1981 WHO formed a working group which studied

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**Table 1. Selected studies on resistance to dapsone in the chemotherapy of leprosy, 1966-1981.**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Date</th>
<th>Drug</th>
<th>Place</th>
<th>No. of patients</th>
<th>Results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pettit, J. H. S. et al.</td>
<td>1966</td>
<td>Dapsone</td>
<td>Malaysia</td>
<td>5,000</td>
<td>Prevalence of resistance: 1 x 1,000</td>
<td>Underestimation for large concentrations of dapsone in the diet of mice</td>
</tr>
<tr>
<td>Meade, T. W. et al.</td>
<td>1973</td>
<td>Dapsone</td>
<td>Malaysia</td>
<td>5,000</td>
<td>Prevalence of resistance: 25 x 1,000</td>
<td>Some patients as study</td>
</tr>
<tr>
<td>Pearson, J. M. H. et al.</td>
<td>1975</td>
<td>Dapsone</td>
<td>Malaysia</td>
<td>100</td>
<td>Incidence of resistance: 0.3 x 100 per year</td>
<td>Resistance verified in all patients</td>
</tr>
<tr>
<td>Pearson, J. M. H. et al.</td>
<td>1976</td>
<td>Dapsone</td>
<td>Ethiopia</td>
<td>1,500</td>
<td>Prevalence of resistance: 190 x 1,000</td>
<td>Patients with monotherapy since 1963</td>
</tr>
<tr>
<td>Peters, J. H. et al.</td>
<td>1976</td>
<td>Dapsone</td>
<td>Costa Rica</td>
<td></td>
<td>Prevalence of resistance: 37 x 1,000</td>
<td>Resistance verified</td>
</tr>
<tr>
<td>Taylor, P. M. et al.</td>
<td>1977</td>
<td>Dapsone</td>
<td>India</td>
<td></td>
<td>Prevalence of resistance: 100 x 1,000</td>
<td>Patients with monotherapy since 1963</td>
</tr>
<tr>
<td>Levy, L. et al.</td>
<td>1977</td>
<td>Dapsone</td>
<td>Israel</td>
<td></td>
<td>Prevalence of resistance: 37 x 1,000</td>
<td>Resistance verified</td>
</tr>
<tr>
<td>Pearson, J. M. H.</td>
<td>1979</td>
<td>Dapsone</td>
<td>Ethiopia</td>
<td></td>
<td>Prevalence of resistance: 50 x 1,000</td>
<td>Patients with monotherapy since 1963</td>
</tr>
<tr>
<td>Balraj, V. et al.</td>
<td>1980</td>
<td>Dapsone</td>
<td>India</td>
<td>1,580</td>
<td>Prevalence of resistance: 2.3%</td>
<td>Patients with monotherapy since 1963</td>
</tr>
<tr>
<td>Lim, K. J. et al.</td>
<td>1981</td>
<td>Dapsone</td>
<td>Malaysia</td>
<td>All cases detected</td>
<td>Prevalence of resistance: 10%</td>
<td>Patients with monotherapy since 1963</td>
</tr>
<tr>
<td>Li Wenzhong et al.</td>
<td>1981</td>
<td>Dapsone</td>
<td>China</td>
<td>Small groups</td>
<td>Prevalence of resistance: 51 x 1,000</td>
<td>Patients with monotherapy since 1963</td>
</tr>
<tr>
<td>Kyaw Lwin</td>
<td>1981</td>
<td>Dapsone</td>
<td>China</td>
<td>11</td>
<td>Prevalence of resistance: 34 x 1,000</td>
<td>Patients with monotherapy since 1963</td>
</tr>
</tbody>
</table>
the problem of resistance, recommended combined treatment for multibacillary and paucibacillary cases, and defined areas for clinical and operational research on chemotherapy. The group’s recommendations included the following:

• The purposes of the treatment program are to interrupt the chain of transmission and to cure the patient.

• Combined treatment prevents secondary bacterial resistance, and therefore the transmission of strains with primary resistance.

• All multibacillary patients (treated or not) should receive combined treatment. It is therefore not necessary to determine bacterial resistance in each patient.

• The basic drugs are rifampicin, dapsone, clofazimine, and ethionamide or prothionamide.

• The intermittent monthly administration of rifampicin (and probably of clofazimine) is effective and permits supervised treatment.

• In paucibacillary leprosy the appearance of resistant strains is very unlikely. Association with rifampicin solves the problem of possible primary resistance and permits a shortening of the treatment period, thereby lessening the workload of agencies and reducing abandonment by patients.

(Source: Leprosy Control Program, Division of Disease Prevention and Control, PAHO.)

Surveillance and Control of *Aedes aegypti* in Bolivia

In February 1980, *A. aegypti* was discovered in Bolivia after 32 years of absence. Findings were made at the Santa Cruz airport, at kilometer 15 of the Santa Cruz-Cochabamba highway, and in the communities of Cotoca, Warnes, and Montero near Santa Cruz.

The following control measures have been taken:

• *Antimalaria vaccination.* Between June 1980 and July 1981 there was 62.5 per cent coverage of the population of Santa Cruz Department.

• *Basic sanitation.* The health authorities, working with civic and development agencies, undertook the collection and disposal of solid wastes.

• *Treatment of positive localities.* The following treatments were applied: focal treatment with abate (1 ppm), perifocal treatment with malathion (50 per cent pH), intradomiciliary treatment using FONTAN packs, and malathion (96 per cent) from the street using ULV equipment.

• *Health education.* All possible means were employed to have the population of reinfested areas take part in health education activities.

From January to May 1981 entomological surveys were made, showing the following rates of infestation: 5.4 per cent in Santa Cruz, 0.0 per cent in Montero, 1.2 per cent in Cotoca, 0.0 per cent at kilometer 15, and 0.0 per cent in Warnes.

Entomological surveillance by regional teams confirmed the absence of *A. aegypti* in all other areas of the country. The inspection of airports and adjacent areas continues as does the spraying of international aircraft and trains.

(Source: Boletín Epidemiológico, No. 73, 1981, Ministry of Social Welfare and Public Health, Bolivia.)

Editorial comment:

A technical meeting on *A. aegypti*, dengue, and urban yellow fever will be held in Mexico City from 1-5 June 1982, in compliance with Resolution XXI of the XXVIII Meeting of the Directing Council of PAHO. Experts from several countries have been invited to present working papers which will guide the discussions on regional action aimed at controlling the *A. aegypti* problem.

An informal group met in Washington, D.C. in January to draw up the agenda for the meeting, which will cover five topics: the vector, the human host, the virus, the disease, and integrated programs for *A. aegypti* control.