Drug Resistant *Mycobacterium tuberculosis*

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In every population of *Mycobacterium tuberculosis* there will be a certain proportion of mutant cells which are resistant to one or another anti-tuberculosis agent. This genetic resistance occurs at a rate of between 1 per million to 1 per hundred million cells. In pulmonary cavitary disease, where there are very large populations of tubercle bacilli in the lesion, the numbers of resistant micro-organisms may be significant. When selected for by an anti-tuberculosis agent this initially predominantly sensitive population can be converted to a resistant one in a relatively short period of time. This is the rationale for giving combination therapy in tuberculosis. Resistance to anti-tuberculosis drugs most often occurs when patients fail to complete the prolonged chemotherapy that is required. Symptoms of patients wane within weeks of starting anti-tuberculosis treatment, and without active intervention many patients may drop out of therapy. Resistance in tuberculosis is termed primary or initial when it occurs in a previously untreated patient and secondary or acquired when it is found in a patient who has received anti-tuberculosis treatment. The primary resistance rate is therefore a reflection of the effectiveness of the treatment and control programmes in a country.

The primary drug resistance rates vary from country to country. In the United Kingdom the primary drug resistance rate among white patients was only 2% in the 1985 to 1989 period, while the corresponding figure for immigrants from the Indian subcontinent was 6.5%[1]. The primary resistance in Western Australia from 1980 to 1989 was 9.9%, with resistance occurring much more frequently among Asian immigrants and aborigines compared to the white population[2]. In the United States the level of primary drug resistance was 9% for the 1982 to 1985 period and again was more frequently seen in the immigrant populations[3]. A similar survey in India from 1983 to 1986 showed the primary resistance rate to be as high as 20%[4]. The primary resistance rate in West Malaysia of nearly 16%, as reported by Jalleh *et al*[5] in this issue of the journal, is therefore quite high although the majority of resistant strains were resistant to only one drug. Primary resistance to rifampicin was also quite low.

There can be several severe consequences of drug-resistant tuberculosis. The minimum period for chemotherapy has to be extended to 18 to 24 months. The cure rate is poor and the mortality in such outbreaks can be very high (72% to 89%). There is also a rapid progression from diagnosis to death (median interval of between 4 to 16 weeks)[6].

In the United States there have been several recent outbreaks of drug-resistant tuberculosis[7]. Many of the patients suffering from drug resistant tuberculosis are also HIV-infected[8,9], thus accounting for the rather severe course of the infection. Drug-resistant tuberculosis is also more likely to occur in the socially maladapted[10], the homeless[11] and inmates of correctional institutions[6]. In Jalleh's paper there were no details of the socioeconomic background or HIV status of the patients with resistant *Mycobacterium tuberculosis*. Such information would have been useful in helping identify patients who are at high risk of harbouring resistant organisms. Nosocomial outbreaks of drug-resistant tuberculosis have been reported with transmission of the infection to inpatients as well as health care workers[12,13]. Restriction fragment length polymorphism analysis has been used to type *Mycobacterium tuberculosis* strains and establish a common source in one such hospital outbreak[14].

To prevent outbreaks of drug-resistant tuberculosis, it is important to ensure compliance in all patients on anti-tuberculosis treatment. The most effective method is through direct observation of therapy by a health care worker. It is also important to reduce risk of transmission of tuberculosis through prompt diagnosis and

isolation precautions. Efforts should also be directed towards improving diagnosis and susceptibility testing. Currently available methods of susceptibility testing are far too slow, requiring several weeks for completion.

There are new anti-tuberculosis agents which may find a role in the treatment of drug-resistant tuberculosis. These include the new quinolones, of which ofloxacin[15] and sparfloxacin[16] are particularly promising. Amoxicillin-clavulanate has been reported to be effective in treating drug-resistant tuberculosis[17]. Other drugs which have been shown to possess good *in vitro* activity against *Mycobacterium tuberculosis* include fusidic acid[18], the oxazolidinones[19] and new rifamycin derivatives[20].

A potentially serious situation with drug-resistant tuberculosis can arise in Malaysia. This is in view of the increasing numbers of HIV-infected persons as well as the large population of immigrants in the country. Continued surveillance of resistance to anti-tuberculosis drugs must be undertaken. The population characteristics of patients with drug-resistant tuberculosis has to be established in order that high risk groups can be identified. Doctors in hospitals who manage HIV-positive patients must be made aware of the risks of nosocomial outbreaks of drug-resistant tuberculosis and all precautions taken to reduce transmission. The tuberculosis control programme in the country should be further intensified as it is only through early diagnosis and effective treatment that drug-resistant tuberculosis can be prevented.

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