Tubercle and Lung Disease (1993) 75, 321–323

Tubercle and Lung Disease

Editorial

Drug-resistant tuberculosis: issues in epidemiology and challenges for public health

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30 years ago, Canetti warned implicitly '... Since optimal chemotherapy of tuberculosis produced by wild strains reduces the frequency of emergence of resistance drastically, the general feeling tends to prevail that resistance has slipped into history ...'[1] The medical community has subsequently learned the hard way, from experience in the USA[2–4] and elsewhere,[5–6] that Canetti really meant optimal chemotherapy and not availability of optimal drugs.

The British Medical Research Council's streptomycin trial[7] revealed early on what is now abundantly clear: in each wild strain of tubercle bacilli, approximately 1 out of every 1–10 000 000 organisms is spontaneously resistant to at least 1 of the known drugs.[8] Because patients with cavitary pulmonary lesions may harbor 10 000 000–1 000 000 000 tubercle bacilli,[1] any patient treated with only a single effective drug has a very high probability that the drug-resistant mutants are preferentially selected while the susceptible ones are killed off. Conversely, a patient continuously treated with 2 or more drugs, in concentrations to which the strain is susceptible, has a very high probability of escaping the fate of incurable drug-resistant tuberculosis. The role of chemotherapy is paramount in the production of all clinically important drug resistance.

Three phases in the development of antituberculosis chemotherapy might be distinguished. They are characterized by increasing knowledge about principles of treatment, accompanied by neglect of that knowledge by large segments of the medical community. The first phase began with the discovery of streptomycin and the early observation of the iatrogenic creation of streptomycin resistance in clinical trials. An insight into the harm inflicted by monotherapy was gained in this period. In the second phase, it was shown that streptomycin resistance could be largely overcome with the addition of para-aminosalicylic acid and isoniazid, and that such 3-drug regimens were able to cure tuberculosis patients who had had no previous treatment in 100% of cases without creating drug resistance.[9] These warnings and insights, however, apparently went unheeded, and isoniazid resistance became a major problem in many areas of the world.[10] Fortunately, the introduction of rifampicin plus pyrazinamide-containing treatment regimens helped to overcome and successfully treat even those patients with strains initially resistant to isoniazid in a very large proportion of cases.[11] The third and most recent chapter in complacency over well-established principles has resulted in the emergence of combined isoniazid-rifampicin resistance, a pattern that currently marks the irreversible end-point of effective tuberculosis control in many parts of the world.

Because the risk of tuberculosis following infection remains lifelong, a crude cross-sectional appraisal of the prevalence of drug resistance carries little information on the susceptibility patterns of currently circulating strains. In the same way that tuberculosis in children is a sentinel event for tuberculosis transmission in the community,[12] so the frequency of drug-resistant tuberculosis in children reflects a precise evaluation of the current situation. Susceptibility patterns from cultures obtained from children with tuberculosis under the age of 5 years should thus be the most informative source of knowledge about susceptibility patterns of currently circulating strains. Unfortunately, such cultures tend to be the most difficult to obtain. In a recent survey in the United States, the crude prevalence of any resistance was 14.2%.[4] Age-specific resistance adjusted for demographic characteristics was highest in children below the age of 15 (21.6%) and decreased with increasing age to 9.4% among patients aged 65 years and older. This strongly suggests that the frequency of any resistance has been increasing dangerously over time in the USA. In contrast, the crude prevalence of rifampicin-isoniazid resistance was 3.5%, but lowest (2.0%) in children under the age of 15 and highest in the 25– to 44-year-old age group, indicating that the circulation of strains with combined resistance might still be limited in the USA.

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To elicit a proper history on previous treatment among patients with tuberculosis is of crucial importance, not only to decide on the correct initial regimen for the individual patient (which should be different for cases with and cases without a history of previous treatment), but also to gain better knowledge about the current circulation of drug-resistant strains. Patients who claim never to have been treated for tuberculosis before, but who are found to have drug-resistant tubercle bacilli, are said to have an initially resistant strain; patients with a history of previous treatment found to have a resistant strain are defined as having acquired resistance.[8] That treatment histories are not always adequate is indicated in the article by Tahaoğlu and collaborators in this issue of *Tubercle and Lung Disease*.[6] Although the authors do not provide the relevant information, it is likely that rifampicin has not been available on a wide scale for more than 25 years in their country; yet half of their patients with any rifampicin resistance who claimed no previous treatment were over 30 years of age; almost 30% were over 50, and thus had a high likelihood of having acquired their infection before the introduction of rifampicin. Unless one is willing to postulate an increasing role of exogenous reinfection tuberculosis with strains resistant to rifampicin, the only other conclusion must be that history of previous treatment was inadequately obtained in a considerable proportion of patients. Initial resistance represents, to a varying degree, a contamination of primary resistance (the result of infection with a resistant strain that progressed to clinical tuberculosis) with acquired resistance resulting from undisclosed previous inadequate treatment. The challenge to the evaluation of a patient's history lies in minimizing this contamination. Structured, and perhaps repeat, interviews combined with a thorough review of all available records enhance the probability that the difference between initial and primary resistance becomes sufficiently small to allow meaningful interpretation of the epidemiologic situation of drug resistance in the community.

A single survey on initial and acquired drug resistance may help to give an idea of the magnitude of the problem in the community and may have important repercussions on the designing of the best regimen for new cases with tuberculosis and the appropriate regimen for patients in need of retreatment.[13] Repeat surveys or a regular surveillance system for initial and acquired drug resistance on the other hand are an essential public health management tool, allowing the observation of deficiencies or improvements in tuberculosis control over time. The Korean Institute of Tuberculosis and the Korean National Tuberculosis Association, for example, have demonstrated with repeat surveys that the level of both initial and acquired resistance can be reduced with a properly structured program, encompassing standardized treatment regimens of high efficacy.[14] Very similar observations have been made in Algeria.[15]

The World Health Organization has taken up the gauntlet, declared war on tuberculosis, and developed a new strategy with two clearly defined objectives, the first being to attain a large cure ratio among diagnosed tuberculosis patients, the second to subsequently expand case-finding.[16] These two objectives must take their place under the hierarchically higher principle which is to avoid at all costs the introduction of drug resistance into the community by inadequate intervention, be it through faulty prescriptions or through failure to guarantee patients' adherence. Situations such as have been reported, from New York City,[2,4] the Philippines,[5] or as are apparently in the making in some areas in Turkey,[6] reflect gross negligence on the part of the medical profession toward the community. Patients have numerous reasons for becoming non-adherent with treatment, particularly if the system fails them from the outset,[17] and the blame for failure must rest with the health care system, not the individual patient.

Adequate chemotherapy can clearly prevent the emergence of drug-resistant tubercle bacilli. It is not possible to assess changes in drug-susceptibility patterns rapidly, because once a new drug is introduced, it will take considerable time for drug resistance to manifest itself in a crude sample of patients. Despite the rapid increase in Tanzania of tuberculosis associated with the epidemic of human immunodeficiency virus, the level of initial isoniazid resistance has not increased over the 15 years of the existing national program,[18] and initial rifampicin resistance is at present below 1%.[19] Antituberculosis drug resistance is a man-made problem and is thus amenable to corrective action. A combination of the best available drugs must be given for patients with the largest bacterial population (sputum smear-positive cases), i.e. isoniazid, rifampicin, pyrazinamide plus a fourth drug (ethambutol or streptomycin), given under direct observation for the first 2 months or until they are sputum smear-negative, if they have not converted by 2 months. Such treatment will overcome even initial isoniazid resistance in most cases and lower the bacterial population to such an extent that a self-administered continuation phase with a fixed 2-drug combination coupled with regular bacteriological controls will prevent the introduction of drug-resistant strains into the community and continue to cure most tuberculosis patients in the world. The potential of introducing drug resistance, resulting from a failure to adhere to these principles, will never be overcome, even by the development of new drugs.

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