Chemotherapy of Drug-resistant Tuberculosis

The treatment of patients with tuberculosis resistant to the standard drugs, streptomycin, isoniazid, and para-aminosalicylic acid (P.A.S.), presents many difficulties, some of which are due to the unfavourable properties of the reserve antituberculosis drugs. Several of these drugs provoke unpleasant or dangerous adverse effects which may necessitate withdrawal of the drug or reduction in dosage to a level at which chemotherapeutic effectiveness is seriously jeopardized.

It is generally necessary to give two years' treatment with at least two drugs in adequate dosage to ensure bacteriological cure, but this is rarely possible when toxic drugs must be used. Another difficulty is that most patients with acquired drug resistance proved uncooperative previously and have failed to take standard drugs as advised. These patients usually prove to be intolerant of prolonged treatment with unpleasant drugs in hospital, become easily despondent, and leave hospital. The unacceptability of some reserve-drug regimens is seen in the results of a co-operative investigation in which 117 patients were treated with ethionamide, cycloserine, and pyrazinamide in many centres in Great Britain. By six months only 49 remained under treatment with the prescribed chemotherapy and by twelve months only 14.[1] Results have been better when small numbers of patients have been supervised by the same physician.[2] There is a need for more effective and less toxic drugs and for more acceptable and easily supervised regimens. Advances along these lines were reported at a recent symposium.[3]

The most promising new reserve drug is rifampicin. It appears to be potent and is remarkably well tolerated.[4] Resistant mutants are exceedingly rare in wild strains of *Mycobacterium tuberculosis*, so that resistance might be expected to emerge less rapidly than with other reserve drugs.[5] Preliminary clinical studies suggest that in combination with other reserve drugs it is effective in the treatment of drug-resistant tuberculosis.[6]

Ethambutol has been used in combination with other drugs in many cases of drug-resistant tuberculosis. Though there is no evidence from controlled studies about its efficacy compared with other reserve drugs, it is generally conceded to be a potent and well-tolerated drug. Reversible retrobulbar neuritis occurs in 5% or 10% of patients receiving 25 mg. per kg. body weight daily. This complication is not a problem at a dosage of 15 mg. per kg. daily, but that dose may not be adequate when the disease is extensive.[7]

Capreomycin is an effective drug and well tolerated. Unfortunately its adverse effects, though rare, are serious and include renal impairment, hypokalaemia, and hypocalcaemia.[8] Until more is known about its toxicity, prolonged treatment with this drug requires careful monitoring of renal function and electrolytes. There is good reason to hope that rifampicin, ethambutol, and capreomycin will prove more successful in the retreatment of patients than the more toxic drugs, ethionamide, prothionamide, and cycloserine.

Intermittent administration of reserve drugs would be a great advantage. It would enable fully supervised therapy to be given more easily to outpatients, thus reducing time spent in hospital, or possibly permitting all treatment to be given in the home. However, intermittent streptomycin and pyrazinamide have been shown to give poor results.[9] In-vitro and animal tests with ethambutol and rifampicin suggest that these two drugs may also be suitable for intermittent administration.[10] The results of clinical studies of intermittency with these drugs are awaited.

Drug-resistant tuberculosis is diminishing in incidence in most economically developed countries, where good primary chemotherapy is available for all. But in many developing countries acquired drug resistance is frequent.[11] Unfortunately, the reserve drugs at present available are too expensive for use in these countries. Until they have a highly efficient and successful organization for primary treatment it would be unwise to divert resources to reserve chemotherapy. Happily there is no reason to believe that the excretion of drug-resistance bacilli constitutes at present a major menace to these communities.[12]

The ideal reserve drug regimen does not exist. The newer reserve drugs offer promise of greatly improved therapeutic results in economically developed countries. The need for a cheap and effective regimen for developing countries remains an unsolved and challenging problem.

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[4] *New England Journal of Medicine*, 1969, **280**, 615.
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[6] Gyselen, A., Verbist, L., Cosemans, J., Lacquet, L. M., and Vandenberg, E., *American Review of Respiratory Diseases*, 1968, **98**, 933.
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[9] East African/British Medical Research Council Pyrazinamide Investigation, *Tubercle*, 1969, **50**, 81.
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[12] Fox, W., *Tubercle*, 1969, **50**, March, *Supplement*, p. 55.

Epiglottitis in Adults

Acute epiglottitis is generally considered to be a disease of infancy and early childhood, and the fact that it occurs in adults, though less frequently, is possibly not fully appreciated. Although the number of adult cases so far documented amounts to no more than 40, the importance of the reports which have so far appeared in the literature lies in their emphasis of the seriousness of the condition. It would seem that the adult sufferer is as prone to laryngeal obstruction as the infant, and that sudden death from respiratory obstruction is not uncommon. The most recent report on this subject stresses the need for increased vigilance in the detection of adult epiglottitis and prompt intervention when the airway becomes compromised.[1]

The initial period of the illness, which is characterized by a sore throat, is often mild, and may last from a few hours to three or four days. There is subsequently an increase in the severity of the sore throat, together with the onset of dysphagia and other symptoms such as cough and voice change. Dyspnoea accompanied by inspiratory stridor comes on suddenly and increases with alarming rapidity over the ensuing hours. The patient at this stage is prostrate and shocked to a degree which is out of all proportion to the short duration of the illness. Restlessness is a pronounced feature, leading in turn to disorientation and in some patients to convulsions. Antibiotics may be sufficient to reverse the earlier changes, but in other cases deterioration is so rapid as to make tracheostomy essential.

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