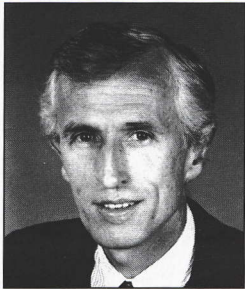# What is New in Tuberculosis?

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Curriculum vitae

Professor Eric D Bateman obtained his MBChB with honours and distinction in the final professional examinations at the University of Cape Town in 1970. His other academic qualifications include the Diploma of Child Health of the Royal College of Physicians and Surgeons (UK) (1973), membership of the Royal College of Physicians (UK) (1974), Fellowship of the Royal College of Physicians in 1986 and a Doctor of Medicine degree from UCT in 1984 for a thesis entitled "Fibrogenetic Mechanisms and Sequence of Collagen Deposition in Pulmonary Fibrosis".

He is currently Head of the Respiratory Clinic, Department of Medicine, Groote Schuur Hospital and University of Cape Town where he has been a consultant since 1980. He was appointed as an Associate Professor in 1986. He is a past President of the SA Pulmonology Society, Scientific Advisor to the National Centre for Occupational health in Johannesburg and is active in many medical bodies including the SA Immunology Society, the Allergy Society of South Africa and the SA Critical Care Society and is a member of both the American and British Thoracic Societies. He has more than 60 publications to his credit. His main area of research relates to cellular immunological and biochemical aspects of interstitial lung diseases including pneumoconioses and disseminated tuberculosis, and the immunology and treatment of asthma. He was awarded the ICI (SA) Pharmaceutical Research Fellowship in 1978, and the Ernest Oppenheimer Memorial Travelling Fellowship in 1991 to enable him to undertake research activities in institutions overseas.

Summary

Tuberculosis was declared a global health emergency by WHO and has been a major challenge in terms of numbers, economic impact and human suffering, world-wide and in SA. With the outbreak of the AIDS epidemic there has been a resurgence of interest and research in this disease, more as a result of its becoming a renewed threat in western countries. This has resulted in many impressive advances in understanding of the immunology, molecular biology and genetics of mycobacterial infections and of the economic, sociological and other epidemiological aspects of the disease. This article deals with issues of immediate interest and relevance to the family practitioner and considers:

1. *the global picture,*
2. *facts about the epidemic in South Africa*
3. *case holding and the development of multidrug-resistant organisms,*
4. *clinical features of tuberculosis in HIV-positive patients,*
5. *prospects for new treatments and,*
6. *the role of the family practitioner in the tuberculosis control programme.*

Introduction

Tuberculosis remains a enormous challenge to humankind, whether viewed in terms of numbers, economic impact or human suffering, and it is thus appropriate that it be included in the programme of a congress of this nature. Sadly, in the 1980's it was in danger of being relegated to an ugly duckling status in medicine, largely because of its rapidly declining incidence in

developed countries. With the outbreak of the AIDS epidemic there has been a resurgence of interest and research in this disease, more as a result of its becoming a renewed threat in western countries than as a result of a global philanthropy. This renewed interest has resulted in many impressive advances in understanding of the immunology, molecular biology and genetics of mycobacterial infections and of the economic, sociological and other epidemiological aspects of the disease. I will confine my comments to issues of more immediate interest and relevance to the family practitioner and will consider:

1. the global picture,
2. facts about the epidemic in South Africa,
3. case holding and the development of multidrug-resistant organisms,
4. clinical features of tuberculosis in HIV-positive patients,
5. prospects for new treatments and,
6. the role of the family practitioner in the tuberculosis control programme.

The Global Picture: Tuberculosis is a Global Health Emergency

Tuberculosis is on the increase and is out of control in many regions of the world. This has prompted the World Health Organisation (WHO) to take the extraordinary step of declaring it a global health emergency. More than ⅓ of the world's population are infected and more than 30 million people are expected to die of tuberculosis in the next decade. It is now the world's leading cause of death from a single infectious agent. This increase is not solely the result of the AIDS epidemic although in Africa the contribution of the latter has been significant. Other

factors cited by the WHO are inadequate programmes for disease control, multidrug-resistance, and a rapid increase in the population of young adults, the age group with the highest mortality. In most countries the incidence of tuberculosis serves as a barometer of socio-economic need and the state of health services. The tragedy of the situation is that the control of tuberculosis is both possible and affordable even for developing countries. The essential components of a successful TB control programme have been established and tested in several countries including Tanzania, China and Mozambique. Such programmes require:

1. political commitment,
2. a secure supply of drugs and diagnostic materials,
3. microscopy with quality control and,
4. proper recordings and reporting of cases on a centralised basis.

They have been subjected to economic analysis and are viewed as a cost-effective intervention. As a consequence, the International Union Against Tuberculosis (IUAT) has received large-scale funding from the World Bank for their implementation in the developing world. The programmes have also been endorsed by the World Health Assembly. In May 1991 the WHA set the following goals: to cure 80% of newly identified smear-positive cases and identify 70% of the total number of smear-positive cases by the year 2000. Full supervision of treatment is considered essential. It was agreed that case findings should only be expanded once the above objectives have been achieved. It is now recognised that these goals are over-ambitious and will not be met by the year 2000.

The AIDS-epidemic made western countries take a renewed interest in TB

TB is out of control in many parts of the world

What's New in TB?

The Epidemic in Southern Africa: Western Cape Epidemic is unexplained

Annual notifications for tuberculosis numbered 77 000 (203 per 100 000) in 1991, and 7 000 deaths were reported. The former figure is higher than in most other sub-continents, but the death rate is lower, reflecting a disparity between preventive and curative health services in South Africa. It is also recognised that notification rates probably represent only ⅓ of patients with active disease. The incidence of disease is however, not uniform throughout the country, but varies according to ethnic group and region. Currently an epidemic of tuberculosis involving predominantly persons of mixed race is in progress in the Western Cape (670 cases/100 000 in 1991).

None of the several hypotheses put forward to explain this epidemic is supported by convincing evidence. It does not appear to be due to falsely high notification rates, non-availability of TB services or changes in the nutritional or socio-economic status of the affected groups.

Countrywide the risk of infection remains considerably higher than the target set in 1979 in the National Tuberculosis Policy. The latter forms the basis for the tuberculosis control programme in South Africa (TCP) and involves reducing the risk of contracting tuberculous infection to 0,3% or less in all population groups, and ensuring effective treatment of all diagnosed disease. The risk of infection is defined as the probability of an individual becoming infected with the tubercle bacillus in one year, and represents the extent of transmission of the organism in the community. Unlike notification and mortality data it is not dependant upon the quality of routine surveillance but is obtained from periodic surveys of tuberculin skin test reactivity. The annual risk of infection amongst mixed race and blacks is currently 3-5 times higher than the target figure, and is highest in adolescents and young adults, in males and in communities living in over-crowded conditions.

The first phase of the TCP involves reducing the infectious pool through active and passive case-findings and supervised short course chemo-therapy (case holding until the patient is cured), and offering protection against infection through BCG vaccination. The aim of the second phase is to reduce the infected pool and endogenous reactivation through secondary chemoprophylaxis and improvements in socio-economic status. The structure of the TCP is a four-tier system comprising a National TB Co-ordinating Committee, regional TB Co-ordinating Committees, local authority teams and community-based services. In spite of improvements in co-ordination at regional level, many obstacles continue to prevent the smooth functioning of the system at local and community level. These obstacles include distances from the clinic, staff shortages, non-availability of all scheduled drugs in some regions, political unrest and other social and economic factors. In order to succeed services must be both accessible and acceptable to the local community.

Case Holding and the Development of Multi-Drug Resistant Tuberculosis

Case-holding is the main determinant of successful treatment and is critically dependent on both patient compliance, which varies from 28% (Soweto survey, 1978) to 82%

WHO declared TB a global health emergency

More than full supervision of treatment is essential of the world has TB

(Western Cape survey, 1984) and compliance of care-givers with TCP policies and regimens. A useful indicator of poor case-holding is the number of patients with active disease who have been treated previously. Amongst such patients are true relapses (where relapse has occurred in spite of full treatment – usually less than 10%) and defaulters – who did not receive full treatment on the first occasion (often 30% or more). Viewed from the perspective of public health, the most serious result of poor case-holding is the development of drug resistant strains of M tuberculosis.

Initial drug resistance is defined as the presence of resistant organisms in persons being treated for tuberculosis for the first time. It results from person to person spread from an open source of resistant organisms. This may occur during ambulatory treatment for open cases, shelters for the homeless or as a result of overcrowding. Health care providers are at special risk and some forms of respiratory apparatus eg nebulisation, particularly in patients with extensive disease and HIV infection may enhance spread. Acquired resistance is defined as resistant organisms found in patients previously treated for tuberculosis and occurs through a process of selection under the influence of partial or inadequate treatment. The most serious form of resistance is multi-drug resistance (MDR) defined as resistance to the two most valuable bactericidal drugs, INH and Rifampicin, and is an increasing problem in many parts of the world. Much publicity has been given to its dramatic increase in New York City, but in terms of numbers, the problem is considerably larger in Africa. In South Africa there has been a gradual decline in both acquired and primary resistance to INH. In 1988 overall drug resistance was as

30 million will die of TB in the next decade

Control of TB is possible and is affordable, even for SA!

Save face...

follows: INH 14,2%, streptomycin 12,1%, rifampicin 1,8%, ethionamide 2,5%, ethambutal 1,2% of cultured specimens.[1]

The incidence of acquired MDR in the Western Cape in 1993 was 4% and initial MDR was 1%.

Resistance to individual drugs occurs naturally by random mutations in the DNA of mycobacteria.[2] These mutations occur with predictable frequencies which vary for different drugs. For example, one organism in a million is resistant to INH and others to ethambutal. One in 108 is resistant to rifampicin, and 1 in 105 is resistant to streptomycin. Fortunately, because the loci are not linked, the likelihood of an organism spontaneously developing resistance to two drugs is the product of probabilities, ie for INH and rifampicin resistance[1] in 1014. Even extensive cavitatory disease rarely contains this number of organisms. Thus spontaneous evolution of multiply resistant bacteria is rare, and singly resistant organisms are eliminated by the other two drugs in a three drug regimen. MDR occurs by selection when only one effective drug is in use as when case-holding is poor and treatment is partial, or drug regimens with a single effective drug are used. Disease associated with large numbers of organisms as in patients with HIV infections, and/or extensive cavitatory disease also favour the development of drug resistance.

The treatment of MDR is approximately 10 times more expensive than usual regimens, and initial response (sputum conversion) occurs in ⅔ of patients. The relapse rate however is high (15-20%). Principles for treatment of MDR TB include the use of at least four drugs, three of which should not have been previously used, treatment should be continued for 18-24 months and be fully supervised. In particular, the addition of one drug to a failing regimen must be avoided. In the Western Cape, treatment of MDR TB has been concentrated in one or two special clinics where rigid criteria for assessing patients, selecting treatment regimens and case-holding, whether as inpatients or through ambulatory care are applied. Only in this setting are satisfactory results obtained.

Tuberculosis and HIV Infection

It is relevant to emphasise some of the important clinical features of tuberculosis in patients infected with HIV, as such cases are on the increase in South Africa. Tuberculosis reactivates early in the course of HIV infection. In spite of their being immunocompromised, HIV-seropositive patients respond to anti-tuberculosis therapy as well as seronegative individuals, provided rifampicin-containing regimens are used.[3] Recurrence rates are also low following rifampicin-containing treatment. The incidence of cutaneous hypersensitivity reactions, particularly to thiacetazone is high.

The prevalence of HIV infection in patients presenting with tuberculosis in Africa ranges from 10-75%, but is still relatively low in South Africa. As lymph node involvement is common, up to 60% of adults presenting with tuberculous lymphadenopathy are HIV positive. Hilar and mediastinal glands are common sites of adenopathy. Unlike the USA where Mycobacterium avium intracellular (MAI) is common, the majority of tuberculous infections in Africa are caused be M tuberculosis. Large numbers of organisms are found in

Currently we have an epidemic of TB in the western Cape amongst coloureds which cannot be explained

Treatment of multi-drug-resistant TB is 10X more expensive

Effective immunotherapy as an adjunct to drug treatment is actively pursued

HIV-related tuberculosis, and may be cultured from blood. Cases are frequently severe and extrapulmonary manifestations are common. Histologically, granulomata are poorly formed.

Prospects for New Drugs and forms of Treatment

Considering the size of the tuberculosis problem, development of new pharmaceuticals has been slow in recent years. Renewed interest has been focussed upon the problem as a consequence of the HIV epidemic and the development of multi-drug resistance, particularly in the USA. Newer agents are costly and provide little advantage over conventional therapy, but may be used as alternatives in MDR TB. Prominent amongst these are rifabutin, and the 4-aminoquinolones (ofloxacin and ciprofloxacin). Rifabutin is 20 times more potent against M tuberculosis than rifampicin, because of greater lipophilicity. 40% of rifampicin-resistant strains are sensitive to rifabutin. It appears to be equally effective in newly diagnosed tuberculosis and in MDR, sputum conversion rates of up to 50% have been obtained. It appears to be safe even in the presence of rifampicin hepatotoxicity.

The possibility of effective immuno-therapy as an adjunct to drug treatment is being actively pursued.[4] The most promising option is the use of several injections of autoclaved Mycobacterium vaccae as a means of modulating the immune response. It is hypothesised that mycobacterial antigens, (termed common antigens), shared by M tuberculosis and M vaccae induce T-helper lymphocytes to differentiate into a class of cell with protective but little tissue destructive effects. The alternative path of

development leads to accumulation of cells that release large quantities of tumour necrosis factor-alpha (TNF-alpha), the cytokine responsible for the pyrexia, wasting, and tissue-destruction in tuberculosis. Preliminary trials with M vaccae performed in the Gambia, India, Iran and Vietnam have shown promising results, and trials are now underway in South Africa. Romania, Vietnam[5,6] and Mexico. In a trial in the Kano district of Nigeria, 98 patients were randomised to receive either a single intradermal injection of autoclaved M vaccae or saline. The M vaccae group gained more weight, had a greater fall in ESR and a greater proportion became sputum negative than in the saline group. Subjective wellbeing improved rapidly in the treatment group.[5]

It is suggested that unless the treatment of tuberculosis can be significantly shortened, it is unlikely that the epidemic in Africa can be brought under control. The addition of new drugs is unlikely to achieve this. The aim of immunotherapy is to eliminater arrest infecting bacilli, leaving the individual protected against re-infection. Secondary objectives are to reduce the degree of host damage caused by the Koch response. An added benefit of reducing the production of TNF-alpha is that in HIV-infected persons this cytokine enhances virus replication. Switching off the Koch response should therefore reduce virus production in HIV.

Tuberculosis and the Family Practitioner

The control and treatment of tuberculosis is correctly viewed as a public health problem, and therefore the responsibility of this state health department. This is a necessary

TB Control programmes will unfortunately have to remain a state health issue

Successful treatment is critically dependent upon compliance over a long period

strategy if tuberculosis control programmes are to succeed. There is abundant evidence that individualised treatment schedules and fragmented control programmes are wasteful and ineffective, and lead to the development of drug resistant organisms. It is thus likely that in the foreseeable future treatment of tuberculosis will remain a state health issue.

This form of vertical control creates several problems. Firstly it is primarily disease-orientated rather than patient-orientated treatment. Furthermore it removes patients from the care of family practitioners who in other respects play a central role in community health issues. Since the success of treatment is critically dependent upon compliance throughout a lengthy treatment period, quality doctor-patient relationships involving education and communication are highly desirable. Separation from family practitioners can mean temporary neglect of other health needs.

Details of future health structures in South Africa are not yet available. Nonetheless, it is worthwhile considering possible new roles for family practitioners in the TCP. This matter has recently been considered in India. Currently in India, as in South Africa, there is a virtual absence of any collaborative effort between private doctors and public health services, and many important deficiencies in the treatment practices of private doctors have been identified.[7] It has been proposed that co-operation and shared responsibility may be achieved through the following:

1. Participation in the planning of the national TCP,
2. Involvement in case finding,
3. Provision of free or subsidised diagnostic services,
4. Making available free drugs for recorded correct treatment practices,
5. Encourage improved case-holding through provision of educational material and the services of a social worker for health education at doctors' surgeries.

Regardless of the nature of future changes to the tuberculosis control programme, it is clear that additional resources will be necessary if the epidemic is to be checked.

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