THE 'GLOBAL EMERGENCY' OF TUBERCULOSIS

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Tuberculosis has had the dubious honour of being among the most feared of all diseases: names such as the 'Captain of all of these Men of Death' and the 'Great White Plague' attest to its dreaded reputation. Until extremely recently, little could be done to alleviate the suffering caused by this disease; indeed, most of the attempts to provide such alleviation were either harmful or horrible. The former included blood-letting, which probably hastened the death from tuberculosis of the poet John Keats, and the latter included the mixture of pigeon's faeces and weasel's blood advocated by John of Gaddeston (1280-1361) in his *Curatio Scrophulorum*.

Doubtless, the majority of physicians in the pre-antibiotic era had a very genuine concern for the welfare of their patients, but they were shackled by the prevailing received wisdom, dogmas and doctrines of their time. As we approach the year 2000 and the world progresses into a state of intellectual liberation, freed from the superstitions and rigid belief systems of yesteryear, medicine in particular should cast off the shackles of past methodology and embrace regimens and therapies based on solid evidence of efficacy. Robert Koch (Figure 1) found the cause of tuberculosis; numerous other scientists and physicians have devoted their careers to this disease and detailed information about the interaction between the causative organism and the infected host has been mapped out. The introduction of effective antituberculosis agents, commencing with the discovery of streptomycin by Selman Waksman and his colleagues, opened the door to the potential conquest of this affliction. The discovery of these agents was only the beginning: other pioneers, notably Sir John Crofton, and subsequently Dennis Mitchison and Wallace Fox of the British Medical Research Council, and their overseas collaborators, laboriously developed the effective drug regimens available today.[1] The development of the modern short-course therapeutic regimens is a shining example of 'evidence based' medical research. Not only was such therapy shown convincingly to be highly effective, but it has been calculated to be among the most cost-effective of all therapeutic interventions.[2]

Far from being conquered, however, tuberculosis is currently the most prevalent infectious cause of human suffering and death. The incidence and predominance of the disease continues to rise in developing countries, while many developed countries have witnessed a reversal of the downward incidence trend that had occurred since the beginning of the twentieth century. In fact, more cases of tuberculosis are diagnosed worldwide today than at any previous time in human history. In 1993, the World Health Organization (WHO) took the unprecedented step of declaring tuberculosis a 'global emergency',[3] yet the incidence still rises. This extraordinary paradox must surely cause the medical profession to consider whether, as the new millennium approaches, we are as much submerged under the waves of obsolete data and observations as John of Gaddeston and our many other forbears had been. In this paper we attempt a re-evaluation of the current worldwide picture of the incidence and distribution of tuberculosis, with an emphasis on what is current, what is new, what is being done and what the future may hold.

FIGURE 1
Robert Koch (1843-1910),
discoverer of the tubercle bacillus in 1882.

'CAUSE' OF TUBERCULOSIS - BACTERIOLOGICAL OR SOCIOLOGICAL?

The obvious answer to the question 'what is the cause of tuberculosis?' is that it is caused by the tubercle bacillus or, more formally, the *Mycobacterium tuberculosis* complex. Most cases are caused by *M. tuberculosis* and a few cases are due to infection with the closely-related species *M. africanum* in certain regions. In addition, an unknown number of cases are caused by the bovine tubercle bacillus, *M. bovis*. The latter organism is almost forgotten in the industrialised world: only a handful of cases are diagnosed annually in the United Kingdom, and these are principally due to reactivation of long-dormant prior infection. It is also

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almost forgotten that the rarity of this form of human tuberculosis in the United Kingdom is the direct result of the bovine tuberculosis eradication programme in cattle which commenced after the Second World War and achieved country-wide coverage by 1960; this was one of the most effective public health measures ever mounted against a bacterial disease, and its singular success proves that, if there is a strong political will coupled to an effective control strategy, a widespread infectious disease can almost be eradicated.[4] Unfortunately, cattle tuberculosis is widespread in the developing nations but, mainly owing to a lack of laboratory facilities, its impact on human health in terms of zoonotic infections is poorly documented.[5]

The sociologist will answer the same question about the cause of tuberculosis in a different manner: tuberculosis is caused by poverty, overcrowding, poor sanitation, malnutrition and grossly inadequate health care services. Worldwide, tuberculosis is undoubtedly a disease of the economically poor: 95% of all cases and 98% of deaths occur in the developing nations.[6] Even in relatively wealthier countries such as Britain, the current increase of the disease is directly related to socio-economic status. Thus, between 1980 and 1992, there was a 35% increase in the incidence of tuberculosis among the poorest 10% of the population of England and Wales, a 13% increase among the next poorest 20%, but no significant increase among the remaining 70% of the population.[7]

The situation is far worse in the developing world; the tragedy is that the very fact that many people live under conditions of abject poverty also implies that they are unable to take the necessary steps to better their condition. Indeed, there is often a vicious cycle with poverty leading to chronic ill-health which, by preventing those afflicted from undertaking gainful work, further exacerbates their poverty. The poor also have few advocates, either in their own communities or in the wealthier nations. Indeed, in comparison with other major afflictions of mankind, tuberculosis is grossly underfunded.[3] Table 1 shows the disparity of funding in relation to the number of deaths in persons aged over five years in 1994. Clearly, in equitably distributing such funds, many factors other than mortality must be considered: for example, leprosy is associated with a low mortality, yet with many years of suffering and severe disability. Nevertheless, there was a very notable discrepancy in funding for the listed diseases in 1994 and, in 1999, the situation is not much different.

TABLE 1

Annual external financial aid given for the control of the major infectious diseases relative to each such death in people aged over five years. (Calculated from data published by the World Health Organization, 1994.)

Disease	External aid (US$) for each patient who died
Tuberculosis	8
Malaria	137
Parasitic disease	370
AIDS	925
Leprosy	38,500

GLOBAL BURDEN OF TUBERCULOSIS

Only approximate estimations of the global burden can be made. Surveys based on case detection and notification are notoriously unreliable, and estimations are largely based on the prevalence of tuberculin reactivity as an indicator of infection by *M. tuberculosis*, and, by extrapolation, the numbers of such infected persons that can be expected to develop active tuberculosis. On this basis, the World Health Organization has calculated that around one third of the world's human population has been infected by *M. tuberculosis* and that, each year, between seven and eight million people develop the disease.[6,8] In most parts of the world, the disease is most frequent in adolescents and young adults.

As only around 15% of patients receive adequate therapy, and as this is a very chronic disease, between 16 and 20 million persons are suffering active tuberculosis at any given time. About half of these patients are infectious and each patient is known to infect between two and 20 persons annually: 100 million persons are thereby being added to the infected pool each year. Almost three million people die of tuberculosis annually, mostly young adults, but also about 100,000 children under the age of five years. Tuberculosis is the most prevalent infectious cause of death, being responsible for one in seven adult deaths and one in four preventable adult deaths. The global burden is increasing and the WHO estimates that, unless there is a radical change in the management of the disease, 10 million cases, and four million deaths, will be recorded annually by the year 2004.[3] The worldwide burden of tuberculosis is summarised in Table 2.

Key points

- **One third of the world's population is infected with the tubercle bacillus.**
- **Each year, 7-8 million infected people develop active tuberculosis.**
- **Each year, 3 million people, including 100,000 children, die of tuberculosis.**
- **Tuberculosis accounts for 1 in 7 adult deaths.**
- **Tuberculosis is responsible for one quarter of preventable adult deaths.**
- **95% of cases of tuberculosis, and 98% of deaths due to it, occur in the developing nations.**
- **Tuberculosis is on the increase in many developed nations, notably among the socio-economically disadvantaged.**

IMPACT OF THE HIV/AIDS PANDEMIC ON TUBERCULOSIS

Infection by HIV is the most important predisposing factor for the development of overt tuberculosis in those infected by *M. tuberculosis*. In the absence of immunosuppression, people who have overcome primary tuberculosis have about a 5% chance of developing post-primary tuberculosis at some other time during the remainder of their lives. By contrast, if such a person becomes HIV-positive, this chance increases to around 8% annually, and to a total of a 50% chance during the remainder of their shortened life-span.[9] If an HIV-positive person is exposed to an infectious source

TABLE 2
The estimated global burden in millions of cases of tuberculosis. (World Health Organization, 1997.)

WHO Region	Total population (=persons at risk)	Number of people infected	Incidence (New cases)	Prevalence	Deaths
South-East Asia	1,458	704	2.8	6.553	1.095
Western Pacific	1,630	610	1.58	3.429	0.591
Africa	611	293	1.65	3.586	0.770
Americas	788	237	0.448	0.988	0.160
Europe	859	205	0.342	0.710	0.118
Eastern Mediterranean	473	161	0.427	1.035	0.173
Total	5,819	2,210	7.25	16.301	2.907

case of tuberculosis, the chance of developing active disease due to primary infection or reinfection is very high, and the course of the disease thereafter is 'telescoped' to months rather than years. This accounts for the occurrence of the explosive mini-epidemics of tuberculosis documented among HIV-infected persons in hospitals and other institutions.[10]

In 1996, an estimated six million people worldwide were infected by both HIV and *M. tuberculosis* and, based on the assumption that 8% of these developed overt active tuberculosis, HIV was responsible for an additional 480,000 cases of tuberculosis in that year, with around 300,000 of these cases occurring in Africa.[11] Several African countries with good notification systems (e.g. Burundi, Malawi, Tanzania and Zambia) have witnessed over the last decade considerable increases in the incidence of tuberculosis and their health services have thereby been seriously stretched.[11] By late 1997, there were an estimated 30 million HIV-infected persons globally;[12] assuming that one third had also been infected with *M. tuberculosis*, around 10 million would be co-infected. If these trends continue, up to 15% of all cases of tuberculosis could be HIV-related by the year 2000, accounting for 1.4 million additional cases of tuberculosis worldwide, with 600,000 of these occurring in Africa.[9]

The burden of HIV-related tuberculosis in Africa has fallen heavily on women and children. In Zambia, HIV seroprevalence rates among hospitalised children with tuberculosis rose from 18% to 67% over an eight-year period, while remaining at a constant 10% among children admitted with surgical conditions.[13] In Zambia, at least one in four pregnant women are HIV-positive and tuberculosis has overtaken intrinsic obstetric complications as a cause of pregnancy-related mortality.[14]

Many variables prevent an accurate prediction of the impact of HIV infection on the epidemiology of tuberculosis beyond the year 2000 but a number of different scenarios for Africa have been postulated.[15] In the worst-case scenario, one in 50 of the total population, and one in 25 of the at-risk population, could develop tuberculosis each year. This would have extremely serious implications for the provision of even the minimum of health care to the sufferers. Though, to date, the major impact of the HIV pandemic has been felt in sub-Saharan Africa, the prevalence of HIV is rapidly increasing in the Asian countries where, as shown in Table 2, the majority of the global population infected by *M. tuberculosis* live.

Key points

- **In the absence of immunocompromisation, a person infected with the tubercle bacillus has a 5% chance of developing active tuberculosis sometime later in life.**
- **An HIV-positive person infected with the tubercle bacillus has an 8% chance of developing active tuberculosis annually, or a 50% chance during the remainder of their shortened life-span.**
- **In 1999, an expected 10% of cases of tuberculosis will be HIV-related, and four-fifths of these will occur in sub-Saharan Africa.**
- **In 1999, a third of the expected 2.5 million AIDS-associated deaths world-wide will be due to tuberculosis.**
- **Even if successfully treated, tuberculosis adversely affects the course of the HIV infection with shortening of the patient's life.**
- **HIV-related tuberculosis may present with atypical clinical and radiological features, especially in the more profoundly immunosuppressed.**

Three other aspects of HIV-related tuberculosis - namely diagnosis, therapy and the effect of tuberculosis on the course of the HIV infection - require consideration. The clinical characteristics and features of tuberculosis in HIV-positive patients with relatively intact immunity are similar to those seen in HIV-negative persons. In the more profoundly immunosuppressed, particularly in those with CD4+ T cell counts of under 50/cu.mm, atypical presentations are common:[16-18] pulmonary cavitation is limited or absent, radiologically non-descript spreading pulmonary lesions are common, extrapulmonary spread (manifesting itself as asymmetrical lymphadenopathy or multi-organ involvement) is frequent. Furthermore, HIV-positive patients with tuberculosis are less likely to be tuberculin-positive and sputum smear-positive than their HIV-negative counterparts. Thus it may not be easy to distinguish tuberculosis from the other infections which occur in HIV-positive patients, such as *Pneumocystis*

pneumonia.

Unless complicated by drug-resistance, HIV-related tuberculosis responds to standard drug regimens, although a higher incidence of adverse drug reactions is encountered. The risk of severe and life-threatening skin reactions, including the Stevens-Johnson syndrome, in those receiving thiacetazone is greatly increased, to the extent that some workers have therefore called for the abandonment of this particular antituberculosis agent.[19]

Even if the tuberculosis responds to therapy, the life-span of the patient is often curtailed as tuberculosis further enhances the pre-existing immunosuppression;[20] indeed, all forms of tuberculosis are currently regarded as AIDS-defining conditions in HIV-positive persons.[21] The specific reasons for this are poorly understood, but it has been postulated that cytokines released from the tuberculous lesion, including tumour necrosis factor (TNFα; see below) enhance the replication of the HIV.[22]

DIAGNOSIS OF TUBERCULOSIS

The clinical diagnosis of tuberculosis has never been easy. Like syphilis, the manifestations of tuberculosis, particularly non-pulmonary forms, can mimic almost all other diseases, and the necessary clinical suspicion and its inclusion in the list of potential diagnoses to consider is not easily maintained in regions where the disease is uncommon. In the pulmonary variety of tuberculosis, chest radiology is sensitive but rather non-specific; sputum microscopy is specific but relatively insensitive; culture of the tubercle bacillus is sensitive but extremely slow, requiring weeks of waiting. Few centres have ready access to the more rapid nucleic acid-based tests (described below) while serodiagnostic tests, despite an enormous amount of research, have in general proved ineffective. The clinical aspects of the diagnosis of tuberculosis are reviewed in detail in recent comprehensive texts.[23,24]

In addition to the problems of diagnosis in those who are HIV-positive, the diagnosis of tuberculosis in children is also problematical as bacteriological tests are only positive in a minority of cases. Diagnosis is therefore usually based on a combination of signs, symptoms and positive tuberculin testing, together with a history of recent exposure to a source case.[25] Algorithms for the diagnosis of tuberculosis in children have been devised and were evaluated in an international co-operative study.[26]

In regions with a concomitant high population incidence of HIV infection, several of the signs and symptoms which enable a diagnosis of tuberculosis in children, as well as radiological changes,[27] are also characteristic of other HIV-related infections and, as in adults, tuberculin tests may be negative.[13] Thus, in such regions, owing to an often unavoidable confusion in diagnoses, some children will inappropriately receive antituberculosis therapy while others in need of therapy will go untreated.

THERAPY FOR TUBERCULOSIS

The aims of therapy for tuberculosis are threefold: to render the patient non-infectious as quickly as possible, to cure the patient and to prevent the emergence of drug resistance. The first aim is achieved by use of an initial intensive phase of therapy, lasting two months, that is aimed to kill the actively replicating bacilli residing in the walls of the well-oxygenated cavities. The second aim is achieved by a continuation phase of therapy that kills residual near-dormant bacilli in closed lesions. The third aim is achieved by giving simultaneously at least two agents to which the bacilli are susceptible.

Owing to the widespread occurrence of resistance to a single drug, most frequently isoniazid, the initial intensive phase should be based on three or four drugs or, in some cases, five drugs.[28] The most powerful drugs in this respect are isoniazid and rifampicin, with the latter having the particular property of killing near-dormant bacilli. Thus the most effective regimens utilise these two drugs throughout, although for reasons of cost it may be necessary to replace rifampicin by a less expensive drug during the continuation phase and to extend this phase for a longer period. The drugs are given daily in most regimens although, if they are given under direct observation, they may be given thrice weekly during the continuation phase.

Examples of treatment regimens recommended by the WHO for various categories of patients are listed in Table 3. Other regimens are in use - some contain thiacetazone but, because of an associated unacceptably high incidence of severe skin reactions in HIV-positive patients, they should not be used.[19] The recommended regimens are suitable for all forms of tuberculosis, although, some physicians recommend a seven-month continuation phase of daily isoniazid and rifampicin for the more serious forms of non-pulmonary tuberculosis, including tuberculous meningitis, miliary disease and spinal lesions with neurological signs. For full details of the doses, monitoring procedures, common side-effects and management of hypersensitivity drug reactions, the treatment guidelines for national programmes issued by WHO should be consulted.[28]

Essential elements of therapy are regular supplies of drugs and their administration to the patients under caring supervision. These elements form part of the WHO's 'DOTS' strategy, as outlined below. The therapy of single drug- and multi-drug resistant tuberculosis is discussed in the following section.

Key points

- **Short-course drug regimens for tuberculosis are optimally based on three or four drugs for two months (intensive phase), followed by two drugs for four months (continuation phase).**
- **Resistance to a single drug is common but has little adverse effect on the efficacy of such drug regimens.**
- **Resistence to isoniazid and rifampicin, with or without other drug resistance, is termed 'multidrug resistance' (MDR).**
- **Standard therapy is ineffective in cases of MDR tuberculosis, and long and very costly alternative drug regimens are required.**
- **Supervision of therapy is regarded as essential to ensure a cure and to prevent a relapse.**
- **Directly observed therapy is therefore the key component of the World Health Organisation's five-point DOTS (Directly Observed Therapy, Short Course) strategy.**

TABLE 3
Antituberculosis drug regimens recommended by the World Health Organization.

Category of patient	Initial phase (Daily or thrice weekly)	Continuation phase
New patients with smear-positive pulmonary tuberculosis; extensive smear-negative pulmonary tuberculosis; severe non-pulmonary tuberculosis	2 HRZE (HRZS) 2 HRZE(HRZS) 2 HRZE(HRZS)	4 HR 4 H_3R_3 6 HE
Cases of relapse, treatment failure or recommencing treatment after interruption	2 HRZES/1 HRZE 2 HRZES/1 HRZE	5 HRE 5 $H_3R_3E_3$
New smear-negative pulmonary tuberculosis (other than those in Category 1); less severe non-pulmonary tuberculosis	2 HRZ 2 HRZ 2 HRZ	4 HR 4 H_3R_3 6 HE
Cases still positive after supervised re-treatment	Treat as though drug-resistant	

Prefixed numbers indicate duration in months of the phase of therapy.
Subscripted numbers in continuation phase indicate intermittent (thrice weekly) dosage.
H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; S = streptomycin.

THE 'THIRD EPIDEMIC' OF DRUG- AND MULTI-DRUG-RESISTANCE

The problem of drug resistance was encountered soon after the discovery of streptomycin and the other antituberculosis drugs, and led to the universal recognition of the need to use multi-drug regimens. Unfortunately, inadequate supervision of therapy, the use of poorly-formulated combination preparations, faulty prescribing practices, unregulated 'over-the-counter' sales of drugs (including cough mixtures containing isoniazid) and erratic supplies of drugs, have led to the emergence of drug resistance world-wide.[29,30]

The most commonly encountered myobacterial resistance is to a single drug, usually streptomycin or isoniazid, but most patients with such resistance respond adequately to modern short-course chemotherapy based on an initial four-drug intensive phase (see above). The emergence of resistance to rifampicin is much more serious, as this is the most powerful bactericidal antituberculosis drug with the unique property of sterilising lesions by destroying near-dormant 'persister' bacilli. Furthermore, most rifampicin-resistant strains are also resistant to isoniazid. By international convention, tuberculosis due to strains resistant to these two agents, with or without additional resistances, is said to be multi-drug-resistant (MDR).

Administration of standard short-course chemotherapy to patients with MDR tuberculosis is not only ineffectual but may be positively harmful as resistance to the other two drugs in the regimens (usually pyrazinamide and ethambutol) readily develops - the so-called 'amplifier effect'.[31] If the cardinal rule of antituberculosis chemotherapy - *never to blindly add a single drug to a failing regimen* - is broken, resistance to even more drugs develops. The 'amplifier effect' was held responsible for a large outbreak of MDR tuberculosis in urban Peru. This has called for a radical reappraisal of standard control measures to be made.[31]

The problems and costs of managing a case of MDR tuberculosis are enormous. Successful therapy requires prolonged courses of less effective, more expensive and more toxic drugs so, in addition to financing the cost of the actual therapy, it is necessary to employ a team of dedicated supervisors. In addition, high-quality laboratory control is essential for the design of the individualised drug regimens and the monitoring of therapy. The incidence of MDR tuberculosis in New York has been reduced by such a strategy, although at a very great cost: the management of a single case can exceed US$250,000. Initially, the results of therapy of MDR tuberculosis were poor, with 45% of patients dying within two years. Better results are now being reported, with up to 85% remaining sputum-negative a year after starting therapy.[31]

The major barrier to a rational approach to the problem of MDR tuberculosis is the lack of good epidemiological data on the prevalence and distribution of such resistance, and the lack of laboratory facilities for its detection and subsequent evaluation, and the monitoring of alternative drug regimens. In view of this barrier, the WHO, together with the International Union Against Tuberculosis and Lung Disease (IUATLD) has undertaken a global survey of drug- and multi-drug-resistance; the two bodies have jointly recommended standardised methods of testing for drug resistance and have established a network of 22 supraregional laboratories (SRLs) to facilitate continuing surveys.[32] Unfortunately, even this network can only undertake examinations for a minority of patients worldwide, and thus many patients are receiving chemotherapy with no bacteriological control.

The WHO/IUATLD survey revealed that resistance to one or more of four commonly-used drugs (isoniazid, rifampicin, ethambutol and streptomycin) is widespread, but that the relative incidence of resistance to these drugs

individually varies enormously from region to region. Thus, the incidence of any form of drug resistance was low in the Czech Republic, Zimbabwe, the United Kingdom and New Zealand, but high in Estonia, the Delhi state of India, Sierra Leone, Latvia, the Dominican Republic and some parts of Russia. Overall, a weighted mean (i.e. adjusted for the incidence of smear-positive tuberculosis in the various countries) of 16.7% of all tested isolates of *M.tuberculosis* showed some form of resistance: 9.1% were resistant to a single drug and 7.7% were resistant to two or more drugs, including 4.3% of the total that were multi-drug-resistant (as defined above). It is indeed possible that even this high incidence of drug resistance is an underestimate as countries that have good laboratory facilities for determination of drug resistance also have more effective tuberculosis control programmes.

The situation in Russia is particularly alarming. According to *Medicins sans Frontiers*, the overcrowded Russian jails have become 'tuberculosis farms' with high infectivity and multi-drug resistance readily developing as a result of suboptimum therapy.[33] These prisons may hold as many as 20,000 inmates with MDR tuberculosis and, when eventually released, these individuals infect members of their family and the community at large. The aid agencies including *Medicins sans Frontiers* and the British agency *Merlin* have been led to conclude that we are witnessing the beginning of an epidemic of MDR tuberculosis that will not stop at the Russian borders. They conclude that 'It is only a matter of time before MDR-TB of Russian origin becomes a daily reality worldwide...the cost of the epidemic to the world will be counted in billions (of pounds sterling) and may become unmanageable'.[33]

Resistance is divided into acquired resistance which occurs in previously-treated patients, usually as a result of repeated suboptimal therapy, and primary or initial resistance which occurs in (supposedly) previously untreated patients as a result of infection from a resistant source-case. The WHO/IUATLD survey revealed that the prevalence of acquired resistance is much higher than that of primary resistance. Thus the prevalence of primary resistance to any drug ranged from 2% (Czech Republic) to 41% (Dominican Republic), while that of acquired resistance to any anti-tuberculosis drug ranged from 5.3% (New Zealand) to 100% (Ivanovo Oblast, Russia).

Therapy of MDR tuberculosis

No standard drug regimens exist for the treatment of MDR tuberculosis. Therapy is individualised, being either empirical, or definitive if and when the results of drug susceptibility tests are available.[31,34,35] Patients suspected of having MDR tuberculosis are those who fail to respond to standard supervised therapy, those with a history of inadequate treatment and those likely to have acquired the disease from a MDR source case. Empirical regimens should, if possible, be based on known prevalent drug-resistance patterns in the patient's community, and on a history of drugs previously received by the patient. Regimens should include at least five drugs, including one injectable drug, to which laboratory results (if available) indicate that the patient is likely to respond. One such regimen recommended by the WHO for patients thought to have tuberculosis resistant to isoniazid and rifampicin consists of treatment with ethambutol, ethionamide, ofloxacin, pyrazinamide and an aminoglycoside - for three months, and the first three of these being administered for at least a further 18 months.[34] Some authorities recommend continuing the aminoglycoside (or other injectable drug) for a total of six months, or for six consecutive months after sputum conversion. The duration of therapy depends on bacteriological, clinical and radiological evidence of cure, but is usually continued for 18 months after sputum conversion. Careful supervision throughout, and monitoring for side-effects of the drugs is an essential, though costly, element of successful therapy.

Other agents suitable for use in unresponsive patients include para-aminosalicylic acid (PAS), thiacetazone and, though evidence of efficacy is somewhat anecdotal, the newer macrolides (e.g. clarithromycin and azithromycin) and β-lactam/β-lactamase inhibitor combinations such as amoxycillin with clavulanic acid. Further details can be obtained from WHO *Guidelines for the Management of Drug-resistant Tuberculosis*.[34]

STRATEGIES FOR TUBERCULOSIS CONTROL - A SEARCH FOR NOVEL TOOLS OR BETTER UTILISATION OF THOSE AVAILABLE

In view of the seriousness of the tuberculosis epidemic and the increasing impact of the HIV/AIDS pandemic and multi-drug-resistance, a radical revision of control strategies is essential. From the biomedical standpoint, the options are either to look for much more effective ways of utilising the currently available control measures or undertaking research to develop new strategies. These would include more effective prophylactic and therapeutic vaccines, 'designer' drugs and more precise diagnostic tests. Fortunately these two approaches are not incompatible and much current activity is taking place in both fields.

From the sociological point of view, effective control of tuberculosis requires rectification of the gross injustices and maldistributions of wealth throughout the world, provision of adequate living standards, and a ready access to effective resources for health care, as enshrined in the Universal Declaration of Human Rights and reiterated in the Alma Ata Declaration of 'Health for All'. This is not an issue that is beyond the remit and concern of the medical profession: throughout history, physicians have been foremost among the advocates for social justice and the creation of healthy societies, and the eradication of this disease is not so different.

USING CELLULAR AND MOLECULAR TOOLS FOR CONTROL

Recent developments in cellular and molecular biology have paved the way to several actual and potential tools for the control of tuberculosis. These include novel vaccines and immunotherapeutic agents, ultra-rapid diagnostic and drug-susceptibility tests, and genetic 'fingerprinting' of tubercle bacilli for epidemiological purposes. Recent sequencing of the entire genome of *M. tuberculosis* has the potential to aid these developments and may permit the development of 'designer' drugs that interfere with metabolic processes unique to this species, such as those involved in the synthesis of the highly complex cell wall of the tubercle bacillus.[36]

Novel vaccines

The only available vaccine, Bacille Calmette-Guérin (BCG), utilises a living attenuated tubercle bacillus derived, by repeated subculture, by Albert Calmette (Figure 2) and

FIGURE 2
Albert Calmette (1863-1933) who, together with Camille Guérin, developed Bacille Calmette-Guérin (BCG) vaccine.

Camille Guérin. Derived from an isolate from a case of bovine mastitis, thus it is presumed to be a strain of *M. bovis*. Present day strains of BCG differ in many respects from wild strains of this species.[37] The vaccine has been used extensively since its introduction into clinical use in 1921, but many of the questions concerning its efficacy and mode of action remain largely unanswered. Its principal protective effect seems to be the prevention of dissemination of bacilli from primary lesions, thereby preventing the serious, but usually not directly infectious, childhood forms of the disease such as tuberculous meningitis. Its efficacy in preventing the development of post-primary, often infectious, tuberculosis in the already infected (tuberculin-positive) person is, unfortunately, very much less.[38] Thus BCG vaccination has had a very limited impact on the incidence of infectious source cases in the community and on the whole it is a poor tool for tuberculosis control.

A further disadvantage of BCG is that its efficacy varies considerably from region to region, from about 80% efficacy in the United Kingdom to less than 0% (indeed a suspected slightly increased risk of developing tuberculosis among vaccinated persons) in South India and Malawi.[39] Speculation as to the cause of this marked variation led to the most widely-accepted explanation that the immune responses of those vaccinated by BCG are already modulated and altered by prior exposure to free-living species of mycobacteria in the environment. Mycobacteria form an important part of ambient micro-flora: they are particularly abundant in marshes, surface water and in piped water supplies,[40] and community exposure to this genus is a regular, recurrent and unavoidable event. One explanation is that populations of environmental mycobacteria induce so much natural immunity in certain geographical areas that BCG can add little to this naturally-acquired innate immunity and is thus ineffective. Another explanation is that there are two principal patterns of inducible immune reactivity to mycobacteria, one conferring protection and the other causing tissue destruction and progression of disease. It is probable that BCG vaccination boosts the predetermined pattern of immune reactivity, thus explaining the considerable regional variation in efficacy and also the apparent ability of BCG vaccination to actually enhance the risk of developing tuberculosis in certain regions.[39]

The nature of the immune responses in tuberculosis and their relation to tuberculin reactivity has been argued about for decades.[41] The Austrian physician Clemens von Pirquet (Figure 3), who developed the tuberculin test for epidemiological purposes (as well as introducing the terms 'allergy' and 'anergy') postulated that tuberculin reactivity was a correlate of protective immunity to tuberculosis;[42] subsequent workers disputed this.[43] One school of thought maintained that protective immunity and tissue-destroying hypersensitivity were distinct and mutually incompatible immune reactions while another considered that they were essentially the same reaction but differing in intensity.[41] This controversy has now been resolved by the finding that T helper cells mature along two different maturation pathways, resulting in two subsets, Th1 and Th2, each of which may be characterised by the cytokines that they release or induce. Evidence is accumulating that protective immune responses in tuberculosis are mediated by cytokines associated with Th1 cells; with a superimposed Th2 response inducing gross tissue destruction characteristic of post-primary tuberculosis.[44] In a Th1 response, tumour necrosis factor (TNFα) plays an important role in granuloma formation, but Th2 cytokines, directly or indirectly, render cells and tissues in the vicinity of the tuberculous lesion very sensitive to destruction by TNFα, thereby leading to areas of necrosis, pulmonary cavitation and progression of disease. TNFα has also been shown to be identical to cachectin, the agent responsible for the gross wasting observed in advanced tuberculosis.[45]

FIGURE 3
Clemens von Pirquet (1874-1929) who developed the tuberculin test for use as an epidemiological tool.

The outcome of any mycobacterial challenge appears to depend critically on the ratio of Th1 to Th2 cells which are induced in response to the challenge. The factors determining this ratio are not fully understood but the immune system appears to be able to 'learn' from past experience, including the host's exposure to saprophytic mycobacteria in the environment.[46] An additional key factor is the balance between the major adrenal steroids, dehydroepiandrosterone (DHEA), and glucocorticoids and their metabolites.[47,48] The former drive newly-recruited T cells along the Th1 maturation pathway, while the latter drive them along the Th2 pathway. It is known that stress is associated with raised glucocorticoid levels and this may explain the many claims that tuberculosis is activated and exacerbated by stressful life events.[49]

A crucial implication of this variability of the immune response in tuberculosis is that protective vaccination against tuberculosis may require more than administration of a specific 'protective antigen'. BCG affords as good, or even better, protection against leprosy as against tuberculosis,[39] and it also appears to protect children against lymphadenitis due to *M. avium* and other environmental mycobacteria.[50] This implies that protection is mediated by antigens shared throughout the genus *Mycobacterium* rather than those specific to the *M. tuberculosis* complex.

The pioneers of vaccination against tuberculosis, including Robert Koch in Europe and Edward Trudeau in the USA, were convinced that the controlled induction of a 'limited tuberculous process' by means of a living attenuated vaccine was essential for the induction of protective immunity and this dogma has been widely held ever since. Although BCG is one of the safest of the live vaccines, it can cause infective complications which may be life-threatening in immunocompromised persons, including those who are HIV-positive.[51] This has acted as an incentive to challenge the dogma of the need for bacterial viability in vaccines and much research is being conducted into the development of non-viable whole cell or subunit vaccines.[52,53] One promising approach is to vaccinate with 'naked' DNA, i.e. mycobacterial core DNA without any of the cell-wall and other antigenic components of the organism. This can then enter antigen-presenting cells and code for the antigen which is presented to the T cell population. Another approach is to develop vaccines that contain adjuvants or cytokines that induce the 'correct' protective immune responses, and suppress those that are inappropriate to protection and intrinsically destructive.

Evaluation of the efficacy of any new vaccine in the human population requires careful consideration.[54] Serious ethical questions will have to be faced if new vaccines are tested against the 'gold standard' of BCG in high incidence regions. At present, no experimental *in vitro* systems of vaccine evaluation are relevant to the human situation, and there is no simple test for the degree of, or changes in, protective immunity in a human population.

Rapid diagnosis of tuberculosis

The most frequently used diagnostic test for tuberculosis worldwide is sputum microscopy, which has the great advantage of rapidity and of detecting those with numerous tubercle bacilli in their sputum, who are consequently highly infectious and a priority group for treatment. Its disadvantages are that it does not detect those who have advancing, not yet 'open', pulmonary tuberculosis and are likely soon to become infectious. It is only positive in around 5% of cases of childhood tuberculosis. In addition, though technically simple, enormous problems are encountered in establishing good microscopy services in developing countries given that the task of searching for the organisms is tediously slow and monotonous - most of these problems being associated with the training, motivation and retention of staff.[55] There may be scope for the development of computer-assisted screening methods as has been done in cervical cytology.

Standard cultural techniques are sensitive, specific, but notoriously slow. More rapid results are obtainable by the use of radiometry (the BACTEC system),[56] or the more recently-introduced non-radiometric systems that depend on colour changes in dyes induced by bacterially-liberated carbon dioxide, or the unquenching of fluorescent compounds when oxygen is consumed by the metabolising and respiring bacilli.[55]

In general, attention is turning to nucleic acid-based diagnostic methods, particularly utilising the polymerase chain reaction (PCR) and related techniques.[57] These tests are based on the *in vitro* replication of DNA or RNA in the presence of polynucleotides, termed 'primers', that are specific for the organism being sought. In principle, PCR is very sensitive and specific but, in practice, problems have been encountered particularly with cross-contamination. Some blind studies have shown very considerable variations in diagnostic accuracy between laboratories.[58] This is a field that is developing very rapidly and many of the original problems have been resolved.[55,57]

Some modifications of the PCR for the detection of *M. tuberculosis* have distinct advantages over the original techniques and some are commercially available in kit forms. One such system is based on the amplification of species-specific 16s ribosomal RNA (rRNA) by reverse transcription to DNA, followed by transcription by RNA polymerase to multiple copies of 16s rRNA, and so on through many cycles. This method is sensitive because each bacterial cell contains about 2,000 copies of the target RNA. In addition, all reactions take place at the same temperature so the expensive thermal cycling machines used in the original PCR techniques are not required, and the inherent instability of the amplified RNA reduces the risk of cross-contamination.[59] The current high cost of the tests makes widespread use in developing countries impractical.

Application of genetic technology to drug resistance and epidemiology

Studies on the mode of action of antituberculosis agents have been facilitated by the ability to determine the genes coding for the sites of action of the various agents.[60] Some examples are shown in Table 4. The ability to characterise such genes has paved the way to the rapid determination of drug resistance by the detection of mutational changes conferring such resistance. A number of methods for detecting rifampicin-resistance have been described; some are already in clinical use.[61] The recent sequencing of the entire genome of *M. tuberculosis* should facilitate the development of similar rapid tests for the detection of resistance to the other antituberculosis drugs.[36]

Epidemiological studies on tuberculosis have been greatly aided by the development of discriminative techniques for subdividing the tubercle bacillus on a genetic basis. The most widely-used technique is known as

TABLE 4
Targets for, and genes determining resistance to, the principal antituberculosis agents.

Agent	Target	Gene(s) encoding target(s) or those in mutations conferring resistance
Isoniazid	Mycolic acid synthesis	*inhA*, *katG, oxyR-ahpC, KasA*
Rifampicin	DNA-dependent RNA polymerase	*rpoB*
Pyrazinamide	Unknown (requires enzymatic conversion to pyazinoic acid)	*pncA*
Ethambutol	Arabinosyl transferase (involved in cell wall arabinogalactan synthesis)	*embA, embB* and *embC*
Streptomycin	30S ribosomal subunit	*rspL* (encodes for ribosomal protein S12)
Other aminoglycosides	30S ribosomal subunit	genes encoding 16S-rRNA (and possibly *aac(2')* encoding aminoglycoside acetyltransferase)
Ethionamide and prothionamide	Mycolic acid synthesis	*inhA*

restriction fragment length polymorphism (RFLP) typing,[62] which relies on the ability of certain enzymes (endonucleases) to cut up, at certain very specific points, the DNA of the chromosome (genome) extracted from a culture of the tubercle bacillus. This gives rise to DNA fragments which may be sorted according to size on a gel in an electrophoretic field. Owing to the large number of such fragments, the patterns given by different bacilli are very difficult to compare. This problem may be overcome by blotting the gel with a probe prepared from DNA sequences that appear at several different and variable sites within the genome - the so-called insertion sequences (IS). Strains within the *M. tuberculosis* complex contain from none to around 20 insertion sequences, and the number of these and their positions on the gel divide the species into numerous sub-types.

The standard RFLP method requires a culture of the bacillus but there are various other typing techniques that may be applied to DNA amplified by the polymerase chain reaction. One popular method is called spacer oligonucleotide typing ('spoligotyping') which is based on the detection of variations in the structure of short sequences of DNA, termed spacer oligonucleotides, that are found in the regions of the genome that harbour the insertion sequences.[63]

DNA typing studies have also been used to investigate the mode of spread of tuberculosis in closed communities and to determine whether post-primary disease is principally due to endogenous reactivation of old disease or to recent exogenous reinfection.

IMPROVING THE USE OF AVAILABLE CONTROLS

The very fact that it has been necessary to declare tuberculosis a global emergency is a certain indication that the currently available control tools are either intrinsically inadequate, or that there has been a widespread and serious failure to use them correctly and universally. The great success of modern short-course chemotherapy under ideal programme conditions indicates that the latter explanation for failure is the correct one. Many publications state that non-compliance with therapy is the major cause of the failure to control tuberculosis. Unfortunately, the term 'non-compliance' implies that the fault lies with the patient, while in fact most breakdowns in therapy are due to failure on the part of the health care provider.[64] Common faults include poor prescribing practices, an interrupted supply of drugs, demands (sometimes clandestine) on patients for payment for the drugs, poor communication, arrogant and patronising behaviour of health care staff and a requirement for excessive travelling to the health care facility.

WHO 'DOTS' STRATEGY

To improve compliance and to standardise the various national tuberculosis programmes, the WHO has advocated the so-called Directly Observed Therapy, Short Course (DOTS) strategy.[8] Despite the name, direct observation of therapy is just one of its five important elements, which are:

- Government commitment to a National Tuberculosis Programme.
- Case detection through sputum smear microscopy for suspects presenting at clinics.
- Short-course chemotherapy under direct observation for all those found to be sputum smear-positive.
- An infrastructure able to ensure an uninterrupted supply of drugs.
- Regular monitoring and evaluation of the efficacy of the programme.

Despite widespread advocacy of the DOTS strategy, programmes that state that they achieve the above criteria are only available to about 15% of all patients suffering from tuberculosis worldwide, although an increasing number of governments are stating their commitment to the strategy. Rather surprisingly, therapy is often not given under direct observation in several Western European and other developed countries. In Great Britain, for example, '...there is a national shortage of clinical nurse specialists in tuberculosis, and district nurses may be unwilling or unable to take on this service. As a result, directly observed therapy cannot be implemented effectively'.[65]

The DOTS strategy has come under some criticism for being too rigid and for not taking into consideration the very wide variations in individual, societal and ethnic attitudes to tuberculosis, and the disruption to everyday

life that a regular attendance at a clinic, or waiting for the supervisor to arrive, may cause. Indeed, the arrangements for direct supervision of therapy may draw the attention of the community to the fact that a person has tuberculosis, thereby breaching confidentiality with, in some communities, a damaging stigmatising effect. Social scientists and anthropologists need to work alongside health care providers to adapt the DOTS strategy for individual regions. Community educators have to strive to abolish the various belief systems, held by patients, health care providers and the community at large, that lead to or enhance stigma. Such belief systems and the stigma that they engender are proving serious barriers to detection and effective therapy of tuberculosis in those regions where many cases are HIV-related, further emphasising the need to attend to local factors when planning control programmes.

Despite these problems, clear examples from parts of China, India and Bangladesh have shown that the DOTS strategy can be applied with great success.[8] Some of these programmes, however, were supported by loans from international agencies, thus compounding the problem of national debt repayment.

The programme conducted by a non-governmental organisation in Bangladesh, in which there was a high cure-rate, and low drop-out and relapse rates, clearly demonstrates that a successful programme requires much more than the mere supervision of therapy.[66,67] The success of this programme was due to the existence of an effective non-governmental organisation which was able to obtain technical and financial support from donor agencies, a well-organised network of laboratories capable of performing sputum microscopy to a high standard and, perhaps most importantly, the supervision of treatment by dedicated community health workers recruited from village organisations that are involved in other aspects of health care, education and general socio-economic improvement.

The use of selected and respected health workers from the local community may provide the ideal 'therapeutic encounter' based on a 'partnership of equals' rather than on the more traditional model of an authoritarian health professional, and a meek and subservient patient. In such a situation, the term 'concordance' - suggested by Robin Fox, a previous editor of the *Lancet* - is more appropriate than either 'compliance' or 'adherence'.[68]

HOPES AND FEARS FOR THE FUTURE

If *Homo sapiens* and *Mycobacterium tuberculosis* were uniform in their respective natures, the DOTS strategy, if rigorously applied universally, could well be the ultimate and complete solution to the problem. However, this is not the case as both species show considerable variation. The wide variation in attitudes, education, pre-suppositions and belief systems in the former call for the forging of a new paradigm of medical care in which sociologists, political analysts, economists, educators, religious leaders, and those from many other disciplines will have to work alongside nurses, bacteriologists, physicians, public health officers, molecular biologists and managers. Such 'interdisciplinarity' and 'skillmix' is not achieved easily. Stephens has adopted the title of the poem 'The Owl and the Pussycat Put to Sea' to stress the need for workers with quite different, and sometimes antagonistic, mind-sets and agendas to unite in the campaign against the common enemy of tuberculosis.[69]

The variation in the tubercle bacillus is particularly disconcerting in regard to its susceptibility to antituberculosis agents. At the time of the introduction of streptomycin into clinical practice in the 1940s, tubercle bacilli were remarkably uniform in their susceptibility to this, and later also to the subsequently discovered antituberculosis agents. Now, multi-drug-resistance occurs with interregional variability throughout the world. If the recommended regimen for use in DOTS programmes is used indiscriminately and without laboratory control, drug-susceptible cases may well be cured but multi-drug-resistant cases will remain infectious and the incidence of such disease will increase. Furthermore, the 'amplifier effect' may well exacerbate the problem. Thus, the DOTS strategy could, paradoxically, lead to a much more serious situation than prevails at present.

Accordingly, a 'DOTS-plus' strategy has been advocated in which each patient's therapy is tailored according to their therapeutic history or the results of drug-susceptibility tests.[31] Although excellent in concept, this requires careful consideration of the cost and organisation of the extensive laboratory facilities with the associated problems of manpower, training, quality control and supplies, the cost of the drugs and the infrastructure for providing supervision of prolonged therapy with drugs prone to cause side-effects. As standard DOTS is only available to around 15% of tuberculosis patients, 'DOTS-plus' will, surely, remain the option for a small and very privileged minority of patients.

The alternative is to hope for the rapid development of a highly effective vaccine that can be given safely to immunocompromised persons and that can also, unlike BCG, be given without adverse reactivity to those already infected with *M. tuberculosis* to prevent the emergence of post-primary, infectious, tuberculosis. Also, an effective therapeutic vaccine that can be given to those with active disease would be of great benefit, especially if it is effective in those with multi-drug-resistant disease. One such agent, a heat-killed suspension of *Mycobacterium vaccae*, has shown some beneficial effect in a series of small pilot studies,[70] and at the time of writing it is being subjected to a study involving around 1,300 patients, both HIV-negative and -positive, in Zambia and Malawi, with results expected in late 1999.

IF NOT DOTS, WHAT IS THE ULTIMATE ANSWER?

Jon Snow remarked that 'If a journalist were to arrive from Mars his lead story would surely be the discovery that some 1.3 billion people on Earth live in absolute poverty'. This brings into consideration, the involvement in the cause of tuberculosis, of poverty, overcrowding, poor sanitation and malnutrition, as well as grossly inadequate health care services. It is evident that the incidence of tuberculosis started to decline in many European countries towards the end of the nineteenth century and, except for slight rises in incidence corresponding to the two World Wars, the trend in incidence continued downwards and the introduction of 'scientific' control measures, rather than socio-economic improvements, had a relatively small impact. Indeed, ironically, subsequent to the introduction of highly-effective modern short-course chemotherapy, the incidence stopped declining and then started to rise in several European countries and in some states of the USA. A recent supplement to the *Proceedings* entitled 'Trial by TB' aptly illustrated the socio-economic and political

influences on tuberculosis control.[71]

It may well be the case that the ultimate answer to the global emergency of tuberculosis lies in a revolution of human conduct and a replacement of the present world order with one based more equitably on natural justice. It is not beyond the bounds of possibility that that a very serious threat from a major epidemic, such as that of multi-drug-resistant tuberculosis, might be the trigger event for such a peaceful revolution. The alternative is too awful to contemplate.

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