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TRIAL BY TB:
a study into current attempts to control the international upsurge in tuberculosis

CHRISTOPHER I HOLME

JOURNALIST

THE HERALD

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PREFACE

Tuberculosis is a disease that respects no age, ethnic, geographical or socio-economic barriers or boundaries, and its incidence has gradually escalated to become the leading infectious cause of death among adults worldwide. It currently kills more women than all other causes of maternal mortality put together and ranks as the main killer of HIV-positive patients. Its chronicity is associated with untold suffering to the patients and their families, a loss of productivity, unemployment, and cascading from it poverty and deprivation on an apocalyptic scale. These stark and disturbing statistics have lead the World Health Organisation to declare tuberculosis as a 'global medical emergency'.

Yet it is a disease that is very cost-effective to control and treat: the World Bank put a figure of $11 per person cured. Treatment strategies have been complacent, and poorly controlled resulting in the inexorable spread of TB and the bacteria acquiring multi-drug resistance. Resistant mycobacteria have been responsible for recent epidemics in Western and Eastern Europe, in the Far East, in New York City, in the Indian subcontinent and in Africa. The increasing ease and expansion of international travel and the ever-increasing problems of population displacements and refugees has brought the problem to the doorstep of Health Ministers worldwide.

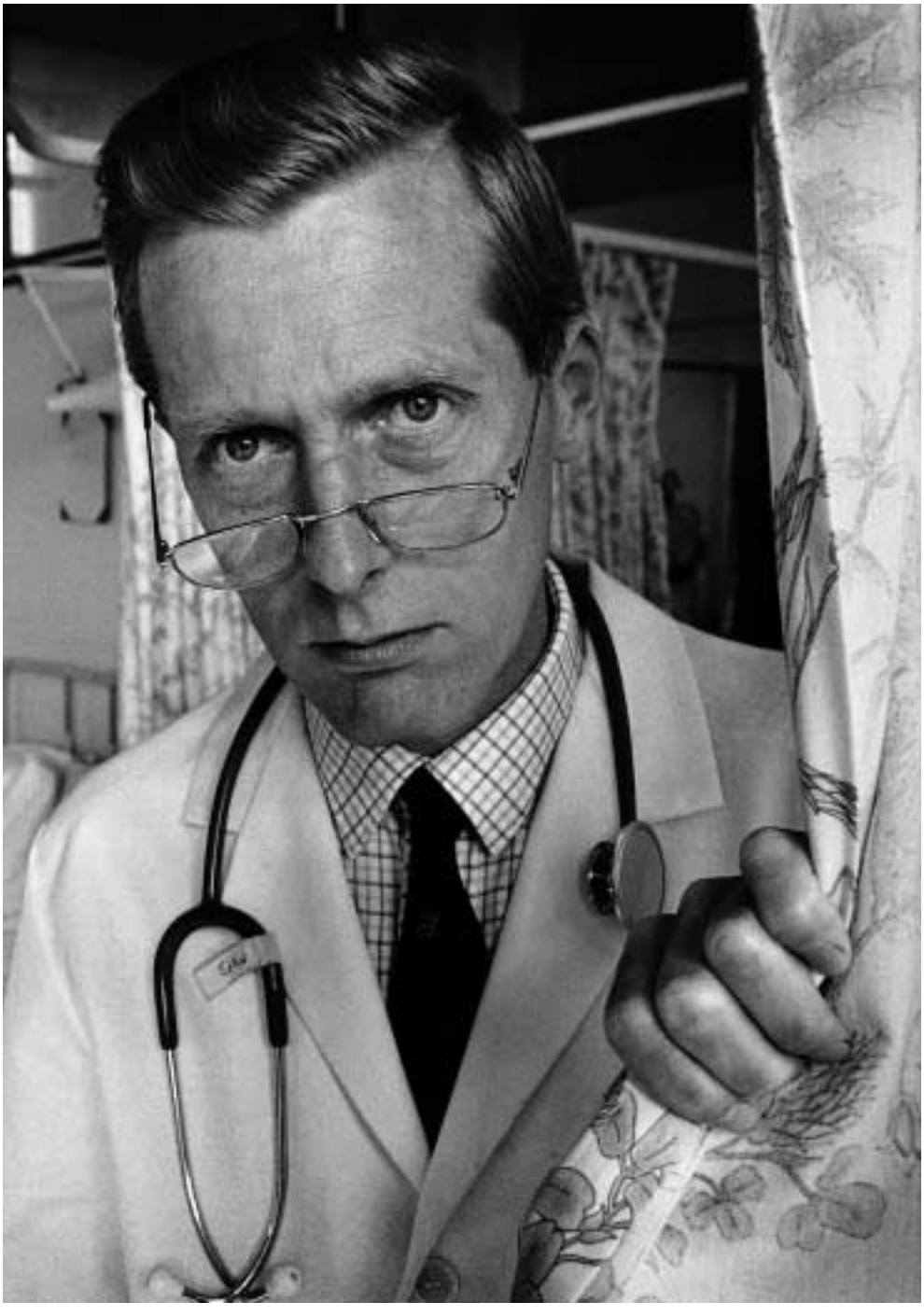
The time is ripe to reassess thoroughly this medical emergency, to take stock and attempt to reassert control over Koch's bacillus.

The Royal College of Physicians of Edinburgh, through a number of its Fellows has been pre-eminent in setting up local standards for the medical treatment, diagnosis, control and eradication of this disease which were emulated and introduced worldwide. Sir Robert William Philip opened the first ever TB out-patient dispensary in Edinburgh in 1894 and Sir John Crofton with his clinico-microbiological team - I. Grant, N. Horne, I. Ross, S. Stewart, A. Wallace, J. Williamson, and more recently A. G. Leitch - have been instrumental in marking out the standards of excellence that need to be adopted throughout the world.

In the spirit of 'seeing ourselves as others see us' and as a tribute to these trail-blazers - not least Gordon Leitch, whose life ended so prematurely - the College has taken the unusual step of agreeing to publish this Supplement to *Proceedings*, written by an informed and caring 'layman' and a prize-winning journalist, who has thoroughly researched this subject and has explored where the medical profession may have lost its way in the eradication of TB. This publication is presented to coincide with WORLD TB DAY organised by WHO and the International Union Against TB and Lung Disease.

> *'The time has now come for the foundation which was so industriously laid.....in Edinburgh to be built upon with equal industry and application by governments and the profession together' A. G. Leitch*

J. D. CASH
President



Dr A.G. Leitch
1946 - 1996
(Photograph courtesy of *The Scotsman*)

FOREWORD

The means to control tuberculosis have been available for over 40 years. It is a sad reflection on the ignorance, incompetence or complacency of societies throughout the world that this age-old enemy is now threatening mankind with a resurgence. The resurgence may be partly due to increased poverty in many countries, but overwhelmingly to the HIV epidemic. This bacterium destroys those very body cells which form the main protection against the disease. Then the tubercle bacilli can rage unchecked.

Moreover, in many countries, through ignorance or neglect, the drugs which should normally cure the disease have been misused. The misuse results in the bacilli becoming drug-resistant. The disease becomes untreatable. Then the resistant bacilli can be passed on to others. They can spread particularly rapidly among those whose defences have been weakened by HIV. The world is threatened with an untreatable epidemic. No wonder that the World Health Organisation has decided that we face a world crisis.

That world crisis can only be outfaced if the governments of all countries are brought to give priority to the threat. It has been shown in some of the poorest countries that an effective control programme can be established if limited resources are efficiently utilised. But many poor countries need international help, partly with expertise and partly with some finance. The main bodies which can provide that help are WHO and the International Union Against Tuberculosis and Lung Disease. Both are themselves grossly underfunded for the crisis they have to face.

We must all be grateful to the Reuter Foundation for providing a fellowship to Chris Holme, a distinguished journalist with a particular interest in this field. The fellowship has enabled him to write a remarkable report, thoroughly researched and appealingly set out. It is all the better for being a review for laymen by a highly intelligent layman. We hope it will help rouse international opinion to the extreme urgency of facing up to the world crisis. The knowledge and the expertise is available. It must be universally applied before it is too late. Failure in one country can infect all the others.

This study is dedicated to the memory of Gordon Leitch who had helped Chris Holme in his research. He had been a close friend and colleague of my own. He was one of the most impressive leaders in the tuberculosis field in the UK. He then became concerned with the vast problem in the Third World. His international reputation was soaring. With his death we have lost a potential world leader. We hope that this report will make its own unique contribution to the global campaign from which Gordon was snatched so tragically and so prematurely. Certainly it is an outstanding tribute to an outstanding man.

JOHN CROFTON

AUTHOR'S NOTE

This paper is intended to honour the memory of Gordon Leitch, an outstanding physician in the field of tuberculosis who offered much enthusiastic and generous support to the author during the research and writing phases. Dr Leitch was drowned in a tragic accident off Cyprus shortly after the paper was completed.

The study was carried out in the course of the inaugural Reuter Foundation Fellowship in Medical Journalism at Green College, University of Oxford, during Trinity term 1996. The author expresses his enormous thanks to George McKechnie, editor of *The Herald*, Glasgow; Stephen Somerville, director of the Reuter Foundation; Godfrey Hodgson, director of the foundation's programme in Oxford; Rosemary Allan, the programme administrator; and to his colleagues on the programme and at *The Herald* for their many kindnesses and support.

Journalists are supposedly engaged in writing the first draft of history and the first thing a physician does is take a history. However, contemporary medical history, particularly concerning the development of tuberculosis chemotherapy, is a much-neglected area. This study aims to fill part of that void and also reach a wider audience. It draws on a series of interviews carried out by the author and on conventional sources which are listed in the references and notes section.

Sir John Crofton has been a source of inspiration and tremendous encouragement for many years. A number of people have also provided much assistance both in the study itself and in revising earlier drafts. These include Sir Richard Doll, Professor Richard Peto, Dr Iain Chalmers and Lynne Parker in Oxford; Professors John Cash and Anthony Busuttil of the Royal College of Physicians of Edinburgh; Sir Kenneth Murray, Dr Karel Styblo, Dr Ian Sutherland, Dr Frank Ryan, Sir William Stewart, Professors Philip D'Arcy Hart, Denis Mitchison and Wallace Fox, Professor Jimmy Williamson, Dr Ian Grant, Dr Norman Horne, Dr Brian Potter, June Andrews, Christopher Hughes, Dr Graham Buckley and Dr Jeroen van Gorkom. Their help has been invaluable but responsibility for any outstanding errors rests with me alone.

In addition, the author expresses grateful thanks to Mrs Sue Simpson, Miss Jennifer Heron and Mrs Carol Knakrick of the Communications Group at the RCPE and to the many librarians in Oxford, Glasgow, London and Edinburgh, who have given freely of their time and energy, and finally to his wife Clair and children for their long sufferance and cheerful tolerance of an otherwise preoccupied dad.

Publication of this study has been made possible by the exceptional generosity of the Reuter Foundation. Additional financial support has been kindly provided by the British Medical Association and *The Herald*.

EXECUTIVE SUMMARY

Tuberculosis will probably kill more people in 1997 than in any other year in history, according to the World Health Organisation (WHO), and an estimated 30 million people will die over the next decade. This appalling level of mortality is entirely unnecessary because a relatively cheap cure has been available for nearly 50 years.

It was the developing world which provided the affluent countries with the expertise through correct combinations of drugs to effect a 100% cure. In exchange, the West offered little but indifference. Poorer countries were largely unable to develop tuberculosis control programmes of their own because of lack of resources. From 1960 there were three decades when a vigorous and co-ordinated international response, requiring relatively modest funding, could probably have controlled the disease.

Instead, it continued to flourish. Poor treatment led to the development of multi-drug resistant strains and the advent of HIV triggered an explosive epidemic TB which may now prove impossible to control. No health system in Europe, the Americas, Africa and Asia is immune from its spread.

Western medicine used tuberculosis chemotherapy to fashion a broad intellectual revolution based on randomised controlled trials. The methodological breakthroughs which made a universal cure possible were wasted because of poor doctoring and a lack of concerted international effort. There is little point in developing standardised therapeutic models if physicians do not apply them in practice and patients do not follow them.

Worthy but sporadic attempts have been made over the years to address the problems of developing countries. More recently, WHO was sufficiently concerned at the dangers to declare TB its first global emergency in 1993. The World Bank has also placed a high priority on tuberculosis control and is providing loans to support major programmes. The resultant DOTS (Directly Observed Treatment, Short-Course) strategy may yet curb the spread of tuberculosis. Such concerted effort is welcome, but long overdue.

C. I. HOLME

ILLUSTRATIONS

Introduction

Tuberculosis (TB) could and should have been relegated to the dustbin of medical history as a spent and conquered illness. Instead, it has flourished and proliferated, retaining its gruesome status as the world's 'biggest killer' by single pathogen, claiming three million lives every year.[1]

No other disease has invoked more terror, nor wreaked so much havoc, on mankind. The 'White Plague' wiped out whole families and destroyed communities. Its slaughter was wholesale and its modes of attack indiscriminate; it could gnaw away at the spinal column or brain, eat away facial flesh or gain access to most tissues and organs of the body via the blood and the lymphatic system. More typically, it chose to invade and slowly destroy the lungs, condemning the victim to the dreadful fate of many consumptives: to drown in their own blood.

Bunyan's 'Great Captain of All the Men of Death' was also able to lie dormant for decades before reawakening to kill, whenever the host's defences were compromised.

Nothing could stop it. Poverty and destitution assisted its passage but wealth and privilege were no obstacles. Western medicine was as powerless as traditional healing methods and nostrums in Africa and Asia.

Then the battle lines suddenly changed. Three new drugs discovered between 1943 and 1952 offered the means both to strike back at the bacillus and to kill it for good, but that opportunity was squandered. This study aims to find out what went wrong. It makes no claim to be an exhaustive analysis since the potential subject matter is virtually limitless and it is written in a style which is intended to be free from unnecessary technical jargon, so that it may prove of interest to the intelligent lay reader.

The paper explores the cultural and historical background to the disease and the various efforts to combat it. It then describes the development of chemotherapy through clinical trial and application in practice. Later chapters are concerned with the widespread failure to implement successful control strategies and the resurgence of the disease alongside the HIV epidemic. The paper draws some wider conclusions about the current practice of medicine and its epistemological framework which was fashioned by the randomised controlled trials of tuberculosis chemotherapy.

No one emerges from this story with much credit. The history of TB shows medicine at its worst and best. For all the bravery and brilliance of some physicians and scientists, there have been many others whose ignorance, incompetence and intransigence have made matters worse. Poor treatment proved worse than no treatment at all. In prescribing single drugs in isolation or dispensing them in wrong combinations they merely exacerbated the prognosis, creating a problem of drug resistance and perhaps ultimately incurable TB.

Third World governments facing rival claims for scarce health resources, have some excuse. Affluent countries had the resources, expertise and money to assist. They still have. In the first two months of 1996 alone, combined pharmaceutical sales in the Western World and Japan actually slowed down to a mere $23bn.[2] At the same time, TB goes largely undiagnosed and untreated in most countries through shortage

of drugs and effective programmes. It gives a new edge to the phrase, 'the politics of consumption'.

Efforts to muster an international response to other dreadful infections have also met with frustration and failure. Poliomyelitis remains unconquered and malaria is resurgent despite the DDT mass dusting programmes in the 1950s.[3] In the wider arena of public health, problems of drug resistance have been compounded by the appearance of hitherto unknown organisms.[4]

Disease control has long been trapped within the complex web of international finance and divisions between rich and poor. It could be argued that affluent nations take justified umbrage at endemic corruption and organisational chaos in poorer countries where genuine humanitarian donations end up lining the pockets of powerful élites. On the other hand, developing countries may take offence at the way the West uses them as dumping grounds for inferior and perhaps unsafe foodstuffs and drugs, frequently in the process adding to the vicious cycle of Third World indebtedness.

Western bleatings on the danger of fresh infection from immigration or increased tourism and business travel do not garner much sympathy from the poor destitute mother in Madras or the KwaZulu mine worker with TB-riddled lungs. Both are increasingly likely to be co-infected with HIV; yet the chances now are that they will not be seen off by a horribly exotic AIDS-related cancer such as Kaposi's sarcoma, but instead by the old bogey, TB.

It was the West which exported the bacillus to the remoter areas of Asia and Africa. Highly virulent transmissions of TB long preceded the growing epidemic of low quality satellite TV now spreading into the developing world.

A measure of responsibility must also lie with international agencies and the media for failing to act sooner. Scores of homeless African Americans and Hispanics had died in the USA from incurable TB before newspaper editors took an interest. It took the death of a white prison guard at Syracuse to catapult the issue on to the front page of the *New York Times*.[5] Similarly in the UK, it would usually require the fillip of an unexpected location like a Scottish public school or an English opera house for an outbreak of the disease to rise up the news and feature schedules.[6]

Current efforts to combat the disease have more than an air of sending in the medical cavalry after the wagon train has been massacred. Ultimately, we only have ourselves to blame. We had our chance and blew it. Only time will tell if we have lost the opportunity for ever.

Chapter 1

THE WHITE PLAGUE

TB has been known to man for at least 6,000 years. No one knows where it came from. Separate but similar strains of the disease also infect birds and animals, which may point to its origins as a soil micro-organism which has since evolved gradually into different and virulent forms.[7] How this disease-inducing microbe subsequently developed into one of the greatest killers of mankind is not clear.

Paleopathologists have documented evidence of mycobacterial infections in several ancient civilisations, and contemporary accounts attest to symptoms which correspond to what we now know as TB. One group has recently reported the discovery of the human strain *(Mycobacterium tuberculosis)* by DNA profiling of material removed from the mummified body of a woman from southern Peru, dating back 1,000 years. US researchers have claimed this organism is more likely to be the bovine strain *(Mycobacterium bovis)* and put forward the theory that it was a virulent mutant of this which changed and evolved into the human form. Thus, a likely evolutionary hypothesis is that over the course of centuries, the organism was picked up from the soil by grazing ruminants and was then passed on to man when he started farming and domesticating cattle and other animals.[8]

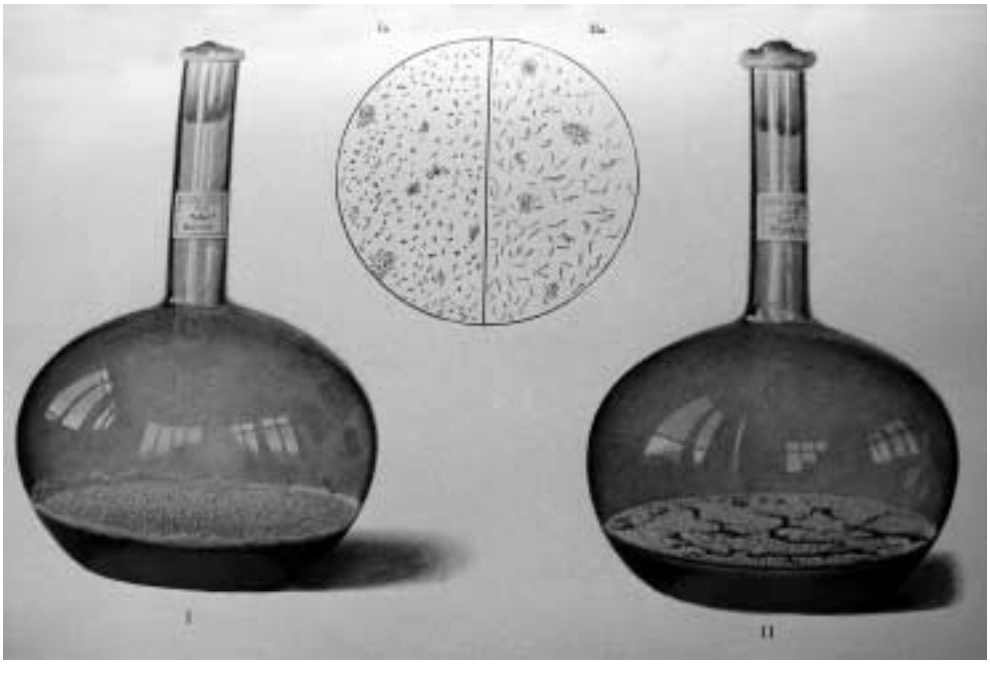


FIGURE 1
Two forms of the tubercle bacillus: the bovine variety *(Mycobacterium bovis)* on the left and the human variety *(Mycobacterium tuberculosis)* on the right.
(The Herald Archive)

One form of TB which was certainly a major cause of morbidity in medieval Europe was *scrofula*, TB of the lymph nodes at the side of the neck, which led to purulent discharges, and much scarring and disfigurement. It was known as the King's Evil and was supposedly curable by the monarch's touch.

TB also acquired other names: *phthisis* from the Greek meaning 'wasting'. It was more commonly referred to as consumption, a reference to the marked loss of weight, wasting away and muscular debility which the disease eventually resulted in. Its ability to manifest itself variously as a chronic, intermittent or acute disease in a variety of organs, often capable of becoming reactivated after long periods of dormancy, made its diagnosis exceedingly problematic.

> More than any other affliction, excepting madness, it appeared to be a generalised condition of disease rather than a specific entity amenable to secure diagnosis and reliable prognosis.[9]

As a result, it became the perfect vehicle both for quack remedies and inappropriate intervention by orthodox medicine, as the French-American philosopher and scientist René Dubos observed, and he should have known: his first wife died from TB and his second wife almost shared the same fate. 'Because of the uncertainty of its prognosis, TB has provided in the past – and remains today – the ideal disease for the promotion of ill-founded methods of treatment,' he noted.[10]

The explosion of TB in Europe occurred in step with industrialisation in the 19th century and the consequent poverty and overcrowding in the urban sprawls established in its wake. The manner in which epidemics of TB peaked later in association with industrial changes in other countries, such as Japan, tends to support this hypothesis. Dubos described TB as the social disease of the 19th century 'perhaps the first penalty that capitalistic society had to pay for the ruthless exploitation of labour.'[11]

By 1840 TB had become the biggest killer in Britain, accounting for around one in every seven deaths. Although predominantly the scourge of the poor, it also left its mark among the literate and affluent classes claiming John Keats, Frederic Chopin, Nicolò Paganini, Anton Chekhov, the Brontë sisters, Franz Kafka, D. H. Lawrence, George Orwell and Fyodor Dostoevsky. For them TB imposed a deadline which was both short and literal.

TB was embedded into the fabric of society as well as in the lungs of its artistic élite where it fuelled a mood of morbid romanticism. The image of the doomed young artist heroically struggling against the monstrous instrument of fate was enshrined by the operatic heroine Mimi in Puccini's *La Bohème* and in Alphonsine Plessis, the courtesan model from Verdi's *La Traviata*. The French poet Millevoye likened the dying consumptive's final days to the falling of leaves, a term later revived in its Greek form, *apoptosis*, to describe the process through which cells are practically programmed to commit suicide.

To prolong the performance and agony there was also no shortage of weird and wonderful bogus cures. These ranged from cod liver oil, lard and the smell of cow dung for the masses, to more exotic remedies like boa constrictor excreta, arsenic, aluminium, digitalis, gold and opium for the rich. The Belgian Adolphe Sax offered the pulmonary exercise required to blow his new instrument and, for those still not out of breath, long sea voyages and horse riding were both supposed to have some effect.[12]

The commonly held belief that the source of infectious diseases was in the atmosphere, particularly in the foul and heavily polluted cities, triggered a growth in

health travel or climatotherapy. The coughing wrecks made the effort to get away to drier and healthier wide open spaces. It was this belief which uprooted Robert Louis Stevenson from Auld Reekie and sent him on his travels. The young Cecil Rhodes was on a similar quest on his early visits to South Africa. The damp climes of Edinburgh and Oxford were not thought to be conducive to recovery.

Nowhere else was this health-motivated diaspora more apparent than in North America where the opening of the transcontinental railroad spawned an exodus westwards of the 'lungers'. By 1880 one third of Colorado's population comprised 'reconstructed invalids', and in Denver alone there were an estimated 30,000 consumptives, the 'one lung army'.[13]

TB also had a profound impact on the development of Albuquerque and Santa Fe in New Mexico, and of Santa Barbara and San Bernardino in California where the coughing masses who had migrated there were accommodated in makeshift houses, shacks and tents. One contemporary observer in 1910 described the plight of the desperate colonies which had sprouted in and around San Bernardino thus: 'There are tents in front yards and back yards, in vacant lots, by country roadside, on farms and ranches, in secluded canyons . . . and away up in the mountains. They are the camps of the Arabs of the Southwest – a forlorn, homeless and almost hopeless multitude of wanderers, chasing the phantom, Health.'[14]

Little good would the journey do many of them. In 1893 Santa Barbara had one of the highest suicide rates in the world and one in three deaths in the town was due to TB.

By this time, however, there was prospect of at last being able to do something about it. There had long been theories of contagion but TB was a notoriously elusive foe. The breakthrough came in 1882 when a German doctor, Robert Koch, announced to an astonished medical audience in Berlin that he had found the causative agent for this disease. He used a new acid-fast staining technique, to highlight the tiny, rod-like bacilli, which, when later modified by Paul Ehrlich, showed them as scarlet ribbons against a blue background.

Robert Koch 1843 - 1910

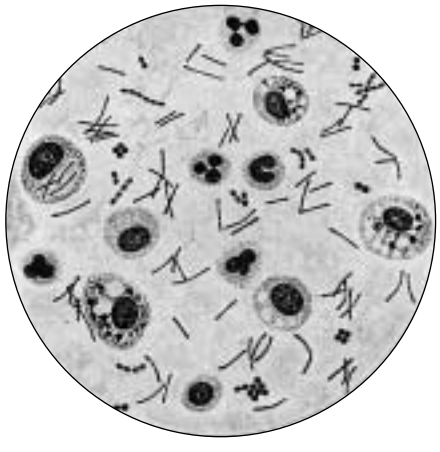


FIGURE 2

Depiction of tubercle bacilli, in a specimen of sputum, stained by the Ziehl-Neelsen method.

In the same year a similar theory was being propounded in Melbourne, Australia, by William Thomson who observed that the disease seemed to be spread by newly-arrived phthisics who expelled micro-organisms in their breath to be inhaled by healthy people.[15]

Koch's achievement was all the more remarkable because he completed the entire process of discovering the tubercle bacillus and carrying out extensive proof in animals to show that it was the cause of the disease, all within the space of eight months.[16] His work was to have profound repercussions throughout the world. Know your enemy is the first mantra of warfare. The centuries-old adversary had finally been identified, prompting a wave of optimism that something could be done to combat the disease. Fatalism of the previous generation gave way to major lay-inspired public health campaigns and fund-raising. In 1897 the first anti-TB charity postage stamps were launched in New South Wales, an idea which spread like wildfire in the USA.[17]

Similarly, the sanatorium movement grew in popularity on both sides of the Atlantic with its régimes of fresh air and prolonged rest. Many establishments like Davos, which first opened in 1841, and Saranac in New York State became celebrated disease palaces. TB control became a fashionable cause for the chattering classes. Edward VII took an active interest. It was assisted by enthusiastic and flamboyant physicians like the Canadian William Osler, later knighted when Regius Professor of Medicine at Oxford.

Osler already had experience of the Grim Reaper's scythe from the 1,000 autopsies he had carried out at Montreal General Hospital of which 216 were due to TB. He had lost several colleagues including his houseman Meredith Reese in 1892.[18] Never afraid, when charm failed, of calling a spade a shovel and then hitting someone with it, Osler berated the mayor of Baltimore at a public meeting in 1899, comparing the paltry provision of sanatorium places in Maryland to that of forward-looking Massachusetts. In Baltimore itself there were enough places for just 5% of TB cases. 'Now, what is the condition in this city and what are we doing for the 10,000 consumptives who are living in our midst? We are doing nothing, Mr Mayor, and fellow citizens, not one solitary thing that a modern civilised community should do . . . it is a disgrace to us as a city of 500,000 inhabitants. It is a story of dire desolation, want and helplessness, and of hopeless imbecility in everything that should be in our civic reaction to the care of this disease.'[19]

Fighting talk indeed. Not to be outdone by its northern neighbour, the Maryland General Assembly took heed and established a TB Commission at its next meeting. Across the world, the anti-TB movement came into the 20th century spoiling for battle. It would take another 50 years and 100 million more tombstones before it could launch an effective attack.

Chapter 2

POST KOCH, PROPTER KOCH: THE PHONEY WAR

Unfortunately for these zealots, armed with a certitude forged on the new anvil of medical science, the enemy was already retreating from the battlefield.

Annual deaths from TB in the United Kingdom were more than halved between 1870 and 1910.[20] The pattern was repeated elsewhere in Europe and North America as each epidemic ran its course and mortality rates went into a gradual but steady decline. There is, indeed, a legitimate epidemiological argument that the disease would have petered out on its own in the Western world thanks to improved social and housing conditions and rising standards of living. In this context, some of the attempts at cure may well have hindered rather than helped.

But for the two world wars, when the downward trend was briefly reversed, the decline would certainly have been more rapid. Quite what predisposed populations to TB and other infections is a matter for interpretation, but overcrowding and absence of ventilation at work or at home, poor hygiene, and other manifestations of poverty undoubtedly played significant roles.

In the UK, the battle against TB was pursued on a number of fronts under the aegis of the National Association for the Prevention of Tuberculosis (NAPT), set up in 1898. Its initial propaganda efforts drew heavily on the North American experience, particularly that of New York, where legislation against spitting had been introduced in 1896, and that of San Fransciso, where offenders could face a $500 fine if caught expectorating on public transport by the plain-clothes detectives who enforced the ban.[21]

There was a heavy air of moralistic social engineering, often fused with religious fervour. Sanatoria provided the institutional basis for control and flourished everywhere, based on régimes of bed rest, diet, and continuous exposure to fresh air. This treatment left an architectural heritage in the former sanatoria now used as more conventional hospitals: the open balconies where beds were pushed out at whatever time of day or night and in all weathers. Apart from a militaristic approach to discipline there was often an emphasis on self-help and more than a sprinkling of the Protestant work ethic amid paternalistic admonitions on the evils of sex and alcohol.

Beneath all this was a lingering culture of misery for patients. Toys and other personal effects were often burned on admission to reduce the risk of infection but this also reinforced the power structure. Patients were quite literally ciphers, their numbers and severity of condition reported as such in newspapers to keep relatives informed on the outside when visiting access was denied. It would be unfair to characterise all sanatoria in this way, but the nature of their régimes certainly gave those who wished to abuse positions of power the opportunity to do so.

At one end of the spectrum was the international sanatorium at Davos where the rich sick of Europe could engage in sexual intrigue and endless philosophical and intellectual debate. Thomas Mann's hero, Hans Castorp, went there intending to stay for three weeks but ended up on the 'Magic Mountain' for seven years under the care of the relatively benevolent Hofrat Behrens. Mann is scathing about patients' demands for excessive use of some treatments such as heliotherapy which involved sun lamps: 'They already had two, but these did not suffice for the demands of those

FIGURE 3
Stannington, Northumbria, was the first British sanatorium for tuberculosis children; these senior girls were surgery cases.
(The Wellcome Institute Library, London)

FIGURE 4
Early public health advice in the Netherlands extolled the virtues of healthy living and warned of the dangers of quack remedies and aerosol spread.
(KNCV The Hague)

who wished to get sunburnt by electricity – it was so becoming of the ladies, young and old, and made all the men, though confirmed horizontallers, look irresistibly athletic.'[22] Whatever palliative therapies a sanatorium life could offer, the natural history of the disease remained the same, as Castorp pointed out to his Uncle James:

> He heard his relative hold forth upon the disease which was the business of life up here . . . upon the attraction the bacilli had for the cellular tissue of the air passages of the throat, bronchial tubes, and pulmonary vesicles; upon the formation of nodules, the manifestation of soluble toxins and their narcotic effect on the system; of the breaking-down of the tissues, of caseation, and the question whether the disease would be arrested by a chalky petrifaction and heal by means of fibrosis, or whether it would extend the area, create still larger cavities, and destroy the organ. He was told of the 'galloping' form the disease sometimes assumed, which made the end an affair of not more than a few months or even weeks; of pneumotomy, of the Hofrat's masterly surgery, of resection of the lungs, an operation which was to be performed tomorrow or the day after upon a severe case just brought to the sanitorium, a charming, or once charming, Scotswoman suffering from gangroena pulmonum, gangrene of the lungs, a green and black pestilence, which obliged her to inhale all day a vaporized solution of carbolic acid, lest she go out of her head from sheer physical disgust.[23]

Some institutions used the term 'sanatorium' and others 'sanitorium', perhaps to reflect the separate Latin origins of these terms, either to heal or simply concerned with health, but régimes were different. The unpredictable nature of TB rendered it open to a variety of treatments, most dependent on whether the supervising physician or the affluent patient thought they worked. Judicious selection of milder cases for admission could greatly improve 'success' rates and the absence of any agreed protocols rendered any objective assessment of cure rates impossible.

In Britain similar establishments were set up with both private and public funding. Papworth in Cambridgeshire opened its doors in 1915 as a 'consumptive garden city' on the basis of long cheap stays, rather than the short-term expensive treatment of conventional sanatoria.[24] By the mid-1920s, however, there were questions asked about whether they actually did any good. They consumed vast sums of money and gathering patients together under one roof, however airy, possibly assisted in cross-infection. They probably did make a significant contribution simply by removing a substantial pool of infection from communities at large, thereby preventing further spread. However, sanatorium treatment was not an option available to the vast majority huddled in the slums of cities like Manchester, London and Liverpool. TB was forever a disease of poverty. In 1931 rates in England and Wales were twice as high among unskilled labourers as among the upper and middle classes.[25]

Another model for treatment was the dispensary. The first was established in Edinburgh in 1887, by Robert Philip, whose influence on the Departmental Committee on Tuberculosis in 1912 under Waldorf Astor MP probably led to the idea being copied throughout the United Kingdom.[26] The dispensary was a visionary concept in public health, focusing on the family as a unit of treatment, and tracing contacts of infected patients using the forerunners of present day health visitors. In Edinburgh, Philip took the model of TB treatment much further, establishing a sanatorium, a farm colony and a separate tuberculin-tested herd for milk supply.

Philip was a charismatic figure, of no small ego, who carried much influence within the NAPT. His great mentor was Robert Koch whose original brilliance soon became tarnished. In 1890 Koch announced he had discovered a potential vaccine, made from extracts of the dead bacilli, but this proved wildly premature and

optimistic. His discovery, tuberculin, was a useful test for TB infection but nothing more, although disciples like Philip remained convinced of its value in treatment for decades afterwards. Koch made another error in 1901 when he opined that bovine TB *(Mycobacterium bovis)* was not transmissible to humans, a statement which was to have far graver consequences.

Whereas there was no effective treatment of human TB *(Mycobacterium tuberculosis)*, there was at least something which could be done against the bovine variety since its principal source was infected milk. Some countries realised this and started culling infected herds and pasteurising milk. Denmark, with a growing dairy export business, led the research work in this area.[27] Pasteurisation programmes were introduced in Chicago, Massachusetts and New York City between 1908 and 1912, policies which seemed to bear fruit in reducing mortality.[28] New Zealand, Finland and Canada soon followed.

In Britain there was much less enthusiasm for such prophylactic measures outside London where pasteurisation was introduced in the early 1920s. Successive governments, under pressure from the agricultural and milk production lobbies and with the support of Philip and others in the NAPT, favoured a graded system of milk classification where market forces and consumer choice would determine types of milk supply. Slaughtering schemes, when introduced, were ineffective and poorly supervised. Repeated attempts by the British Medical Association and others to extend and enforce pasteurisation met with stubborn governmental and public resistance.

The end result was that thousands of British children died in the interwar period through exposure to bovine TB in infected milk. As late as 1931 the Ministry of Health stated that more than 1,000 children died each year from bovine TB and many more were crippled. At the same time, more than 40% of cows were infected with TB. Three years later it was estimated that 6% of all farms were sending out milk containing tubercle bacilli and therefore all bulk milk was liable to be infected.[29]

A similar sorry tale emerges from the NAPT's antipathy to BCG vaccine developed from a bovine strain by the French scientists Albert Calmette and Camille Guérin in 1922. It was dogged by a lack of authoritative testing and a disaster at Lübeck in Germany in 1930 when a laboratory mix-up led to the death of 73 infants who had been infected. Philip himself had a stormy friendship with Calmette[30] which probably delayed any proper evaluation and testing in the UK until 1950, well after Sir Robert's death when a Medical Research Council trial conducted by Dr Philip D'Arcy Hart established BCG's worth and ensured its rapid introduction as part of the new National Health Service.

Calmette pleaded in 1932 for Britain to carry out a trial of his vaccine, but died a broken man soon after. The vaccine which he and Guérin had discovered was the only positive and demonstrably efficacious preventive measure science had actually managed to produce in the fifty years after Koch's discovery. It deserved a better contemporary reception, and remains misreported in Britain to this day.[31]

This was an era when any idiot could voice a clinical opinion and many did, including surgeons who had long had a dubious role in therapy. TB formed the second largest part of Joseph Lister's caseload in Edinburgh during the 1870s. Two of his patients later wrote of their experiences: Margaret Mathewson from Yell, Shetland, whose family was almost annihilated by the disease, and the poet William Henley, subsequently editor of the influential literary magazine, *The National*

Observer. Henley was also a collaborator of the consumptive Robert Louis Stevenson, who possibly used Henley's crippled leg and gait as a model for Long John Silver.[32] In *Invictus* Henley went on to write: 'Under the bludgeonings of chance, my head is bloody, but unbowed.'

As surgical practice developed, so did specific treatments for pulmonary disease. Collapse therapy, through the artificial pneumothorax where air was introduced into the membrane surrounding the lung in an effort to kill off the bacillus or, more radically, thoracoplasty, where whole sections of the rib cage were removed for the same purpose, was crude, brutal and sometimes in itself fatal. Although some thoracic surgeons became active votaries, others were less enthusiastic and, even in those studies which showed good survival rates, relapse was common within five years.[33]

It could be argued that physicians and surgeons were doing their best in the light of conditions and knowledge of the time, a proposition which might be tenable but for the fact that so many unwarranted and allegedly scientific claims were made on their behalf.

Perhaps if they had done nothing more quietly, critics would not have noticed. Among literary sufferers there was a well observed condition *spes phthisica* which supposedly added piquancy and urgency to their work in the latter stages of the disease. The English novelist David Herbert Lawrence summed up sceptical lay opinion of treatment with this poetic rebuke in his final consumptive months:

> When I went to the scientific doctor
> I realised what lust there was in him to
> Wreak his so-called science on me
> And reduce me to the level of a thing
> So I said: Good morning! and left him.[34]

The American tennis star Alice Marble evinced similar disdain to conventional medical orthodoxy in 1934. Aged just 20, she collapsed on court in Paris and was told her career was over because of newly diagnosed TB. Transferred on a wheelchair back home she was admitted to Pottenger's sanitorium at Monrovia, California, but, encouraged to fight on by her coach and the actress Carol Lombard, she walked out and went back to serious training. Marble then went on to win three consecutive US women's single titles and live well into her pensionable old age.[35]

Chapter 3

GERMS AND GERMANS

It is impossible to escape militaristic metaphors in the literature and history of pathology, particularly TB. This reached its apogée during World War II. The most celebrated literary allusion is in Albert Camus's *The Plague*, first published in 1947, which equates the plague outbreak in Oran in Algeria with the spread of the Nazi sickness:

> He (Rieux) knew what those jubilant crowds did not know but could have learned from books: that the plague bacillus never dies or disappears for good; that it can lie dormant for years and years in furniture and linen-chests; that it bides its time in bedrooms, cellars, trunks, and bookshelves; and that perhaps the day would come when, for the bane and enlightening of men, it roused up its rats again and sent them forth to die in a happy city.[36]

Camus was also able to draw on his own personal experience of TB in the same way fellow Nobel laureate Thomas Mann had done with Hans Castorp, last depicted charging off into the bloody carnage of World War I.[37] Franz Kafka, who like Thomas and his brother Heinrich Mann had spent time at the Hartmann Sanatorium at Riva in 1913, described TB in a letter to his fiancée, Felice Bauer, as 'a knife that stabs not only forward but one that wheels around and stabs back again.'[38]

Kafka likened his pulmonary and laryngeal tuberculosis to his being impaled. It was also a different manifestation of the madness which he believed he had inherited from his mother's family, prompting him to reflect further:

> I am willing to believe that tuberculosis will be controlled; every disease will ultimately be controlled. It is the same with wars – each one will come to its end but none ever stops. Tuberculosis no more has its origins in the lungs than, for example, the World War had its cause in the ultimatum. There is only a single disease, no more, and medicine blindly chases down this one disease as though hunting a beast in endless forests.[39]

Kafka died three years later in June 1924. He was Jewish and had he lived longer he might have equated the rod-like bacilli with the rods that became the emblem of fascism. This was an era when genetics was hijacked by eugenicists. Hitler added further poison to the concept by depicting Jews as weak carriers of disease, infecting the 'healthy' Aryan race. He forged his policy of genocide around it, murdering millions of people, including Kafka's three sisters who had escaped the pestilence which had claimed him twenty years earlier.

Camus's allusion was not lost on the younger generation of TB doctors in Britain. Some, like Archie Cochrane, had enlisted as medical auxiliaries in the International Brigade in Spain whilst others helped form the British committee to give medical assistance to the Republican side. Others like Philip D'Arcy Hart also wrote papers for the influential Socialist Medical Association. He stumbled into a career in TB almost by accident in 1930, taking over a clinic at the Royal Northern Hospital in London when the TB officer failed to turn up.[40]

Prior to the actual outbreak of war, the enemy could be seen in London. D'Arcy Hart recalls the visit of a group of German air force officers to see a fascist sympathiser friend working as a biochemist at University College alongside a Jewish colleague

FIGURE 5
Italy, the first fascist state, claimed to have the largest sanatorium in the world, the Sanatorio Mussolini in Rome.
(Wellcome Institute Library, London)

who had fled from Germany: 'They started off on the biochemist and said what are you doing with a Jew in the lab? We learned afterwards that they had gone on to boast about Guernica. They had learned quite a lot from it.'[41]

Wary of the lessons from World War I and the dangers of resurgent TB to the fighting forces and war production, the British Ministry of Health appointed a committee to investigate the problem. D'Arcy Hart was its secretary and its guiding influence was an earlier Socialist Medical Association pamphlet written by him and his colleague Marc Daniels, who advocated use of the newly-available miniature X-rays to help diagnose cases. This was not the resounding success which the committee had hoped for, but another of its recommendations, for the pasteurisation of milk on a national basis, at least remedied a long-standing gap in effective prevention.

The expected resurgence of TB did indeed materialise in combatant countries. In Britain deaths from the disease rose by 15% in the first two years of the war[42] and in Japan TB mortality actually reached its 20th century peak at 147,000 in 1943.[43]

Ironically, anti-TB research flourished despite the war. The motif of the International Union Against Tuberculosis, the principal agency for international collaboration against this disease, had long been the Cross of Lorraine, which itself became the symbol of the French resistance to the Nazi swastika.

Equally ironically, much of the impetus to finding anti-TB drugs came from within Germany itself. Some years previously, Paul Ehrlich had articulated the concept of the magic bullet, using chemicals to kill bacteria but save the patient. The discovery by Gerhard Domagk in 1935 of prontosil, the first effective antibacterial drug, earned him a Nobel Prize which Hitler refused to allow him to accept; the Gestapo arrived at Domagk's house and kept him in jail for a week's interrogation,

an experience which he found terrifying and exhausting.[44] His potential value to the Reich in combating gas gangrene and other front-line infections probably saved him from a worse fate.

Domagk was an inspiration to Fleming, Florey and Chain in the development of penicillin but neither it nor prontosil was effective against TB. After so many failures, any compound which did work would justify the cliché of medical breakthrough. It eventually came from an unlikely source – the soil. Allegories of agricultural fecundity had their place in wartime vocabulary, Dig for Victory and Scorched Earth destruction, but the subject had also attracted the interest of soil scientists interested in the mechanisms of how various micro-organisms managed to establish and feed themselves whilst also possessing anti-bacterial properties to ward off rivals.

Selman Waksman had pursued this line of research at the then unfashionable Rutgers Agricultural College in New Jersey. He was joined by a 23-year-old student, Albert Schatz, in June 1943. Part of Schatz's PhD brief was to search for a specific anti-mycobacterial agent. He tested all the colonies of actinomyces he could find against a disease-causing germ. On 19 October he hit the jackpot with two colonies, one found on a throat swab from a sick chicken and the other from heavily manured soil.[45]

The discovery was utterly astonishing. Despite some problems in testing and manufacture, the new compound, streptomycin, appeared to be remarkably effective against a number of infections, including TB. The first victory in the war against TB had been achieved by two Jewish men just at the time when the military war had turned against the Nazis.

As Schatz later recalled, the process of discovery was simplicity itself. Many colleagues had repeatedly warned him that he was wasting his time: 'They told me that the tubercle bacilli were covered with a heavy waxy capsule and nothing could get in. And that's why the drugs were not effective. My feeling was that if nothing got in we wouldn't have tuberculosis, because nutrients would have to get in and waste products would have to get out. If food and waste products could get through, so could an antibiotic. So that argument did not hold water with me. I therefore kept on working.'[46]

Despite daily Allied bombing, Domagk and his colleagues at Bayer's Elberfeld laboratories continued to work on thiosemicarbazones, which had putative anti-TB properties. It was an earlier Bayer discovery, aspirin, which opened up the second front in 1943. It was well known that aspirin itself seemed to encourage growth of the bacillus, and to some researchers it was apparent that by interfering with this mechanism there could be a possibility of reversing this process. The Danish scientist Jorgen Lehmann, working in neutral Sweden, had suspected that the para-amino salt of common aspirin had anti-tuberculous properties as far back as 1940. Para-aminosalicylic acid (PAS) was used on the first patient in October 1944 in Gothenburg, one month before the first clinical use of streptomycin in the USA.[47]

In the same month Nazi tolerance of Domagk and his circle was beginning to wear thin. His friend Philipp Klee, who had supervised the early prontosil treatments at the Wuppertal-Elberfeld Hospital, had since 1939 used his status as a distinguished doctor to protect his Jewish wife, Flora. This time, however, the SS came and took her away to Theresienstadt concentration camp in Czechoslovakia. By sheer chance and good fortune through the camp's early liberation, she survived. As Domagk remarked in his diary: 'The National Socialist system started with lies and suffocated in cruelty and blood.'[48]

The real truth of Nazi medicine was even more horrific. A series of experiments were carried out late in 1944 at the Neuengamne concentration camp in Hamburg by Kurt Heissmeyer, whose uncle August was chief of the SS's central organisation. Twenty Jewish children aged between five and twelve were deliberately infected with live tubercle bacilli through injections, cutaneous scarring or direct introduction to the lungs via a tube. Surgery was also carried out on them and adults to see how the disease was developing. By the spring of 1945, the impending arrival of the Red Army had forced him to abandon the project. The infected children were taken out and murdered.[49] After the war, Heissmeyer returned to his home in Magdeburg where he was highly regarded as a lung and TB specialist.[50]

The death of Hitler and his ideology coincided with the death of man's helplessness against TB. The evolution of an effective range of therapies was a genuine pan-European achievement with a major contribution from European immigrants in the USA. It was fitting then that the new European anthem, the *Ode to Joy*, was the product of a TB victim, Friedrich von Schiller.

But, as Camus pointed out, disease, like Nazism, was always capable of returning.

Chapter 4

HOW THE CHEST WAS WON

Streptomycin may have been a wonder drug but it did not produce miracles.

Initial euphoria waned when it emerged that a significant proportion of those treated began to develop resistance. This disappointment was compounded by the antipathy between Waksman and Schatz over who was to inherit the public acclaim that went with the discovery. Their friendship was irrevocably wrecked by quarrels over the resultant credit, academic prestige and financial benefits. As with Banting and Macleod with the discovery of insulin in Toronto in 1922 and Gallo and Montagnier over the AIDS virus identification in 1984, remarkable scientific achievement was overshadowed by subsequent inter-scientist squabbling. The decision to award the 1952 Nobel prize for medicine to Waksman alone merely made matters worse.

The problem with the newly-discovered drugs was that nobody knew exactly what to do with them or knew their proper dosage. Treatment was haphazard and necessarily opportunistic since streptomycin in particular was very hard to obtain. From the patient's point of view, high expectations nourished by credulous newspaper coverage were often cruelly dashed, as George Orwell's letters reveal.

His efforts to write *1984* on the Scottish island of Jura in 1947 were frustrated by a more serious manifestation of earlier TB. Orwell was terrified of infecting his adopted son Richard and went to the lengths of buying a TB-tested cow to ensure a safe milk supply. In December 1947 he was admitted to Hairmyres Hospital in East Kilbride and in the spring of 1948 his editor David Astor cabled his New York contacts for some supplies of streptomycin.

FIGURE 6
George Orwell (1903 - 1950)
(The Herald Archive)

Orwell bore the treatment with fortitude, writing in April: 'I suppose with all these drugs it's rather a case of sinking the ship to get rid of the rats. However they've stopped the strepto & evidently it has done its stuff.'[51] Unfortunately, as Jimmy Williamson, the junior doctor administering the injections realised, it had not. Orwell had experienced a terrible reaction to the drug which could not be controlled and the remaining supplies were given to another patient who recovered well.[52] He finished *1984*, acknowledging it would have been a better novel but for his illness. His alternative working title was *The Last Man in Europe*, which is what the author became in the sense that he was the last major literary figure to die prematurely from TB. Another attempt at streptomycin therapy in the Cotswold sanatorium at Cranham in Gloucestershire in April 1949 had equally ghastly results and Orwell died at University College Hospital in London in January 1950, a few days before he was due to travel to a Swiss sanatorium.[53]

Orwell's case and thousands of others highlighted the need for a rational approach to use of the drugs. The British Medical Research Council invited one of its staff, Philip D'Arcy Hart, to run a TB research unit. They made him an offer he could not refuse: 'I was just told to form a unit and get on with it, otherwise they would say bye-bye to me. It was rather an unusual way of being made a director but they really did not know what to do with me at that time.'[54] He chose Marc Daniels, a former TB officer, who had developed a special interest in statistics and epidemiology, as his deputy and their first task was to run a trial on streptomycin. The resultant unit was to change not only treatment of TB but also to revolutionise the entire Western approach to medicine.

D'Arcy Hart is a remarkable man. Few doctors are still writing letters to the *British Medical Journal* just before their 96th birthday, even fewer have them published, and none of sufficient importance to cause a revision of textbook footnotes. The 1948 streptomycin trial was not the world's first randomised controlled trial. The same techniques pioneered by Austin Bradford Hill were in fact deployed four years earlier in the 1944 MRC trial of patulin against the common cold among more than 1,000 factory workers and civil servants. This was both double-blind and placebo controlled but since it produced a negative result, it was largely ignored whereas the successful streptomycin trial made medical history.[55] Other trials in the USA and the Netherlands may have some claim to the title[56] and there are serious question marks as to whether the patulin trial itself was truly randomised. One eminent authority points to the MRC whooping cough vaccine trial as the first to use randomisation techniques which completely ruled out the possibility of investigator bias. It started in 1946 but did not report until 1950.[57]

Hitherto, the assessments of new treatments had been largely based on administration by a physician who then judged the efficacy on whether he thought the patient's condition had improved. Such an approach was, by definition, subjective and a wider picture only emerged through the doctor's treatment of other patients and reports from colleagues. Medicine had not been devoid of rationalistic practitioners nor even of those who saw the value of impartial assessment: the naval surgeon James Lind had applied this principle nearly 200 years earlier in the use of lime juice for the treatment of scurvy. The lesson had long been forgotten. Bradford Hill's thesis that - by random selection of patients and application of basic statistical principles to eliminate bias - one could arrive at an objective appreciation of therapeutic worth, was considered both novel and dangerously subversive. If this notion took root, as it certainly did, it necessarily threatened those physicians who

viewed themselves as the sole and supreme arbiters of what was right for the patient. It could lead to standardisation of regimens where the doctor's role was diminished. Worse still, it could even hit his income.

What helped sustain the new approach was a young generation of doctors, many of whom had just returned from wartime service, and the establishment of the National Health Service. It was indeed a climate of radical change. If the randomised controlled trial became the seed of an intellectual revolution in British medicine, the NHS provided the greenhouse in which it could take root and flourish.

The trial was conducted in several centres and Daniels collated the results. Supplies of the drug were provided by the United States. The trial was deemed ethical since only a small amount of the drug was available, its effects were not known, and the control group was being given the best existing treatment. It demonstrated that while streptomycin worked well, it only had a temporary effect and also produced problems of resistance and toxicity.

Public interest, particularly among relatives of those with the disease, which in its pulmonary form still killed half of all sufferers, was intense. Some unfortunates even turned up in the night outside the MRC's buildings in Hampstead pleading for supplies of streptomycin. There was also an ethical dilemma in dealing with a consultant at the Hammersmith Hospital who was seriously ill with TB. D'Arcy Hart turned him down since all supplies were for the trial. A phone call by the secretary of the MRC, Sir Edward Mellanby, to a friend in America obtained an alternative supply and the consultant later recovered.[58]

A second trial was carried out using streptomycin and PAS. It was of critical scientific importance in that it provided the basis for TB chemotherapy for the next 20 years. What it showed for the first time was that combined treatment diminished the emergence of drug resistance. Mutant bacilli, present at levels as low as one in 10 million, were prevented from growing by PAS whereas streptomycin prevented the growth of PAS-resistant mutants. It was an entirely hypothetical approach and novel in that the same method did not work in other infections. A further series of trials between 1951 and 1955 used a new and extremely effective drug, isoniazid (isonicotinic acid hydrazide) which had evolved simultaneously in Germany and America. As the trial results gained acceptance, so did the MRC's science.

Generational gaps invariably produce divisions in medicine: younger doctors with a radical vision against a cautious old guard with a vested interest in maintaining the status quo. The old guard's power of patronage usually enables it to dominate, but in the immediate postwar period the young radicals were riding on a wave of a new therapy and socialised organisational culture.

This division was certainly apparent at the Brompton, England's foremost chest hospital. Ian Grant, then a junior physician, developed a disdain for his senior colleagues who sent him out to the Fulham Road to collect black market deliveries of streptomycin.[59] Private practice certainly offered the opportunity for ignorant doctors to inflict the worst treatment on frightened and gullible patients who thought they were buying the best. It was all too easy to prescribe the first wonder drug and then, when it failed due to resistance, try the next until resistance rendered it ineffective and so on. The patient by this stage would be incurable - and probably bankrupt - as a result of the long periods on successive single drug treatment. When the patient died, the physician could blame the dreaded tubercle bacillus and claim he had tried everything. It was a no-lose strategy for the greedy and unscrupulous.

Among the radical group there were some who had experience as patients, including Georges Canetti at the Pasteur Institute in Paris, Bradford Hill, and Wallace Fox, whose tuberculosis was diagnosed six weeks after he qualified. After two years off, he served his TB apprenticeship working at a sanatorium near Maidstone: 'I was learning a lot about tuberculosis. I knew more than most of the Brompton consultants who at that time were a shockingly ignorant lot. In Harley Street they saw West End people and they really did not understand what tuberculosis was all about. In a place like the Brompton when they had 12 consultants, every one of them had their own treatment for tuberculosis and when you could offer them standardised treatment, that wasn't good enough for them. They thought they had good results and why should they change? So they carried on.'[60]

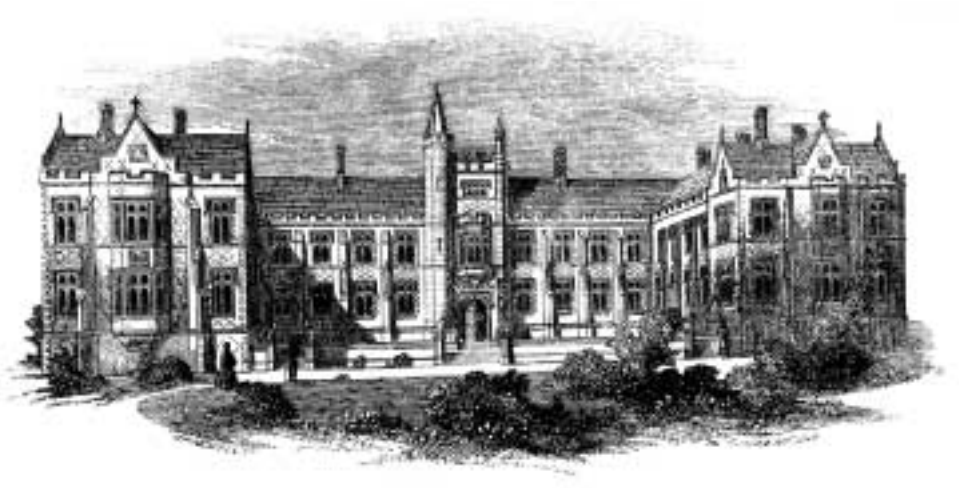


FIGURE 7
England's most celebrated chest hospital, The Hospital for Consumption, Brompton Road, Fullham, London.
(The Wellcome Institute Library, London)

The old guard could only be removed by promotion, retirement or death. Dublin-born John Crofton, who was involved as a junior doctor in the initial MRC trials at the Brompton, was the first among the radical group to put some of the new ideas into clinical practice. In 1952 he was appointed to the chair of tuberculosis at Edinburgh University. If London had examples of incompetent consultants, Edinburgh had one who combined misogyny with sadism. TB rates were highest among young women and, it seemed from the feverish flush associated with the disease, among beautiful women. This consultant delighted in going round the wards telling them: 'You are all rosy red apples, rotten to the core.' On another occasion he is reported to have told one patient who asked why she was suddenly being transferred from the Royal Victoria Hospital to the City Hospital, which dealt with more serious and terminal cases: 'You see, my dear, there is no post-mortem room at the Royal Victoria Hospital.'[61]

This consultant's retirement allowed Crofton to reorganise the service entirely and establish continuity of treatment. Previously, out-patient and hospital services were separate entities, allowing doctors to transfer their failures elsewhere. He assembled a talented group of physicians including Williamson, who had treated Orwell; Grant, formerly of the Brompton; Norman Horne and Ian Ross. They inherited a grim situation. Scotland and Portugal were the only countries in Europe where the numbers of new notifications of TB were rising after the war. Death rates in Scotland in 1948 were almost twice those of England and a special committee was set up to advise the Scottish Secretary.[62] By 1954, although mortality from the disease was dropping, annual numbers of new cases in Edinburgh reached 1,000, but there were only 400 beds, and 400 more people waiting for admission.[63]

The Edinburgh group used both the endowments left by Robert Philip's earlier fund raising and his techniques of contact tracing with good effect. Since TB was a social disease, it was not one where hospitals alone could provide the cure. As it developed, the technique of triple chemotherapy for TB could be described in popular parlance as 'kill it once, kill twice and then kill when it was dead, just to be sure.' The task itself was infinitely more complex. It began by examining treatment failures in depth. The Edinburgh group was supported by two bacteriologists, Archie Wallace and Sheila Stewart, whose contributions were critical in establishing that all failures were due to drug resistance, which, in itself, was largely the product of inappropriate combinations of previously administered drugs.

If all three available drugs were given from the beginning of treatment, the Edinburgh group found that they could cure even patients who were resistant to one drug. Paradoxically, milder cases treated for short periods fared worse than more severe cases treated over a longer period. For this reason, treatment for 18 months became standard to eliminate the risk of relapse. Each patient's progress was monitored scrupulously through bacteriological analysis and close surveillance to ensure that medicines were actually taken. Previously rising notification rates in Edinburgh were halved in Edinburgh between 1954 and 1957.[64]

Crofton's other great gift was as an organiser, capable of bringing out the best in others. It was a team effort and he took trouble to involve all his medical, nursing, paramedical and scientific colleagues as well as treating the patient as an individual. Traditional professional rivalries were not allowed to fester and colleagues met frequently to review treatment. If hard work was the order of the day, at least it was shared, and soon it became apparent that it was bearing results.

Establishing chemotherapy as a treatment in its own right was no easy process. TB therapy had seen many false dawns only to be overtaken by darkness. René Dubos, writing soon after the advent of isoniazid in 1952, was not optimistic: 'Unfortunately, the 'miracle' drug which made for such exciting headlines and photographs in mid-Feb 1952, will probably be regarded as just another treatment when re-evaluated in the light of experienced judgement.'[65]

Even by 1955 and 1956 when the MRC carried out the first national drug resistance survey which showed 3% primary resistance, usually due to one drug, and thus paved the way for triple chemotherapy, eminent figures like Canetti at the Pasteur Institute remained sceptical: 'Short of spectacular progress in one way or another, it is unlikely that chemotherapy will become the exclusive treatment of pulmonary tuberculosis. There are too many factors against it . . .'[66]

This was the critical period in Edinburgh when Crofton's group were discovering that chemotherapy was not ancillary to collapse treatment or surgery but a substitute

for them. Moreover, it was also emerging to the better-informed that the best way to prevent the spread of TB was to treat active cases by chemotherapy. Mass X-ray campaigns of the general population identified new, and often earlier, cases. By 1958 Crofton and his colleagues were sufficiently confident to postulate that a 100% cure for pulmonary TB was both a reasonable and achievable target in new cases, providing that their rigorous model was followed.[67] The Edinburgh group had optimistically estimated it would take 20 years for them to control TB in the city. In fact, they achieved it within six.

FIGURE 8
A queue for X-ray screening in Princes Street Gardens, Edinburgh, 1958.
(The Herald Archive)

The trouble was that nobody believed the results. Some even accused Crofton of fiddling his figures. By that time, however, Canetti was convinced, along with his colleague Noel Rist. In 1959 they helped arrange an international co-operative trial, the first of its kind, ostensibly to test treatment failures, although the covert aim was to gain acceptance of the Edinburgh method in the leading hospitals of 23 countries.[68]

It achieved its goal. The results were increasingly accepted, at least in Europe. The real challenge was in the rest of the world.

Chapter 5

THIRD WORLD FIRSTS

Conventional wisdom panders to Western conceit that it provides the technological, economic and medical advances to the developing world. In the field of TB therapy the reverse is true. It was the West which copied the efficacious regimens developed in India and Africa.

Wherever it may have existed in previous millennia, TB was certainly re-exported by hordes of infectious European colonists during the 18th and 19th centuries. Recent biographers have refuted previous suggestions that Cecil Rhodes suffered from TB. Rotberg dismisses it entirely, pointing out that, although the evidence is not conclusive, the stated cause of death was congenital heart disorder which may have accounted for his previous episodes of ill-health.[69] Rhodes himself was as enigmatic about his morbidity as he was about his sexuality. It probably would not do for the doyen of the derring-dos to be done in by a disease of the weak or effete. Contemporary medical records are incomplete and diagnosis was very imprecise by modern standards. An alternative explanation is that he suffered from TB of the lining of the heart's sac, the pericardium, a manifestation of the disease which was rare in most parts of the world but now relatively common in the Transkei.

If Rhodes himself was not capable of coughing up live tubercle bacilli over native Africans as they dug out his diamond fortune, his friends certainly were. His partner Charles Rudd, who manned the Kimberley operation when Rhodes returned to Oxford, had left England in 1865 on doctor's advice because of pulmonary TB.[70] After suffering a serious 'chill' Rhodes boarded the *SS Asiatic* in December 1873, apparently convinced that a sea voyage would save his life. Half-way through he felt able to write to his father that he was still suffering from his lungs, but nothing like he used to.[71] On board the steamship he also met a second class passenger, a Mr Williams, on whose behalf Rhodes later made a request for financial help, describing him thus: 'He went out to Natal very bad with consumption and hard up; no friends; packed off from England to die abroad.'[72]

One of the legacies of mine working, which made countless billions of rand for the white settlers, was rampant TB in the lungs of generations of black mineworkers already damaged and scarred through inhaling dust. Conditions both underground and on the surface in crowded barracks were ideal for its dissemination. Since most were migrant labourers, they could also take it home to their families, a feature noticed as early as 1908 by the Scottish-born doctor Neil MacVicar in his study *Tuberculosis Among the South African Natives*. He helped lay the foundations of public health in that country and the training of African nurses. His attempts to establish a hospital in the Cape Colony were met with this response from an irate official: 'I do not approve of hospitals for kaffirs.' MacVicar's investigation into the spread of TB among the African populations of the High Veld and Northern Cape, the supposedly dry, healthy areas for which Rhodes craved, concluded that bovine TB was not the cause. Instead it was due to immigration of Europeans and of workers from the Indian sub-continent brought by the British into Natal.[73]

Black populations usually fell victim to the galloping form of the disease, often dying within months, whereas among Europeans it was more chronic and often contained. The phenomenon was well-known to contemporary observers and it provided the basis for two theories which were to shape South African medicine. According to the conservative interpretation, indigenous blacks represented 'virgin' populations lacking any inherited 'herd' resistance to the infection. This assumed a measure of historical inevitability. As such, according to its most ardent votaries, there was little point in improving living and working conditions of blacks since they would still retain this vulnerability. The contrary liberal view was that the whites had introduced this infection and should be held responsible for its devastating effects.[74] Given the fact that most epidemiological analysis is complex, it may well be that both theories applied in some measure. They are not mutually exclusive. The danger lay in developing health policies based on a slavish adherence to a single explanation.

As usual, there was also a military dimension. In the mid-19th century TB was more common among British soldiers in India than in their Indian counterparts. Black troops in British and French armies serving their colonial masters during World War I also took TB back to sub-Saharan Africa.[75]

Whatever the causal explanations developed later, native peoples around the world hitherto unexposed to a variety of infections were the easiest of targets. There is some evidence in the early colonisation of North America of deliberate application by the British of live smallpox viruses to annihilate obstructive tribes.[76] TB was certainly a far more dangerous foe for American Indians than the Seventh Cavalry. In 1886, ten years after General Custer was despatched by their Sioux and Cheyenne brethren, native Americans were suffering the highest TB death rates ever recorded in the world.[77] European emigrants to Australasia in the 19th century were full of praise for the effects of the salubrious air on consumptives and Dr Samuel Bird asserted in 1863 that the Australian climate had saved him from almost certain death. Sixty years later, research in a Maori district in New Zealand's East Cape found an incidence of TB ten times higher in the natives than in the general population.[78]

The latter study was funded by the British Medical Research Council, which in the age of chemotherapy led the way in developing treatments with truly universal application. Once the earlier domestic trials on streptomycin, PAS, and isoniazid were completed, the MRC turned its attention abroad and embarked on a series of more than a dozen trials which were truly remarkable both in their foresight and impact.

Wallace Fox joined D'Arcy Hart's TB research unit in 1952. Two years later Denis Mitchison was appointed head of a new MRC unit for laboratory studies in TB. Its job was to co-ordinate the bacteriological studies essential to give validity to work in the field. Chest X-rays could give some clues in diagnosis, but it was microscopic examination of sputum and cultures of the microbe which provided the proof of the efficacy of any therapeutic regimen. Similarly, it was the systematic application of statistical techniques applied to the trials which made the investigations truly valid. At the MRC these epidemiological studies were led by Dr Ian Sutherland and they later helped provide benchmarks which were used internationally.

From the outset, the MRC realised the great problems with triple chemotherapy. It was too expensive, treatment of up to two years was too long and it was very difficult to supervise and ensure compliance. Western countries with relatively small populations, ample resources and sophisticated health systems found it difficult

enough, but it was wellnigh impossible for developing countries lacking basic infrastructure and funding.

The MRC's first foray into this complex area was a well-planned trial in East Africa in the early 1950s. Thiacetazone had previously emerged as a good alternative to PAS but studies in the United States ruled it out on the grounds of toxicity. The MRC unit demonstrated that, with careful monitoring of dosage, problems of toxicity could be overcome, in East Africa at least. Further studies were then carried out in India and Hong Kong. The new combination was just as effective but much cheaper, thus making a cure available to many more patients.[79]

At the same time Mitchison, Fox and colleagues also became involved in a much more ambitious trial in India, where the Government asked the World Health Organisation (WHO) for assistance in developing TB control measures. D'Arcy Hart, Fox and Guy Scadding from the MRC visited India in 1955 to assess the problem. Instead of a 'treatment and demonstration' centre, Fox advocated a chemotherapy research centre; the only problem was its location. The first trial was to test treatment at home against sanatorium treatment. Bangalore, with its mild climate and opulent surroundings, which had been favoured for decades by the British, was offered along with other sites.

Instead, Fox chose the slums of Madras. If a treatment worked among the teeming, poverty-stricken, hungry hordes of this city, it would work anywhere: 'We deliberately picked Madras because everything was unfavourable. I think people believed these results for the reason that we had patients with very severe disease so they couldn't say it was trivial. It was an appalling climate and an appalling diet: short of protein, fats, vitamins, minerals, short of everything except carbohydrate in the rice. All of that was fully documented. We did extremely intense bacteriology. We were doing three tests on cultures a month, as well as smears, on every patient all the way through the first year. Nobody in any of the technically advanced countries had ever done such intensive study. We did this because we said nobody would ever believe you could do these studies in developing countries.'[80]

If the planning of the study and its execution had been meticulous, its results were sensational. Published in 1959 with the benefit of the WHO imprimatur, it showed conclusively that patients could be treated just as effectively at home with chemotherapy as in sanatoria, hitherto considered by many to be essential to any treatment. Moreover, patients being treated at home were not a serious risk of infection to their families, as had been previously thought.

Few trials in medical history can have had such a diverse and profound impact. The observations on the health of 190 citizens of Madras had a distinctly tangible effect in the West. Almost overnight the sanatorium's *raison d'être* was removed and with it a huge industry. Mitchison, who came out in 1956 to set up and supervise the new laboratories which provided the proof for the trial's findings, was conscious of the contemporary reaction: 'People were certainly influenced by the results, all over the world, especially the English-speaking part of the world. There were still a number of important vested interests that fought this sort of conclusion, particularly the Swiss sanatoria.'[81]

Closure of British sanatoria alone led to annual savings of more than £30m in taxpayers' money and represented the biggest boost in bed complement the NHS has ever received. It saved the developed world billions of dollars for which it contributed virtually nothing. Funding for the Madras Tuberculosis Research Centre, as it was later named, came from the Government of India, the Madras State

Government and WHO. What the MRC provided was the scientific expertise of Mitchison, Fox (on a five-year secondment to WHO) and their colleagues. As its reputation grew, particularly for long-term follow-up of patients, it also began to attract talented Indian researchers back from America.

FIGURE 9
Lack of good infrastructure makes follow-up medical visits difficult, as in this area in Indonesia.
(KNCV, The Hague)

Closing sanatoria, however, opened a pandora's box of nightmares which have bedevilled treatment for the last 40 years and continue to do so. Whatever their deficiencies, these institutions at least provided the discipline for administering regularly and meticulously whatever therapy was on offer. Chemotherapy could cure virtually all patients; but without the mechanisms for delivering the correct drugs, and ensuring patients actually took all the medicines and completed their course of treatment, it was worse than useless. Developed countries with sophisticated public health surveillance, health care systems and technical support, could manage, but it was an entirely different proposition in many Third World countries with no money and hardly any health infrastructure.

The enormous problems associated with the new drug treatment were apparent to both the Edinburgh and Madras groups. In India, cost was another crippling constraint. Sanatorium treatment with surgery was up to 20 times more expensive than chemotherapy, but its removal from the agenda did not make an appreciable impact in a country where the annual budget stood at just 2.20 rupees or 46 cents per head to cover all health services in 1960.

Isoniazid alone cost less than 10% of the more effective combination of isoniazid and PAS. The Madras researchers were sympathetic to the dilemma facing the

physician looking after a sick patient. If the only affordable and realistic option was monotherapy with isoniazid, it was reasonable to prescribe it, and this became official WHO policy. The alternative was to let the patient die untreated. At the same time, this left the danger of isoniazid-resistant TB being passed on to others. 'As a result it is possible that a long-term public health risk will be created', Fox noted with prescience.[82]

By 1960, Crofton and Rist had identified drug resistance through errors in treatment as a growing problem. In that same year Crofton also warned of the dangers of complacency. TB would remain undefeated unless concerted action was taken internationally and the lessons of scrupulous bacteriology, adequate resourcing, strict adherence to proven therapy and team work were applied with rigour.[83]

That warning was to prove tellingly prophetic.

Chapter 6

HOW THE CHEST WAS LOST

The speed with which Western countries expunged tuberculosis from their consciousness was matched by the indifference demonstrated to continuing problems in the rest of world. TB had long carried a dreadful social stigma. It went far beyond awkward glances from neighbours and avoidance in genteel society of even mentioning the word. Rehabilitation was always difficult. Prolonged treatment and absence from home broke up marriages and families. Finding work afterwards could be equally problematic in a society still swimming in the seas of superstition about the disease. Since TB was known to be infectious, it also assumed an additional dimension of terror whereas cancer, which was to displace it in the public imagination, was not contagious. It is perhaps understandable why people wanted to forget. As the TB wards and sanatoria were either closed or put to other uses, so too were the chest physicians who ran them. As early as 1965 tuberculosis had been dropped from courses at the Harvard School of Public Health, as D'Arcy Hart discovered to his astonishment on a visit there.[84] Wallace Fox succeeded him as director of the British MRC's unit that year, and it continued the search for improved treatments which could work in the Third World. The sheer logistics of a conventional two-year course of chemotherapy were horrendous, involving more than 2,000 doses of medicine on the basis of several doses a day. Intermittent regimens pioneered by the MRC in India eventually managed to reduce this to 62 doses in a six-month period, effecting considerable savings in drugs and ensuring greater patient compliance.

At this time the concept of fully supervised treatment was developed not only to find the right dosage of drugs but also how to keep patients taking them as they got better and started to feel well. Since intermittent regimens were the only feasible option for most countries, further trials were also carried out to find out the limits of the interval between doses which would still retain efficacy. The early work in Madras also disproved a long-standing tenet of WHO orthodoxy that poor compliance was due to the bulky and unpleasant nature of PAS. In fact, patients were just as likely to stop taking isoniazid, or even a placebo.[85]

The nature of the overseas trials was essentially collaborative. There was little point in further trials in the West since the real problem of TB, both in terms of the range and severity of manifestations, was firmly in the Third World. Put crudely: this is where the clinical material was, but the trials were not a medical extension of neo-colonialism. The MRC provided the scientific expertise and training for indigenous researchers and geared its studies to developing solutions to suit particular problems in each country. Host governments were expected to provide the drugs and supply them free to the patients.

In 1970 it embarked on a series of trials in East Africa, initially in Uganda, Tanzania and Zanzibar, and then in Zambia. These were the first to use a new drug, rifampicin. They also led to the resurrection of pyrazinamide, hitherto regarded as too toxic to be used in first-line therapy. The trial demonstrated that reports of toxicity had been grossly exaggerated and, if used carefully, this drug could be very effective. It was also cheap, which led to its widespread adoption in African countries.[86]

The East African studies demonstrated the efficacy of short-course treatment and once again Western countries eagerly seized on the results for their own benefit. Further investigations in Hong Kong, Singapore, Africa and India refined the six and eight month regimens still further and provided the basis for current guidelines used by WHO. Hong Kong introduced fully supervised intermittent regimens on a three-times-weekly dosage early on, thereby establishing one of the most efficient TB treatment services in the world. Other trials were related to how local problems in specific areas could best be dealt with, such as how to assist nomadic peoples in Algeria with pulmonary TB; how to best manage TB of the abdomen, lymph nodes and TB meningitis in Madras; TB pericarditis in South Africa; and spinal TB in Korea, Hong Kong and elsewhere, which showed that surgery and prolonged bed rest of up to three years were no longer necessary in dealing with this particularly gruesome form of the disease.

This was a critical period. Science had provided the therapeutic answers. All that was required was the political will and the resources to put them into practice world-wide. Neither was forthcoming.

Internal difficulties at WHO, which still favoured monotherapy using isoniazid, and other demands led to TB sliding down the priority ladder. Early attempts to apply chemotherapy in some African countries were dismal failures. In the West, its status as the head of the family of infectious killers had also taken a tumble. To all intents and purposes, TB was downgraded in the medical curriculum, not worthy of being taught in medical schools, not meriting a new textbook for two decades and not deserving any media or political interest.

Interest in developing countries was largely sustained by the Paris-based International Union Against Tuberculosis (IUAT). Founded in 1920, its early record was inauspicious. According to one historian its annual congresses were an excuse for delegates to mix with the great and good, eat and drink too much, squabble over national rivalries, and give the odd paper on abstruse pathology or how wonderful they and their local campaigns were.[87]

By the late 1950s it was certainly more active. It was the Union which arranged the international trial of the Edinburgh group's treatment, and in 1961 it launched a mutual assistance scheme whereby bodies in affluent countries provided money to support national TB programmes in poorer countries. Despite major contributions from organisations in Canada, Germany and the Netherlands, overall support was poor - amounting to just over $1m in the first fifteen years. The Union was conscious that donations were low because former TB associations were moving into campaigns against smoking and other respiratory diseases. Paradoxically, the Union itself did precisely the same thing in 1986, changing its title to International Union Against Tuberculosis and Lung Disease (IUATLD).[88]

In 1977 the mutual assistance scheme was changed to involve the host government directly and the first such agreement was concluded the following year in Tanzania. Under its National Tuberculosis and Leprosy Programme, funding was provided by the Swiss Government and others, and stocks of drugs and equipment imported, including 90 motorcycles for health workers in the field which instead were sent to the front because of the war with Uganda. Most were recovered some 18 months later.[89]

The Tanzanian project was led by the Union's new director of scientific studies, Dr Karel Styblo, who had contracted TB as a prisoner in a Nazi concentration camp. He had carried out innovative work in his native Czechoslovakia in conjunction with WHO. Styblo's earlier studies had discounted the use of BCG vaccination as a

means of preventing spread of TB, although it was useful in protecting children against primary infection.

Organising the service was a massive task. Use of X-rays as an accurate diagnostic tool had long since given way to sputum microscopy, principally due to an IUAT trial which showed that sputum examination was not only prone to fewer errors than X-ray assessment but was also much cheaper. Presence of tubercle bacilli in a patient's sputum was evidence that he or she had the active disease and was infectious. Treating these active cases properly was the best method of preventing its spread and subsequent testing could establish cure or containment of the contagion, by achieving negative sputum.

However, initial results were disappointing. Using conventional chemotherapy the programme staff only managed cure rates of 50%. From 1982, they opted for short-course chemotherapy, developed by Mitchison and Fox. There was a large element of risk involved: rifampicin would have to be used which was more expensive and, if the programme failed, there would be an awful legacy of rifampicin-resistant disease.[90] In addition, the initial treatment would have to be directly supervised. It took four years to extend short-course chemotherapy to all 20 regions in the country.[91] But it was worth the wait. Cure rates of 75% were reported, rising to nearly 90% if patients who absconded were excluded. Tanzania had demonstrated what many had thought impossible. TB could be controlled in a poor developing country in just the same way as in the West, providing that enough care and effort was invested in making the programme work and ensuring that patients took the medicine. The tragedy was that it had taken 30 years since Fox and Mitchison started their work in Madras to achieve this. Three decades, when much could have been done but was not, largely due to Western apathy.

Formal confirmation of British complacency came in 1986 with the disbandment of the MRC Tuberculosis Unit. Ostensibly the Thatcher Government's rationale was that the unit had completed its research tasks and it was now up to WHO and the developing countries to apply the results themselves. There were also acrimonious internal divisions within the MRC between those wishing to defend the unit and those who wanted it closed and its resources transferred to high technology projects elsewhere in the organisation. Fox was due to retire and there was no obvious candidate of his calibre and scientific eminence available to succeed him and carry the unit's work on further. It was common policy for the MRC to close a unit down on the retirement of its director.[92] Others suspected a hidden agenda of simply wishing to save money, and perhaps a certain disdain for altruistic foreign aid. The combined annual costs of Fox's unit and the laboratory unit headed by Mitchison was £1.5m. Few research bodies have been more cost-effective in terms of the worldwide savings in treatment and drugs which resulted from their research over 35 years.

The MRC owed its very existence to TB research, since the idea of state-funded medical research arose in 1911 from the Royal Commission on Tuberculosis. TB studies accounted for nearly half of its funding grants in 1914.[93]

The former director, D'Arcy Hart, was not consulted over the closure.[94] The decision was as unexpected as it was peremptory for Mitchison, and Fox who recalls: 'No one ever saw the actual piece of paper, but the gossip was that she (Mrs Thatcher) did not favour wasting British money on developing countries.'[95] The result was that the world's foremost centre for TB research was shut down just at the time when its expertise was needed.

By 1987 TB had found a new friend in the Human Immunodeficiency Virus and it was ready to make a big comeback.

Chapter 7

CAPTAIN DEATH RETURNS

The first danger signs came from Africa. Just as it was celebrating its great success, the Tanzanian programme was encountering an inexplicable rise in new cases. Rates in Zambia doubled between 1985 and 1990 and those in Malawi were not far behind.[96]

Despite all the historic fears, TB is a very difficult disease to contract. Those infected with the bacillus have only a 5% to 10% risk of actually contracting the disease and becoming infectious themselves. In the vast majority of cases, the body manages to cope with the intruder, attack it and seal it off. Most people remain latently infected but totally asymptomatic. The advent of HIV changed this entirely. In destroying the body's immune systems the virus lays it open to reactivation of dormant bacilli and any new infection.[97] People with HIV are far more likely to become sick with TB, and unless treated, are likely to pass it on to others. In Africa, and now also in India, TB is the commonest first indicator that a person is HIV-positive.

The advent of HIV in sub-Saharan Africa swamped TB control programmes, which could scarcely cope with their existing workload. It posed additional problems in clinical practice. Diagnosis through tuberculin skin testing and sputum examination became more problematic and, furthermore, TB manifested itself in different forms, away from the more usual and classical sites such as the lungs, lymph nodes, brain or chest wall. It also revealed very unpleasant side effects in one of the common cheap drugs, thiacetazone, which in some cases caused the skin of HIV-positive TB patients to peel off.[98]

At this time the legacy of poor treatment was also beginning to show itself in increasing numbers of patients who had developed resistance to first-line drugs. The USA had failed to follow the examples of Algeria, Tanzania, Korea and its old adversaries Libya and Vietnam, and by 1990 was starting to pay the price in the form of HIV-associated multi-drug resistant TB. Despite long-standing warnings from some quarters and limited successful application in Denver, Mississippi, Texas and Baltimore, directly observed therapy was largely ignored in the USA and only became accepted standard practice in 1993. In New York City TB rates had nearly tripled, less than half the patients who began treatment were cured, and in some hospital and prison outbreaks mortality rose beyond 80%.[99] TB cruelly exposed the deficiencies of fragmented health care in the large cities and the stupidity of the earlier decisions to dismantle public health infrastructure. There was little point in offering the poor, homeless, alcoholic, immigrant and other disadvantaged groups the finest medications in the world without the elementary precaution of ensuring that they were taken.

America woke up quickly to the everyday risk, however remote, that a single cough in the subway or on the sidewalk could infect anyone, whether they were heading for Wall Street or Harlem. The federal TB programme budget was increased more than tenfold, and state and city authorities also made major investments in TB control measures. Since treating a single patient with multi-drug resistance could cost $200,000 and the same sum could provide directly observed treatment for 700 patients, the economic case was unanswerable.[100] Such measures appear to have been

successful. Over the last three successive years notification rates, as monitored by the Centers for Disease Control and Prevention, have dropped, although within foreign-born ethnic groups they are still on the increase.[101]

Similar rises were experienced after 1990 in western European countries before levelling off and falling, but a major component of new infection came from overseas.[102] However, official statistical data can be misleading. Dismantling the US programmes on the basis of apparently reassuring notification figures would invite another catastrophe along the lines of the 1990 disaster.

Well-established surveillance and control measures in the United Kingdom are also not without flaws. Notification rates may be well below actual incidence and screening of incoming refugees and immigrants is inefficient.[103] The actual experience of health visitors and TB nurses, who do the work of contact tracing, suggests further problems. The system does not ensure that all new arrivals from high-risk areas are seen by the communicable disease consultant where they settle and it does not cover illegal entrants at all. Fear that a TB diagnosis may lead to deportation, ignorance about the availability of a simple cure, and social stigma still attached to TB add to existing difficulties.[104]

More worrying for affluent nations in Europe and North America is that relatively little is actually known about recent TB epidemics. Western faith in the efficacy of its health and disease control systems is grounded in their historical record rather than their contemporary or future capability to control infections which can mutate and re-emerge in unexpected locations at any time. Western media reporting also tends to sensationalise certain features such as the threat of multi-drug resistance. As in New York's case, this triggers a rapid political response and a huge amount of dollars and resources are thrown at the problem which then appears to vanish.

But it doesn't. Drug resistance is nothing new. It has been present since the advent of chemotherapy and escapes wider attention only because it is self-limiting. Sufferers disappear because they die. In this context, blaming HIV alone is a convenient excuse. A more persuasive argument in the developed world is that it is merely a catalyst for more rapid transmission of TB. Hence, addressing the needs and problems of refugees, immigrants, the homeless, drug addicts, prostitutes and other disadvantaged groups is the real issue - but it is one which wins few votes and grabs even fewer headlines. The underprivileged exist in Tower Hamlets as well as Harlem and Tokyo as well as Tashkent. Every city has its underclass.

Good TB control programmes are usually associated with socialised health systems which discourage private practice and provide adequate drug supplies free to patients. A measure of administrative and organisational efficiency is also essential. The republics of the former Soviet Union met these criteria but evolved a system of treatment unique to themselves. It was, and still remains, heavily reliant on the use of BCG as the main form of prevention (a practice adopted only by some countries in western Europe and never attempted on any significant scale in the USA); extensive use of mass X-ray screening; hospitals, sanatoria and surgical intervention; and use of single drugs or dual combinations adapted to suit each individual patient. Little or none of the research which developed and modified chemotherapy in the rest of the world filtered through. Mortality rates were higher than in western Europe, although there was scant evidence of any additional impact as a result of HIV infection at the start of this decade.[105]

Economic dislocation, civil war and increasing levels of poverty in the wake of the collapse of the Soviet empire, however, have made an impact. TB in Russia has

risen by 40% in the last four years.[106] Rates are higher in Siberia where there are also significant problems of drug resistance, a result, at least in part, of a breakdown in drug supplies.[107] A team from the British medical charity MERLIN (Medical Emergency Relief International) went out to Tomsk in 1994 to offer an alternative and less expensive model based on short-course chemotherapy, assistance in developing laboratories for sputum testing, and enough drugs to last for three years.[108]

Across the world the resurgence of TB in the 1990s ruthlessly exposed the inadequacies of health care systems in every country.

In the Indian sub-continent, problems have developed on a scale of magnitude unknown elsewhere. TB had an indirect role in the establishment of the partition of the Raj in 1947. Jinnah, the Moslem leader, had been diagnosed as having advanced pulmonary TB in June 1946, but this was kept a closely guarded secret, particularly from Nehru, Gandhi and Mountbatten. Had they known, they might have planned their negotiating strategy differently. Jinnah managed to hold on for a year after partition, latterly trying desperately to get hold of some streptomycin.[109]

Gandhi's vision was for the health service to develop along traditional Indian, rather than Western, lines, with responsibility going back to small communities and individuals. This did not materialise, as a joint report in 1980 from the Indian medical and social science research councils indicated: 'The imported model of health services is top-heavy, over-centralised, heavily curative in its approach, urban and élite-orientated, costly and dependency creating. The serious shortcomings of the model cannot be cured by small tinkerings or well-meant reform.'[110]

It was difficult enough for the Edinburgh group to achieve its goals in a compact city with a population of around 500,000 but this was as nothing to India with 1,600 times that number sprawled across a vast subcontinent. The Prime Minister Pandit Nehru opened a National Tuberculosis Institute (NTI) in 1960. Its brief was to set up a National Tuberculosis Programme (NTP), train its staff, initiate research, and later monitor its operations. The fact that it was in Bangalore, 220 miles away from the Tuberculosis Research Centre in Madras with which close working links were essential, did not augur well for the future.[111]

The NTP itself proved woefully inadequate. By 1994, more than 100 of the 496 districts still had not implemented a TB programme. In those that had, training and supervision were poor and they were failing to reach rural populations.[112] These shortcomings were matched in the NTI itself which was unable to recruit key staff and by serious doubts about the quality and efficacy of drug preparations.[113]

India, which had shown the world how to use chemotherapy correctly, proved shockingly incompetent at delivering these benefits to its own citizens, despite a pharmaceutical industry and health resources which would be the envy of other developing countries. Some studies showed 40% mortality after five years on standard drug regimens treated at home against a 50% chance of death, if untreated. This perhaps also explains lack of enthusiasm to complete standard drug courses by as many as 80% of those who started on them[114] and the marked preference by patients in India to go first to private doctors rather than rely on free services offered by the state.

A study of the prescribing habits of private general practitioners in the slums of Bombay, a mixture of both Western trained doctors and those qualified in indigenous systems, revealed a grim picture. The 100 doctors involved prescribed no less than 80 different regimens based on two or more of the five major drugs. Only four actually conformed to one of the six standard recommended regimens. As well as

giving more powerful drugs inappropriately and continuing treatment long after it was necessary, such indiscriminate prescribing sows the seed for potentially disastrous drug resistance. Moreover, patients were not supervised in taking their medications. In addition to doctors' fees, they also paid twice the going rate for their drugs.[115]

Given the inadequacies of the government's TB control programme and the fact that it does not cover private practice which is preferred by patients, it is no wonder that standardised treatment has failed in the country that spawned it. Nor does Pakistan fare any better: a similar picture of irrational treatment and failure to use sputum examination in diagnosis emerged from a study in Sindh.[116]

The cumulative result of all these failings is continued mass misery: one TB death is recorded every minute in India, which means one grieving family without a father, mother, wage-earner, carer or child, a lingering morbidity and stigma for sufferers, particularly women, like these three from the Pune district in Maharashtra:

> Laxmi, Shantabai and Vuvarna were all TB patients who had been deserted by their families by marriage as soon as they knew them to be suffering from TB and in the case of Vuvarna, in spite of her brother-in-law also having the disease. In Laxmi's case the decision was forced by financial rather than social reasons. Her husband had exhausted all his resources trying to get a diagnosis for her illness and when finally told she had TB, he had no money left to treat her. Shantabai, a fifty year old woman, had to face the ignominy of being sent to her brother's house by her own grown-up son on the premise that a woman's treatment cost has to be borne by her maternal family.[117]

Disillusion with control models from the top have shifted ideas back to the Mahatma's original vision of community-based solutions, particularly in rural areas. One experimental programme in Bangladesh, has achieved notable success in keeping patients on treatment regimens. It is based on village health workers, *shebikas*, usually young women, who receive basic medical training and ensure patients receive and take their drugs. Patients have to put down three days' wages ($3) half of which is returned if they complete the 12-month course. The *shebika* also receives a financial incentive both to identify positive sputum cases and maintain treatment to its conclusion.[118]

If Gandhi had lived longer he might have been disappointed by the results of treatment in his own country but he undoubtedly would have expected better in his erstwhile home, South Africa. With an annual budget of $100m for TB control (enough to have a decent stab at treating all active cases in the entire African continent), with a long tradition of highly sophisticated medical services based on European models and at the forefront of current research into new treatments, one might expect that it would deserve an accolade as the jewel in the crown of TB therapeutics.

Not so. Alarming reports towards the end of June 1996 told a different story. Not only was South Africa's notification rate the worst in Africa, it was also the worst in the world, reaching in a nation of 30 million people the horrific levels previously recorded among small communities of Maoris and American Indians some 60 and 120 years earlier. Parts of two adjacent suburbs in the Western Cape Province, Ravensmead and Uitsig, have incidence of 3,000 cases per 100,000 of population, almost one house in every three reporting at least one case of TB in the previous decade. DNA fingerprinting of the strains involved suggests this is reactivation of old latent disease.[119]

The announcement of South Africa's overall rate of 310 per 100,000 people (three times as high as Tanzania's) was the result of a six month review by WHO officials, the SA Department of Health and a team of international experts. Dr Donald Enarson, scientific director of the IUATLD, was prompted to remark: 'I have investigated the TB situation in over 150 countries, and South Africa's epidemic is the most frightening situation I have ever encountered.'[120]

Unpublished WHO estimates suggest that if the situation is left unchecked, some 3.5 million South Africans, more than 10% of the entire population, will not simply be infected but actually get sick with active TB within the next decade. Published data suggest an equally frightening existing scenario: 140,000 people became ill with TB last year. Of these 2,000 were resistant to both isoniazid and rifampicin and mortality in this group was 80%. 'In many ways, multi-drug resistant TB is much more frightening than AIDS since you can protect yourself from AIDS by avoiding unsafe sexual behaviours. But there is virtually nothing you can do to protect yourself from TB, as the primary risk factor for acquiring TB is simply breathing,' Enarson added.[121]

The review was ordered by Dr Olive Shisana, director-general of the Department of Health, in the wake of increasing concern of an epidemic which is associated with increasing HIV infection. Its genesis, however, was in the TB policy administered by the Nationalist Government during the apartheid years. The explosion was entirely predictable, even without the accelerator of AIDS, and indeed it was predicted in 1989: 'The current push by conservative whites for strong segregation and stiffer laws aimed at controlling the spread of illegal squatter communities would seem to indicate that a 1950s-like exercise is in the offing. If this course is chosen, the next generation of South African leaders, whatever their political or racial complexion, is likely to face an even greater epidemic of the *white plague*.'[122]

Far-sighted public health officials like East London's medical officer of health saw it coming some sixty years earlier: 'The well-being of one section of the community, whatever its colour, is of necessity dependent upon the well-being of all other sections, whatever their colour . . . We have now reached the stage where 'development along their own lines' would produce merely a black reservoir of tuberculosis, venereal disease and typhus, which from time to time would overflow.'[123]

The diamond and gold mines which underpin the economy also provide a reservoir for TB and its wider transmission. TB rates among mineworkers have historically been at least five times the national average. They fell progressively between 1910 and 1935. Diet and working conditions during the interwar years improved as a result of a threat of Government sanctions against the mine owners in 1913. Even so, malnutrition was common. Despite falls in scurvy rates, outbreaks at the Randfontein gold mine in November and December 1926 led to 84 cases and three deaths from scurvy.[124]

Economic segregation between the races was transformed after 1950 into a political credo. Demography, migration from the north and the relatively recent arrival of TB in Southern Africa all may have made substantial contributions to current epidemics but apartheid did nothing to address the underlying causes of the disease among blacks: poverty, overcrowding and malnutrition. Nevertheless, perhaps prompted by white fears, the Nationalist Government tripled the number of TB beds for blacks between 1952 and 1957. Even then, with notification rates among blacks ten times those for the white population, there were proportionately three

times as many beds available for whites as for blacks and a huge backlog of African patients waiting for admission. Most black workers lost their jobs once diagnosed and in the absence of adequate social welfare provision, the imperative to return to work overrode the therapeutic need to complete drug treatments. Moreover the apartheid system, the Group Areas Act, and dependency on migrant labour were quite inimical to efficient contact tracing and chasing up of defaulters.[125] Banishment to homelands, the so-called independent Bantustans, merely shifted the infections away from white suburbs and the eyes of statisticians, a great disappearing act which accounted for the decline in official South African notification rates. More recent studies have shown the previous shambles of treatment in areas like Zululand where fewer than 20% of patients actually completed treatment. The development of community-based programmes, under proper supervision by both medically trained and untrained workers, has shown that treatment completion rates of 90% are achievable.[126]

South Africa is unique in another sense that both its temporal and spiritual leaders after the transition from apartheid, President Nelson Mandela and Archbishop Desmond Tutu, literally bear the stigmata of TB in their own lungs. Mandela contracted TB in 1988 on Robben Island. The overcrowding and the general atmosphere of prisons have always favoured the spread of TB and he became the first black patient at the luxurious Constantiaberge clinic near Pollsmoor.[127] Tutu was sufficiently supportive of WHO's World Tuberculosis Day in March 1996 to lead a commemorative service in Cape Town.

The external members of the review team found it very difficult to persuade senior health officials of the scale of the disaster facing South Africa.[128] Perhaps the blinkers on parts of the white South African medical establishment which led to other ethical, epidemiological and clinical oversights during the apartheid era are still there.

All along, TB had never recognised any racial barriers.

Chapter 8

FIGHT BACK

The advent of HIV sounded alarm bells in 1989 and for the first time galvanised the international community into devising an effective and co-ordinated response to TB. There was a lot to do. Neglect at the WHO had reduced its entire TB monitoring and control operation to one man and his dog - without the dog.[129]

Major investments by WHO and the establishment of a strong TB programme were accompanied by reawakening of epidemiological interest at Harvard. Rather than rely on crude mortality figures, researchers developed a more sophisticated econometric model, DALY (Disability-Adjusted Life Year), which measures health life years lost as a result of premature mortality and those lost as a result of disability. This was considered a far more useful indicator of the actual burden imposed by disease. A survey of 47 treatments revealed TB chemotherapy to be one of the most cost-effective health interventions in the world.[130]

WHO, meanwhile, adopted the model of supervised short-course chemotherapy, coined a catchy new acronym DOTS (Directly-Observed Treatment, Short-course) and vigorously pushed for its universal application. In essence this is what the USA adopted as standard in 1993 and South Africa with increased urgency in 1996. It was based on the Tanzanian IUATLD treatment introduced by Styblo, which itself was modelled on the earlier trials by Fox and Mitchison. What Styblo did almost single-handedly was lay the foundations for the practical application of a universal TB cure. It was perhaps fitting that the first success was in Tanzania. The much-travelled Robert Koch, who first isolated the bacillus, would have approved. In the days when the country was a German colony, he himself had worked there for some time in the laboratory at Dar es Salaam.

It is curious that 80 years later that support for TB control in the developing world has tended to come from smaller nations rather than the large former colonial powers. This applies to both governments themselves and voluntary groups. During her term as President of Ireland, Mary Robinson attributed the hugely disproportionate resources the Irish people devote to international humanitarian causes to the legacy of their own suffering during the 1847 Potato Famine in which TB played a significant role in despatching the starving hordes.

Ireland is a constituent member of the IUATLD. The United Kingdom is not, although some financial support is channelled from a voluntary group in Scotland. Of the governments of the 'Group of Seven' world's richest industrialised nations only Japan and France have contributed substantially to IUATLD programmes for the developing world. If Germany were to match *per capita* spending by Norway or Switzerland, all the African countries currently without donor partners would have sufficient resources to tackle TB. The cost would be less than that of a single military aircraft.[131]

It was Norwegian and Swiss support which helped replicate the Tanzanian success in Malawi, Benin, Mozambique and Nicaragua. The leading non-governmental organisation has been the Royal Netherlands Tuberculosis Association, KNCV (Koninklijke Nederlandse Centrale Vereniging tot bestrijding der Tuberculose). Unlike others which moved into other areas of chest disease, it stuck to its original

brief and has been the only private body to organise, fund and manage TB control programmes in several developing countries. In 1996 it was active with local health workers in Benin, Gambia, Kenya, Malawi, China, Indonesia and was preparing to launch projects in Ethiopia and Zambia.

FIGURE 10
Three TB patients share the same bed in Benin.
(KNCV, The Hague)

FIGURE 11
A hospitalised TB patient in Benin.
(KNCV, The Hague)

Both in supporting Styblo's research and implementing it in practice, KNCV delivered the DOTS strategy as an example for every developing country to follow. The strategy itself, as currently promoted by WHO, contains five essential elements: a well-designed and managed national programme, adequate and regular funding, uninterrupted supply of drugs and equipment, well-trained staff from the front-line health worker upwards, and a rigorous and accountable monitoring system to record patients' progress.

What this represents is simply good practice, distilled from experience of past successes and failures. Over-ambitious attempts to cover an entire country at the outset have tended to flop. Thus the preferred way is launch pilot programmes which can then show success to others and in the process overcome hostility of officials and medical vested interests in preserving the status quo.[132] The emphasis is on education via self-help rather than coercion and criticism. Each country or region can also adapt the programme to suit local circumstances and resources, so long as the key features remain. Thus one might choose hospitalisation or a district nurse to oversee the first intensive phase of medication whereas others might use a village health worker. What matters is that treatment is supervised. Like justice, it must not only be done, it must be seen to be done.

Critics of WHO argue that it is the World Health Organisation itself which is in need of a cost-benefit analysis which would find it excessively bureaucratic, wasteful and ineffective.[133] However much that might be true of the organisation as a whole, there is little evidence to sustain the charge against its TB programme. Indeed, a feature of the response to the resurgent epidemic has been the remarkable degree of unanimity and collaboration between the various organisations, including the IUATLD, WHO and the World Bank. It is the latter's involvement which has been the catalyst for change and actual application of WHO protocols which previously had attracted worthy plaudits, but in the absence of guidance and finance, could not be implemented in poorer countries.

The World Bank too has long been criticised for its lack of concern for health and the depressive effects of its fiscal policies on developing countries and their health care systems. There are broader signs that not only is it listening but is also prepared to put its money where its ear is, in terms of low-cost loans for health projects, particularly TB control.[134] Nevertheless, there are doubts as to the prolonged effectiveness of this type of fixed-term arrangement in disease control. Hopes that malaria would be eradicated were dashed after it made a comeback when money for control programmes ran out.

The first fruits of the concerted international approach were evident from major programmes in China, covering 12 provinces with a population of 573 million. Results from 112,000 patients undergoing DOTS treatment showed initial cure rates of 90% among new cases.[135] More than 25 developing and middle-income countries have started to use DOTS in addition to a further 20 where it is already well established. However, out of eight million new cases a year, only five million will receive some treatment and just 10% of these will receive DOTS.[136]

This is clearly insufficient to deal with the expected rise in mortality as a result of the epidemic. Past experience suggests it will take at least five years before effective treatment can actually be delivered to the mass of people in a moderately-sized country. India's problems are more acute in view of an anticipated explosion in HIV infection. Successive efforts over the last two years have attempted to remodel the National Tuberculosis Programme so that it is fit to deliver DOTS. A series of pilot

studies are under way, supported by the British Overseas Development Administration and others, before considering extending the programme to cover the entire country. It is a delicate balancing act: leave it too long and the epidemic may prove uncontrollable, but premature intervention without proper regulation could lead to disastrous levels of rifampicin resistance. The dilemma is all the more excruciating since the Government of India faced exactly the same scenario in 1956 over the widespread application of isoniazid. By the end of January 1997 the World Bank had made its decision with the announcement of a $142m loan for TB control in India, the largest single programme devoted to tuberculosis in the bank's history.

Following Osler's example of nearly a century ago, WHO has not been backward at coming forward to explain the horrendous consequences of inaction for the benefit of the media and politicians. Sometimes it gets too excited and a bit careless on detail: according to its annual reports TB mortality among children dropped from 300,000 to 170,000 between 1995 and 1996, which seems unlikely. WHO's own calculations of total global TB mortality are also slightly higher than Harvard researchers' estimates.

These, however, are marginal quibbles. There is a degree of epidemiological consensus on the current crisis: around 3 million people will die from TB this year, surpassing the 2.1 million figure for the earlier peak in 1900. Around 15 million people have active TB and there are 8 million new cases a year. The increase in mortality and morbidity is due to overall growth in the world's population, the advent of HIV and failure to apply correctly the cure which has been available for nearly 50 years. TB kills more adults than all other infectious diseases combined and causes one quarter of preventable deaths in the developing world.

If there are some optimistic signs, there are also many dark clouds on the horizon. All of WHO's eggs are in one basket. Not only is DOTS the only effective way of curing sufferers it is the only effective means of prevention. If it fails or falters, there is nothing else. Even if the strategy achieves its ambitious target to detect 70% of all infectious cases and cure 85% of these, that still leaves a sizeable number of cases untreated and infecting others. It is also subject to two entirely unpredictable forces: the spread of HIV and multi-drug resistance.

Furthermore, DOTS treatment is founded on technology and drugs which are at least 20 years old. Efforts are being made to develop new pharmaceuticals for treatment. Some quinolones have shown anti-TB properties and other drugs may be on the horizon, but any trials are likely to take a decade to complete and it would probably take another decade for any products to become affordable in developing countries. Currently the cheapest DOTS regimen costs around $11 per patient through bulk buying of supplies.

Some interest has been shown in potential vaccines which, unlike BCG, might have universal application and long-lasting efficacy. A British biotechnology company, Stanford Rook, has high hopes for its *Mycobacterium vaccae*, cultured from soil samples found in Uganda, and this is undergoing trials in South Africa. In May 1996, however, its managing director resigned, reportedly because of his doubts over claims on its behalf.[137] In 1993 Glaxo Wellcome set up an international research programme, Action TB, providing £10 million over five years to groups working in South Africa, England and Canada. As yet, it has not provided any quick solutions.

Basic research has been sidelined in the understandable rush to develop effective treatments over the last 60 years. We still know very little about the precise relationship between bacillus and its human host, about how and why the body

usually manages to contain it and render it harmless, and what precisely causes it to reactivate. Some clues might have been found in studies on cattle, which have provided much information in the past, but if human TB studies have had the status of Cinderella, bovine TB research has been reduced to one of her pumpkins. It is still unclear why bovine TB is common in certain areas but unknown elsewhere, both within African countries and across the continent itself: this might imply some kind of environmental influence.

Bovine TB is also remarkably versatile, having been identified in the Arabian oryx, buffalo, bison, badger, possum, llama, camel, wild pig, antelope, and almost every domesticated animal including man. In 1993 an HIV-positive patient infected five others in a Paris hospital with a multi-drug resistant strain of *Mycobacterium bovis*.[138]

Molecular genetic techniques have been applied to TB including use of DNA profiling to identify particular strains. Researchers also hope to map all the genes in the bacillus by March 1997, if not sooner. This will undoubtedly yield much information for potential therapies but the question remains as to who would want to exploit it.[139] Any potential drugs with general antibacterial properties will have much more lucrative applications than mere TB therapy and a familiar Catch-22 also applies: the countries with the greatest need have the least resources to buy, so the drugs are not taken to the manufacturing stage. Given estimated developmental costs of $100m or more for a new drug of this nature, there is no great surprise at the lack of any significant progress. Different methods of delivery of drugs have also been tried, including a depot system where long-term medication can be provided in one dose, but these remain unproven.

The net result is that, barring a freak breakthrough, the likelihood is that the world is going to have to face a growing epidemic with the cumbersome therapeutic tools that it has at present. Almost every aspect of detection and treatment is problematic. For all these reasons, a successful campaign against TB looks unlikely over the next decade. We will do very well just to hold the line. Therein lies the most compelling argument for funding DOTS programmes: the alternative of doing nothing is too dreadful to contemplate. As the next millennium approaches, the very least mankind can do is to use the weapons it already has to fight the bacillus. Otherwise, the war is lost completely.

CONCLUSION

One does not need to be too much of a cynic to argue that the only reason affluent countries rediscovered their concern for this forgotten disease was self-interest. TB showed that it could strike again, anywhere, at random and with devastating effect. WHO's current slogan, *There is no hiding place*, is spot on.

Demographic changes and the revolution in air transport spell the potential of universal transmission and it comes equally easily via Club Class in a 757 as in an overcrowded, leaky boat. With an estimated 500 million people crossing international boundaries by air each year and at least 50 million refugees and displaced people in the world, the reality of widespread transmission of infectious diseases is with us already.[140] In the case of TB, all it takes is a cough or a splutter to release drug-resistant bacilli for which there is no cure. If the epidemic proceeds unchecked, there will be a need for exclusion facilities to protect against wider infection. We could even call them sanatoria.

A cynic in 1950 might have predicted the sorry saga which ensued. Humanity came off the Magic Mountain, developed the Magic Bullets to kill the Magic Dragon – but ended up slaying itself. It is never easy to ascribe causes to epidemics of apathy, indifference and neglect. Assuming that governments act on the will of the people and that international organisations act in accordance with governmental wishes, we must all share the blame. This study has attempted to show that the relationships were far more complex, particularly in the inter-reaction between the affluent and poorer countries. It was the latter which provided the assistance and certainly the example for the former. To the developed world's shame, it offered virtually nothing in return.

By its nature, however, this study has also concentrated more on the role of doctors who have had the lead part in the tragi-comedy of TB treatment. The epistemological framework of modern medicine was developed both as a result of and alongside tuberculosis chemotherapy through the introduction of the randomised controlled trial. If the streptomycin trial was not actually the first, its success certainly ushered in the new era of scientific medicine.

The age of antibiotics encouraged a culture of doctor-dependency and an undying faith in the power of scientific medicine to solve all problems with a pill. The actual impact of scientific medicine on improving health may have been grossly exaggerated.[141] It could also be argued that most infectious diseases were petering out on their own by the 1950s and that their later resurgence was not due to antibiotics and their misuse but rather to the explosion in world poverty.

In choosing the controlled trial as its intellectual foundation, however, medicine laid itself open to the risk of being hoist with its own pétard. Physicians may have accepted the concept of proven treatment but many were less keen on following the resultant standardised protocols. Poor doctor compliance by Western doctors has been well documented. Indeed it probably is more important to follow standard regimens in countries like the UK and Switzerland since low TB incidence means physicians see far fewer cases and therefore expertise is lacking.[142]

The spread of multi-drug resistant TB worldwide has been largely iatrogenic. Treatments are initiated by individual doctors or through tuberculosis programmes designed by doctors. As a result of their failures, TB has, in some cases, become incurable. It could be argued that if patients fail to complete treatment or do not follow instructions, the fault lies with themselves. Such a view is tenable if a narrow

view is taken of the physician's function: that in essence he simply has to hand out prescriptions and advice. If so, pharmacy should beckon as a more suitable career. Unsupervised therapy may work with an educated and disciplined group of patients but it had disastrous consequences in the United States and much more so in India. The ethics of entrusting powerful drugs to patients, knowing full well the consequences of failure to observe strict adherence both to the individual patients and the wider public health, are extremely questionable. But this is exactly what happened.

It is easy to blame poor compliance on patients themselves, but such an argument is specious. Failure on their part to take medicines as directed is as old as medicine itself. So too is the pressure from patients on the physician to provide any kind of treatment, the public's insistence on 'being poisoned', as the American poet and physician Oliver Wendell Holmes once described it.[143]

Perhaps doctors need to rethink their role. Perhaps society expects too much from them.

In this context, criticism of simplistic media coverage, usually in terms of brave doctors in search of medical breakthroughs, medical historiography which sometimes borders on hagiography, and, above all, a broader culture which falls over itself to support the mythology of scientific medicine, is probably justified.

The idea of standardised treatment did not rule out the wider role of compassion, understanding and treating patients as individuals. If they had TB, they were certainly in need of such consideration in view of the social aspects of the disease. The classical medical rubric *guérir quelquefois, soulager souvent et conforter toujours* places actual cure within a context. It was such an holistic approach which characterised the Edinburgh group's treatment in the 1950s. In Crofton's scheme, it started with civility by the doctor standing up and shaking the patient's hand on arrival and ended with writing letters late at night to try and find a job for the cured but still stigmatised individual. In Madras, Fox followed exactly the same precepts. A TB control programme could never be imposed on a reluctant population. It was only through close and careful collaboration with communities and a range of other health workers, but above all with informed and co-operative patients, that it could work.

Poor treatment may sometimes be the result of greedy private practice in that continuing with successive drugs prolongs therapy and therefore fees. A potential constraint, particularly in the Indian subcontinent and in the United States, is to resort to the law and sue the doctor concerned for the consequences. Doctor compliance would certainly be reinforced if judges recognised clinical freedom as a contributor to, or actual cause of death, and imposed an appropriate financial penalty.

The overriding lesson from TB therapy is that valid medical interventions are by themselves utterly useless and potentially lethal, unless properly supervised and effectively delivered.

Paradoxically, the intellectual edifice built on the randomised controlled trial flourished as TB disappeared from the curricula of Western medical schools and the agenda of medical journals. Those specialists and public health doctors who retained an interest in tuberculosis were marginalised. TB conferences still have the occasional air of unreality, even of colonialism, in both senses of the word, evinced by a patronising view for the problems in developing countries and a collective sense of self-righteousness apart from everyday life. Pompous utterings before well-lunched colleagues at a smart conference centre about the failure of the media and politicians to follow the speaker's own well-thrashed hobby horse do little good for the poor patient.

Mainstream medicine and surgery, meanwhile, was heading up a different path, far removed from both ordinary medical practice and patients. The boom in medical publications based on reporting of randomised trials shows no signs of abating. Publication in one of the more respected of the estimated 22,000 biomedical journals around the world is deemed essential to further a doctor's career. The volume is such that errors in methodology and interpretation and reporting go unchecked, prompting calls for less research, better research and research done for the right reasons.[144]

For the public there are many legitimate but unanswered questions about the relevance and effectiveness of the medical research which it pays for. Why, for example, despite the million randomised controlled trials on every treatment under the sun, which followed the initial ones on TB chemotherapy, have we not actually applied the cure for TB? How is the average hospital physician or general practitioner supposed to keep up with all this outpouring of information? The underlying impression is that the early TB trials spawned a monster of uncontrolled research activity using the rationalistic principle of controlled trials. Trials undoubtedly have an essential place in shaping medical practice, but patients do not get better on statistical confidence intervals. Evidence-based medicine can never work if a significant minority of doctors deem it inadmissible at the outset.

The information glut in Western medicine is only one symptom of the divide between affluent and poor countries. Whereas the West may look at how MRI or other sophisticated diagnostic tools might be applied to a rare form of TB, the developing world is still waiting for microscopes to do basic sputum testing. Similarly, efforts to find second and third line drugs might be considered misdirected when many parts of the world are still awaiting their first delivery of isoniazid. Some efforts have been made to redress this imbalance. Fred Miller, Crofton and Horne have produced a non-technical and easily readable guide to clinical TB designed to be freely available and used by village health workers as well as physicians.[145] The passive tense is banned. Active efforts against TB are favoured by linguistically active usage. And in the right language. Already it has been translated into Chinese, French, Spanish, Arabic, Mongolian, Portuguese, Thai, Vietnamese, Turkish and Farsi. Editions in Russian, Indonesian, Italian, and Urdu are in the pipeline.

The principal driving force behind the work of Styblo, Mitchison and Fox was the hope of finding cures which the Third World could use. Instead of learning from clinical trials, western medicine became obsessed by methodology, as opposed to their usefulness and application. Review articles and computer searchlines offer ways of collating information and presenting it in a digestible form. A new international initiative, the Cochrane Collaboration, has started producing systematic reviews of randomised controlled trials, which are updated on computer disks. The design of its logo is based on the failure to apply the benefits of corticosteroid treatment for women giving birth. Despite trials which proved the technique's worth, no systematic review was carried out for 17 years and it was not brought into everyday obstetric practice. Tens of thousands of babies may have suffered or died as a result.[146]

The collaboration takes its name from Archie Cochrane, the Scottish medical volunteer who went out to join the Republicans in Spain. He later specialised in the epidemiology of TB, having witnessed its manifestations earlier among Yugoslav, French and Russian prisoners in the camps following his own capture in Greece in 1941.

We still have a lot to learn from those doctors who saw TB at first hand and at its most frightful. We are fortunate that many of them are still with us and still at work. Defeating TB will require the kind of enormous effort, good science, pragmatism and ingenuity which they demonstrated 30 and 40 years ago.

For a disease that frequently results from inspiration, there is always room for inspirational leadership.

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