'The Captain of All These Men of Death'

Aspects of the Medical History of Tuberculosis

A thesis presented in partial fulfilment of the requirements for the degree of

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Kenneth Dawson

MA, MSc, MD, PhD, DHSc, FRACP, FRCP(G) FRCPCH.

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Figure 1.   **The Sick Child by Edvard Munch**

Edvard Munch, *The Sick Child,* 1885-86, oil on canvas, (Oslo, Norway: The National Gallery)

This painting is said to reflect the death of Munch's sister, Sophie, who died in 1877 at the age of 15 from tuberculosis. The mother is based on Munch's aunt, Karen Bjølstad. Munch's own mother had died in 1868 also from tuberculosis.

Abstract

Current evidence suggests that some time in pre-history the ancestor of the modern tubercle bacillus evolved from a soil organism into a human pathogen. Since that time it has caused death and misery to millions of human beings by causing the infectious disease we now call tuberculosis.

This dissertation examines some of the aspects of the history of tuberculosis and specifically how it has affected humans from early times not only medically but socially. It looks at mankind's struggle to overcome the disease, those who introduced scientific methods in attempts to halt and defeat the organism and its associated infectious disease. There are descriptions of the effects of the disease on prominent people and how the disease often cut short their productive lives. Stress is placed also on the organism's ability to adapt and survive in a latent form and to develop virulence factors as and when necessary for its own survival. The advent of the co-infection with HIV/AIDS has caused a major setback in control methods and our attempts to halt the progress of the disease and these are factors in the resultant worldwide epidemic of tuberculosis.

Particular importance is placed on the public health measures used in the past and the importance of continued and improved control measures at the community level now and in the future.

The implementation of the knowledge gained about the disease and the organism to date, the avoidance of the errors made in the past, is emphasised if we are to make progress in the future. To totally defeat the organism remains the major goal of public health agencies, medical researchers and social scientists so we can say that, at last, tuberculosis is no longer the 'Captain of all these Men of Death'.

Acknowledgements

*No Man is an Island, entire of itself.*
John Donne (1571-1631)

My wife, Mairi, a registered nurse, has been a major supporter in the production of this thesis. Not only has she acted as a proof reader but a constant source of encouragement, stimulus and common sense. I am, as ever, grateful to her and acknowledge her contribution with thanks.

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Above all I have to give thanks to the doctors and nurses of the former Tor-na-Dee Sanatorium in Aberdeen, Scotland who were responsible for restoring my health and making it possible for me to pursue a career in Academic Medicine and Paediatric Respiratory Medicine and hence ultimately to submit this dissertation.

Preface
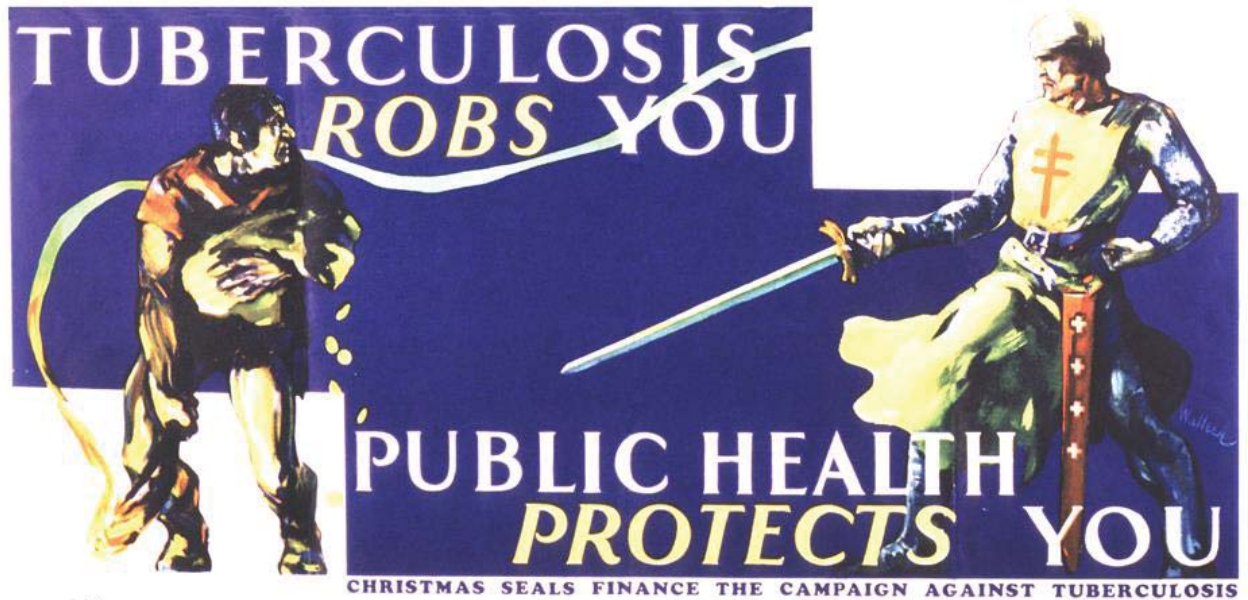
> *'Pasteur worked to protect individuals through immunization, Koch worked to protect communities through better hygiene and Public Health'*
> Blevins and Bronze (2016)

'The Captain of all these Men of death'. 'Under Captain Consumption, he rots away, and dies in sinful security'.

John Bunyan (1680). The Life and Death of Mr. Badman. (Chapter XVIII)

Abbreviations

1. HIV: Human Immunodeficiency virus

2. AIDS: Acquired immunodeficiency syndrome

3. TB: Tuberculosis

4. MDRTB: Multiple drug resistant tuberculosis

5. XDRTB: Extensively drug resistant tuberculosis

6. XXDRTB: Extremely drug resistant tuberculosis

7. WHO: World Health Organisation

8. MTB: Mycobacterium tuberculosis

9. DNA: Deoxyribonucleic acid

10. PCR: Polymerase chain reaction

11. USA: United States of America

12. UK: United Kingdom

13. AAFB: acid and alkali fast bacteria

14. BCG: Bacille Calmette-Guérin

15. PAS: p-aminosalicylic acid

16. MMR: mass miniature radiography

17. IUAT: International Union Against Tuberculosis

18. IUATLD: International Union Against Tuberculosis and Lung Disease

19. bTB: Bovine tuberculosis

20. DOTS: Directly observed treatment – short term

21. WW2: World War Two

22. ART: Anti-retroviral treatment

23. IGRT: Interferon gamma release test

24. ARV: antiretroviral drugs

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Chapter 1   Introduction, Methods and Materials

If men could learn from history, what lessons it might teach us.
S.T. Coleridge (1772-1834)

Chapter 1.1   Introduction

Tuberculosis is a disease that has had a major impact on mankind and has remained a scourge up to and including modern times. Despite this, the disease has captured the imagination of scientists, epidemiologists, artists, humanitarians, sociologists and physicians (Schwartz, 2009). To study the history of tuberculosis, therefore, there must be an examination of the lives of many people drawn from many aspects of life. One must take note of the literature, poetry and paintings that are associated with them and the disease that has affected them. As Thomas Carlyle (1795-1881) has succinctly put it 'history is the essence of innumerable biographies'. No disease, perhaps save leprosy, has run such a protracted course affecting almost any part of the body and giving rise to such a long period of ill health and debility.

The main thrust of this dissertation, while covering some of the many medical aspects of tuberculosis, is not intended to review and detail the vast historical literature that has accrued about tuberculosis but to study the areas of particular relevance to the specialty of Public Health. The thesis is divided thus into two parts. The first part is concerned with the relevant general historical background and includes aspects of the social, cultural and artistic features of the disease that make it so relevant to Public Health. The study features those pioneers of the basic science relating to the disease, those who contributed to its treatment and those who contracted it. In so doing examples of the large output of relevant paintings, illustrations, posters, postage stamps and seals produced on and about the disease and its victims and researchers will be included to illustrate the narrative. This is based upon the established power of visual imagery that can portray events and prevent information overload (Isaacs, 2016). The aim of this part of the thesis then is to outline and demonstrate how terrible the disease tuberculosis is and how it has robbed many people of their full potential and cut short the lives of many ordinary productive people as well as

those with specific talents. It also reflects on the journey towards a possible cure and the hope that the disease could be removed from those affecting the public at large.

Part 2 looks at selected specific historical topics about tuberculosis that are much more relevant to community strategies that have been employed to combat tuberculosis. This is, however, not a disease of the past but one that continues to cause death and chronic ill health globally. It has been given a new lease with the advent of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) as well the development of multiple drug resistant (MDRTB) and extensively drug resistant tuberculosis (XDRTB). The latest reports suggest extremely drug resistant tuberculosis is occurring in Europe (XXDRG) (Migliori et al., 2007). These happenings make the study of the history of how mankind has dealt with the disease highly relevant and hopefully we may learn from the past and as Coleridge outlines in the above quotation and refute the words of Hegel (1770-1831) '...that people and governments learn nothing from history'.

The importance of this disease and the stimulus to this thesis is well encapsulated in the following facts. Tuberculosis due to infection with the Mycobacterium tuberculosis complex (*M. canetti, M. africanum*, *M. microti* and *M. bovis*) accounted for 8.7 million new cases in 2011 worldwide and of these 1.4 million people had died (WHO, 2011). By 2013 this figure had risen to 9 million of whom 1.5 million had died (WHO, 2014). Professor Bloom of the Harvard Medical School has illustrated the extent of the problem in terms of a single country namely, India. Tuberculosis kills one Indian every 90 seconds and between the years 2006-2014, the disease overall cost India in financial terms $340 billion. The problem is compounded by the fact that India has the highest per capita rate of MRTB (Pai and Bloom, 2016). It is thus, an enormous public health problem and a massive global burden. The problems of tuberculosis control have been exacerbated by the emergence of drug resistance as discussed above. These facts make tuberculosis the leading cause of death from a potentially curable disease (Glaziou et al., 2013).

A vast literature about tuberculosis has accrued over the years. This ranges from books specifically written for the general public (Bynum, 2015) to diary records of a patient in a sanatorium in the 1940s (Hurt, 2004), as well as the mass of research reports about the organism and the disease per se (Gutierrez, 2005). In the light of this, it seems more

practical to cite the appropriate literature review in each aspect of the dissertation rather than one very large isolated chapter.

The structure I have employed is to review the information we have to establish initially that tuberculosis is an ancient disease. Thereafter, there will be an overview of the historical aspects of the disease up to the present time. The main essence of the dissertation will be concentrated on the pioneers of research into the disease and those who contributed to advances in knowledge about the condition and especially to those who made therapeutic advances. An important aspect of this discourse will be discussion of a selected group of those well known people drawn from the arts, literature and politics who became victims of the disease. This is intended to illustrate the devastating effects of the condition on humanity and the loss of talent that has ensued. Finally as stated above the remainder of the dissertation focuses on facets of the past more related to Public Health practice.

I have felt it important to illustrate this presentation with as much visual material as space permits. I have thus chosen photographs, art works and posters to accomplish this. In addition, I have made frequent use of postage stamp images. Why postage stamps? Stamps can have impact and present a fresh approach to subjects and objects. Postage stamps have also now established themselves as very useful objects for educational purposes (Nuessel, 1996). Many stamps do contain semiotic messages but this role here is intended only to be of secondary importance. However, stamps are now accepted as part of popular culture and as they cover a vast range of subjects they can provide a useful alternative method for illustration (Child, 2008). They have had a major role to play in propaganda and have been used extensively to raise funds for tuberculosis charities. Countries such as Belgium, Finland, the Philippines and the Dominican Republic have produced such stamps annually for a period of over thirty years. In addition, Christmas seals linked to anti-tuberculosis appeals are another method to raise funds and advertise the cause. Their role will be discussed in regard to the sanatorium movement.

Art works and especially paintings provide a potentially rich source of information and illustration with regard to the disease. This is well exemplified by the frontispiece (figure 1).Tuberculosis had a major impact on the life of the Norwegian artist, Edvard Munch, as he lost both his mother and sister to the disease. His famous painting of the *Sick Child* reflects

this as do his works labelled *The Scream*. The effects of the disease on the work of other painters such as Watteau and Beardsley will be discussed later in the dissertation.

We need to look, therefore, beyond the medical writings to see how the disease, 'consumption', affected people. Chalke (1962) states that more information can be gained by studying biography and contemporary literature and especially painted portraits of the appropriate time periods (figure 2). In other words to understand the historical significance of the disease we need to look not only at the medical facts but the social experience.

Figure 2. *The Head of Medusa representing Tuberculosis*, Basel 1913, lithograph
Welcome Institute no. Loo34019

Chapter 1.2   Methods and Materials

Nothing is so hard that a search will find it out
Robert Herrick, 1591, Seek and Find

The initial thrust of the literature research involved searching the website of the United States National Library of Medicine at the National Institute of Health (PubMed). Citations which were linked to 'history and tuberculosis' and 'tuberculosis and therapeutics' were sought and then selected. Thus a vast number of citations were obtained in the first

instance and these were refined to those deemed of specific relevance to the project. The original papers were obtained and read as appropriate. Thereafter, additional information was obtained from the Turnbull Library, Wellington and the Wellington Central Library. Further material was gathered from the Medical History collection of the libraries of the Royal Australasian College of Physicians in Sydney, Australia and the Royal College of Physicians and Surgeons of Glasgow, Scotland. This access was possible because of my being a Fellow of both Colleges.

Reproductions of pictures, drawings, posters and paintings have been obtained from a wide range of sources and each of these is acknowledged beside the respective figures. The Curator of Posters at the Museum of New Zealand (Te Papa) supplied me with one image as it was not otherwise available on the public domain. Each image was scanned using a Brother MFC 9340CDW Scanner and was graphically manipulated, as necessary, using the Adobe Photoshop Elements 7 program (Adobe Systems) to form a jpeg image.

The finding of relevant postage stamp images was more involved. Reference was made to the Stanley Gibbons Simplified Catalogue of Stamps of the World (Stanley Gibbons Ltd., Ringwood, UK. 2015). These volumes list over 500,000 stamps plus hundreds of images and from this listing a search was made for appropriate stamps. An additional check was made by consulting the Smithsonian Institute's National Postal Museum in Washington, USA[1]. Their website allows access for research into postal and stamp matters. This was, therefore, consulted for additional information and relevant stamps. Once identified the stamps were obtained from either e-Bay, stamp dealers and/ or stamp fairs. Thereafter, once purchased they were scanned and manipulated in the same manner as the art works and posters.

The material for the section on R.L. Stevenson's home at Vailima, Apia, Samoa was obtained during my visit there. The photograph of the house was taken with a Nikon 1500 Digital Camera.

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[1] www.postalmuseum.si.edu

Part 1:   The Historical Background
Chapter 2   In the Beginning

The Lord shall smite thee with consumption and with a fever and with an inflammation....and they shall pursue thee until thou perish.
Deuteronomy 28:2

Paradoxically, the sequencing of the genome of *Mycobacterium tuberculosis* (MTB) in 1998 proved to be a key event that has enabled investigators to gain insight into the early history of tuberculosis. The sequencing of the genome of has cast new light not only on the origin of the human disease, tuberculosis, but also upon the origins of the genus. It had been postulated that the genus Mycobacterium originated some 150 million years ago (Hayman 1984). Gutierrez et al., (2005) concluded that the earliest progenitor of M. tuberculosis was present in East Africa some three million years ago. This estimation and calculation is based upon the slow mutation rate of the organism. The current strains of MTB appear to have had a common ancestor about 15,000 – 20,000 years ago. These strains probably diverged from their common ancestor between 250 – 1,000 years ago (Gagneux et al., 2006). Comas et al. (2013) analysed the whole genomes of 259 MTB strains and used the data to characterise their global diversity and to reconstruct the evolutionary history of the organism. They concluded the MTB emerged some 70,000 years ago and moved out of Africa as human populations expanded and migrated. Eventually, these populations carried the organism around the world as humans explored, traded and conquered. Gagneux (2012) examined the paradox that while MTB is a very effective killer to its human hosts, it still manages to survive. The explanation for this is that the organism developed the ability to remain dormant and re-emerge decades later. It had also developed an ability to have a hypo-inflammatory effect upon the macrophages. Gagneux postulates that the recent success of MTB may be due to modern variants having changed and thus acquired a high virulence and also a short latency period. Further genomic analysis of the smooth tubercle bacillus has provided insights into how this virulence adaptation mechanism may have been achieved (Supply et al., 2013).

The evolutionary success of MTB genotypes may be due to the wide demographic expansions of humans suggesting that co-habitation led to mycobacterial evolution and the

eventual development of bacterial virulence. If these migrations had not occurred humans would have counter-reacted to minimize virulence by co-evolution. This feature may be defined as adaptive changes in the host as well as the pathogen (Brites and Gagneux, 2015).

Wirth et al. (2008) have added very important information, by using the technique of tandem repeat sequences, they have shown that the MTBC consists of two clades[2], one composed exclusively of *M. tuberculosis* lineages from humans and the other of mixed human and animal lineages. Their findings support the hypothesis of an original human host rather than an animal one. This study rebuts the former claim that there was a bovine origin to human tuberculosis. In this study, they provide genetic evidence indicating that the most common ancestor of the bacterial complex emerged some 40,000 years ago from its progenitor in East Africa. This is the region from where modern human populations disseminated around the same period. This initial step was followed 10,000 to 20,000 years later by the radiation of two major lineages, one of which spread from human to animals. In more recent years (approximately 180 years ago), coinciding with the human population explosion and the industrial revolution, the human-associated pathogen lineages have strongly expanded. These results thus reveal the strikingly parallel demographic evolution between humans and one of their primary pathogens.

Some 17,870 years ago, a bison, of a now extinct species of the Pleistocene era, fell to its death. The animal had fallen 30 metres into a chamber of the Natural Trap Cave in Wyoming, USA. In doing so the animal joined many others who had met the same fate as they travelled along an established game track. When the bones of the animal were found in the present times it was noted that they had pathological changes in keeping with osseous tuberculosis. Carbon dating confirmed the age of the bones and polymerase chain reaction amplification (PCR) of material from the lesions determined that they had been caused by an organism belonging to the Mycobacterium tuberculosis complex (MTBC). This important discovery, documents that TB infection occurred, in a now extinct animal and it is the oldest record of TB yet discovered. Further analysis of the DNA used spoligotyping[3] and sequencing distinguished the organism from modern MTB and from modern *M. bovis* and from non-MTBC mycobacteria.

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[2] A group of organisms evolved from a common ancestor.
[3] Spoligotyping – 'spacer oligos'- PCR amplification of 43 non-repetitive short spacer sequences.

These findings are in keeping with the hypothesis that animals were first to cross the land bridge at the present day Bering Strait bringing with them the disease TB. It is also in keeping with the idea that TB was in North America before the first human settlers arrived (Rothschild et al., 2001). Daniel (2000) has provided evidence to support the contention that the Asian immigration to the Americas was 10,000 or even 20,000 years ago and these people brought TB with them. It persisted in small dispersed social groups for thousands of years. However, an epidemic occurred some 1,500 years ago. Eventually, this subsided well before the arrival of the first Europeans. MTB was then re-introduced with their arrival. Daniel (2000) again reiterates that the evidence now points to the fact that the animal form, *M. bovis* was not the cause of the infection. In the context of the Americas, the earliest proven TB was in a pre-Columbian Peruvian mummy (Salo et al. 1994) and subsequently eleven other pre-colonial sites with skeletal remains have shown evidence of TB. This has been by PCR amplification, acid and alkali staining of the bacilli (AAFB) and or pathological findings in the bones. These findings date from 1,000 years ago (figure 3).

Bos et al. (2014) have added a further dimension to this debate by their examination of one thousand-year old skeletons from Peru. Examination of mycobacterial genomes extracted from these skeletons revealed a distinct form different from the known human adapted forms. These were more closely related to those adapted to seals and sea lions. The group suggest that their findings implicate sea mammals playing a role in transmitting the disease to humans across the ocean.

The earliest confirmed humans with proven TB come from a finding of skeletal remains of a mother and her child at Atlit-Yam. This is a now submerged pre-historic site several hundred metres off the current shoreline and at some 10 metres below sea level. It is one of the first sites with evidence of agriculture and animal domestication and dates from 9,250-8,160 years ago. The nearest current population centre is Haifa in Israel. The rib and long bone samples obtained showed changes of hypertrophic osteoarthropathy and extensive bone remodelling and these were in keeping with TB infection. DNA was obtained from these bone lesions and PCR examination revealed five genetic loci for MTB. Thus the finding of MTB genetic material in keeping with present day MTB supports the theory of the long-term co-existence of this pathogen with the human host (Hershkovitz et al., 2008).

There is mounting scientific evidence that TB was present in much of the world before large scale recent colonisation took place. The study of Zink et al. (2003) characterised MTBC from Egyptian mummies obtaining ancient DNA from tuberculous lesions. Their findings showed the presence of MTB and *M. africanum*. This work further rebuts the role of *M. bovis*. Indeed, they support the concept that the precursor complex to current MTB was from *M. africanum*.

Similar laboratory identification of human MTB infection has come from Korea and Japan from 1st Century remains. Chinese MTB DNA has been found in 2,000 year old Chinese populations and Iron Age people of Thailand (Geffin, 2011).

Figure 3.   Mayan figurine depicting a tuberculous spinal kyphosis
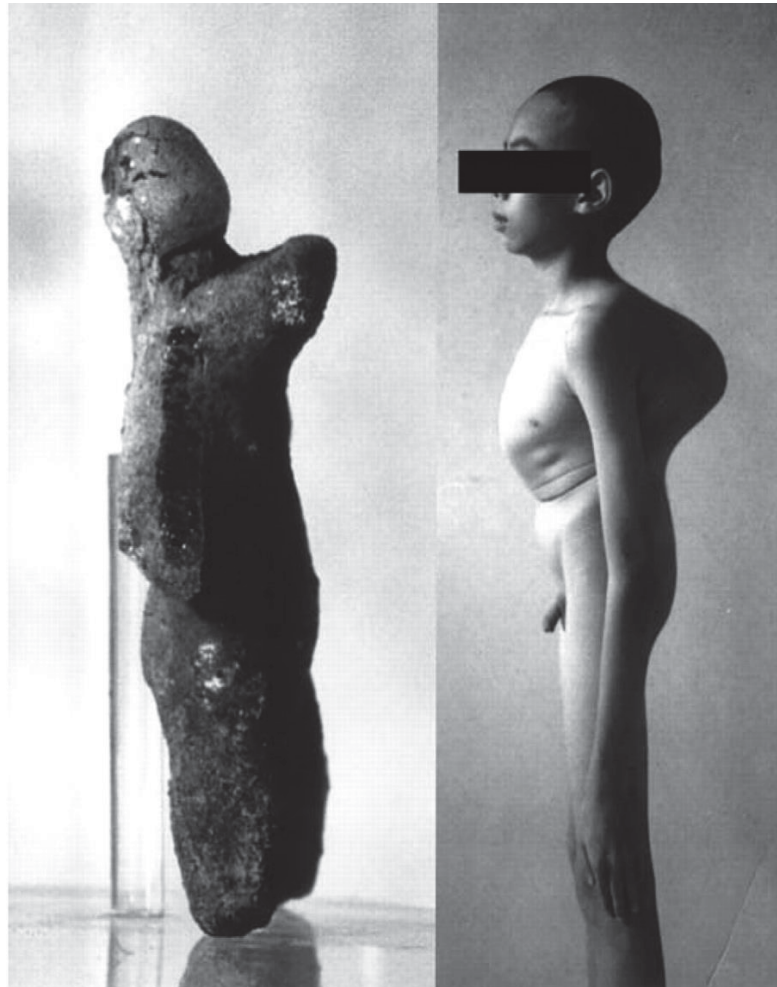
On the left, a Mayan terra-cotta figurine from the postclassical period (900–1521 C.E.) discovered inside the Temple of the Seven Dolls at the Dzibilchaltun archeological site in Yucatan, Mexico (photograph provided by and published with the permission of D. Trejo, Museo del Pueblo Maya de Dzibilchaltun, Instituto Nacional de Antropología e Historia). The boy on the left shows a characteristic kyphosis and gibbus formation associated with spinal tuberculosis as does the terracotta figurine.
Picture reproduction permitted for teaching and learning purposes.

Chapter 3   The Era of Phthisis and Consumption

Consumption was the most considerable of the diseases which then prevailed and the only one which proved fatal to many persons
Hippocrates of Cos (460-370 BC)

Chapter 3.1 The Early Years

Hippocrates is often credited with being the founder of Western Medicine (figures 4, 5). He used the terms 'phthisis[4]' and 'consumption' for the disease we now call TB. These terms continued to be used right through to the 18th Century. Hippocrates describes the disease as a 'weakness of the lung' in his Book 1 of the Epidemics (410-400 BC) (Frith, 2014). He describes the clinical features which included sweats, rigors, sputum production and its predilection for young adults. He states further that there is a high prospect for death for those with the disease. While still recognising that phthisis is highly contagious, by advising physicians not to contact those in the final stages of the disease, he still considered it, however, an inherited disorder (Hertzog, 1998). This contrasts with the views of Aristotle (384-322 BC) who believed phthisis was a contagious disorder (Hertzog, 1998).

The hereditary basis for the disease was further dismissed by two later physicians. The first was Caelius Aurelianus, a Roman physician, who wrote detailed clinical descriptions of TB after studying patients with consumption and by doing so established in his mind that there was an infectious nature to the disorder.

Galen of Pergamum (c 120-201 AD) (figure 4) was a Greek physician who moved to Rome in 162 AD and later served as physician to the Roman Emperors Marcus Aurelius, Commodus and Septimus Severus. He further established the infectious nature of phthisis and warned in his writings of the dangers of intimate contact with consumptives (Boire et al., 2013). He also described the clinical features such as night sweats, fever and the coughing up of blood. Galen stressed that anatomy and dissection were the foundations of medical knowledge. In turn he described tubercles in the lungs of deceased patients and called these findings phuma. He was perhaps the first to do so.

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[4] Phthisis is derived from the Greek word 'phthiein' meaning to waste away or to dwindle -φθϊόϊς

Figure 4. Hippocrates and Galen

Greek Stamps, 1996, Hippocrates on the right, Galen on the left

Figure 5. Hippocrates and an Allegory of Health

Greek stamps of 1934 and 1948-51 respectively reflecting Hippocrates's important place in the beginning of scientific medicine.

Chapter 3.2   **The Middle Years: 'The King's Evil'**

...strangely-visited people,
All swollen and ulcerous, pitiful to the eye.
Shakespeare, Macbeth Act IV, scene 3

The fall of Rome brought a fall in living standards in early medieval times and brought with it an upsurge in disease and especially TB. There is archaeological evidence of this from many sites throughout Europe (Daniel, 2006). Of special interest at this time was the appearance of scrofula or tuberculous adenitis. There are reports from England and France dating from 1066 to the reign of Queen Anne who died in 1714. *M. bovis* was a common cause of scrofula as well as non-tuberculous mycobacteria. Scrofula[5] was also known as the King's Evil especially in England and France. It was believed that a touch from royalty could result in healing of the skin lesions. Special ceremonies were held known as 'touching for the King's Evil' (figure 6). This was based on the concept that the God-given right of kings to rule had given them special abilities. The affected received special coins called 'touchpieces' and these angel coins were often used as amulets. The diarist, John Evelyn, described these ceremonies for the 6th June 1660 (Bohn, 1862).

> *His Majesty began first to touch for evil, according to custom, thus, His Majesty*
> *sitting under his state in the banqueting house, the chirurgeons cause the sick to*
> *be brought, or led, up to the throne, where kneeling, the King strokes their face*
> *or cheeks with both hands*

Meanwhile, in the Islamic World the distinguished Persian physician Avicenna or Ibn Sina (980-1037 AD) had written his Cannon of Medicine (al Qanum fi'l tibb). These writings were in accordance with Islamic teaching and culture and soon spread to Europe in translation. His writings are still highly regarded and his work is credited as being the foundation for the present day concept of Evidence Based Medicine (Shoja et al, 2011). Avicenna recommended honey as one of the best remedies for TB. Interestingly, it has been shown recently that honey, in fact, stimulates inflammatory cytokine production and has other positive attributes (Ahmed et al., 2012).

Europe was now taking a divergent course. On the one hand, people such as Versalius (1514-1564) were carrying out autopsies and correlating these with clinical presentations. Sylvius de la Boc of Amsterdam was producing detailed information about pathological

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[5] Scrofula translates from the Latin – morbis regius or royal disease.

findings on the morphology and pathology of pulmonary tuberculosis. He described details of tubercles in the lungs and other organs. Richard Morton of London published a detailed description of the disease and case reviews in his book *Phthisiologia* (Keers, 1982). It appears that 20% of deaths in London at this time were due to TB. By 1720, Benjamin Martin (1704-1722) had proposed his theory of an infectious basis for the disease.

These activities contrasted with the developing superstitious beliefs that were becoming intertwined with Christianity such as the King's Evil and King's Touch. The Church's religious views tended to dominate the medical world (figure 7). Illness was looked at as a punishment from God and those who were ill were sinners. Suffering was part of the human condition. Ideas on the origin and cause of disease were based on destiny, sin and heavenly influence (Hajar, 2012).

Figure 6. Touching for the King's Evil

The Royal Gift of Healing

Charles II touching for scrofula circa 1660
Wellcome Library, London

Figure 7. Medieval Doctor making a diagnosis

A diagnosis made on the colour of the urine
Heart Views 2012

Chapter 3.3   The Patron Saints

I would never have believed it was possible to suffer so much.
Saint Thérèse of Lisieux circa 1897

In the absence of any real cure and in light of the limited therapeutic options available for those with consumption, the populace turned to the Church for succour despite its known punitive attitude to illness. The obvious choice for those afflicted was to appeal to the specific Patron Saints to ask them to intercede on their behalf.

Saint Pantaleon (c 275-305) (figure 8) was the earliest relevant Saint to acquire this status and to be regarded as a Patron Saint for consumption and tuberculosis. He coupled this with his care of physicians and midwives. Saint Pantaleon studied medicine under Euphrosinos and eventually became physician to Emperor Maximinian. The Saint's death was due to his refusal to pray to the Roman Gods thus declining apostasy and heading for martyrdom. He heeded the words of Saint Hermolaus that 'faith' is to be trusted over medical advice. A sentiment which was probably true in those days and typified European thought until later centuries.

The reason he became a Patron Saint for those with consumption is not quite clear but the fact his name derives from 'all compassionate' and he was a physician may be the explanation for his special status. His feast day is the 27th of July.

Figure 8. St. Pantaleon

13th Century Icon, Monastery of St Katherine, Mount Sinai,
Source: Wikipedia

The second Saint regarded as a Patron Saint of tuberculosis was Saint Gemma Galgani (1878-1903). She was known as the Virgin of Lucca and the Daughter of Passion. St. Gemma Galgani was born in Lucca, Italy. During her childhood and early years she experienced many mystical experiences. Among these were the marks of the stigmata and many 'ecstasies'. Her mother contracted TB when she was only two and a half which required her to go to a boarding school. Her brother also died of TB while studying to join the priesthood. She herself died of TB aged 25 years and hence was well qualified to be a Patron Saint for the disease.

By far the best known Saint regarded as a Patron Saint for TB was Saint Thérèse of Lisieux (1873-1897) (figure 9). Known as the Little Flower, she was born near Alençon, France and became a nun at 15 years of age. She joined the Carmelite Community of Lisieux. She also died of TB at the age of 24 and experienced a drawn out demise as a result of the disease.

Pope Pius Xl said of her that she was 'the greatest Saint of modern times'. She, therefore, is the third Patron Saint for TB and had the added portfolio of 'lung ailments'.

It will be seen that all these Saints died before any real progress was made in the treatment of TB and two of them had the disease themselves. Hopefully, those that sought spiritual help from them experienced some comfort mentally and emotionally if not physically.

Figure 9   St. Thérèse of Lisieux

Photograph circa 1888 from Wikipedia

Commemorative stamp, France 1973, Alençon Cathedral

Chapter 4
Towards a Scientific Based Solution: the Research Pioneers

It is the over-crowded dwellings of the poor that we have to regard as the real breeding places of consumption.
Professor Robert Koch, 1882

By the end of the 18th century, knowledge regarding the basis of phthisis and consumption was slowly expanding with clinical, anatomical and pathological descriptions having been published (figure 10). There was increasing recognition that the disease was probably due to infection rather than heredity. Indeed, it was also being debated that scrofula and consumption may be the same disorder and that tubercles found in the lungs and elsewhere may be an integral part of the disease process (Lennox, 1977). In 1834, the German physician Johann Schönlein coined the term 'tuberculosis' to cover diseases that involved the presence of tubercles. The term tubercle, itself, had been coined previously by the English physician Richard Marten. Schönlein made a large contribution to medical knowledge giving his name to one form of purpura (Schönlein–Henoch Purpura) (Hierholzer et al, 1994).

Figure 10   Jan Steen (1626-1679), *The Doctor's Visit,* 1662, (UK: Wellington Museum)

The picture in Figure 10 was painted between 1658-1662 by oil on a panel, and it is held by the Wellington Museum, Apsley House, London. Steen illustrates the pontificating of the doctor and his pretentious manner and unscientific approach.

By 1676, another Dutchman, Anton van Leeuwenhoek (1632-1723) had developed the first real steps in the commencement of the scientific era. While the development of the single optical and then compound microscopes is attributed to Zacharias Jansenn in the Netherlands, about 1595, van Leeuwenhoek's superior lenses were able to identify bacteria, yeasts and blood corpuscles. Figure 11 illustrates some of these early microscopes. Further development of microscopes was carried out by Robert Hooke in England.

Figure 11 Early Microscopes (1740-1873)
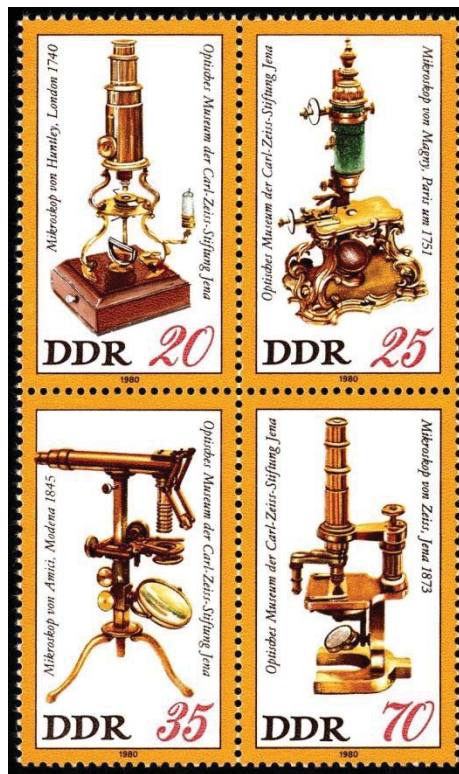
Stamps issued by German Democratic Republic (DDR), 1980

Chapter 4.1

René Théophile Laënnec (1781-1826)

The cure of phthisis by nature is possible, but not by art.
R. Laënnec[6]

Figure 12   Portrait of Laennec

French stamp, 1952

Laënnec must rank as one of the first of the renowned medical researchers (figure 12). He was born in Quimper, Brittany, France in 1781. In his early life his mother died from tuberculosis. He later studied medicine and received his degree from the Ècole de Santé in Paris in 1804. Thereafter, he studied dissection, pathology and surgery under Giullaime Dupuytren[7]. By 1816 he was working at the L'Hospital Necker in Paris. It was during this period that he invented the stethoscope[8]. Initially, he simply referred to it as 'le cylinder' but later changed it to stethoscope. It is said that Laennec was a shy man and the innovation was due to his feeling uncomfortable examining the chest of a young woman (Vatanoglu-Lutz and Ataman, 2016) (figures 13, 14). Laennec is quoted as saying:

> *I therefore took a paper notebook, rolled it up tightly, applied one end to the all pericardiac region and listened to the other. I was surprised as I was pleased to hear the heart beat much more clearly and distinctly (Frith, 2014).*

In relation to TB, his innovation enabled Laennec to compile accurate descriptions of lung sounds and to publish his findings in his work, *De l'auscultationn des Pouman et du Coeur*.

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[6] Quoted in *From Consumption to Tuberculosis: a Documentary History* B. Rosencrantz (ed) 1994 p 148
[7] Eponym: Dupuytren's Contracture
[8] Stethoscope: Greek stethos (chest) and scopos (examination) 'I look into the chest'.

He originated many medical terms such as 'auscultation', 'rhoncus', 'râles' all of which are still used in clinical practice. His major work, however, was in relating clinical findings to post mortem appearance. He identified consolidation, pleurisy and cavitation. Laennec later went on to describe miliary TB, extra pulmonary tubercles and "caseous" material in large tubercles. He also showed tubercles within the collapsed vertebrae of Pott's disease[9] (Frith, 2014). His ability to achieve these advances was based on his enormous experience with autopsies on people dying of tuberculosis at the Necker Hospital. At this time TB had reached epidemic proportions in Europe and the death rate had reached 100/1000 of the population per year (Daniel, 2006).

Laennec achieved high professional advancement and was also made a Chevalier de Legion d'Honeur. However, his health had remained poor and this was due to pulmonary tuberculosis. This is not surprising with his close involvement with patients and post mortem examinations. Unfortunately, his health deteriorated further and he died in Kerlouarnec, France on the 3rd August 1826 at the age of 45.

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[9] First described by Sir Percival Pott, a British surgeon in 1779.

Figure 13   Laennec auscultates a patient at the Necker Hospital
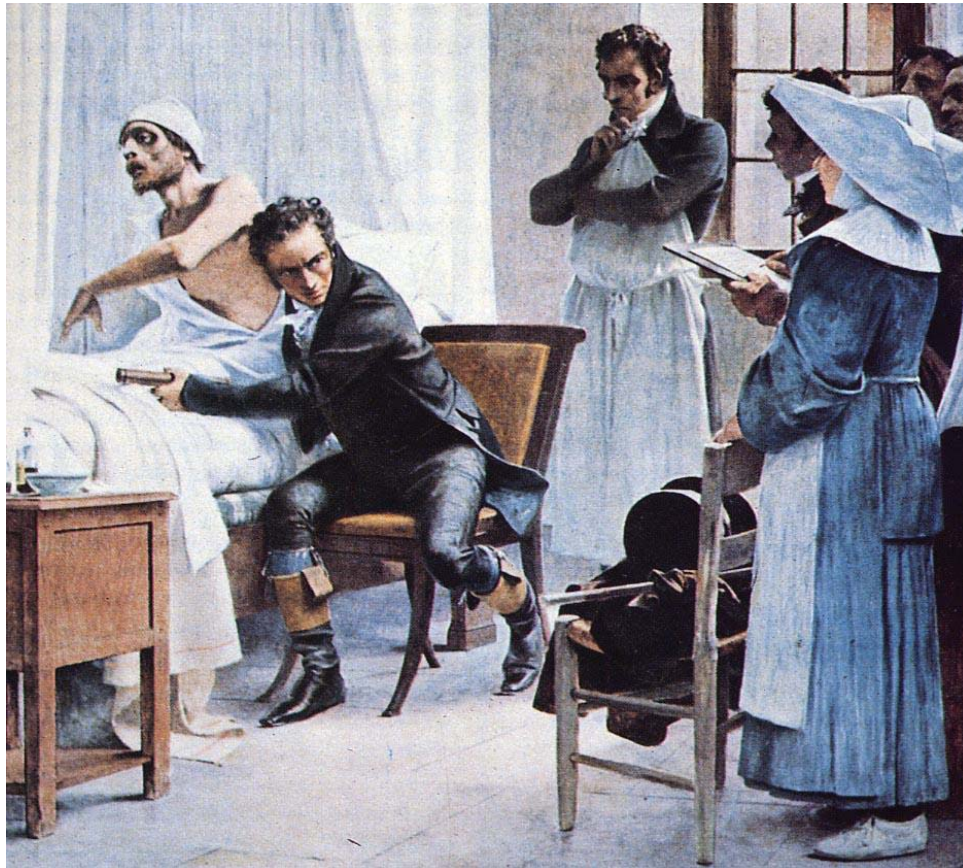
Thébold Chartran (1849-1907),
Laënnec à l'hôpital Necker ausculte un phtisique devant ses élèves, 1816
(Bethesda, USA: National Library of Medicine)

Figure 14

Original Laennec Stethoscope and modern equivalent

Science Museum, London, Picture Library

Danish postage stamp, 2003

Chapter 4.2

Jean-Antoine Villemin (1827-1892)

A phthitic soldier is to his roommates what a glandered horse is to its stable mates.
J-A Villemin, 1865

Figure 15   J-A Villemin

Source: Wikipedia   Military Physicians including Villemin, France, 1951

Villemin was born in 1827 in Prey in the Vosges Region of France. He studied at the Military Medical School in Strasbourg and qualified as an army physician in 1853. He completed his MD degree in 1863 in Paris, and was appointed to a position in the Army Medical School at Val-de-Grâce where he remained until his retirement (figure 15). His early observation was that young healthy men from the country often developed tuberculosis after living in close quarters in the military barracks (Shampo et al., 2009). He was aware that glanders[10] in horses was transferable in the horse stables. This prompted him to study TB.

In 1865 he demonstrated the infectious nature of TB when he inoculated a rabbit with a small amount of purulent liquid material, obtained at autopsy, from a cavity found in a tuberculous patient who had died of the disease. The animal remained apparently healthy but was sacrificed three months later. The findings showed extensive TB within the animal. Interestingly, it has been subsequently shown that rabbits are usually resistant to MTB and a

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[10] Glanders is an infectious disease of horses, mules and donkeys caused by infection with *Burkholderia mallei*, usually contracted from infected water or feed.

guinea pig would have been a more appropriate choice (Daniel, 2006). Villemin then using the scientific method demonstrated the infectious nature of the disease.

This now proved that TB was infectious beyond doubt. This concept was now slowly being accepted by other workers who were studying the effects of TB on previously naive populations. Villemin died in Paris in October 1892.

Chapter 4.3   Robert Koch (1843-1910)

From my numerous observations, I conclude that these tubercle bacilli occur in all tuberculous disorders and they are distinguishable from all other microorganisms.
Robert Koch, 1882

Figure 16 Robert Koch
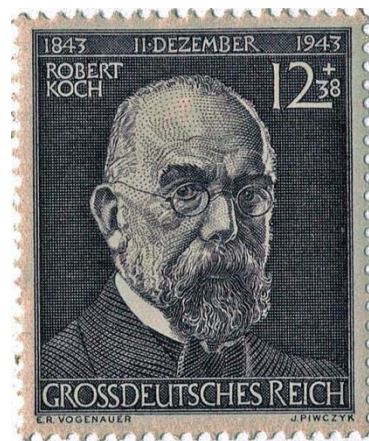
German charity stamp, 1943

A dramatic turning point in the history of TB took place on the 24th March 1882, when Robert Koch (figure 16) presented his seminal paper 'The Aetiology of Tuberculosis' to the Berlin Physiological Society. In it he announced the discovery of the tubercle bacillus (figure 17).

Koch was born in 1843 in Clausthal, Germany He showed early evidence of having an outstanding intellect. He received his medical degree from the University of Göttingen in 1886, graduating with distinction.

In 1875 Koch visited the major scientific research centres in Germany and was thus exposed to the 'germ theory' of contagious disease which was gaining ground at that time. After his

appointment as a district medical officer in Wöllstein he began investigating anthrax which was a major health problem there. Koch developed culture techniques which allowed him to grow the anthrax bacilli in vitro. He injected the cultured organisms into various animals and demonstrated that this induced anthrax in mice and other creatures. He then progressed to try and link specific bacteria with specific diseases and developed staining methods suitable for each organism.

When he eventually moved to Berlin following a promotion he became interested in tuberculosis. He faced two problems. The organism's unique protein coat resisted conventional staining and its slow growth rate and growth requirements resisted conventional media. Robert Koch experimented with different culture techniques and media until he was able to grow the organism and develop a workable stain. He was aided in this advance by Julius Petri (1852-1921), a German microbiologist, who developed the Petri Dish and the use of agar. To this substance the various nutrients and chemicals were added. This work was expanded further by Hans Gram, Franz Ziehl and Friedrich Neelson. Thus the Gram stain and Ziehl-Neelsen stains developed (ZN stain) and acid and alcohol fast bacilli (AAFB) terminology.

Among Koch's other achievements was to develop his so called Koch's Postulates[11]. Following the publication of his work on the tubercle bacillus he hoped to discover a cure or a vaccine. However, this work was not as successful. He obtained a glycerine extract from tubercle bacilli, which he called Tuberculin, but this proved to be an ineffective therapeutic agent. Instead what he did discover was that when injected into healthy people tuberculin had little or no effect. However, when injected into people with TB it caused a marked reaction. The work of others later developed this finding into a diagnostic test (Blevins and Bronze, 2010).

Robert Koch was awarded the Nobel Prize for Medicine and Physiology in 1905 for his work on anthrax and tuberculosis. He continued his work with tuberculin but at age 67, in 1910, he died from heart failure (figure 18).

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[11] Koch's Postulates: coincidence of bacteria and disease, isolation of bacteria in pure culture and induction of disease by inoculation with bacteria from pure culture.

Figure 17 Centenary of Koch's Discovery of the Tubercle Bacillus

Koch and his original clinical paper, East Germany (DDR), 1982

Figure 18   Examples of the International Centenary Celebration of Koch's Discovery

Cuba, 1982

West Germany, 1982

Poland, 1982

Chapter 4.4 Wilhelm Röntgen (1845-1923)

It is clearly something new, something unrecorded.
Wilhelm Röntgen, 1895

Röntgen must be included in the group of pioneer researchers whose work aided in the

advancement of knowledge and management of TB. He was a German engineer and

physicist who obtained his PhD from the University of Zurich in Switzerland. His major achievement was to produce and detect electro-magnetic radiation in a wavelength range he called X-rays. Röntgen published his findings in 1895 under the title *On a new kind of rays*. For this work he was given the Nobel Prize in Physics in 1901 (figure 19).

The use of X-rays in the diagnosis and management of TB advanced from the chest film only onto X-ray fluoroscopy screening (figure 20) and then to computerised axial tomography. Despite these advances the basic chest X-ray has continued to be of value in the detection of TB in urban groups (Abubakar et al., 2010).

Figure 19   Celebration of Rontgen's Achievements

Figure 20 Fluoroscopy

Birth centenary and 50th anniversary of the Nobel Prize
Germany (DDR) 1965, and West Germany, 1951

Russian TB publicity label

Chapter 5   Culture and Romanticism

Youth grows pale, and spectre thin and dies.
John Keats, 1819

Chapter 5.1   The Victims

In Europe and North America during the 19th Century, tuberculosis was so widespread that it influenced manners and aesthetic taste (Dubos and Dubos, 1952). Indeed, *the fragile silhouette, with long limbs, long fingers, long throat, and the tired head leaning on a pillow* became the unhealthy symbol of Romanticism (Lamlein, 1981).

There was a popular belief, however, that talent was somehow aided by tuberculosis, because several outstanding artists were so afflicted. This may have stemmed from the work of the novelists alluding to pale heroines languishing in decline and even children as little heroes *consumption whose tainted breathe destroys unhappy children*[12] .

Antoine Watteau (1684-1721), was regarded by many as the greatest painter of the 18th century. He developed tuberculosis during his adolescence. He was described as a gaunt man with an expression of suffering and lacked flesh and muscle. His temperament was described as difficult. Despite this, Watteau was able to produce many paintings of the romantic style labelled Rocco. He worked in great haste as if he knew that his life would be shortened. As his health failed he consulted a well-known London physician, Dr. Richard Mead, with regard to his tuberculosis. Unfortunately, he did not improve and died in Paris at the age of 37. It is suggested that this was due to terminal laryngeal tuberculosis. His art legacy, however, continues up to the present day (Lemlein, 1981).

The Pre-Raphaelite painters such as Millais and Rossetti, chose as their model, Elizabeth Siddal. She was pale, thin, long limbed and graceful (Lemlein, 1981). Siddal was also described as death-like and beautiful (Dubos and Dubos, 1952). She thus fitted well into the idealised vision of early Victorian women. Siddal had tuberculosis but committed suicide, at the age of thirty, by taking laudanum. This was said to be as a result of her advanced tuberculous condition.

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[12] Jonathan Swift *The Tales of a Tub* (1689)

Those who fell victim to tuberculosis came from all walks of life. However, it tends to be the celebrities of the time that we have written accounts and knowledge about the effects of the disease. Celebrity victims are numerous and include amongst their ranks Samuel Johnson, the Brontë Sisters and Jane Austin. Bynum, (2015), has described the effects of tuberculosis on the life of George Orwell in great detail.

The next sections give a brief account of the effects of tuberculosis on other well known people most of whom are still held in high regard to this day.

Chapter 5.2

The Poets: John Keats (1795-1821)

Mortality weighs heavily upon me.
J. Keats

John Keats fulfils many of the attributes discussed in Chapter 5.1. He died very young, as did his two brothers, and he became famous through his romantic poetry. Keats' mother died of tuberculosis when he was only 14 years of age. Following this event, he became apprenticed to an Apothecary. Later he became a medical student and qualified as a Licentiate of the Society of Apothecaries at the age of 22. He did not pursue a career in Medicine but chose poetry instead. His first signs of ill health were in 1817 when he had a major haemoptysis. Despite this he chose to carry out an arduous walking tour of Northern England and Scotland, even climbing Ben Nevis. After this, he was never quite the same. Unfortunately his brother Tom died of tuberculosis shortly after this walking trip.

By February 1820 he had another massive haemoptysis and looked very ill. He is quoted as saying *that drop of blood is my death warrant. I must die* (Smith, 2004). Thereafter he had bouts of fever and multiple episodes of haemoptysis. He then set out for Rome in the forlorn hope that a change of climate would result in a cure. His physician there was Dr. James Clark who was equipped with the latest aid to diagnosis, namely a stethoscope. Unfortunately, despite this he felt that Keats had a stomach problem. When Keats died six months later his autopsy revealed severely damaged lungs (Smith, 2004). At the time of his

death his caregiver described in a letter how Keats would sometimes cry upon waking to find that he was still alive.

> *Keats raves till I am in a complete tremble for him…about four, the approaches of death came on. [Keats said] "Severn—I—lift me up—I am dying—I shall die easy; don't be frightened—be firm, and thank God it has come". I lifted him up in my arms. The phlegm seem'd boiling in his throat, and increased until eleven, when he gradually sank into death, so quiet, that I still thought he slept.[13]*

His reputation as a poet grew after his death and he became one of the most highly regarded poets in the English language. He was buried in Rome with a simple inscription on his tomb (figure 21).

Figure 21: Keats'Grave Stone and Stamp Image

'Here lies One / Whose Name was writ in Water. 24 February 1821' (Source: Wikipedia)
Depiction of John Keats, UK stamp 1971

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[13] Refer: www. lumibyte.eu/microbiology-news-keats-died-of-tuberculosis. (cited 16-8-216)

Chapter 5.3

The Writers: Robert Louis Stevenson (1850-1894)

Under the wide and starry sky,
Dig the grave and let me lie..
Stevenson: Requiem on his tomb

Stevenson was a world famous Scottish writer and author of such books as *Treasure Island* and *Kidnapped*. His father Thomas Stevenson was a lighthouse engineer based in Edinburgh. He died from tuberculosis and was probably the source of his son's disease. Robert eventually qualified as a lawyer, never practising, choosing instead to be a writer.

In 1873 Robert Louis Stevenson developed the first signs of chest disease. Subsequently, he was diagnosed by several doctors as having consumption. His disease remitted and relapsed over time. Eventually, after much travelling, he met and married an American divorcee. She described him at that time as *a mere complication of cough and bones, much fitter for an emblem of mortality than a bridegroom*[14]. To improve his health, he was advised to move either to an area with fresh air such as the Swiss Alps or an area with a mild climate such as the South Pacific. Initially, he went to the USA, to the mountains of Colorado and as he had been informed these had a favourable fresh air climate. While there he learned of the successful treatment results of Dr. Edward Trudeau at his Adirondack Sanatorium at Saranac Lake[15]. He arrived there on the 3rd of October 1807 and occupied a small cottage, the Baker Cottage, which had fine views of the Saranak River. He formed a friendship with Dr. Trudeau, his physician, and spent the best part of a year trying to cure his tuberculosis. Their relationship was said to have its ups and downs[16]. It was a meeting of great minds and to celebrate Stevenson's stay, many years later the sculptor Gutzon Borglum created a plaque which is now attached to Baker Cottage to celebrate Stevenson's time spent in the sanatorium[17] (see figure 22).

Following his time there, he moved to explore the South Pacific visiting Tahiti, Gilbert Islands and finally settled in Samoa. He built a house in Vailima near Apia (figure 23). He appeared

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[14] The letters of Robert Louis Stevenson volume 1 Chapter 5, 1881
[15] See Chapter 5.5 for a discussion of the Sanatorium Movement and Dr. Trudeau.
[16] www.biography.com/people/robert-louis-stevenson.9494571 (accessed 18/8/2016)
[17] www.localwiki.org/hs/Gutzon_Borgum (accessed 19/8/2016)

to enjoy life in Samoa and was held in high regard by the local people who called him 'Tusitala', the teacher.

In 1894, Stevenson died of what was described as a stroke and was buried on Mount Vaea with a view overlooking his house (figure 24). Examination of the details of his illness by Dr Jonathan H Cossar, from Glasgow, who visited Samoa in 2013 with the Robert Louis Stevenson Society of Edinburgh made this comment:

> *In my professional opinion, based on the history of RLS' illness from his writings and other sources, it was certainly compatible with the diagnosis of pulmonary tuberculosis causing lung damage - lung cavitations (bronchiectasis) this in turn pre-disposing to recurrent lung infections with fever, cough and coughing up blood (haemoptysis).*

Despite his early death at age 44, Stevenson achieved much in his life despite his chronic relapsing tuberculosis and one wonders what he may have achieved if he had not contracted this debilitating disease.

Figure 22: Plaque celebrating Stevenson at Adirondack Sanatorium, USA and Stamp of Dr. Trudeau, USA, 2008

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Source: localwiki.org

Figure 24: Postcard photograph of Robert Louis Stevenson and a stamp showing his grave
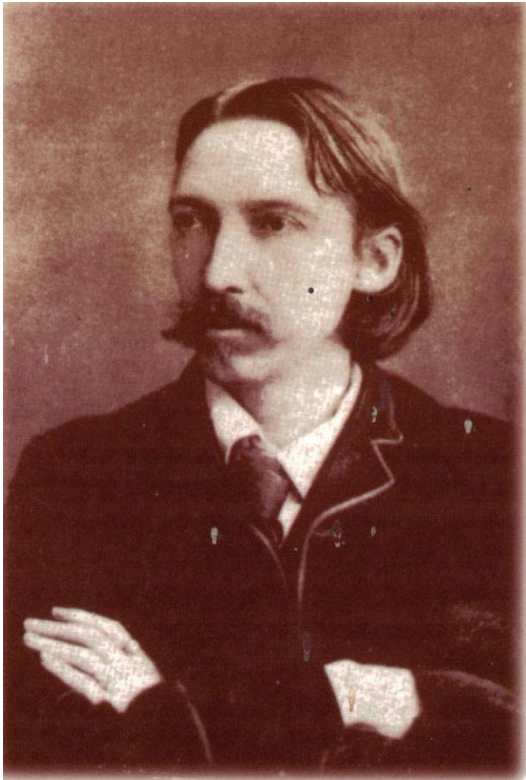
From a postcard obtained by the author at the Robert Louis Stevenson Museum at Vailima, Apia, Samoa
Postage stamp image of Stevenson's grave, Western Samoa, 1939.

Figure 23: Stevenson's home in Vailima, Samoa

Photograph by the Author

Chapter 5.4

The Painters

It was the fashion to suffer from the lungs...to spit blood....and to die before reaching the age of thirty.
Alexandre Dumas (Morens, 2002)

The artists have provided us with a visual perspective of how they perceived that the disease had affected them, their relatives or sufferers in general. Their works can be viewed as realist, romanticised or visionary. I present, therefore examples of the various genres to further illustrate the human dimensions of the disease rather than the medical or purely scientific facts (figures 25-29).

Figure 25: Alice Neel (1900-1970) *TB Harlem*, 1940, (Washington, DC: National Museum of Women in the Arts), Oil on canvas.

The painting is a portrayal of Carlos Negrón, a Puerto Rican living in Spanish Harlem, New York. The bandage covers the wound from the thoracoplasty he received in the treatment of his tuberculosis.

Figure 26: Christobal Rojas (1857-1890) , *Le Miséria*, 1886. (Caracas, Venezuela: Galeria de Arte Nacional).

Christobal Rojas was a Venezuelan born painter, who developed tuberculosis and died from it at aged 33. This painting depicts the social aspects of the disease and the living conditions in the late 19th century. The gloom creates a metaphysical element and also engenders sympathy for the victim.

Figure 27: Fidelio Ponce de Leon (1895-1949), *Tuberculosis*, 1934. (Havana, Cuba: Museo Nacional de Belles Artes)

Fidelio Ponce de Leon (Alfredo Fuentes Pons), 1895-1949, was a Cuban painter who developed tuberculosis in 1943 and died of complications of the condition.

Figure 28: Richard Cooper (1885-1957), *Sickly female invalid sits covered up on a balcony*. circa 1912

Richard Cooper's painting is an allegorical painting. It symbolises 'Death' rising over the invalid with tuberculosis. The metaphorical aspect was intended to show the negative effects of both disease and medical cures. Welcome Institute.

Figure 29: Pablo Picasso, *Pobres Genios*, 1899-1900, (Barcelona, Spain: Museo Picasso)

The sketch shows a sick patient with Tuberculosis. Picasso is known to have been devastated by the death from tuberculosis of Marcelle Humbert (known as Eva Gouel, 1885-1915)[18]. She was described as being frail, slender and enigmatic. She was also the subject of Picasso's cubist painting *I love Eva.*

I have already shown an example in Figure 1 (page ii) of the influence tuberculosis had on the life and works of the Norwegian painter Edvard Munch. Not only did he lose his mother and sister from the disease but it is felt that these experiences in early life resulted in such paintings as *The Sick Child*, *Chamber of Death*, *Spring* and probably his versions of *The Scream* (Messer, 1987).

Many other painters suffered from tuberculosis and among these are Aubrey Beardsley (1872-1898). He shocked the Victorians by his bizarre works and his 'indecent' portrayal of his subjects. He died aged 26 from a pulmonary haemorrhage. Amedo Modigliani (1884-1920) was another famous painter who suffered from tuberculosis during his short and productive life. However, his demise was hastened by alcohol, a diet of sardines and kidney disease. He died at 36 years.

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[18] Letters by Juan Gris, Private printing, 1956, letter XLI, page 34

Chapter 6

Progress in the Management and Treatment of Tuberculosis

My faith in the possibilities of chemotherapy for tuberculosis is based simply on what Ehrlich has demonstrated – namely that a chemical compound could be discovered which killed the germ without injuring the cell.
Edward Trudeau, 1916[19]

Chapter 6.1

The Early Steps

Professor Paul Ehrlich (1854-1915), a German physician and scientist (figure 30) is credited with the development and naming of the concept of chemotherapy. His early work on cell stains and their effects on different tissues prompted this concept. He developed the 'magic bullet' idea in which selected targeting of an organism by a chemical compound would kill that organism either directly or by adding a toxic agent to the 'bullet'. In so doing the host would not be harmed. While conducting his experiments with stains, he is said to have isolated AAFB from his own sputum, having contracted the infection in his laboratory.

His first experiments in this field were with dyes. He used methylene blue to study its effects on malaria and tuberculosis. Indeed, he demonstrated a fall in temperature and a slight improvement in a woman with TB following injection of the dye. Eventually, in his laboratory, the discovery of arsphenamine (Silvarson) took place. This proved to be the first agent that was effective in the treatment of syphilis. This use of screening of compounds is still practised to this day in the pharmaceutical industry (Bosch and Rosich, 2008).

Ehrlich received the Nobel Prize in Physiology and Medicine in 1908.

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[19] Quoted in *Relative immunity in tuberculosis and the use of tuberculin,* British Journal of Tuberculosis 1916; 10:29-30

Figure 30: Paul Ehrlich and von Behring

Postage stamp of West Germany, 1954

Chapter 6.2

The Sanatorium Movement

Look to your health; if you have it, praise God.
Izaak Walton (1593-1683)

The first sanatorium was opened by Herman Brehmer (1826-1889) in 1862 at Görbersdorf in the Silesian Mountains (now in Poland). He called it Heilanstalt Sanatorium[20]. His thesis was that the hearts of tuberculous patients were smaller than normal and by placing them at high altitude, the heart would expand and improve the patient's health (Daniel, 2011). He added to this hydrotherapy, with the patients standing under streams of cold water. However, he was the first to take regular temperature readings and to advocate for milk intake and exercise. Later he changed this regimen to rest and outdoor living and a healthy diet.

The sanatorium treatment and care concept dominated the management of tuberculosis for the next hundred years. Sanatoria proliferated around the world, spurred on by the

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[20] The etymological origin of the word is from the Latin **sanare,** to heal. Sanitarium, however, is derived from the word **sanitas** meaning healthy.

apparent early success of Brehmer's strict methods and improved results (figures 31 and 32). One of the best known was that founded in 1882 by Edward Trudeau at the Saranac Lake and he named it the Adirondack Sanatorium (later the Trudeau). Trudeau had had tuberculosis himself and was influenced by the fresh air and bed rest concepts of Brehmer, and his disease went into remission after spending time in the Adirondack Mountains (Murray et al., 2015). Trudeau lost his brother to tuberculosis and this event probably also greatly influenced him to establish his hospital (figures 24 and 33).

Figure 31: Leysin Sanatorium
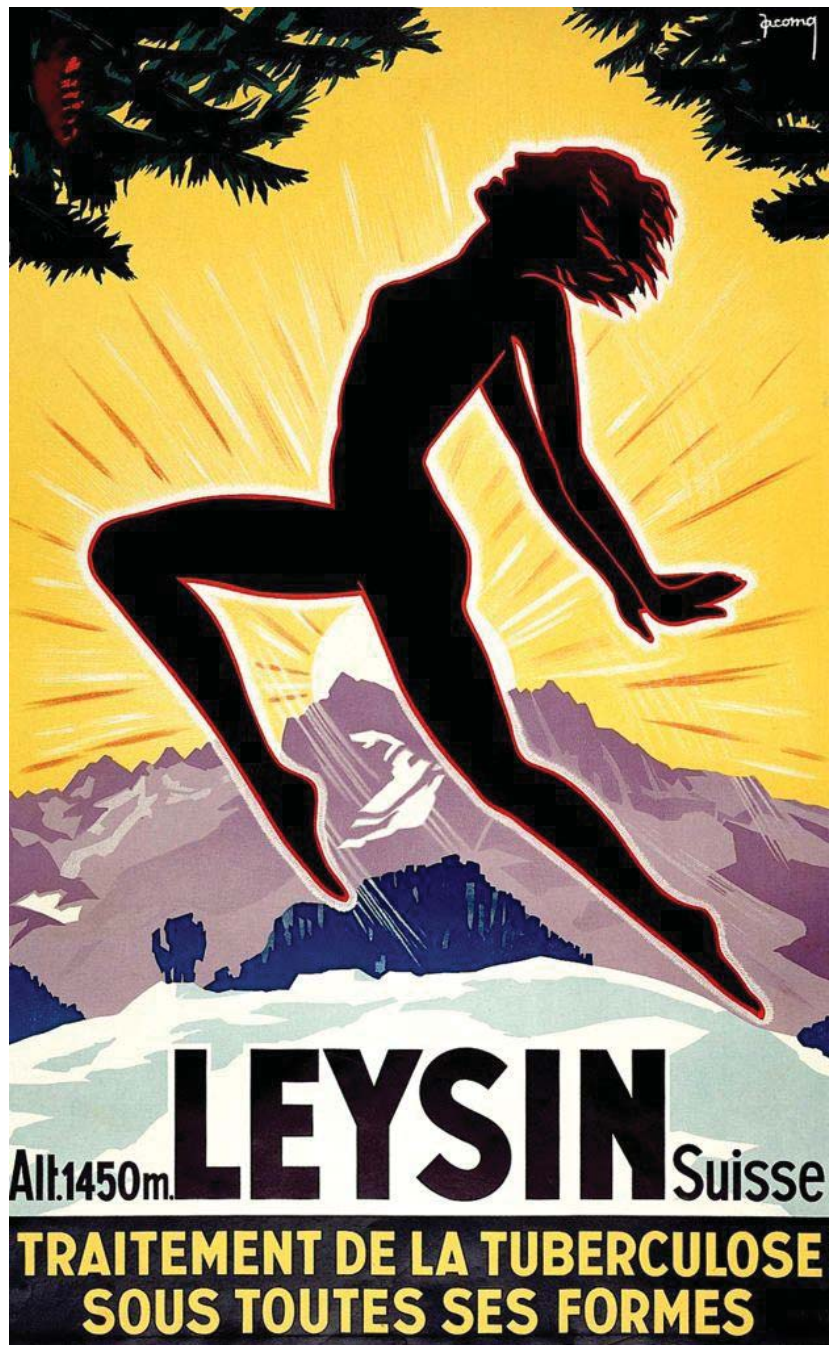
Promoting the Town of Leysin in Switzerland for the treatment of tuberculosis circa 1930.
Wellcome Library

Figure 32: Treatment for TB at Mearnskirk Hospital Sanatorium, Glasgow, Scotland

Fresh Air and Heliotherapy for Tuberculosis, 1933
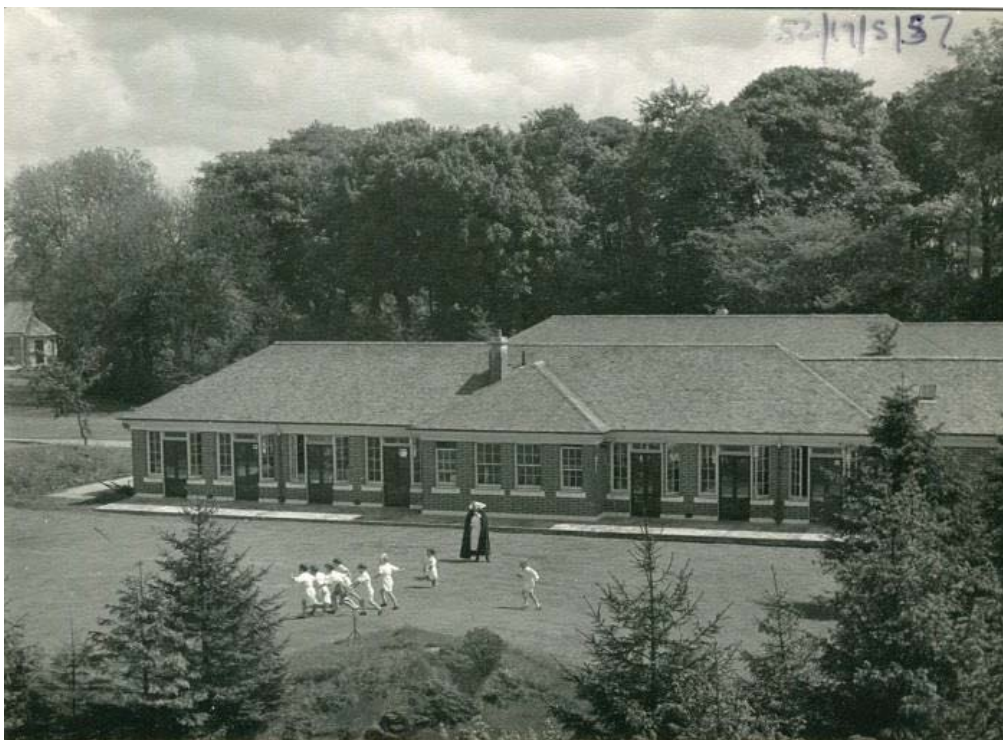
TB isolation ward for children, Mearnskirk Hospital, 1940

Underwater exercise and hydrotherapy bath, Mearnskirk Hospital, 1959

Courtesy of the Royal College of Physicians and Surgeons of Glasgow's archives (RCPSG 52/19/2/14: 52/19/5/57; 52/19/2/50/1).

Figure 33: The Statue of Edward Trudeau at the Trudeau Institute
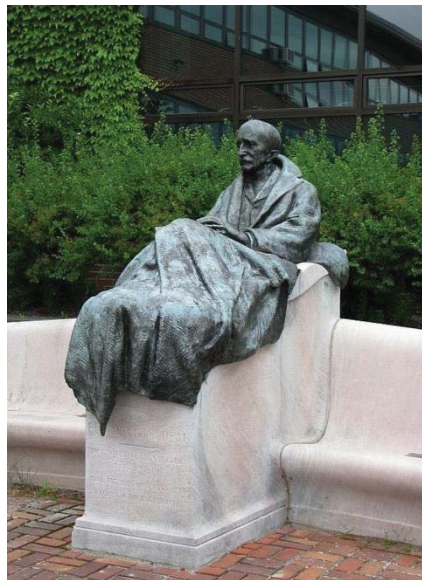
Source: Wikipedia

The rest, fresh air and good nutrition became the standard regimen for sanatoria. Additional therapies were added at times such as hydrotherapy and heliotherapy. Importantly, the removal of infected people from the general population would have certainly helped in

reducing the spread of the disease. The strict and, at times, harsh life in sanatoria has been well described by Bynum (2015) and a patient's diary of her experience in 1940 has been published (Hurt, 2004).

The development and provision of sanatoria became a large industry and it was based on benevolence, government provision or pure profit. Figure 31 shows an interesting advertisement seeking clients for the sanatorium at Leysin in Switzerland in 1930. There were claims made for the superior results of one sanatorium over another often on the basis of their regimen being able to promote a greater immune response by the patient. In reality, many commercial sanatoria would only admit afebrile patients as their chances of improvement were greater. The government and charity run organisations had to cope with the more seriously affected patients. What was not recognised or was ignored were the effects of reducing overcrowding, improving nutrition, housing, hygiene and medical services in many societies. Figure 34 shows quite dramatically the fall in mortality trends in Western Europe up to 1950 when there were no specific anti-tuberculous chemotherapy treatments available.

Figure 34: Trends in mortality from tuberculosis in Western Europe, 1774-1985.
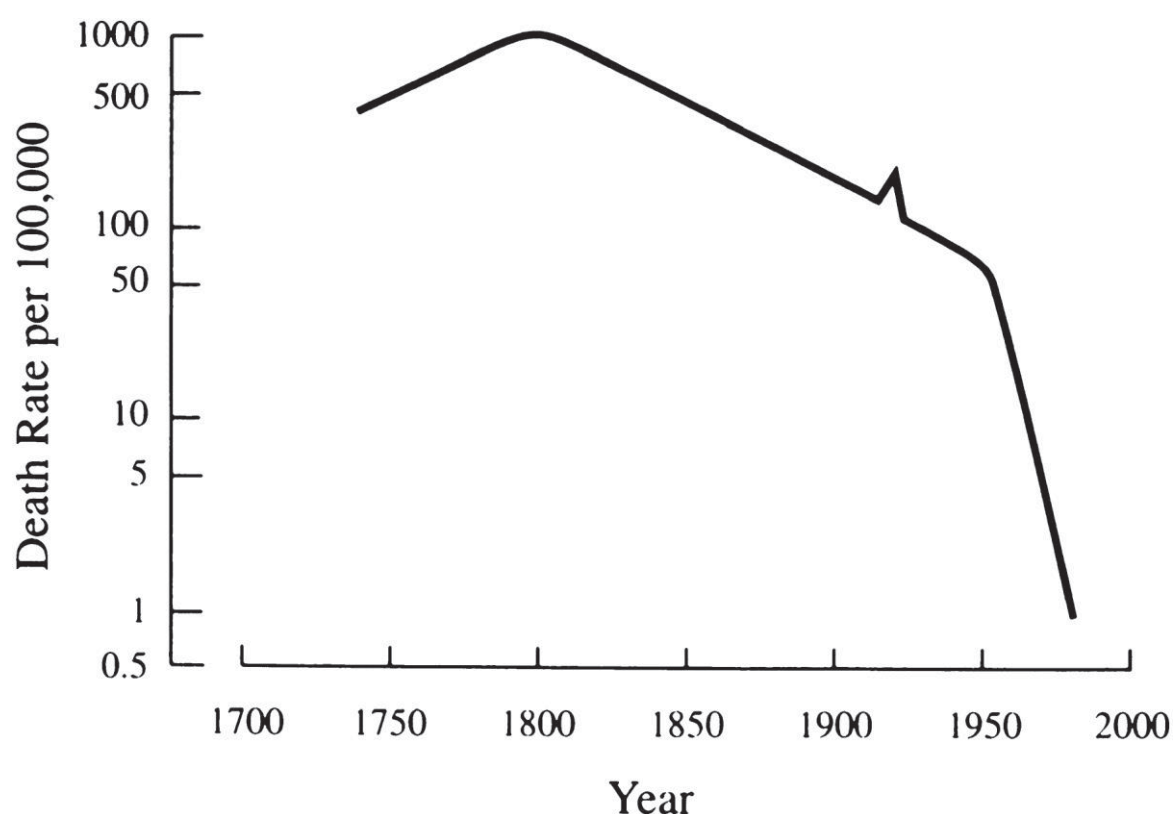
Based on Murray, 2004[21]

How useful was sanatorium care? Cox (1923) published a follow up study in 1923 comparing those patients treated in a sanatorium with those treated at home. It revealed that those who were sputum negative on admission had a 14% mortality while those treated at home who were also sputum negative had a 38% mortality. With sputum positive patients the mortality was 61% and 81%. A similar study from New York State revealed that those with minimal disease on admission did well while those with advanced disease did not (Alling et al. 1960).

Was there any scientific basis to the rest hypothesis? It was claimed that bed rest in the horizontal position reduced the gravity effects on pulmonary circulation. Pulmonary blood flow being less in the apical regions with reduced oxygen saturations and where most TB lesions and cavities were situated. The horizontal position caused an increase in oxygen tension in the apices, and hence this would lead to lower multiplication rates of MTB (Murray, 2003). Other theories around the benefit of the fresh air, sunshine and nutrition

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[21] Murray JF. A century of tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 2004;169:204.

are based on the idea that the exposure to sunlight and food intake would restore depleted vitamin D levels and this in turn, would improve macrophage activity. Perhaps not enough to justify the message in figure 35, however.

Figure 35: Advertisement for Sanatorium Care
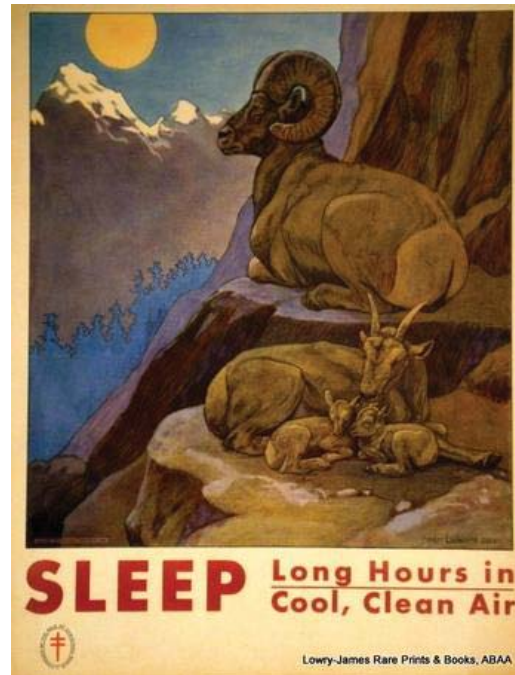
Source: Lowry James Books circa 1930

It had been assumed that some mysterious factor in certain climates would heal consumptives. Gradually medical care with close supervision, nutrition, rest and surgical procedures (see Chapter 6.4) were the standard regimens used. The decline of the sanatorium came about with the discovery of specific chemotherapy (qv). By the 1950s it was clear that TB mortality was falling irrespective of tuberculosis treatment (figure 34). Sanatoria were now expensive to run with competition, improved building standards, staff salaries increasing and the financial crisis of the 1930s saw a fall in charitable contributions. By the late 1960s, the sanatorium movement was over, and the research institutes took their place, and many of the former sanatoria buildings evolved into geriatric care centres (Editorial, 1968).

Chapter 6.3

Bacille Calmette-Guérin

En toutes choses, je crois, le secret du success est dans les longs efforts. Par la perseverance dans la recherché, on finit par acquérir ce que j'appelle volontiers l'instinct de verité.
Louis Pasteur

Robert Koch in his search for a cure of tuberculosis produced a glycerine extract of tubercle bacilli which he called Tuberculin. Tuberculin proved ineffective as a therapeutic agent, but with later modifications, it became a standard for the diagnosis of tuberculosis (Blevins and Bronze, 2010).

In the 1880s Pasteur had invented the principle of attenuating the virulence of microbes to produce successful vaccines. Beginning in 1908, Albert Calmette and Camille Guérin (figure 36) used the techniques of Pasteur to create a vaccine against tuberculosis. They passed a single isolate of MTB, 230 times through an ox blood medium to render it non-fatal to a range of animals. The attenuated organism when formulated into a vaccine did, however, produce a self-limiting infection as well as partial resistance to vaccine reinfection with a virulent MTB strains and *M. bovis* (Murray, 2004). The researchers called it Bacille Calmette-Guérin[22] (BCG).

BCG was cautiously used with no apparent further side effects of note in animals. In 1921 the first human administration occurred (figure 37) and later, up to one hundred thousand children were immunised. Disaster struck in 1930 in Lubeck, Germany when 250 children were given BCG vaccine that had been accidently contaminated with a virulent strain of MTB. Seventy-three children died within a year, and 135 were infected but eventually recovered (Frith, 2014). Following this tragedy, confidence slowly recovered and at one time it was the world's most used vaccine (Murray, 2004). Brewer (2000) carried out a meta-analysis of published studies on BCG use. He concluded that it provided a 50% protection rate. It also appeared to be most helpful in infancy and does protect children from military TB and meningeal disease. Later age infection may be retarded by prior BCG vaccination.

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[22] Originally called Bacille Bilié from the ox bile used in attenuation, later changed to BCG.

BCG is not now given routinely except in places with a very high TB rate in order to prevent meningeal disease and in situations where the healthcare of military personnel is at high risk.

Who were these men who developed the first useful tool against TB? Albert Camille (1863-1933) was born in Nice, France (figure 36). In 1885 he completed his medical studies and proceeded to an MD in 1886 with a thesis on filariasis. In 1895 he was appointed as the first Director of the Pasteur Institute in Lille. In 1897 he was joined by Camille Guérin as his assistant.

Camille Guérin (1872-1961) was born in Poitiers, France and he trained at the Ecole Alfort, the Veterinary School near Paris. He undertook research into infectious disease in the veterinary field and was eventually appointed to the Pasteur Institute.

Following the disaster in Lubeck, both men came under considerable strain, but they were both exonerated by the Germany enquiry, and they remained confident about the safety of BCG (Sakula, 1983). Their contribution to the work against tuberculosis has been widely acknowledged in many forms including postage stamps (figure 37, 38).

Figure 36: Albert Calmette and Camille Guérin

First Day of Issue, Monaco, 1996

Figure 37: Celebration of First Human Innoculation of BCG

First Day cover from Wallis and Futuna Islands, 1981

Figure 38: Promoting BCG Use

Stamps of the Dominican Republic (1956) and Ghana (1982)

Chapter 6.4

Forlanini and the surgical approach

Dr. James Cameron in Edinburgh observed that a patient who developed a pleural effusion subsequently had an improvement in his tuberculosis. Ramage in London in 1884 carried out the first artificial pneumothorax for TB and reported that his patient was cured. However, it was Carlo Forlanini (figure 39) in Italy, who created the first pneumothorax by

collapsing the lung and filling the pleural space with nitrogen. The rationale behind this treatment was the concept that by deflating the lung, movement is stopped and this relaxation would allow cavities to close and the lung to heal naturally. In so doing the sputum would become free of organisms. Following the documentation of Forlanini's results in 1894, the procedure became widely used (figure 40).

Roger Mitchell (1951) reported the outcome of 557 patients who had undergone the procedure at the Trudeau Sanatorium. Of these patients, 326 were working and classed as well. Sixty were chronically ill while 119 had died from tuberculosis. No control group was available making an assessment of these results difficult.

Other surgical methods were tried such as thoracoplasty. Ribs were surgically removed to cause lung collapse. This had the possible advantage of avoiding actually entering the pleural cavity. Plomage or extra pleural pneumolysis involved placing inert foreign objects in the pleural cavity to induce lung collapse (figure 41). Phrenic nerve crush was used to cause diaphragmatic paralysis and stop lung movement.

With the advent of chemotherapy, these procedures became redundant. However, antimicrobial cover did permit lung segmental or lobar resection to occur more safely and in some situations, pneumonectomy.

Figure 39: Carlo Forlanini (1847-1918) pioneer of the artificial pneumothorax

Belgian charity stamp, 1953

Figure 40: Pneumothorax procedure, 1941

Source: museum.aarc.org/gallery

Figure 41: Radiograph of plomage performed many years previously
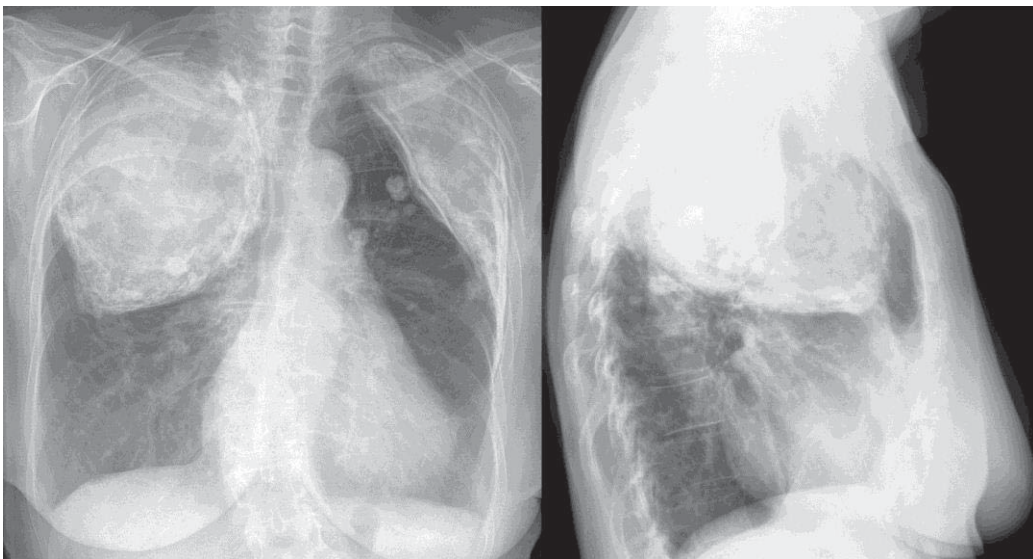
Source: Wikipedia

Chapter 7

Chemotherapy for Tuberculosis: the End or Just the Beginning?

Near this place in 1887, Dr Robert Philip founded a tuberculosis dispensary, the first clinic in the world dedicated to fighting a disease of which he foretold Man's eventual mastery. That vision has brought hope to many lands.
Plaque opposite Law Courts, Edinburgh, Scotland

With the discovery of penicillin in the 1930s, effective chemotherapy became a reality. Unfortunately, this group of drugs was not effective against MTB. The finding that soil microbes were capable of producing substances capable of preventing the growth of other microbes opened a new door for investigators. In addition, the sulphur compounds were reassessed by Gerhard Domagk in 1932. From these investigations, the development of sulphonamides occurred. Domagk received the Nobel Prize for this work. Meanwhile, Hinshaw and Feldman had developed a guinea pig model to test the efficacy of any newly developed chemotherapeutic agents (Murray et al, 2015).

Chapter 7.1

Waksman et al.

Stimulate the phagocytes. Drugs are a delusion.
George Bernard Shaw, *Doctor's Dilemma.*

In 1944, Albert Schatz, Elizabeth Bugie and Selman Waksman from Rutgers University reported the isolation of streptomycin, claiming it had bactericidal effects against MTB. Waksman had sent 10 grams of streptomycin to Hinshaw and Feldman which was capable of testing four guinea pigs infected with a virulent strain of MTB. Their report was to the effect that there was a steady improvement in the infected animals which were treated as opposed to that of the controls.

Streptomycin went on the market in 1946, heavily promoted and the demand for the new 'miracle' drug was enormous. For some, however, it proved not to be a miracle and hard to obtain. George Orwell, the author, was an example of one of these. He died of TB despite receiving streptomycin. He tolerated it poorly and responded badly (Bastion, 2006).

Selman Waksman (1888-1918) was born in Priluka in the Ukraine. He later immigrated to the United States. He eventually obtained his PhD from the University of California in biochemistry. Thereafter, he moved to Rutgers University in New Jersey, USA. When Waksman learned about the origins and source of penicillin, he switched his laboratory's line of research to finding new antibiotics convinced that soil organisms were capable of generating antibiotic substances. He thus, started screening organisms capable of producing these (Mistiaen, 2002).

Albert Schatz (1920-2005) was a graduate student at Rutgers University in Waksman's Department. He first isolated an antibiotic substance from *actinomyces griseus* in November 1943. He showed it was active against various bacteria including MTB. He called it streptomycin. Schatz's role in the discovery was eclipsed by that of Waksman, and this eventually led to litigation.

The background to this dispute lies in the facts that the success of penicillin stimulated Merck Pharmaceuticals to fund research by Waksman, as a soil scientist, into the collection of *actinomycete*s that he had assembled over thirty years. He applied the systematic, uncreative testing techniques that had made the German pharmaceutical industry so successful to these untested organisms and this led to streptomycin being discovered.

Waksman received the Nobel Prize for this discovery in 1952. The test that turned out to be the crucial one could have been carried out by any of his several students, but the lucky one was Albert Schatz. Schatz then sued the University for a share of the royalties payable by Merck and also petitioned the Nobel committee to include him in the award. Although he obtained a very substantial out-of-court settlement, this probably damaged his subsequent academic career, and he never ceased to argue his case for recognition and to claim that Waksman took the credit. Kingston (2004) has pointed out that Schatz failed to understand that once pharmaceutical research had become primarily a matter of large-scale, routine testing, little individual creativity was left in this work. Credit for any successful results must be given to whoever is the originator or director of a particular program.

 The drug was developed by a large American pharmaceutical firm, Merck, with which Waksman had had a commercial agreement since 1940. From this agreement, Waksman

was to receive 20% of all streptomycin royalties. The Royalties eventually amounted to some $12 million of which a large portion funded the Waksman Institute of Microbiology at Rutgers University.

Figure 42: Selman Waksman
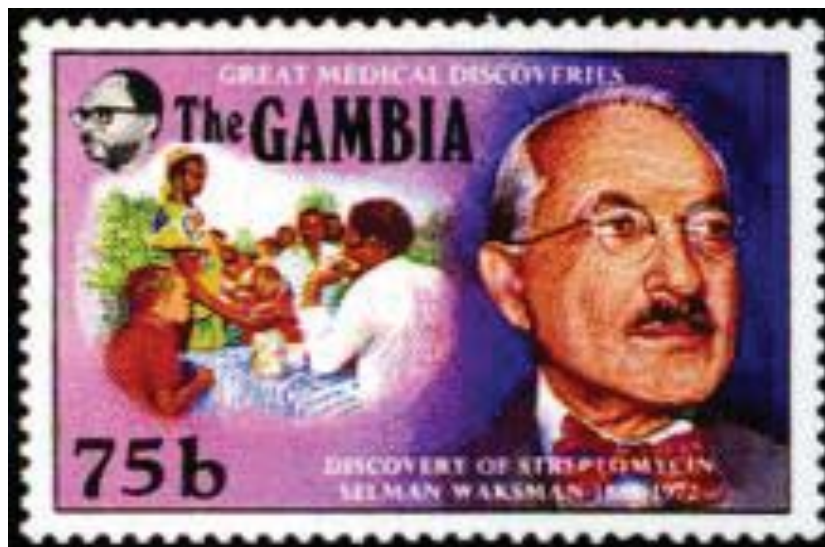
Postage stamp from The Gambia, 1972

Chapter 7.2

Towards a 'cure' for tuberculosis

Desperate diseases need desperate cures.
Latin Proverb

Just prior to the period when streptomycin was being developed, Jörgen Lehmann in Gothenburg, Sweden, had designed and developed a chemical agent that would kill MTB. This compound was para-aminosalicylic acid (PAS). Due to the Swedish safety requirements, it was only available two years after streptomycin was released onto the market but had actually been discovered before streptomycin. PAS proved to have a bacteriostatic action only.

The first setback to progress was the discovery that both drugs could have serious side effects. The first major clinical study took place in 1948 when the results of the UK Medical Research Council's randomised controlled trial of streptomycin efficacy was published (Yoshioka, 1998). The results revealed that monotherapy with streptomycin produced good results with sputum clearance and improved chest X-ray findings. However, Crofton and Mitchison (1948) reported the first streptomycin resistance. The Medical Research Council's follow up study revealed a significant relapse rate and the five year survival rates were the same between treated and untreated patients (Fox et al., 1954).

The major discovery of isoniazid in 1952 produced another advance. Two pharmaceutical companies, Hoffman La Roche and Bayer Chemicals discovered its action against MTB at the same time. However, it was revealed that the compound had first been synthesised in 1912 by two Czechs. It was soon discovered that resistance rapidly developed to this drug when given alone.

It soon came apparent that combination therapy was needed and triple therapy regimen was advocated, namely – streptomycin, PAS and isonazid. It was found that drug resistance occurred to only one of the drugs when they were given in combination (Keshavjee and Farmer, 2012).

Progress, thereafter, was aimed at shortening the treatment time which had been 9-12 months of drug therapy. Newer drugs became available such as pyrazinamide (PZA) in 1952,

cycloserine (1952), rifampin (1957) and ethambutol (1962). All these drugs were subjected to trials to establish the best combination and the shortest duration required.

Rifampicin was discovered in Italy, and it allowed real progress in reducing therapy time and improved compliance. When combined with isoniazid and ethambutol, treatment times were reduced to less than nine months. The avoidance of frequent intramuscular streptomycin was a real boon to patients. Thereafter, further drugs were found with varying efficacy and these are listed in table 1.The progress in drug therapy was not accompanied by progress in diagnosis. Most centres still used the microscope to diagnose tuberculosis and relied on the staining techniques of Ziehl and Neesen founded in the 19th century.

As pointed out earlier the mortality from TB was falling steadily prior to the discovery of chemotherapy (figure 34) and the decline in the disease accelerated thereafter. This was the final blow for the sanatorium movement and a steady closure of most sanatoria occurred subsequently. The feeling at this time was summed up by Waksman (1965):

> *Antibiotics have appeared, sanatoria have disappeared; as far as the public are concerned the problem is solved the disease has been conquered.*

The reality was more in keeping with the title of the paper by Boise et al. (2013):

Tuberculosis: from an untreatable disease in antiquity to an untreatable disease in modern times?

Table 1.   Anti-Tuberculous Agents Available in 2013

Category	Indication for use in TB treatment	Drugs
1.	First-line, oral anti-tuberculous agents	Isoniazid (INH) Rifampin / Rifampicin Ethambutol Pyrazinamide Rifabutin
2.	Injectable anti-tuberculous agents, second-line anti-tuberculous agents	Streptomycin Kanamycin Capreomycin Amikacin
3.	Fluoroquinolones, second-line anti-tuberculous agents	Levofloxacin Moxifloxacin Gatifloxacin
4.	Oral bacteriostatic, second-line anti-tuberculous agents	Ethionamide Prothionamide Cycloserine p-Aminosalicylic acid Terizidone
5.	Anti-tuberculous agents with unclear efficacy and/or role	Linezolid Clofazimine Clarithromycin Thioacetazone Imipenem Amoxicillin/ Clavulanate Dapsone

Table is based upon that of Boire et al. (2013).

Part 2: The Public Health Dimension

Chapter 8: Early Days in the Antipodes

The cure for this ill is not to stand still.
Rudyard Kipling, Just So Verses.

Chapter 8.1
The Arrival of Tuberculosis in New Zealand and the Aftermath

There is no evidence that the Maori brought TB with them when they arrived in New Zealand from Polynesia. In contrast, the first reports describe them as a vigorous people. It seems certain that tuberculosis arrived with the first European settlers in the early 19th century. Indeed, it has been surmised that many immigrants came with the thought that the sea journey and the climate in New Zealand would benefit their pre-existing tuberculosis (Bryder, 1991).

The estimate of the rates of TB in New Zealand in 1872, when the first national statistics were collected, was 126 per 100,000 of the population[23]. By 1899, TB accounted for 10% of all deaths in the settler community (Registrar-General, 1900), Maori TB deaths statistics being excluded at that time. No specific measures were taken during this period to address tuberculosis as a health problem, victims being left to be cared for by the charitable organisations (Bryder, 1991).

With the setting up of a Department of Public Health in 1901, with Dr. J.M. Mason as the Chief Health Officer, attention eventually focused on tuberculosis. The discovery of MTB by Koch was well recognised, and moves to treat the disease were started. Mason in his 1901 annual report stated: *..until some place has been erected where patients can be treated in accordance with the latest scientific manner, the best results cannot be hoped for* (Bryder, 1991)*.*

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[23] The equivalent rate in the UK at that time was 300 per 100,000 of the population.

Subsequently, the first sanatorium was set up in 1903, Te Waikato, in Cambridge and it closed in 1922. The principles of treatment were the same as in Europe – good food, fresh air, rest and to this was added graduated labour. The latter part failed as not many patients could be persuaded to take up work. Sanatoria spread across the country[24]. In 1909, Cashmere Hills Sanatorium was opened and run by the North Canterbury Hospital Board (figure 43B). There was a steady decline in the rates of TB infection over the next number of years, and by the 1980s it had stabilised to a rate of 10 cases per 100,000 of the population. Despite this, the Maori population had a ten times greater incidence than the non-Maori (Das et al., 2006)[25]. The reason for this lay partly in the fact that the Department of Health directed their anti-tuberculous campaign entirely at Europeans in the early twentieth century. An action of stupidity they would later regret. By the 1930s enthusiasm for the sanatorium form of treatment waned in New Zealand (as elsewhere). It was replaced by surgery, albeit with little more success. Surgery was quickly abandoned once effective anti-tuberculosis drugs appeared. In the 1960s sanatoria were closed or converted to geriatric homes.

Although New Zealand had one of the lowest rates in the world (Maori rates excluded), this did not lead to complacency, especially in relation to school children. School nurses were involved in searching for children who were likely to be infected with tuberculosis. After discussion with their parents the children would be offered convalescent home care or be sent to a health camp.

The health camp movement was a uniquely New Zealand concept. Originally they had started as camps for malnourished children predisposed to tuberculosis. The scheme with modifications has been running now for over 95 years. The first camp was held in Wanganui and was the result of the ideas and work of Dr. Elizabeth Gunn. Dr Gunn was a school medical officer in Wanganui (figure 47). She had qualified in medicine at Edinburgh University, Scotland and had spent time as a medical officer in the military. She had been impressed with the open-air schools she had seen in Britain for TB sufferers, and it was these that gave her the idea of a camp system to improve child health. The success of the

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[24] A brochure about a South Island sanatorium published in 1928 said: 'It would be hard to find a happier, more healthy looking lot of men and women than those at Waipiata'. (sic)

[25] The 2014 rate for Maori was 5.3 per 100,000, equates to 36 people per year. www.surv.esr.nz

early camps led to the foundation of the National Federation of Health camps. By then the original stress on tuberculosis had shifted to child health and welfare in general.

Funding of the health camps came partially from the Government and from the sale of health stamps (figure 44) and later TB seals (figure 46). These were intended also to raise the awareness of health camps and bring them to the consciousness of New Zealanders. Their issue was accompanied by posters which were said to promote New Zealand images as a supposed healthy, humanitarian country concerned with its future (figure 45) (Tennant, 1994).

While these camps have continued into the 21st Century there is debate as to their continued existence in light of the changing concepts of what is therapeutic about camps (Kearns and Collins, 2000).

The immediate post war period of New Zealand TB history has been well described by Dunsford (2008) and includes the introduction of the TB Act of 1948. She points out that the continued improvement in living standards and drug therapy saw a dramatic fall in mortality and incidence. This also applied to the Maori population but their rates still lagged behind those of the European population. This was the situation by the end of the 1970s. Das et al. (2006) pointed out that from 1996 the incidence rate for tuberculosis did not fall. They attributed this state to the migration of infected people from high incidence areas to New Zealand with refugees contributing at least 25% of all new tuberculosis cases. Despite this the rates for New Zealand born people were falling except for Maori and Pacific people (figure 43A). The rate for the Pacific group, in 2010, reached 19.5 per 100,000 of the population and the other ethnic groups are shown in table 2 (Bisielo et al., 2011).

These observations were developed further by O'Toole and Freeman (2013). Between 1995 and 2011 the proportion of TB cases occurring in overseas-born persons had increased from 47.5% to 75.4 % by 2011. A large proportion of overseas born individuals appear to have been infected by the time of their arrival in New Zealand. This is supported by molecular epidemiological evidence from the genetic lineage of the MTB strains causing infection (Yen et al., 2013).

Figure 43A: Tuberculosis notification rate: crude rate per 100,000 New Zealand born population, 1922-2004
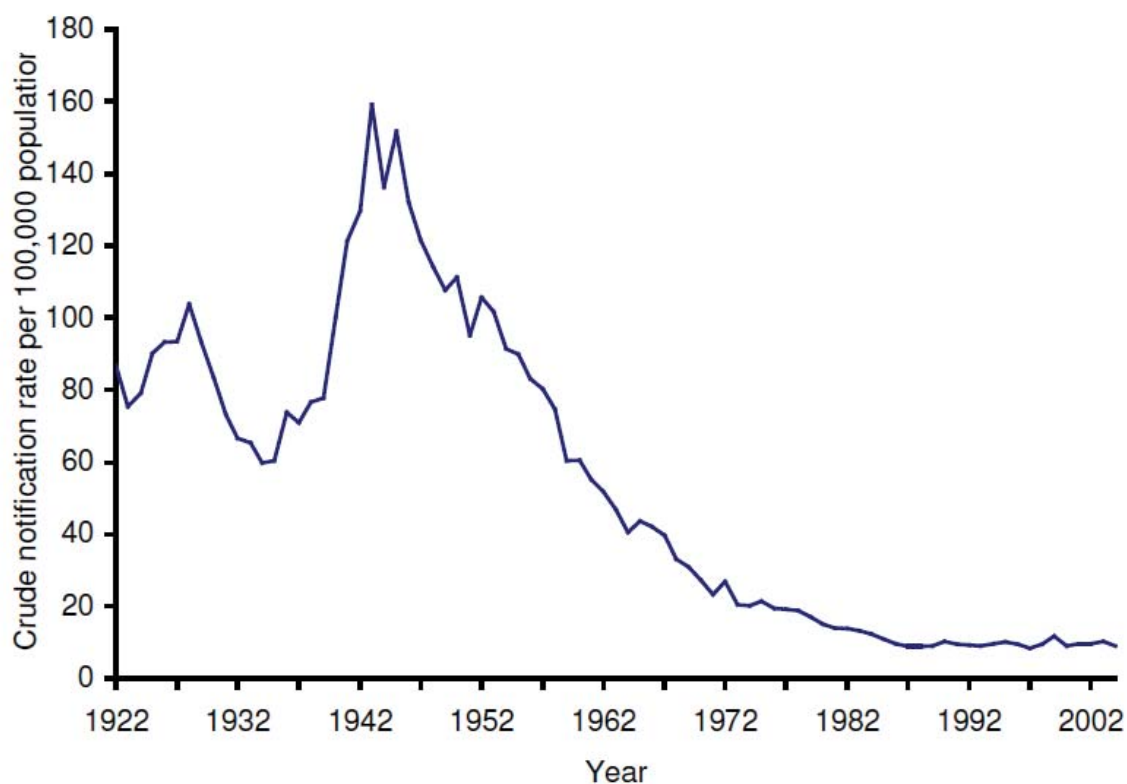
Source: TB Annual Report, 2013 New Zealand, Ministry Health, Wellington

Trend in tuberculosis incidence, 1980-2009
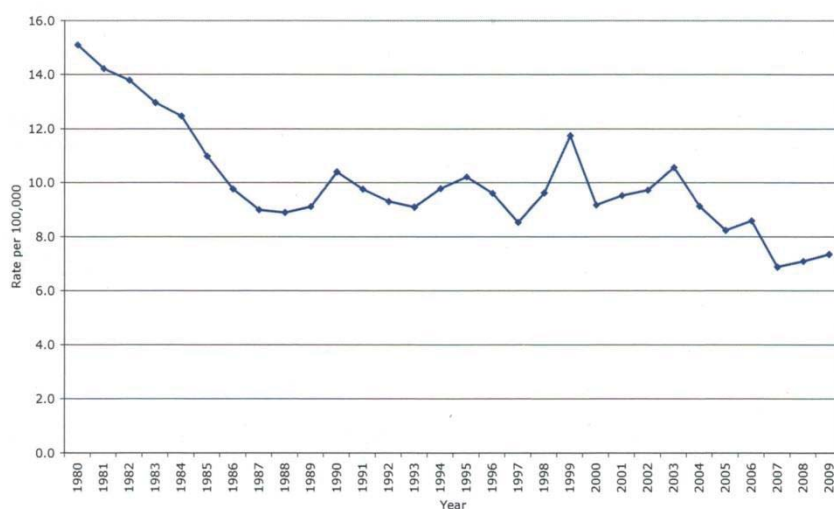
Source: Ministry of Health: guidelines for tuberculosis control (2010)

Table 2:   Ethnic distribution of notified tuberculosis in 2015

Ethnic Group	Rate of TB per 100,000 of the population
Maori	3.9
Asian	36.7
Pacific	19.5
Middle Eastern, Latin American, African	15.8
Other	0.6

Source: Notifiable diseases in New Zealand: Annual Report 2015

Figure 43B: Cashmere Hills Sanatorium, Christchurch, circa 1920.

Exposure to fresh air and sunlight were critical elements of the treatment. These are the women's shelters at the Cashmere Sanatorium near Christchurch, which were located on the north-facing side of the Cashmere Hills. The large windows and multiple sliding doors were designed to let as much air and sun in as possible. Some of the shelters were on wheels so they could be moved to catch the sun.
Source: Encyclopaedia of New Zealand www.teara.govt.nz accessed 30th August 2016.

Figure 44: First New Zealand Charity Stamps

'Help stamp out Tuberculosis' and 'Help promote health'

Charity stamps of New Zealand, 1929 and 1930. Designed by Stanley Davis and produced by the Government Printer, Wellington. Strictly called semi-postals as one penny covered postage and the other penny went to charity use.

Figure 45: Health Promotion Poster, 1930
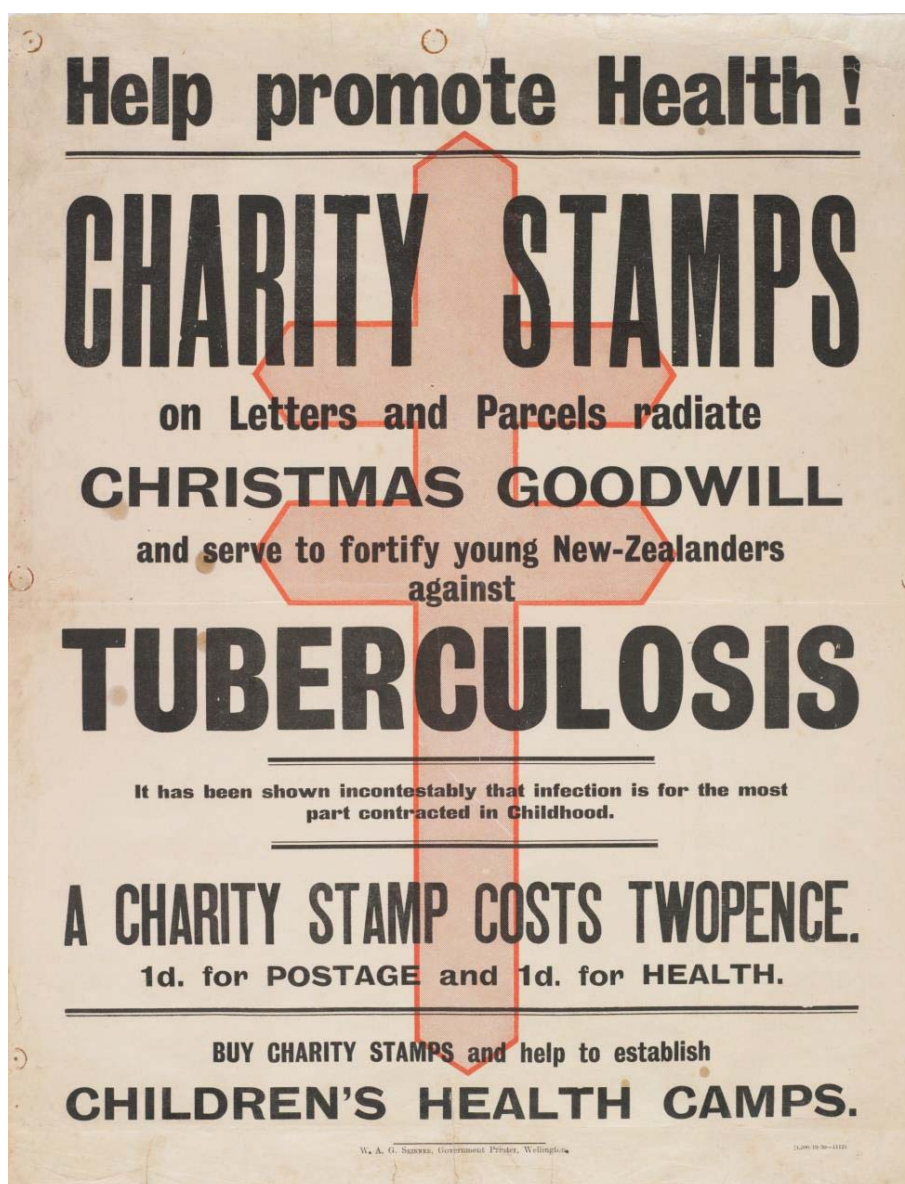
'Help promote Health! Charity Stamps': 1930. Lithograph 570x445 mm. Printed by WAG Skinner, Government Printer , Wellington.
Copied by permission of Te Papa, Wellington (GH.009878)

Figure 46: Early New Zealand Christmas Seals

Christmas seals, 1946, 1960, 1967 raising funds for tuberculosis relief, no postal value.

Figure 47: Dr. Elizabeth Gunn, Health Camp Founder

New Zealand Post 1969

Chapter 8.2

A brief summary of the Australian experience of tuberculosis

The first confirmed death from tuberculosis in Australia was that reported by Captain Cook. A seaman, Formby Sutherland, from the *Endeavour* died of consumption on May 1st 1770 and was buried at Botany Bay (Proust, 1991). The disease was brought to Australia en masse by the First Fleet in 1778. It did not present as a major health problem until the massive influx of immigrants at the time of the Gold Rush in 1851-1861. This created the squalid, overcrowded conditions that TB thrives on. Dr Harry Wonderly was the first in Australia to carry out important tuberculosis screening prior to the Second World War, when he developed a method of radiological screening. This was designed in particular to protect health workers from those patients with unidentified tuberculosis (Wunderly, 1940).

The recognition that tuberculosis was a national health hazard occurred when the Ministers of all the States held a conference in 1943. From this meeting stemmed the creation of the Tuberculosis Act (Williams and Phelan, 1995). Following this Dr. Wunderly was appointed as Director of Tuberculosis in the Commonwealth Health Department. He proposed that each state develop adequate facilities to control the disease and there should be an effective national campaign. In New South Wales, Dr. Cotter Harvey was a strong advocate for tuberculosis care; examination of the archives of the Royal Australasian College of Physicians reveals a great deal of active work by him (figure 48).

Following the active campaign against TB and the introduction of compulsory notification of the disease, there was a steady fall in the rates of tuberculosis up to 1990 (see figure 49). Thereafter, the rate remained constant at about 8 per 100,000 of the population. The major change was in the community pattern of those affected. Those not born in Australia constituted 37% of those notified in 1970 while by 1981 this figure had risen to 81% (Toms et al., 2015). By the years 2012 and 2013 progress had been made in the rates of TB with a general population rate of 5.8/100,000 and 5.5/100,000 respectively. However, those born overseas had a rate of 19.5 and 18.4/100,000. Fifty percent of all overseas cases came from five countries with India providing the most. Specifically, the rate for those born in Somalia was 243/100,000.

It will be seen from this comparison with New Zealand that the patterns have been very similar with both countries experiencing that the main prevention strategies need to be directed now at those individuals born in high incidence areas.

Figure 48: Archival letter on tuberculosis control
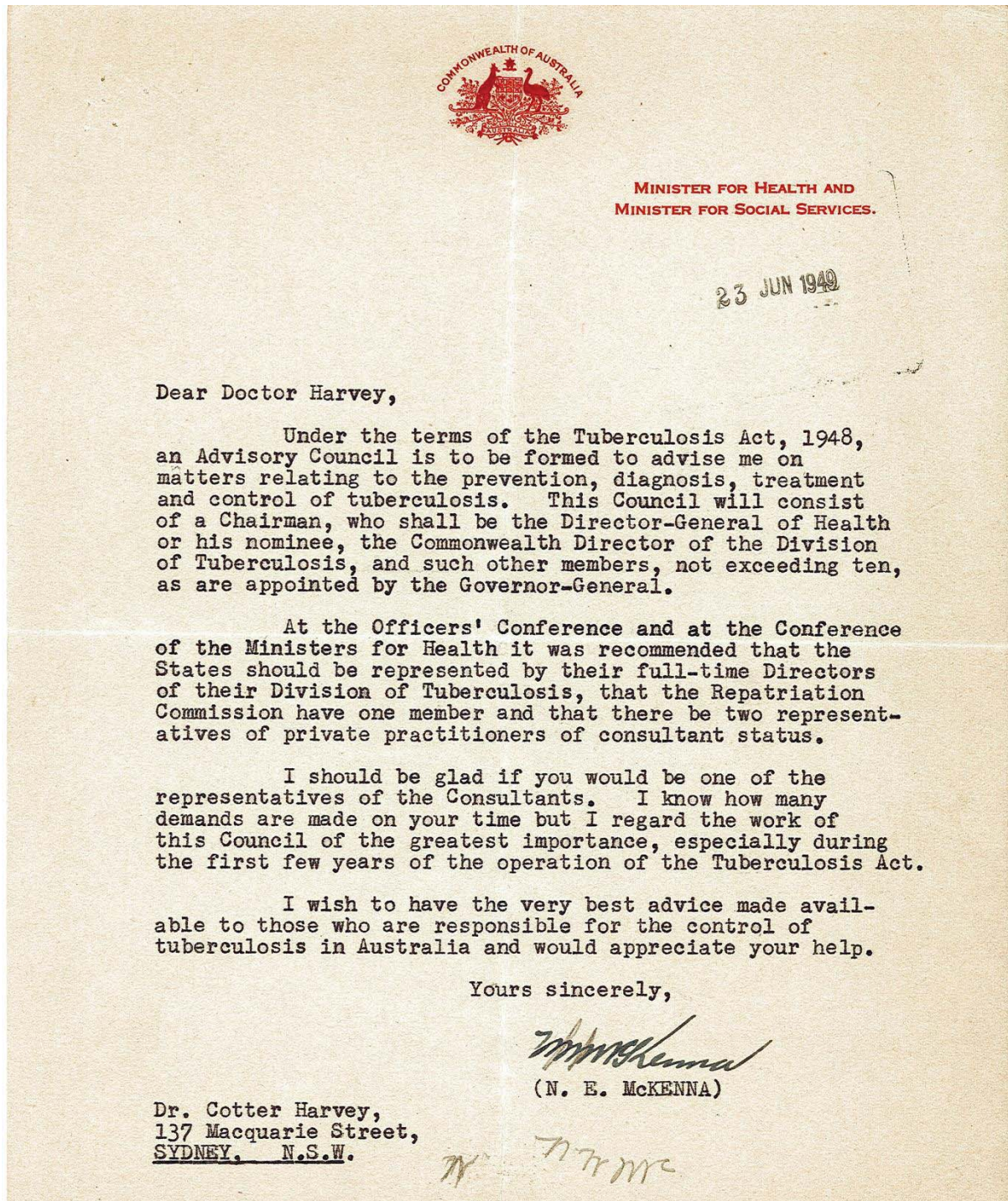
Figure 49 : Notification rates for tuberculosis, Australia, 1960-2013
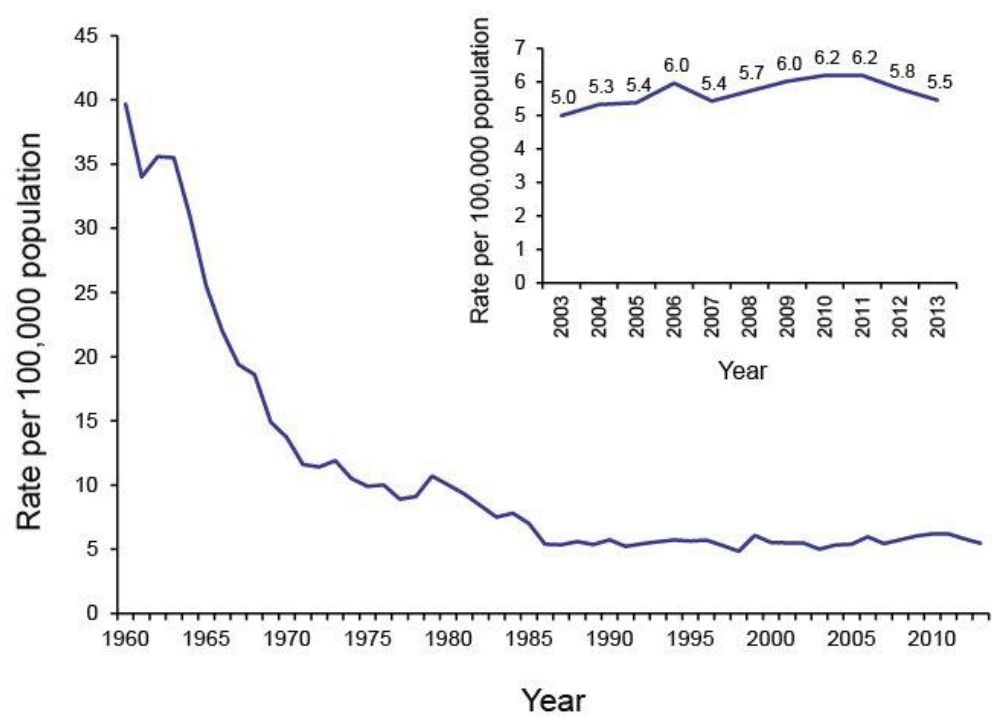
Source: Toms et al. (2015)

Chapter 9:

Public Health and Mass Miniature Radiography

The picture is worth a thousand words.
Anonymous

9.1 The Background

The place of radiology in the diagnosis and management of tuberculosis soon became established and proved extremely useful in clinical practice. However, the need for mass screening of recruits in the First World War revealed the limitations of the single plate X-ray method.

An epidemic of tuberculosis in Rio de Janeiro in 1930 stimulated Dr. Manuel de Abreau (1884-1962)[26] , a Brazilian respiratory physician, to develop a system for mass miniature radiography (MMR)[27]. Subsequently, his original method was modified and improved. However, the principle of using fluoroscopy images which were then photographed remained. Improvements involved the use of fast film and improved cameras. The roll of film was held within a 70mm. cassette and eventually the process became fully automated and the pictures obtained were stored on microfilm. When the film was in due course read by the radiologist, and if any doubts existed as to the diagnosis or quality of the image, a full plate X-ray was requested. This method also reduced the extent of the radiation exposure overall for staff and patients (Kerley, 2014).

The MMR method soon became popular worldwide and was deemed a cost effective way of detecting those with tuberculosis and symptom free carriers. By 1936, Britain had MMR in full use nationally. The MMR unit became installed in trucks and buses and thus formed a mobile Public Health screening tool which could visit any part of the country (figures 50, 51, 52). Figure 53 shows a model of the layout of a typical mobile unit. Its design allowed a rapid flow of patients through the system.

Sweden soon followed this model and employed MMR from 1940 to 1970 throughout the country. Over a ten year, period 90% of the Swedish population had been x-rayed. The

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[26] Dr. De Abreau, a smoker and a respiratory physician, died of lung cancer.
[27] Sometimes referred to as 'abreugraphy', 'abreaugrafia' or 'radiophotography'.

service was free and remained a voluntary act for the population. The success of this scheme was said to be due in part to the close cooperation forged between the media and the health professional groups. The engagement of journalists during each phase was said to be the reason for the high coverage rate (Julich, 2016).

During the Second World War, the USA forces successfully screened 20 million men as part of their recruitment examination, all by MMR. The procedure became very popular in factories and mines for health monitoring during the 1950s. The first unit in New Zealand was a mobile Xray unit in Taranaki that had been funded by the Taranaki Maori Trust Board (Francis, 1956).

As the incidence of tuberculosis fell in the developed countries, the World Health Organisation (WHO) in 1970 recommended that routine MMR should be stopped. The reason behind this was the dramatic fall in incidence from rates of 150/100,000 in 1900 to levels of 5/100,000 in 1950. This rate made the process no longer cost effective and other screening methods would be more appropriate. MMR no longer justified the risks associated with ionising radiation.

The procedure was still used in prisons and immigration centres and was justified by advances in digital radiology and the requirement for lower doses of radiation in more modern X-ray machines. There may still be a return of MMR with the changes which are occurring in the 21st century in tuberculosis rates.

Figure 50: Public Health posters advertising MMR

Source: The Stroke Association, UK

Figure 51: South Korean postage stamp advertisement for MMR

South Korea: Miniature postal sheet, 1961

Figure 52: Samoan Stamp illustrating MMR

Western Samoa 1967

Figure 53: Model of Mobile MMR Unit
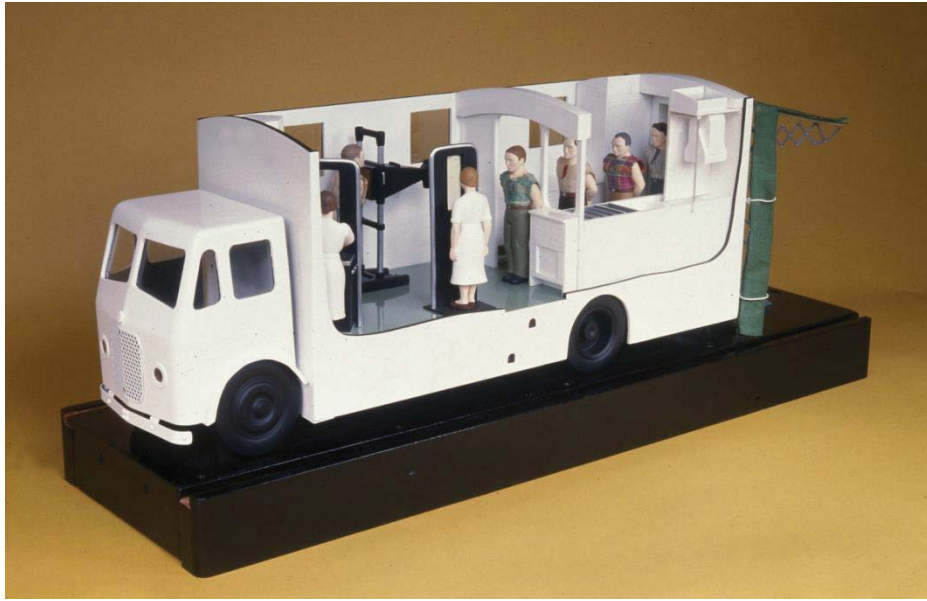
Source: The Science Museum, London

Chapter 9.2
The Glasgow Mass Radiography Campaign, 1957.

Be X-rayed don't trust to luck.
Glasgow Campaign slogan

Following the Second World War, the incidence rates of TB were falling overall within the UK, however, Glasgow, Scotland remained a 'black spot' with the highest incidence of the disease in Western Europe. This was attributed to and exacerbated by the poor housing stock, malnutrition and the poverty that still remained in the city. In fact, Glasgow's TB incidence had actually risen from 139/100,000 in 1945 to 200/100,000 in 1956, and the death rate in 1956 was 25/1,000 of the population. This latter figure was twice that of the South of England. This situation created a political storm among the Scottish members of Parliament (Levitt, 2003). Eventually, after several pilot schemes, not always successful, a decision was made in February 1956 to carry out 'the detection of the infectious person, his treatment and his contacts' (Levitt, 2003). The principal weapon was to be an X-ray survey by MMR.

The advent of the MMR Campaign, as proposed, would be at that time the largest public health campaign undertaken in UK history. Considerable advanced publicity took place with billboard and radio advertising. In addition, special sponsorship by companies occurred and films were prepared. The opening events were of Hollywood proportion (figure 54). Some 12,000 volunteers had been recruited, and every household in Glasgow had received a letter inviting them to have an X-ray and follow up checks were instigated for those who did not come forward. The volunteers carried out house to house visits. The whole gamut of propaganda was instituted and consisted of films, advertisements, posters, stickers, loudspeaker vans, prize competitions and even aeroplanes dragging banners (figure 56). The main sponsors were the Glasgow Corporation and the Western Regional Health Board.

The Campaign started on the 11th March 1957 and finished on the 12th April 1957. During this period 37 mobile MMR units were employed from all over the UK and 714,915 people were X-rayed. This amounted to 76% of the Glasgow population (Figure 55). From this group, 2,842 people (0.4%) were detected with tuberculosis and subsequently treated.

The success of this campaign led to similar schemes throughout Scotland and overall 50% of the adult population were screened. Subsequently, there was a dramatic fall in the mortality and a reduction in notifications. A childhood scheme of BCG vaccination had been commenced a decade before and this itself was now reaping its reward.

The Glasgow campaign was described as a 'blitzkrieg' on the disease. Not everyone was convinced of the success of the scheme without addressing the underlying problems of the city. Glasgow had the bulk of Scotland's unemployed, and there was poverty and overcrowding, poor housing and other health related problems[28]. Certainly, many people received treatment before it became obvious they needed it resulting in a reduction in spread of disease. Even in 2012, while the TB rate was 6.5/100,000 for the UK nationally, for Scotland overall it was 8/100,000 while Glasgow's rate remained at 13.7/100,000[29].

It would appear axiomatic that housing would play a major role in the causation of this state of affairs (figure 57). However, a paper published soon after the Glasgow Campaign finished

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[28] Victorian Realist Artists such as Cruikshank portrayed similar problems as poverty, unemployment, alcoholism, forced emigration and overcrowding one hundred years before with little subsequent remedial action taking place in Glasgow.

[29] Scottish Government Publication (2013) www.gov.scot/publications/2013

suggested that the highest incidence of tuberculosis was not related to the worst houses themselves but to the degree of overcrowding (McMillan, 1957). McFarlane (1989) developed this theme and showed the critical discriminating factor did appear to be overcrowding and to a lesser degree the state of the houses themselves. Be that as it may Glasgow was awarded a greater share of council (State) housing as a result of the campaign results.

Figure 54: Invitation to the opening reception of the MMR Campaign

THE LORD PROVOST
AND
CORPORATION OF THE CITY OF GLASGOW
request the pleasure of the company of

Dr Dale

at a Reception in the City Chambers, Glasgow, on Friday, 8th March, 1957, at 7.30 p.m., to the Staffs of the X-Ray Units coming to Glasgow for the Mass X-Ray Campaign.

MUSIC   DANCING   BUFFET REFRESHMENTS

DRESS INFORMAL

City Chambers, Glasgow   A reply by return is requested to
February, 1957   The Lord Provost's Secretary.

THIS CARD TO BE SHOWN AT THE DOOR
MOTORS AT 11.30 P.M.

Source: Courtesy of the Royal College of Physicians and Surgeons of Glasgow

Figure 55: Queues forming for X-ray, 1957

Source: Burrell Collection Photographic Library, Glasgow, Scotland

Figure 56: Advertisement by local tramcar
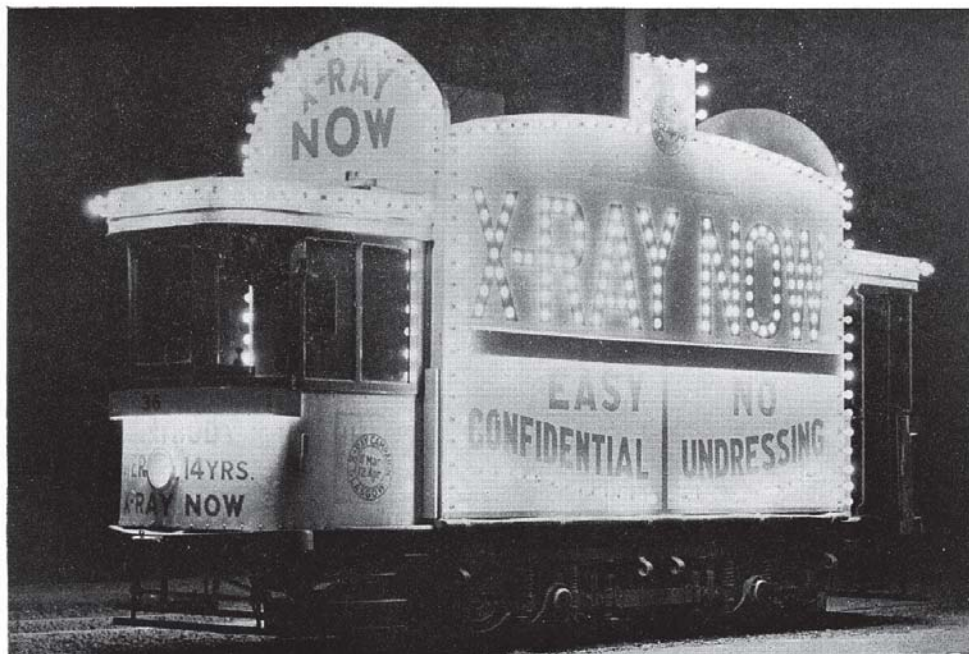
ILLUMINATED TRAM-CAR (page 16).

Source: Wellcome Library L0016012

Figure 57: Housing, Glasgow, 1957

Source: Glasgow City Archives

Chapter 10:
Health Promotion and Tuberculosis: Strategies for Funding, Education and Public Awareness

In general, the use of internationally recognised symbols is now more effective than the rendering of messages in words.
World Health Forum, 1989

The first meeting of tuberculosis experts took place in 1867 with the intention of sharing strategies to fight tuberculosis. In 1902 a similar meeting, held in Berlin, established the Central Bureau for the Prevention of Tuberculosis. It adopted as its symbol the Cross of Lorraine. World War 1 saw the closure of the organisation. However, in the 1920s, 31 nations founded the International Union against Tuberculosis (IUAT). This was later amended to include Lung Disease (IUATLD). The Cross of Lorraine was retained as its logogram.

Figure 58: Original Cross of Lorraine Symbol and Current Modification

Source: IUAT

The Cross of Lorraine is a two barred cross with the upper bar shorter (titulus). Its use as the symbol of opposition to tuberculosis was suggested by Dr. Gilbert Serison at the 1902 meeting of the Central Bureau. It symbolised the 'crusade' against tuberculosis and as the Duke of Lorraine was a distinguished Crusader and Governor of Jerusalem his symbol was suggested and adopted and later modified by the Union (figure 58). A double crescent was adopted by Islamic Societies as their motif.

The IUATLD has been active for many years now in organising conferences, coordinating clinical trials and conducting TB surveillance. Recent activities have been directed at Developing Countries and HIV and TB. It is linked with the WHO and the publishing of the annual report which gives a comprehensive assessment of progress in tuberculosis control programmes, research and funding. This report summarises the situation in over 200 countries and has done so for 20 years. The Red Cross is the other agency involved with TB, running programmes involved with increasing public awareness, prevention and treatment protocols.

The following sub-chapters illustrate specific practical methods that have been used to educate, fund and raise awareness of tuberculosis. There is a definite historical aspect to these methods as with time the approach changes as the priorities change. This is exemplified by the stopping of funding for sanatoria to the need to fund HIV education and information. Illustrated examples are, therefore, presented of many of these past and present approaches using a number of different media.

Chapter 10.1   Posters

Illustrative posters soon became an effective tool in public health education and fund raising. Among the more eye-catching and emotionally evocative tuberculosis posters were those designed to raise funds for veterans who had contracted the disease while serving in the First World War. An annual fundraising campaign backed by a private French group with support from the French and American governments, the Journée Nationale des Tuberculeux, used posters commissioned by leading artists. Figure 59 is an illustration from French caricaturist Abel Faivre. Faivre became famous for his posters supporting the French military effort during the war. This image of a weary soldier with a nurse's hands on his soldiers is accompanied by the powerful message, 'Save them'.

In figure 60, the poster by the celebrated French symbolist painter, Lucien Lévy-Dhurmer, is entitled *A retired soldier under a blossoming tree supports himself with a walking stick*. An impressionistic sea separates the soldier from the city in the background. Contrasting the

soldier's feelings of isolation and despair with the beauty of the landscape, the painting is designed to provoke an empathic response from the viewer.

Raising funds for sanatoria and advertising specific institutions was an early use of posters. Figures 31 and 61 are examples of posters celebrating the place of these institutions for the care of patients with tuberculosis. There are a large range of posters that were produced for educational purposes. I have included a selection from different cultures to stress the worldwide problem of tuberculosis (figures 61-66).

Figure 59: National Tuberculosis Day

Source: Abel Faivre, Paris circa 1919, Image A026647 History of Medicine

Figure 60: Old Soldiers: National Tuberculosis Day

Source: Lucien Lévy-Dhurmer, National Library, USA

Figure 61: Sanatorium Poster, 1905

Source: Drawing/print after H.C. Ulrich (1905)
Sanatorium Appeal for Tuberculous Children, Zurich Colour Lithograph
Welcome Institute WI no. L0073310

Figure 62: Belgian Red Cross Poster for TB Hygiene
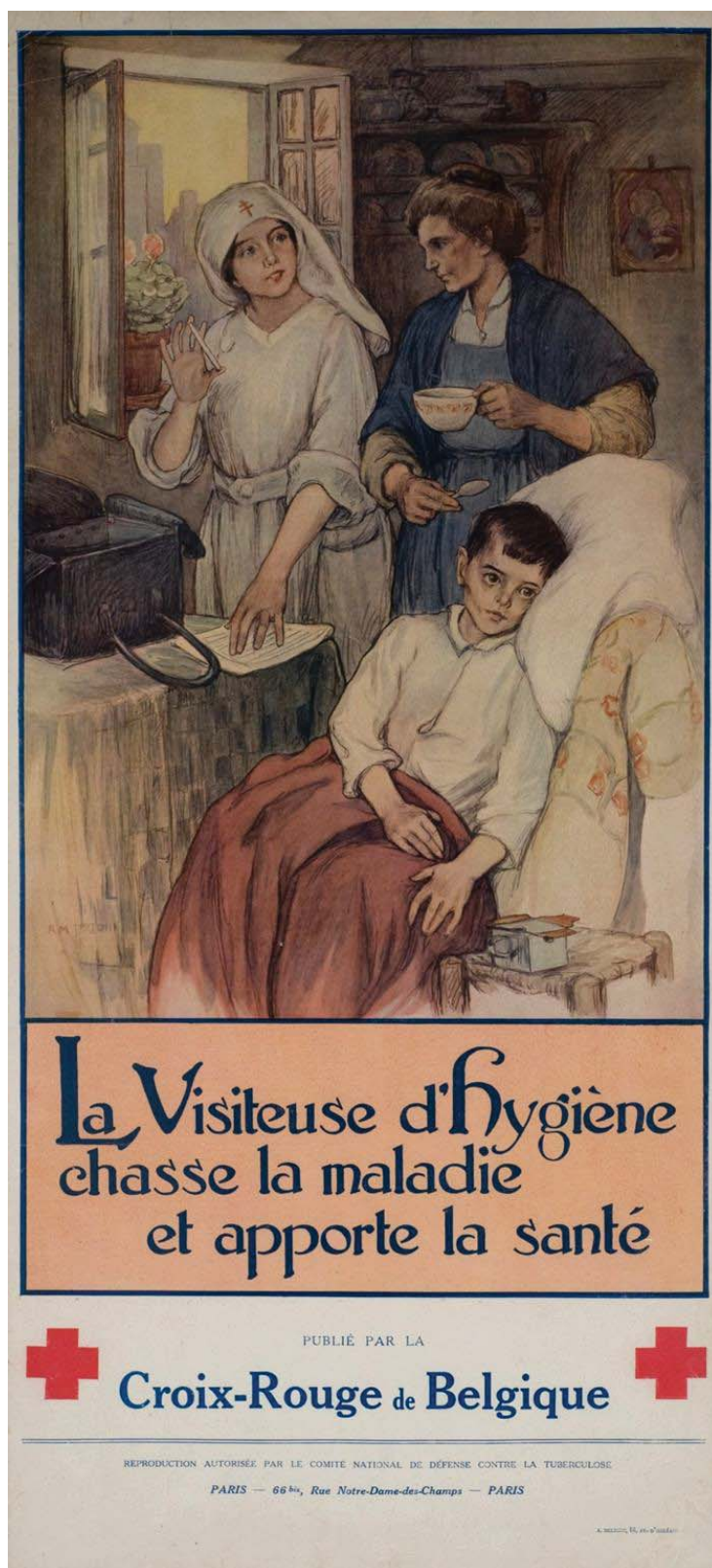
Source: US National Library

Figure 63: "Think TB" USA
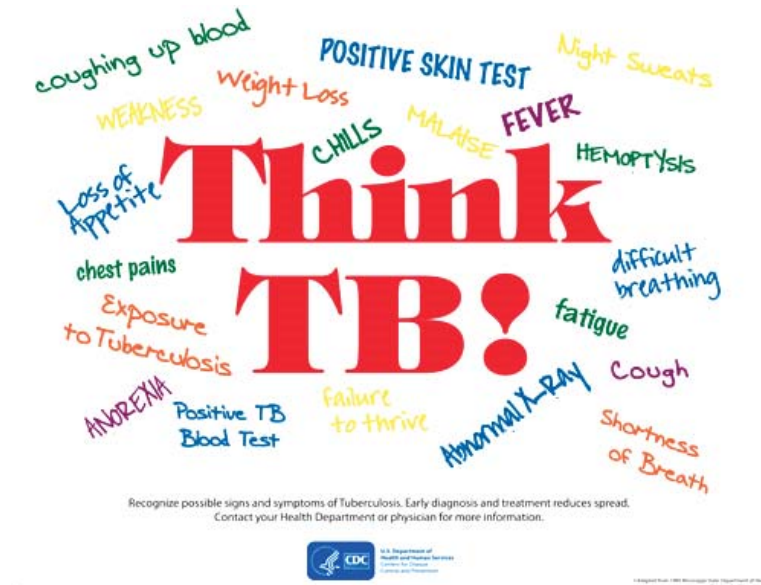
Source: Centres for Disease Control and Prevention (CDC), USA

Figure 64: MMR Campaign, China

预防肺结核
要定期进行肺部透视

北京市结核病防治所　东城区结核病防治所 印

Source: MMR Campaign China, US national Library

Figure 65: TB Campaign, Canadian First Nations
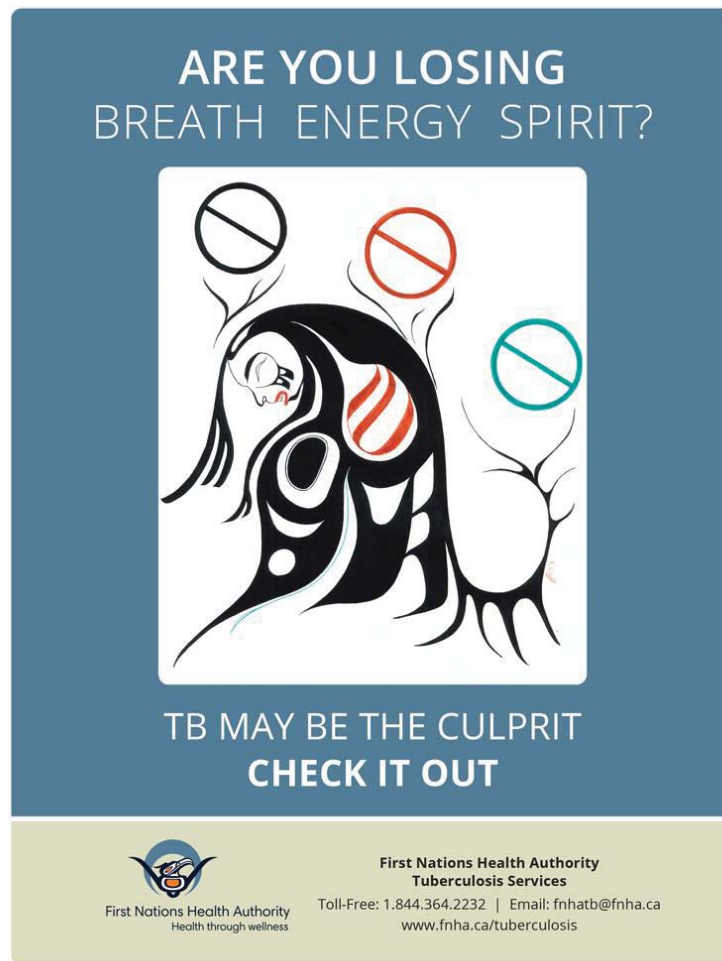
Source: First Nations Health Authority, Canada

Source: Works Progress Administration - Public Health campaigns tried to halt the spread of TB. This poster, created between 1936 and 1941 advised the public to have good sleeping habits, eat well, and get enough sunlight exposure.

Chapter 10.2 Postage Stamps

Many health campaigns have been promoted on postage stamps.
World Health Forum, 1989

Since their introduction in 1840, postage stamps have evolved over the years into potent propaganda agents as well as their initial primary role as pre-payment of mail. The post, bearing stamps, goes from hand to hand, town to town and can reach the furthermost corners of the world (Stoetzer, 1953). This attribute provides a great medium for passing on messages – good or bad. These messages, once perceived, may be carried subconsciously and subtly conveyed and the process of repetition consolidates the message (Childs, 2008). It seems that for these reasons stamps have had a major role in tuberculosis funding and education.

The term 'Charity Stamp' was applied to certain issues when they carried a premium which was, in fact, a compulsory contribution to the funds of a specific charity. These stamps were also referred to as semi-postals. In certain countries, during a fixed period, they became the only postal stamps permitted and therefore became a direct tax. Many stamps have been produced which simply carry a message, and no premium is attached. In terms of tuberculosis these stamps usually bore the Cross of Lorraine somewhere in their design.

The first ever Charity Stamp was issued by New South Wales in 1897. It was in aid of the Consumptives Home (figure 67). Similarly, the first Charity Stamp in Europe was issued from the Netherlands and again for Prevention of Tuberculosis and for children (Voor het kind) (figure 67). New Zealand was early in producing a TB issue - 'help stamp out tuberculosis' (figure 44 & 45). Subsequent issues were in support of Health Camps (see Chapter 8.1).

Figure 67: The world's first Charity Stamp and Europe's first Charity Stamp

New South Wales, 1897   The Netherlands, 1906

Many stamps were intended to help fund sanatoria, and Finland, Belgium and the Philippines were prominent in this field (figure 68). Cuba, the Dominican Republic and many other countries were active in bringing TB to the notice of their citizens and especially the use of BCG (figures 36, 37, and 38). Examples of other TB stamps are given in figures 68 and 69.

Figure 68: Belgian and Finnish TB Stamps

Belgian Charity Minisheet May 1941

Finnish TB stamp, 1947

Figure 69: International Tuberculosis Charity Stamps

Kuwait, 1963   Belgium, 1936   Morocco, 1949   Belgium, 1950

Venezuela, 1976

Chapter 10.2.1 Cancellations and Slogans

An additional way of adding more advertising impact on the mail was to add a slogan as the method of cancellation of the stamp that is used to prevent re-use. The introduction of franking machines made this possible and made it independent of the actual postage stamps. This method did not raise revenue but was often used to encourage people to have an X-ray or to buy Christmas seals (qv) which in themselves raised funds for tuberculosis charitable activities. Figure 70 illustrates examples of these cancellations and Figure 71 shows an anti-tuberculosis stamp of Belgium with an additional postal cancellation with a TB message. Finally, certain postage stamps had an overprint added as a TB message.

Figure 70 Examples of TB Postal cancellations

Figure 71: TB slogan on a Belgian TB stamp and overprint on a Philippine stamp

Chapter 10.3   Christmas Seals

Probably the best known of the fund raising methods for tuberculosis is that of the Christmas Seal. Einar Holbøll, a Danish postal clerk, developed the idea of adding an extra charitable stamp on mail posted as Christmas greetings. The money so raised could help those sick with tuberculosis. His idea was rapidly approved to the level of King Christian IX of Denmark.

The first seal was issued in 1904 and was based on a likeness of the Danish Queen Louise and the word Julen (Christmas) (figure 72). Over four million of the seals were sold in their first year. These sales raised sufficient money over the next few years to help fund a new

sanatorium which opened in 1911. Denmark has continued to produce Christmas seals up to the present day, and the sales and profits are managed by a special committee (Julenmaerkefonden).

The success of the scheme resulted in a rapid spread of the idea through the Nordic countries and subsequently, the Christmas seal idea spread worldwide. Most seals included the Cross of Lorraine to indicate the association with tuberculosis (figure 73).

The concept was brought to the United States by Emily Bissell in 1907 after she had read of the Danish experience (Sanitize and Shengelia, 2015). Her work in the field of fund raising was acknowledged by the US Postal Service in 1980 when they issued a stamp to commemorate her success. Currently, the bulk of the money raised from the sale of seals goes to the American Lung Foundation (figure 74).

The seals are sometimes referred to as Cinderella stamps but have no postal value and are only added to mail after they have been purchased. The proceeds as stated before go to charity. Most carry the name of the issuing country and are often found with postal cancellation by error. They have become items collected in their own right.

Figure 72: The First Danish Seal, the Danish seal of 1999 and Einer Holbøll

Figure 73: Examples of International Tuberculosis Seals

New Zealand (1969), South Africa (1914), Canada (1959), France (1926-29), Philippines, Hungary, Ecuador (1951), Mexico 1061-2)

Figure 74: USA Emily Bissell Postage Stamp and Seals

'Crusade against Tuberculosis': Emily Bissell, USA (1980),

Chapter 11: Public Health and Bovine Tuberculosis

Bovine tuberculosis is one of the most complex, persistent and controversial problems facing the British cattle industry.
Brooks-Pollock et al. (2014)

A history of tuberculosis would not be complete without a discussion of the role of *Mycobacterium bovis* (bTB) and the important part played by public health practice in its management and prevention. There has been in the past a strong link between animal and human tuberculosis. In New Zealand bTB has been present for as long as cattle and deer have been there. However, it is only when the TB caused by this organism entered into the possum population did it become a potentially serious threat.

Much of the scrofula seen in the Middle Ages was probably due to bTB (see The Kings' Evil). It was Villeman (Chapter 4.2) who showed clearly that tuberculous infected material could be transferred from one species to another. It was later recognised that there was a high incidence of TB in farm workers, slaughter house attendants and meat packers.

The organism bTB has a vast number of hosts ranging from domestic to wild animals. These include goats, bison (USA), badgers (UK), deer and bush tailed possum (NZ), elk (Canada) and kudu (South Africa). The total elimination of the organism and disease thus appears impossible. In terms of humans, the clinical infection is determined by the route of infection. Drinking infected milk usually results in cervical and mesenteric lymphadenopathy. Inhalation of airborne aerosols will lead to pulmonary disease. The disease caused by MTB as opposed to bTB cannot be distinguished clinically or radiologically. It requires specific laboratory tests to determine the type of mycobacterium[30] [31]. As a generalisation infants and young children are particularly susceptible to bTB (Kleeberg, 1984).

It was not until the 1920s that the dangers of animal transmission to humans was fully recognised and subsequently the dangers of infected milk. Prior to this in the Victorian era, most of the city milk came from cows living in sheds within the city limits. Thus it seems

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[30] Spoligotyping for rapid identification of bTB.
[31] bTB are naturally resistant to pyrazinamide (Bilar et al, 2010)

likely that much of the morbidity and mortality associated with tuberculosis at this time could have come from such a source (Davies, 2006). In certain areas of the world, some interesting cultural practices probably reduced this mode of infection. Some African people stored their animal milk in calabash[32] containers, and this resulted in the souring of the milk and this process destroyed bTB. It was also happenstance that in Turkey it was a traditional practice to boil milk thus sterilising it (Kleeberg, 1984).

By the 1930s it was realised that 40% of slaughtered cattle in England and Wales had obvious signs of tuberculosis. Once this was appreciated and the danger to milk was recognised, significant public health actions were invoked. Tuberculin skin tests for cattle were developed to enable routine testing of cattle for bTB (tbfreeengland, 2016). Animals testing positive were then slaughtered. In the UK, it was made illegal to sell infected milk and the tuberculin test was used to determine those infected cows. By 1935 a scheme to develop an 'Attested Herd' was introduced and later that year pasteurisation[33] of milk took place (figure 75).

By the 1960s there was regular compulsory testing of cattle and the slaughter of tuberculin reactors. These actions resulted in a very low level of the disease in cattle in the UK, and it appeared the problem had been solved.

However, in the UK in the 1980s it was noted that there was a rise in the number of infected cattle and this increase was found to be exponential. It was then found to be related to the rapid rise in the badger population (at that point a protected species) and the high incidence of bTB in the species. Culling of the badgers then took place but it did not solve the problem. The incidence of TB in badgers had however, risen from 5% in 1972 to the order of 38% by the year 2016 (tbfreeengland, 2016)[34].

This initial rapid fall in cattle in the UK did not hold true for the rest of the world. In Nigeria for example, 14% of cattle were found to be tuberculin positive and 12% of milk specimens

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[32] The gourd of the *Lagenaria sicerania* has been used in Africa for food storage, goblets and even fishing floats for many hundreds of years.

[33] The original concept was invented by Pasteur. Heating of milk to 60° C. for 20 minutes kills and reduces viable pathogens (e.g. tubercle bacillus, listeria and salmonella) for a defined period (expiry date). It does not involve boiling the milk hence it does not sterilise. UHT (ultrapasteurisation) sterilises the milk at 140°C for four seconds.

[34] Badgers have a latrine system, members of the same sett use the same defined area and grazing cattle can be exposed to infected material (Hardie and Watson, 1992).

were culture positive for bTB. This is explained by the introduction of larger herds of cattle and modern farm methods without the introduction of TB eradication methods and exacerbated by the African custom of free movement of cattle.

The infection of cattle and wild animals remains a major problem in many parts of the world. The UK example indicates that the problem is far from solved and the recent finding that alpacas exported from the UK to Norway were infected with bTB indicates the scale and intricacies of the problem (Brooks et al., 2014). The scale of the potential problem of infected possums was not recognised in New Zealand until 1967, and it was in 1971 that the link to cattle was confirmed. It was later shown that direct contact with dying tuberculous infected possum was necessary before cattle infection could take place. Thus, as with human TB, the problem of bovine tuberculosis, the potential for cattle infection and their milk contamination is far from solved. However, by 2011, New Zealand had a bovine TB rate some twenty times less than the UK due to possum control and by 2016 the rate had plummeted further. New Zealand had spent, however, some $NZ 80 million between 2013 and 2014 to achieve this result (www.bovinetb.info, 2016).

Figure 75: Louis Pasteur

Source: photograph by Nadar (Wikipedia)   France: commemorative stamps 1923-25

Louis Pasteur (1822-1895) (figure 75) became famous for his work on vaccines. However, he showed that heat treating wine and milk stopped bacterial contamination. He had established that the growth of microorganisms spoiled milk and by heating it to a temperature between 60-100°C most bacteria were killed (now termed pasteurisation).

Chapter 12: The Resurgence of Tuberculosis: 'How, When and Why' did it all go wrong?

Poverty conspires with the most deadly and painful diseases to bring a wretched existence to all who suffer it.
World Health Organisation, 1995

In the world of the 1970s, there was talk of the eradication of tuberculosis. What happened to cause the WHO to declare tuberculosis a 'global emergency' in 1993 (WHO, 1993)? The very success of chemotherapy for TB, with the closure of sanatoria had spelt out to the general public that the disease was no longer a health problem. The resurgence of TB was, however, more complex than simply the waning of public awareness.

There was also decreased attention to tuberculosis control and a reduction in public health infrastructure and funding. This again was probably due to the gains made and the falling population rates of morbidity and mortality from TB being seen in the developed countries.

Four main factors have been put forward to account for the resurgence (Murray, 2004). These are:

1. The development of 'Hot Spots' where TB flourished.

2. The deterioration of TB control.

3. Immigration of people from high prevalence countries to countries of low prevalence.

4. The arrival and spread of HIV infection and AIDS.

To this, I would add the effects of poverty and the development of drug resistance. While these factors can be discussed separately, they need to be regarded as interdependent and cumulative.

'Hot spots' are regarded as situations such as prisons, shelters for the homeless and even hospitals. The best reported and studied example of a 'hot spot' was New York City, USA. The incidence of TB within the USA as a whole was declining annually by 5-7% in the 33 years prior to 1986 (Division of TB Elimination, 2003). However, for the first time, in that year it was noted that the incidence rose. However, closer examination indicated that this

trend had started in New York, as early as 1978. This was even further exaggerated in the Harlem area of New York and the incidence rates are shown in Figure 76. By 1992, it was further shown that the New York TB cases represented 14% of all known USA cases and from this city alone 61% of all drug resistant strains (MDRTB) in the USA had emanated.

The USA Congress had decided during 1970-1 to change the funding methods for tuberculosis and revoked the funds earmarked for TB control. Instead, they bulk funded for communicable diseases en bloc. The resultant of this was that in New York the TB control services shrank considerably. During the same period, there were large numbers of immigrants entering the city from high prevalence areas carrying a considerable TB burden. The final elements were the arrival of HIV and AIDS in the city and just at the point when TB services were contracting. Thus hospital follow up of cases was disrupted and failures occurred in follow-up. The latter event certainly contributed to exacerbating the development of a drug resistance problem (Frieden et al., 1995).

Figure 76: Incidence rates of tuberculosis per 100,000 persons in Harlem, New York City
from 1970 to 1989
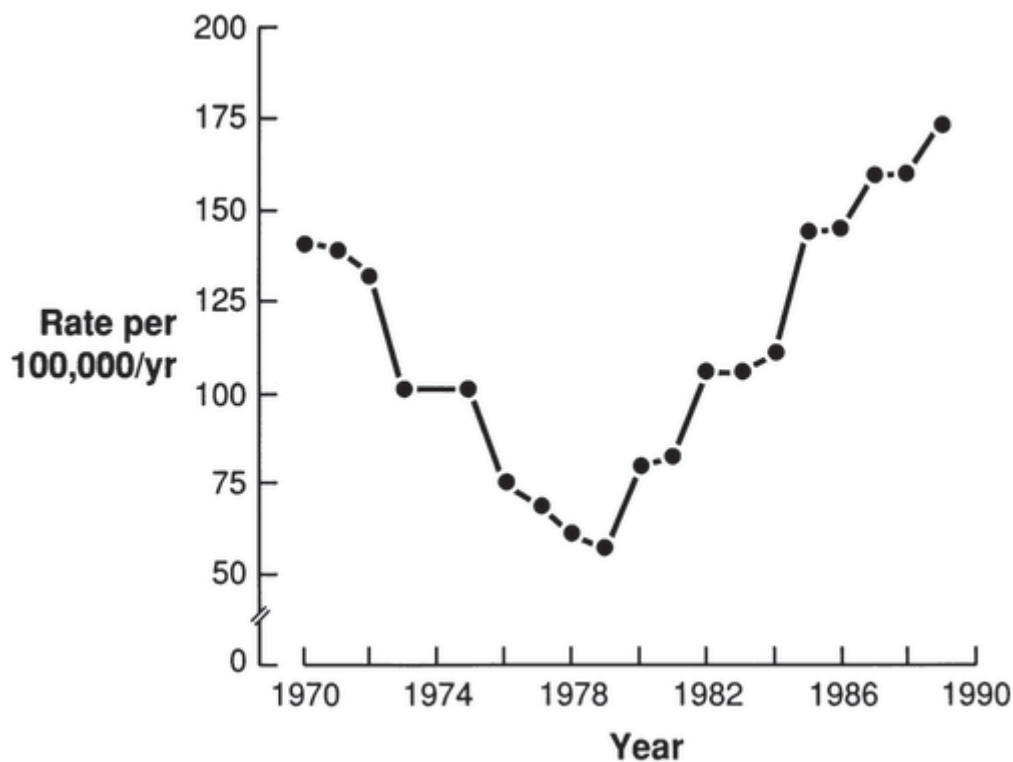
Source: Murray JF. (2004)

The New York 'hot spot' characterised all the individual factors that were implicated in the resurgence and when they all occurred together this resulted in a total breakdown of TB control. This all took place in an area that was also characterised by low income and frank poverty. Those in poverty suffered disproportionally from the disease as was demonstrated clearly by Barr et al. (2001) and shown graphically in Figure 77. This finding adds further evidence to the concept that social determinants have an important effect on the extent and severity of the disease. It should be pointed out that in the Barr et al. (2001) study the effects of poverty held true when controlled for race, AIDS, foreign birth and ethnicity.

Figure 77: Tuberculosis incidence per 1000,000 in New York City in 1992 plotted by decile of neighbourhood rates of poverty and abject poverty.

Percentage of Neighborhood Residents in Poverty
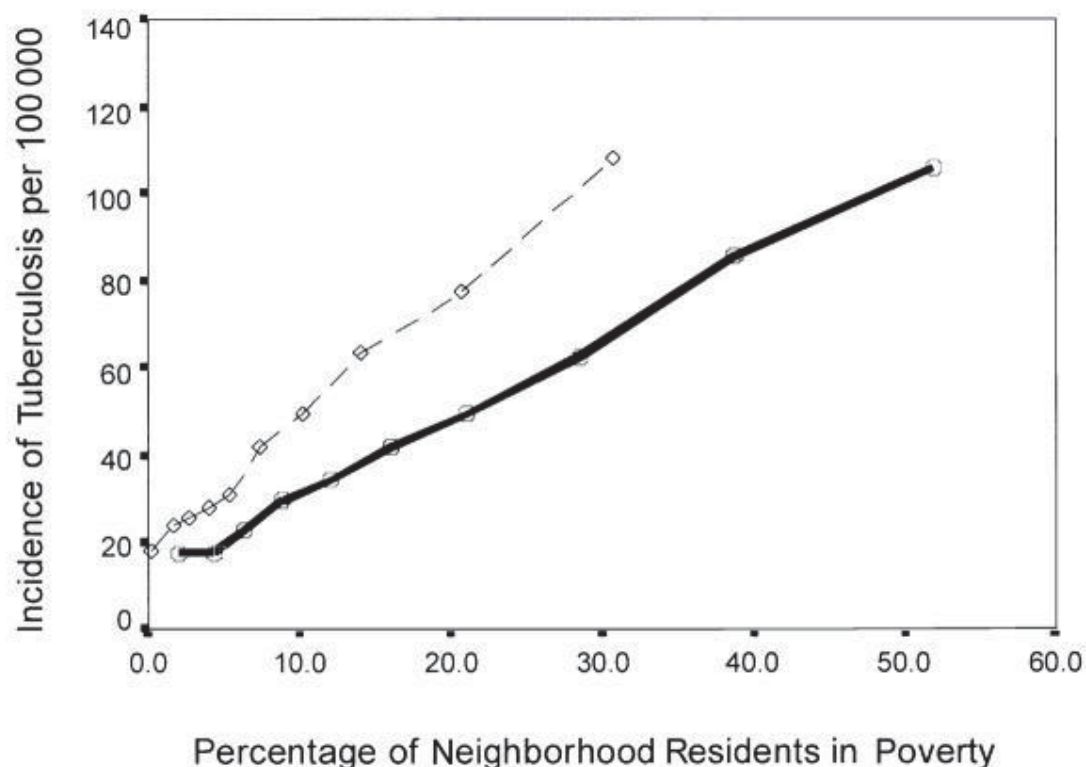
Key: -O- = poverty   -□- = abject poverty

Source: Barr et al. (2001)

The phenomenon reported above was not unique to the USA. The dissolution of the Soviet Union into several states saw the breakdown of public health controls there and subsequently the rapid emergence of multi resistant tuberculosis (MDRTB). This is defined as resistance to isoniazid and rifampicin. This problem has rapidly escalated, and extremely high rates of resistance have been reported from Azerbaijan, India, the Russian Federation and China. It appears that 62% of the global incidence of MDRTB occurs in these countries (Zignol et al., 2006).

The problem of drug resistance has been compounded by the emergence of organisms resistant to some of the second line drugs as well as resistance to the first line. The drugs concerned are amikacin, kanamycin and the fluorquinolone group (XDRTB). Disease caused by XDRTB is present worldwide, and rates as high as 18.7% have been obtained from isolates in Estonia (WHO, 2011). The extreme situation has occurred in Italy with patients

who were found to be infected with organisms that were resistant to 17 known chemotherapeutic drugs. This has been labelled extremely drug resistant TB (XXDRTB) (Migliori et al., 2007). Finally, four Indian patients with TB, all known to have had TB previously were shown to have infecting organisms resistant to all known 1st and 2nd line drugs, referred to as totally drug resistant TB (TDRTB) (Udwadia et al., 2012).

It is believed that the precursor of HIV passed from red capped mangabey monkeys to chimpanzees and then to humans in the form of HIV around 1920 probably in Kinshasa, Democratic Republic of Congo (Faria et al., 2014). Since then HIV/AIDS has become recognised as the most powerful risk factor identified that enhances the progression of TB. The synergy of the two has led to an unparallel catastrophe. The risk of developing TB is 28-30 times more in those with HIV infection. TB remains the commonest cause of death among patients with AIDS. By 1992 over four million people worldwide had dual infections of TB and HIV and this number had risen to 8.3 million by the year 2000 with 95% of these in the developing world. The clinical presentation of tuberculosis in those with co-infections can be atypical and extra pulmonary disease is frequently seen (Raviglione et al., 1992).

Further, the TB disease may not be recognised in the early stages of HIV infection as the fevers, weight loss and malaise can be explained by or attributed to the HIV infection itself. In recent onset HIV infection, TB can present as a classical re-activation type of disease. Those with advanced disease and severe immune-suppression are likely to present with a primary tuberculosis infection.

The reasons for this negative impact of co-infection have been studied. It has been hypothesised to be attributable to increased expression of the CCR5 and CXR4 co-receptors on CD4 cells (Vanham et al., 1996).

The emigration of people from high prevalence areas to low prevalence areas has been one of the factors that have contributed to the upsurge in tuberculosis in the developed world. This has prompted a close review of the need for and value of immigrant and refugee screening for tuberculosis. The evidence to base this on comes from studies such as that of Liu et al. (2009). They showed that in 2007, 57.8% of new cases of TB in the USA were diagnosed in foreign born people, with this rate being ten times that of US born people. It must be remembered, however, that the rates for US born people in New York City had

fallen from 52/100,000 in 1992 to 9/100,00 by 2013 (Ahuja et al., 2015). This is illustrated further for New York in figure 78.

Figure 78: Number of Tuberculosis Cases in New York City, According to Birthplace, 1992–
        2013.
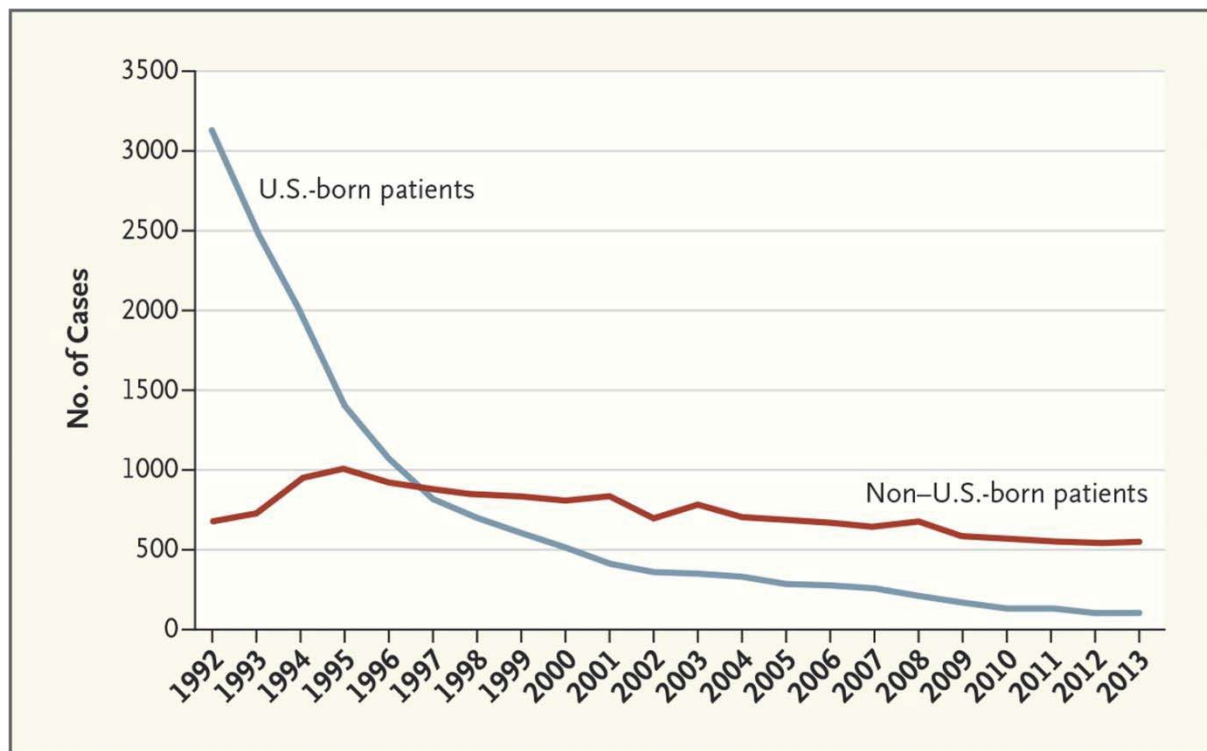
Patients considered to have been born in the United States include those born in the USA territories. Data are from the New York City Department of Health and Mental Hygiene, Bureau of Tuberculosis Control (Ahuja et al., 2015).

Immigration to the USA annually is in the region of 400,000 people of whom 50-70,000 are refugees. Active TB has been found in 7% of immigrants and refugees, and an additional 1.6% had a diagnosis of inactive disease. This study shows clearly the importance of screening of immigrants which would help reduce the incidence of TB cases among foreign born people in the USA. In the year 2012, the main flow of refugees to the USA was from Bhutan and Burma. Immigrants came mainly from Mexico and China. By this time these immigrants were subjected to mandated medical examination (Centers for Disease Control and Prevention, 2016).

The results of the first year of screening detected approximately 1,100 cases of TB. In addition, the screening process included testing for MDRTB. Of importance was the fact that 60% of cases detected were smear negative but culture positive. This indicates that sputum culture is mandatory and sputum smear alone is insufficient and will not detect all cases of active disease.

A further important finding was that those immigrants from high TB prevalence areas had a high rate of developing TB and this tendency lasted for up to ten years following their immigration to the USA. This held true even when those cases occurring within six months of arrival were excluded (Cohen and Murray, 2005). It can be concluded from these observations that immigrants carry with them a higher TB incidence and /or drug resistance rate from their place of origin. In the experience of Leung et al. (2015) there is a higher drug resistance rate in immigrants on arrival in the USA, poorer treatment outcomes and excess relapse risk after their immigration to the USA. This raises, therefore, concerns over secondary transmission of drug resistant tuberculosis within the local community. The detection rate for immigrants and refugees is 20.6 per 100,000 (Liu et al., 2009) and the relapse rate appears to be in the order of over 10% of those actually identified at screening to have TB (Binkin et al., 1996).

It is clear that contact tracing will be important after immigration and that the long term solution to these problems requires increased investment in global TB control (Dasgupta and Menzies, 2005).

The findings described above in the USA regarding immigration and TB appears to hold good for New Zealand. The studies of Das et al. (1995) have shown that the main source of TB in New Zealand is also as a result of migration from high TB incidence countries. Of those who develop TB after arrival in New Zealand 25% do so within a year of arrival. A quarter of this group, who are mainly refugees, are thought to have had pre-existing disease at the time of entry.

Chapter 13:   The Fight Back

*The tubercle bacillus is an index by inversion of the real progress of the human race.....
the disease will surely increase as civilisation retrogrades.*
John B. Huber, 1907

The first stage of correcting the problem of tuberculosis was the recognition that there was, indeed, a major global problem. The WHO drew attention to the situation by the following facts:

- Someone was newly infected with TB every second.

- One percent of the world's population is newly infected with TB each year.

- Overall, one third of the world's population is currently infected with the TB bacillus.

- Five to ten percent of people infected with TB become sick or infectious at some time during their lives.

This prompted the WHO to declare TB a Global Emergency in 1993 (WHO, 1993). The next strategy employed was the issuing of the WHO Millennium Development Goal to halt and reverse the TB epidemic by 2015. These aims have been achieved, and the next subchapters outline the approach that had been adopted. The new target is TB elimination, defined as one case of active TB per million of the population per year, which should be reached by 2050 (Weise, 2015).

Chapter 13.1

Direct Observed Treatment –Short Term (DOTS)

A treatment system of checks and balances that provided high cure rates at a cost affordable for most developing countries.
The Economist, 1995

Karel Styblo (1921-1998) who was born in Klaster, Czechoslovakia was the pioneer of the strategy of what was later called DOTS. Like many pioneers in the field, he had become infected with TB while in a Nazi concentration camp during WW2. His work in the 1970s showed that TB could be controlled in extremely poor countries such as Tanzania. Styblo combined the gathering of high level political commitment with his treatment plan as

outlined in table 3. The programme ensured that the patient actually swallowed the medication by this direct observation (Enarson, 1991). The DOTS concept no longer permitted self-administration of TB drugs. The method, however, had been pioneered before the HIV/AIDS epidemic had taken place.

The concept was adopted and promoted by the WHO under the title 'DOTS' (directly observed treatment – short term). Thus by definition, treatment schemes had to be shortened and could involve as little as 62-78 encounters over a six month delivery period to bring about a curative treatment. DOTS proved to be an effective method of treatment delivery (Bayer and Wilkinson, 1995). Figure 79 shows the positive effects of a DOTS regimen in New York City.

However, Styblo's system had a major drawback. Sputum microscopy, not culture, was insensitive and did not identify drug resistant strains. The sputum only method detects patients with very extensive disease, usually with cavity formation.

Table 3: DOTS based upon the original work Karel Styblo**.**

1. **Sustained political and financial commitment.** TB can be cured and the epidemic reversed if adequate resources and administrative support for TB control are provided

2. **Diagnosis by quality ensured sputum-smear microscopy**. Those with respiratory symptoms examined in this way helps to reliably find infectious patients.

3. **Standardised short-course anti-TB treatment given under direct and supportive observation (DOT).** Helps to ensure the right drugs are taken at the right time for the full duration of treatment.

4. **A regular, uninterrupted supply of high quality anti-TB drugs.** This ensures that a credible national TB programme can be inclusive.

5. **Standardised recording and reporting.** Helps to keep track of each individual patient and to monitor overall programme performance

Figure 79: Number of Patients with Tuberculosis in New York City (Solid Line) and Number Receiving Directly Observed Therapy at the End of Each Year (Shaded Bars), 1978 - 1994.
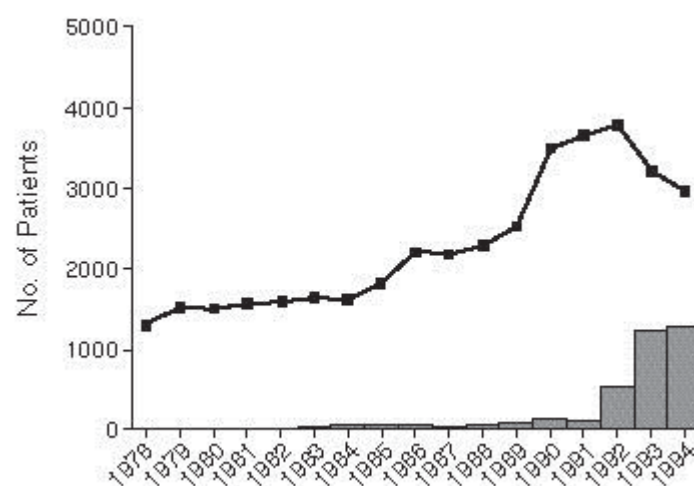
Source: Data are from the New York City Department of Health (Frieden et al., 1995).

Fifty percent of the patients with active disease would not be detected by this method. However, despite this, the increase in the proportion of people screened for TB rose from 40% to nearly 80% at the cost of $10 per life saved and $3 per new infection avoided (The Economist, 1995). These claims of cost effectiveness for DOTS were examined by Baltussen et al., (2005) for the period 2000-2009 and they confirmed that it was indeed, cost effective.

A Cochrane Systematic Review, however, could not demonstrate that the DOTS method was more efficacious than self-administered treatment (Volmik and Garner, 2003). Despite this, the WHO and the IUATLD continued on the assumption that this method is an important strategy to reduce the likelihood of drug resistance.

Chapter 13.1.1   DOTS-Plus

In 1999, the WHO developed the concept of DOTS-Plus to address the problem of MDRTB. Its design was intended to be implemented in selected areas to combat an emerging epidemic. It was to utilise First and Second line TB drugs and the intention was as outlined in

Table 4. By 2005, 36 DOT-Plus pilot projects had commenced in 27 countries treating 10,000 MDRTB patients. These pilots showed that the project was feasible and cooperation with the pharmaceutical industry to allow preferential access to drugs at a cheaper rate. In 2000 the first pilot scheme was launched. The actual format of the scheme was effective in resource-poor countries (DOTS-Plus, 2000), (Stop TB Working Group, 2003). In the pilot schemes, 70% of patients were treated successfully, out of these 50% had been treated previously with First and Second line drugs and 65% were resistant to both First and Second line drugs. Treatment had to be stopped because of adverse drug reactions in 3.2%.

Some doubts arose regarding DOTS-Plus plans and Sterling et al., (2003) concluded that if DOTS-Plus was implemented with minimal decreased effectiveness substantially more patients would die worldwide than under DOTS alone.

Based on a lack of a sound approach to MDRTB, the lack of a political will and public health infrastructure as well as a laboratory capacity and human resources, the DOTS-Plus scheme was cancelled (Stop TB Working Group, 2006).

In 2006, the WHO decided that a redefinition of DOTS should take place. DOTS would be about the provision of diagnosis, treatment and care for all patients. This would include those with drug resistant TB and patients with co-infections with TB and HIV. Effectively DOTS-Plus would no longer exist and would be included in a redefined DOTS programme[35] .

Table 4:   Outline of DOTS-Plus proposed programme

1. Second line anti-tuberculosis drugs (more toxic and expensive, and less effective, than first line drugs) are used. The regimen includes two or more drugs to which the isolate is susceptible, including one drug given parenterally for six months or more. Total duration of treatment 18-24 months; treatment is directly observed

2. Treatment regimen is either:

(a) Individualised according to drug susceptibility test results of the *M tuberculosis* isolate identified on culture; or

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[35] See: www. TB facts.org/dots.tb/

(b) Given as a standardised regimen to patients who fail supervised re-treatment (for example, when culture and drug susceptibility testing are not performed).

(c) Mycobacterial cultures and drug susceptibility testing may be performed.

Chapter 13.2   STOP-TB

Every breath counts – stop TB now.
World Tuberculosis Day slogan, 24th March.

At the onset of the 21st Century the WHO underwent a paradigm shift. This comprised a Global Plan to end TB and the provision of a road map to do so. Over the last decade and a half the Stop TB Partnership has issued five and ten-year global plans. These plans provide estimates for the resources needed every five years to achieve the goals the world has set for TB.

The first plan covered the period of 2001 - 2005. The plan was bold in its ambition and was the first of its kind following the Millennium Development Goals. Subsequently, five year plans have been produced for up to 2020. An example of the objectives of one of these plans is given in table 5.

The end strategy is to show an 80% drop in new cases by 2030, a 90% drop in deaths by 2030 and a 100% success in providing protection for families from the catastrophic costs of TB by 2030. The road map method of achieving this has modifications for childhood TB and a copy of this is presented in figure 80.

In 2006, the Partnership launched the Global Plan to Stop TB 2006-2015 in Davos, Switzerland at the World Economic Forum. The total cost of the Plan - US$56 billion - represented a threefold increase in annual investment in TB control compared with the first Global Plan. The Plan set out to reduce TB incidence in line with the Millennium Development Goals (MDGs) and reach the Partnership's targets for 2015 of halving TB prevalence and deaths compared with 1990 levels.

Table 5: Eight specific objectives of the WHO Secretariat for 2006–2015

Objective 1:
Promote accountability, flexibility and coordination in the management of partnership resources.
Objective 2:
Stimulate the mobilization of the resources needed to permit the implementation of the Global Plan to Stop TB (2006–2015).
Objective 3:
Ensure the effective functioning, growth, dynamism and catalysing effect of the GDF in global TB control.
Objective 4:
Facilitate relationships between and with existing partners and strengthen our coalition by reaching out to new or potential partners.
Objective 5:
Build skills, resources and capacity at regional and national level to enable successful partnerships to be developed.
Objective 6:
Place TB on the global development agenda, while at the same time mainstreaming pro-poor approaches into TB control.
Objective 7:
Take TB beyond the existing reach and scope of traditional disease control programmes by catalysing new opportunities and promoting the aims and objectives of the Global Plan to Stop TB (2006–2015).
Objective 8:
Monitor and evaluate the impact of the Secretariat and Partnership in delivery of the Global Plan to Stop TB (2006–2015).

Source: www.stoptb.org/global/plan/

Figure 80: Roadmap and key actions to address childhood tuberculosis
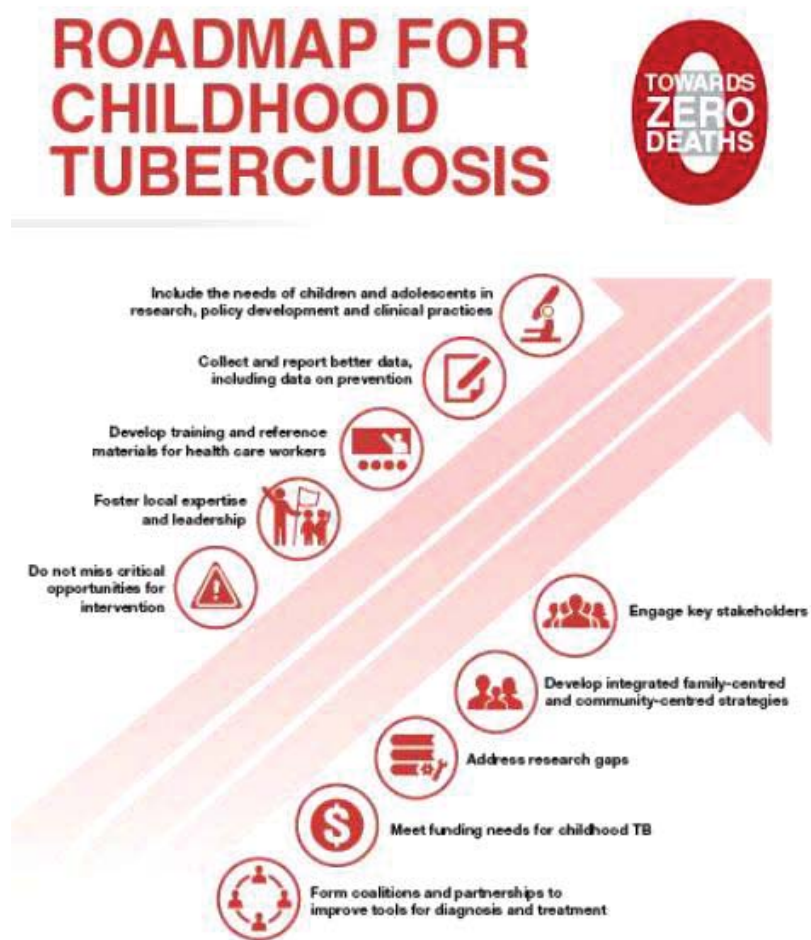
Source: Marais and Graham (2014)

Chapter 13.3   HIV/ AIDS

Behold, a pale horse: and his name that sat on him was Death.
Revelation of St. John

There is little doubt now that the spreading of HIV infection is the main driving force of the global resurgence of TB and this is especially so in sub-Saharan Africa where 75% of individuals with TB are co-infected with HIV. In those with HIV alone initially, the most common opportunistic infection is MTB. This pattern can be clearly seen in figure 81, and it is stressed in the health promotion poster shown in figure 82. However, figure 81 could be misleading in relation to the breakdown and degradation of the public health services in the former Soviet Union and cause some bias in the comparisons with relation to Eastern Europe. Thus not only have the treatment plans been directed at TB but the strategies have been directed at HIV/AIDS (Dlodlo et al., 2005). Patients with HIV infection and tuberculosis have an increased risk of death, treatment failure and relapse.

While no curative regimen has been found for HIV/AIDS the introduction of antiviral treatment (ART) has made an enormous difference in the management of the co-infection.

Treatment progress has been made as a result of responding to three basic problems:

1. Treating latent TB in HIV infection.

2. Avoiding drug interactions in the treatment of HIV related TB.

3. Co-treatment of multi-drug resistant TB.

It is not the remit of this dissertation to examine the details of the various drug regimens. However, the topic of drug resistance is well covered by Falzon et al. (2011). Success has been achieved in the management of latent tuberculosis by a nine month course of isoniazid in HIV infected individuals. It is said that 90% of tuberculosis is due to reactivation of an earlier infection hence the importance of this prophylaxis.

Advances in HIV therapy are required before this dual problem can be totally defeated. Despite the 30 ART drugs currently available from six classes there is no evidence of elimination of the virus. A vaccine is the next required major step[36].

Figure 81: Trends in tuberculosis case notification rates for selected countries
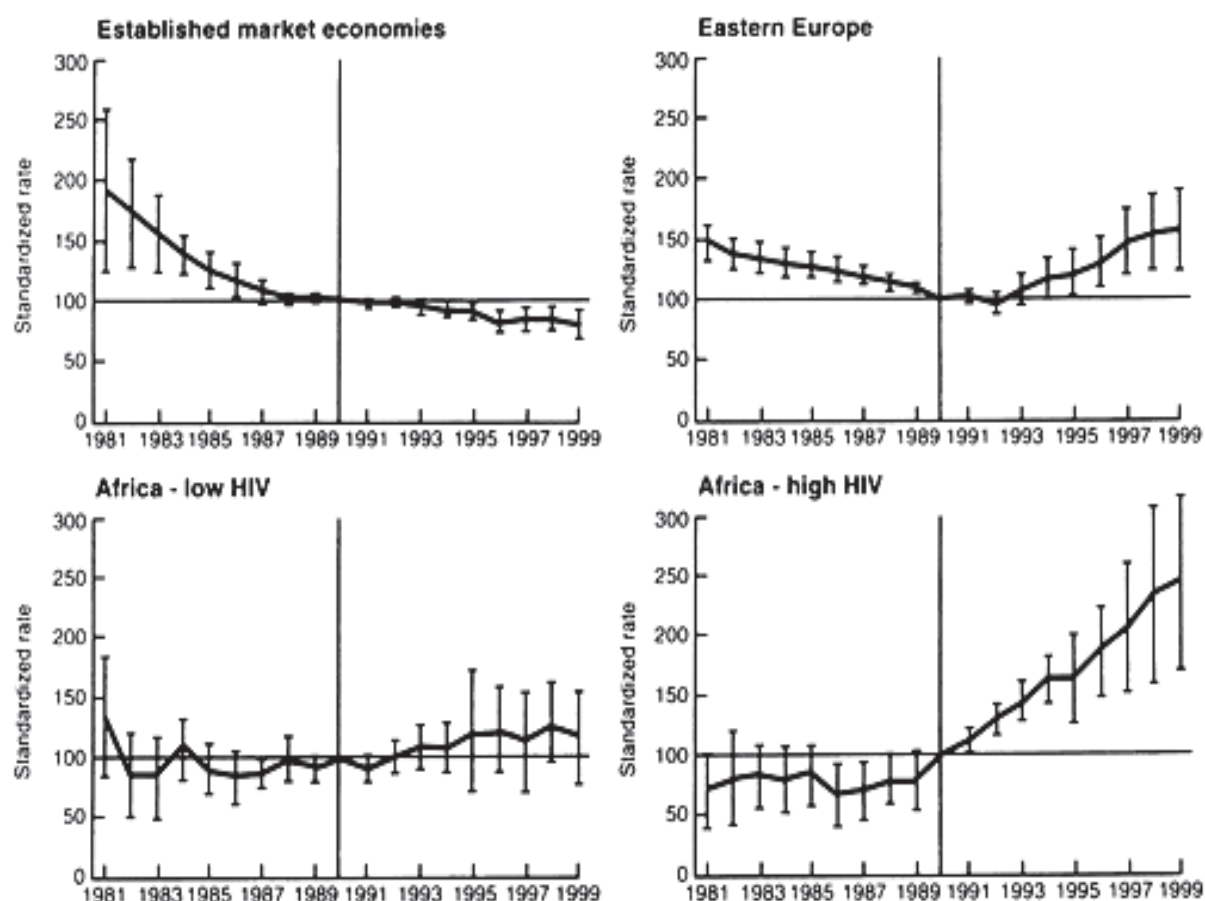
Figure shows tuberculosis notification rates for countries with established market economies, those from Eastern European countries, and from African countries with low and high HIV seroprevalence rates (below and above 10%, respectively) among adults 15–49 years of age. The rates for all countries have been expressed relative to an arbitrary standard of 100 in 1990. Vertical bars show 95% confidence limits.

Source: Murray JF. (2004).

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[36] See www. niaid.nih.gov/topics/hivaids/pages/Default.aspx

Figure 82: Double Trouble – TB and HIV
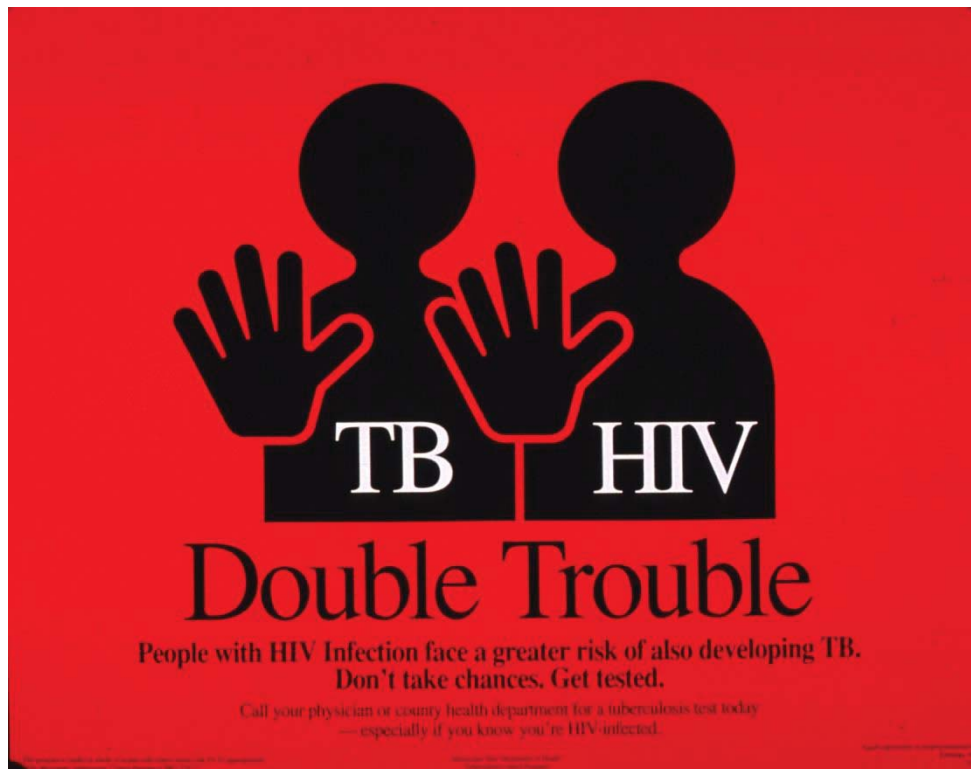
Chapter 13.4   Immigration screening

In Chapter 12 there was a discussion of the role of immigrants from high prevalence areas to low prevalence in introducing TB into the latter countries. This had been specifically found in New Zealand and the USA. As part of the strategy to overcome the import of tuberculosis a screening program has been introduced into the USA for refugees and immigrants. This plan is listed in table 6.

The need for this is based on the fact that for more than two decades, as the number of tuberculosis cases overall in the United States has declined; the proportion of cases among foreign-born persons has increased. In 2013, the percentage of TB cases among those born outside the country was 64.6%. To address this trend, the Centers for Disease Control and Prevention (CDC) has developed strategies to identify and treat TB in USA-bound immigrants and refugees overseas. Each year, approximately 450,000 persons are admitted to the United States on an immigrant visa, and 50,000–70,000 are admitted as refugees. Applicants

for either an immigrant visa or refugee status are required to undergo a medical examination overseas before being allowed to travel to the United States. CDC is the federal agency with regulatory oversight of the overseas medical examination, and panel physicians appointed by the U.S. Department of State perform the examinations in accordance with Technical Instructions provided by CDC's Division of Global Migration and Quarantine. In 2007, CDC issued enhanced standards for TB diagnosis and treatment, including the addition of sputum cultures as a diagnostic tool and treatment delivered by DOT. In 2012, the year for which the most recent data are available, 60% of the TB cases diagnosed were in persons with smear-negative, but culture-positive, test results. The results demonstrate that rigorous diagnostic and treatment programs can be implemented in areas with high TB incidence overseas.

New Zealand requires all those who intend to stay in New Zealand for a period in excess of 12 months to have a medical examination and a chest X-ray prior to their arrival. Thus the tests must be carried out in the immigrant's home country (Ministry of Health, 2010).

Table 6: Tuberculosis screening algorithm for applicants aged ≥2 years in countries with a tuberculosis incidence rate estimated by the World Health Organisation at ≥20 cases per 100,000 of the population.
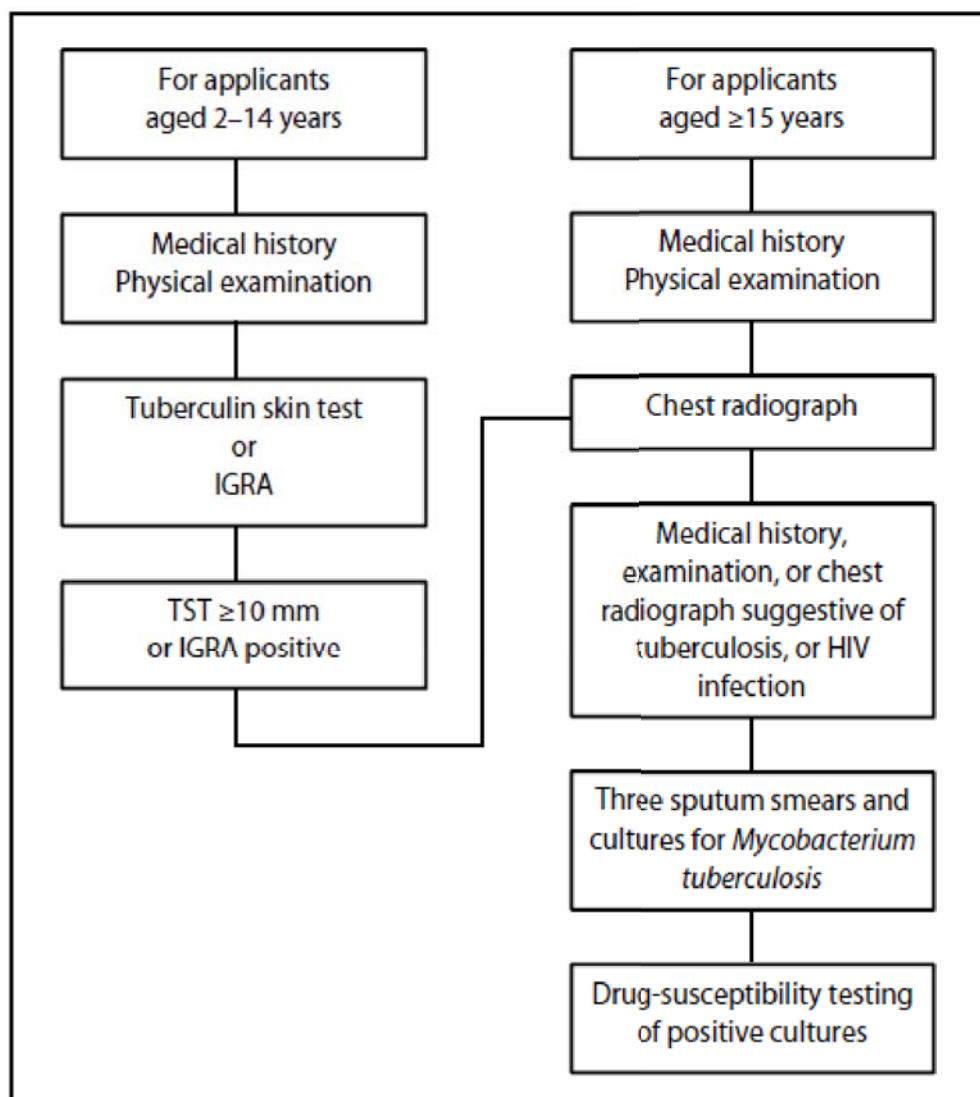
Technical Instructions for Tuberculosis Screening and Treatment Using Cultures and Directly Observed Therapy, United States, 2009

Key: IGRT = Interferon Gamma Release Test,   TST = Tuberculosis skin test

Source: New TB Screening Requirements for U.S.-Bound Immigrants and Refugees — 2007–2014, CDC (2013).

Chapter 13.5   Advances in Diagnosis

This new test represents a major milestone for global TB diagnosis and care. It also represents new hope for the millions of people who are at the highest risk of TB and drug resistant disease.
Dr Mario Ravihlione, Director of WHO Stop TB Department

1. GeneXpert (Cepheid Inc.)

Traditional tests for the diagnosis of TB include the chest X-ray, sputum smear microscopy and bacterial culture. The disadvantages of these methods are numerous. Sputum microscopy can be inaccurate and sputum culture may take up to six weeks to be established. Neither test helps in determining drug resistance. Further culture tests are required for this. Culture is also expensive and time consuming.

GeneXpert uses sputum and a result can be obtained within two hours. It can also detect rifampicin resistance. The test is based upon nucleic acid amplification and detection of an MTB specific region of the rpoB gene. It uses real time polymerase chain reaction (PCR). The test also detects mutations associated with rifampicin resistance as a proxy for MDRTB. The test was first launched in 2004. Its early clinical evaluation took place in 2009 (Jones et al, 2010) and the WHO put together all further evidence and reported a summary of supportive evidence from all relevant studies (2016). A subsequent paper (Piatek et al., 2013) has reported that while GenXpert is a fully automated system molecular test it is expensive ($US 9-17) does require technical support and the initial machine costs in the order of $US 17,000 (figure 83).

A true point of care TB test is what is really needed similar in its 1operational simplicity to the HIV antibody test. It needs to be suitable for use in situations where there is no electricity supply, and where there may be considerable temperature extremes. It also needs to be available at a much lower cost.

Figure 83: GeneXpert 4 module machine

2. Interferon Gamma Release Test (IGRT)

IGTR is a whole blood test introduced to aid in the diagnosis of MTB infection. It does not, however, differentiate between latent TB and active TB, but is based upon the immune reactivity to MTB. White blood cells from infected subjects will release interferon gamma when mixed with antigen derived from mycobacterium tuberculosis. Thus fresh blood is used and controls then antigen is added. The interferon is then measured and an answer is available within 24 hours. As opposed to the Mantoux test the patient need only present once. An additional advantage is that previous BCG does not provide a false positive result (Metcalfe et al., 2011).

Chapter 14
Dealing with Mycobacterium Tuberculosis Drug Resistance

Antimicrobial resistance poses a fundamental threat to human health, development and security.
Margaret Chan, Director General of the WHO, 2016.

In Chapter 7.2, the historical background of chemotherapeutic drugs against MTB was outlined. Table 1 listed the drugs developed that could be used against MTB. Subsequently, it was discussed that DOTS methods of delivering these medications and the upsurge of drug resistance that occurred at the time of the HIV epidemic. The rising incidence of MDRTB and the appearance of XDRTB and even XXDRTB in resource rich countries as well as resource poor countries required a new approach. However, it is important to note that these new strains of MTB emerged in unrelated geographic areas and afflicted people in all levels of society (figure 84). However, close contact with similarly infected people is an important aspect in the spread of these organisms (Boire et al., 2013).

In the previous chapter we have seen the progress made in making a more rapid diagnosis of tuberculosis using techniques like GeneXpert. However, the defeat of drug resistance requires the effective use of the current drugs and the introduction of novel agents and the strictest control and supervision of their use to prevent further bacterial resistance occurring.

The re-evaluation of existing drugs demonstrated, first of all, that rifampicin could be more effective at a higher dose. Further, rifapentine was shown to be more potent than rifampicin itself (Schechter et al., 2006). However, its use requires another drug which would be active against dormant (non-multiplying) bacilli. Drugs such as the fluoroquinolones, Linezolid and Clofazimine may have a place in MDRTB but not in MTB that do not show resistance (Murray et al., 2015). In the main this is due to their toxicity and less potent action. It has become thus apparent that rifampicin antibiotics are the keystone of modern short course therapy and that future strategies must focus upon conserving susceptibility to these agents (Iseman, 2002).

Table 7 lists some of the newer drugs which are being assessed for their suitability for the treatment of MRTB and XXDRTB. Any of the new drugs developed must be able to replace

those lost by resistance factors and hopefully be able to have a superior performance in terms of killing power over MTB. It is axiomatic that the introduced new drugs must be accompanied by the best care practices to prevent future resistance developing.

As stated above it is important to find compounds which are active against the non-multiplying organisms as well as those actively dividing. Of relevance is the recent finding showing that the glyoxylate shunt could be a major target in the destruction of latent bacilli. Particularly the enzymic pathway isocitrate lyase appears to be a vulnerable site. Research directed at disruption of this system may be capable of destruction of all bacilli present in the patient (McKinney et al., 2000).

Most authorities suggest that regimens that are effective among non-HIV infected patients are effective also in those with HIV/AIDS. However, several reports suggest that relapse rates are higher in the presence of AIDS. This is perhaps related to the fact that current anti-retroviral AIDS therapy prolongs the life of the individuals making relapse more likely. The other problem related to TB and HIV drug therapy is the 'immune reconstruction system' phenomenon or a paradoxical late worsening of TB. When anti-retroviral therapy helps restore immunologically mediated inflammation, the paradoxical response occurs. This response is also associated with tuberculin skin reactivity after anti-retroviral therapy. It converts a negative tuberculin skin test from negative to a strongly positive reaction. This happening is of great importance from the public health perspective (Breen et al., 2004).

Table 7: Selected new anti-tuberculosis drugs

Drug class	Investigational drug	Stage of clinical development#	Drug target and/or mechanism of action	Drug activity against			
				Drug-Susceptible TB	Drug-resistant TB	Replicating *M. tuberculosis*	Non-replicating *M. tuberculosis*
				data based on *in-vitro* AST			
Oxazolidinones	Sutezolid (PNU-100480)	Phase II	Inhibition of protein synthesis	ü	(ü)	[0]	[0]
	AZD-5847	Phase II		ü	ü	ü	ü
Diarylquinolone	Bedaquiline TMC-207	Phase II	Inhibition of ATP synthase	ü	ü	[0]	[0]
Nitroimidazo-	PA-824	Phase II	Production	ü	ü	ü	ü

oxazines	Delamanid (OPC-67683)	Phase III	of NO and Inhibition of mycolic acid synthesis	ü	ü	ü	ü
	TBA-354	Preclinical		ü	ü	ü	ü
Ethylenediamine	SQ109	Phase II	Inhibition of cell wall synthesis	ü	ü	[0]	[0]
Pyrroles	LL-3858	Preclinical	Unknown	[0]	[0]	[0]	[0]
Benzothiaziniones	BTZ043	Preclinical	Interferes with cell wall synthesis by epimerase inhibition	ü	ü	[0]	[0]

#Phase of drug development based on Working Group on New TB drugs website accessed April 28, 2013

[0]: denotes no drug activity or no data available for sufficient assessment

Abbreviations: TB: Tuberculosis; AST: Antimicrobial Susceptibility Testing; ATP: Antimicrobial Susceptibility Testing; NO: Nitric Oxide

Source: Boire et al., 2013

Figure 84: Tuberculosis Sufferer in India

Prittam Priyalochan, *Still a Ray of Hope* 2011, Acrylic on Canvas, 60" x 60"

This work bears the signature of suffering from the killer trauma of TB. This is a man I met who badly needs a helping hand to recover, an expression of hope written in his eyes. He is a man who needs someone to rescue him. But we do not want to show him pity. We want to see his dignity. Love and dignity is the boat in the river we have to cross. Let us live in such a way that we plant smiles on pale faces and wipe out the agony of dying and helplessness. Are you not one of his saviours? P. Priyalochan, 2011.

Chapter 15:   What does the future hold?

Histories make men wise.
Francis Bacon (1561-1626)

One would hope that tuberculosis in humans would follow the route of smallpox and be eliminated from the list of diseases that mankind is subject to. This hope is shared by the WHO whose plans include the elimination of tuberculosis by the year 2050. If this was to come about we would hopefully see no more paintings as portrayed in figures 85 and 86. We have already learned that tuberculosis has an ability to stay one step ahead of human attempts to eliminate it and adapt to new opportunities. Let us hope that mankind will learn from history, as suggested by Francis Bacon, and not place the knowledge we have gained about tuberculosis in the 'that great dust-heap called history'[37] or let 'history repeat itself'[38].

As discussed in Chapter 14, there is a great need for new drugs to treat TB. Ideally, the future drugs will have a potent action with few, if any, side effects and a short treatment regimen. The 'Working Alliance for Tuberculosis Drug Development' was formally launched in Cape Town, South Africa in February 2000 (Working Alliance, 2000). It involves the partnership of non-governmental organisations, private philanthropists and governmental agencies. New antibiotic strategies will involve study of the genetics, the signalling and metabolic pathways of the MBT to find its vulnerabilities and to target these potential sites by suitable drugs.

The human immune system produces antibodies as its first line of defence against infection. Their role in TB has not been studied in great depth. Now several workers are looking at these antibodies with a view to developing a vaccine. While a vaccine has remained elusive to date, it is probably the only goal which could address the problem of the 10 million people worldwide who become infected each year with the organism MTB. Of particular relevance here is the difference, if any, in antibody production of patients with acute illness as opposed to those with latent disease. Any molecular modifications in these antibodies may be the key factor in the development of a vaccine which can generate a T-cell response and hence protect the individual (www.hsp.harvard, 2016). At this stage, it is known that

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[37] Augustus Birrell (1850-1933)
[38] Proverb

there appears to be a shift from T-helper cell type 1 (Th1) protective response to T-helper cell type 2 (Th2) pathway which is less effective and more injurious to tissues.

Several new approaches to treatment hold hope for the future. These include the use of interleukin 12, interferon-a, interferon-c, imiquimod (immune response modulator), granulocyte-macrophage colony stimulating factor and levamisole (Iseman, 2000).

The lethal combination of HIV and TB will hopefully be addressed. The spreading of HIV is established as a major factor in the global resurgence of TB. While progress has been made in anti-retroviral drugs (ARV), a cure for HIV infection would be of major importance in the defeat of TB. Towards the goal of HIV infection cure, there is perhaps some light at the end of the tunnel. Kaminski et al. (2016) have described a method of using a DNA editing system which can enter the CD4+ T cells and eliminate HIV-1 DNA. This has the potential to cure HIV/AIDS. Another cure strategy is directed at eliminating the long lived viral reservoir by using drugs called HDAC inhibitors to induce the virus to leave the cell with the hope that ARV treatment will destroy them. Recently, there is a report suggesting that this approach has been successful but it will take time to ensure that all the virus has indeed, been eliminated and the patient remains well without further ARV treatment (www. ndtv.com/health, 2016). If these advances in HIV control can be established and confirmed then these are major steps not only in the controlling the epidemic of HIV but towards the elimination of MTB.

It may be possible, in the future, to eliminate HIV and have a range of treatment options available with the potential to cure TB. However, there will be a fundamental need to have a foolproof Public Health control system in place. This will be essential to prevent a recurrence of what took place in the 1980s and 1990s, namely a relaxation of supervision with complacency and even neglect. This was accompanied by the advent of epidemic HIV/AIDS and drug resistance developing. It is also of paramount importance to recognise that tuberculosis is not just a medical issue, but has complex social aspects as well. Its treatment has political overtones also. It is thus important in the future that all aspects of the disease management are considered as well as provisions for advocacy, financial support and security. It has been calculated that in New York City, USA it has cost $1 billion

to correct and reverse the TB failure of the 1990s and institute a new control system (Murray, 2004).

To plan a robust system of public health control of TB several countries have formed working groups of advisers to format such plans and keep them updated in light of current and future changes in circumstances. The guiding principles for such control methods include:

1. Conducting overall planning and development of policy,

2. Identifying persons who have clinically active TB,

3. Managing persons who have or who are suspected of having disease,

4. Identifying and managing persons infected with M. tuberculosis,

5. Providing laboratory and diagnostic services,

6. Collecting and analyzing data, and

7. Providing training and education.

The Canadian Centre for Disease Control (2014), (Murray, 2006), has published its own guidelines for such a Current and Future Control System. Table 8 outlines the main feature of the Canadian scheme. Similar systems have been published for many countries and states and these include USA, Australia and China. Table 9 shows the main areas globally where special attention needs to be paid. Control of TB is hampered by poverty, overcrowding, health system shortfalls and understaffing. Thus the future of TB elimination is not just a question of which drugs to use and when but the whole concept of public health needs changes in all aspects of welfare.

Table 8: Twelve essential components of TB prevention and control programs

|	
1.	**Management of cases of active TB disease** Preventing the transmission of TB requires prompt diagnosis and treatment. Best practices underscore the importance of effective case management in controlling the spread of TB, from both a prevention and treatment perspective.
2.	**Contact tracing and outbreak investigation**

	Because the contacts of infectious TB cases are at risk of progressing to active TB disease, investigations must be carried out in a timely and organized fashion. Best practices are documented step by step with special consideration given to maximizing existing public health resources.
3.	**Screening for latent TB infection and active TB disease** Screening should be considered for groups at high risk for active TB disease or latent TB infection. With a focus on at-risk groups, best practices are drawn from proven strategies for early preventive intervention.
4.	**Surveillance and data management** The collection, analysis, and interpretation of epidemiological data are essential features of public health practice. The Public Health Agency of Canada maintains a comprehensive surveillance system for active TB disease which is used by all orders of government to ensure continuous improvements in service delivery and the monitoring of disease trends and treatment outcomes over time.
5.	**TB laboratory services** The diagnosis, treatment, and prevention of TB depend on a high standard of laboratory practice. Best practices provide a blueprint for coordinating laboratory services to best support provincial and territorial TB programs.
6.	**Education and professional practice** Ensuring that healthcare providers have the training and knowledge they require to enable optimal TB prevention and control is an aspect of a successful TB program that is sometimes overlooked. Best practices point to a diverse range of educational opportunities supported by strong partnerships with educational institutions, training providers, and professional organizations.
7.	**Community-based awareness** The history of TB in Canada has had a profound impact on the beliefs, attitudes, and behaviours of Canadians most at risk for the disease. Best practices emphasize community engagement and the need to tailor awareness activities to the cultural and linguistic needs of populations at risk.
8.	**Monitoring and evaluation** Measuring program performance is the key to ensuring that resources are being used effectively and having the intended impact. The establishment and monitoring of performance targets has been adopted as a best practice in a growing number of jurisdictions.

Table 9: Global distribution of Tuberculosis by WHO region with estimated incidence and related mortality, 2003.

WHO region	Cases, % of global	Per 100,000 population	
		Cases (% smear-positive)	Deaths
Africa	27	345(42)	78
The Americas	4	43(44)	6
Eastern Mediterranean	7	122(45)	28
Europe	5	50(44)	8
Southeast Asia	35	190(45)	38
Western Pacific	22	112(45)	28
Global	100	140(44)	28

Figure 85: Edvard Munch, the Dead Mother
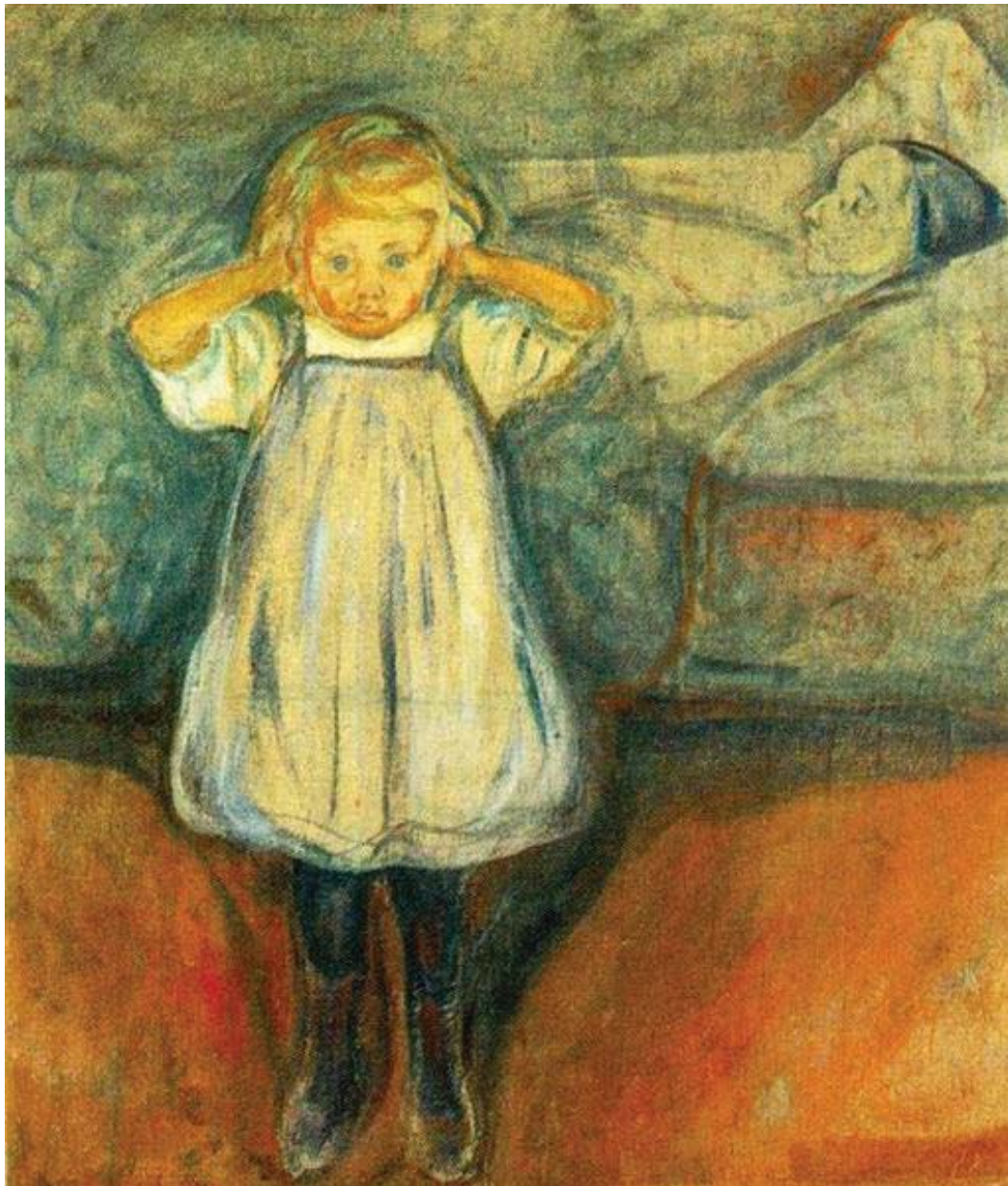
Edvard Munch, *The Dead Mother,* 1899-1900, (Bremen: Kunsthalle) oil on canvas 100x90 cms.

The subject of sickness was so widespread in the late 1800s that those years have been called the 'pillow period' in Scandinavian painting. 'Sickness, madness and death were the black angels who watched over my cradle', Munch wrote about his works: 'I paint not what I see, but what I saw'. Munch was 8 years old when his Mother died. His sister Sophie died 9 years later of TB.

Figure 86: The Dying Wife

Eugeen van Mieghem: *Facing Death*, 1904, (Belgium: van Mieghem Museum)

The drawing depicts, Augustine Pautre the dying wife of Eugeen van Mieghem. She died in 1904 from tuberculosis.

Chapter 16   Discussion and Conclusions

History is philosophy derived from examples.
Dionysius of Halicarnassus, Greek Historian, in Ars Rhetorica

In this dissertation I have attempted to emulate Dionysius. I have reviewed aspects of the history of tuberculosis by a selection of examples. These are intended to illustrate those who have contributed to our knowledge about the disease, and to learn something about the effects upon those who have suffered from it. The remainder of the dissertation has focused on the historical facts which are of relevance to the maintenance of public health in the past, and I have offered a glimpse into what the future might hold.

Like many others who have chosen professionally to care for those with respiratory disease and in particular, tuberculosis, my motivation to write this dissertation comes from personal experience of the disease. The time spent in sanatorium care and the impact of the anti-tuberculous drug regimens does bestow some insight into the effects of the disease and remains with one for the rest of one's life. This certainly held true for the Norwegian artist Edvard Munch who lost his mother and sister from the disease. The effects of this experience clearly influenced his personal life and were reflected in his artistic work during the whole of his subsequent career (see frontispiece and figure 85).[39]

It is with this in mind I have looked not only at the medical aspects of the disease but have tried to touch also upon the societal effects of the disease. It is well established that visual imagery compliments the written word or has an impact even greater than the written word alone (Isaacs, 2016). Thus I have deliberately included a selection of images ranging from photographs, postage stamps and posters to supplement the impact of the historical facts and to add, I hope, some emotional impact also.

The sequencing of the genome of *mycobacterium tuberculosis* complex has provided a new window into the history of TB and takes our knowledge of the organism and disease causing ability to a new level. It has also opened our ability to understand the biology of the organism and has presented new opportunities for therapeutic attacks upon it, based on sound scientific knowledge of its structure and metabolism. Explanations are potentially

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[39] Reference: *Edvard Munch*, Thomas Messer, Thames and Hudson, 1987

available to understand the special features of the bacillus such as its slow growth, dormancy, its complex cell envelope, intracellular pathogenesis and its genetic homogeneity. All of these features have helped make it a difficult organism to conquer (Cole et al., 1998). Initial findings from the sequencing suggest that the progenitor of MTB complex arose from a soil bacterium. The studies of the genetic makeup suggest that its lack of diversity is in keeping with a relatively young evolutionary history. However, it does seem to have emerged from strains of tubercle bacilli with smooth colony morphology and subsequently gained persistence and virulence mechanisms. What has been demonstrated is that the common ancestor of the tubercle bacillus of today resembled the MTB complex and did not diverge from *M. bovis* (Brosch et al., 2002) as was once thought.

Tuberculosis has been a curse on mankind since ancient times. Evidence of this has come from relics in Egypt, India, and China and from findings in Egyptian mummies. In Chapter 3, attention was drawn to the findings of spinal tuberculosis in the local populations in pre-Columbian times. Latter, in Greek and Roman periods, phthisis as it was then called was clearly recognised. In the 19th Century a name change to consumption occurred to describe the wasting away of the victims of the disease. The Medieval Period proved a depressing era for those who had survived epidemics of Black Death and then fell victim to endemic scrofula. The only possible help for these sufferers was the touch from Royalty (King's Evil) or from the Church. Both proved to have poor therapeutic potential but perhaps brought some psychological comfort to those with tuberculosis.

The peak of misery from the disease may well have occurred in the 18th century when it is estimated that the death rate was as high as 900 deaths per 100,000 of the population. At that time there were present the elements that MTB thrives upon such as overcrowding, poor ventilation, poor or absent sanitation and malnutrition. These were the contributors to the origins of the 'White Plague' – the pallor produced in the victims.

The 19th century brought more vivid reports of the effect of TB on individuals and especially in those who were the 'celebrities' of the time. While I have selected and outlined examples such as Keats and Stevenson from the poets, painters and writers of the time, there were

many others who contracted the disease with fatal results in the 19th and 20th centuries. Among these we should include Percy Shelley, Emily Bronte, Sir Walter Scott, Eleanor Roosevelt, Chopin and Henry Thoreau. In terms of New Zealand, Katherine Mansfield who died in Paris in 1923 from TB, is the outstanding example. A good description of the effects of TB and the treatment failure of the author, George Orwell, can be found in the book *Spitting Blood* (Bynum, 2015). The thousands of others who died of the disease from peasants to Saints need to be remembered when considering the human costs of the disease.

The beginning of the scientific approach to TB was heralded by the work of important pioneering individuals like Laennec and Villemin. The peak of these early years was the discovery by Koch of the tubercle bacillus in 1882. While this in itself was a major advance, therapeutic gains due to this discovery were minimal. The period did see the use of antiseptic systems and an improvement in hygiene. Greater attention was paid to stopping the spread of disease and the pivotal importance of better housing, reducing overcrowding and diet. The therapeutic vacuum led to the use of a variety of different substances with the hope that they would have had some value. These included gold, arsenic, carbolic acid and cod liver oil. The first real steps towards a possible cure were the development of the sanatorium movement employing the concepts of fresh air, nutrition and rest to promote healing of the lungs. Edward Trudeau's contribution to this field in the USA is described in Chapter 6.2. Probably a major role, however, of the sanatorium was to isolate the highly infectious patients from the rest of society.

I have described the use of surgical procedures such as plomage, thoracoplasty and phrenic nerve crush as the next step in trying to help patients. It would appear that some patients did benefit from these interventions or at least gained some respite from the progress of the lung destruction. However, this type of surgical approach soon fell into disrepute with the advent of tuberculous chemotherapy. However, the success of chemotherapy did permit more curative surgical procedures such as lobectomy and even pneumonectomy. By this time BCG vaccination was being used extensively with the hope that it may be more effective than it proved ultimately to be.

When the initial impact of chemotherapy began to reduce the incidence of TB, the odd anomaly occurred, as exemplified by Newfoundland, where it was found that TB rates were not falling. This has been attributed to several possible factors. Of interest was the concept that during the cold Canadian winters it was the custom to heat only one room in a house in which up to ten people would live. In addition, the chewing of tobacco was common and spitting the tobacco juice into a cuspidor was common and it was argued that this could have been a common way of spreading the germs[40].

From the public health perspective great hopes were held that the new chemotherapy would end TB. However, it was evident by 1990 that progress was not being made and in that year alone, it was calculated there were 8 million new cases of TB in the developed and developing world of which 95% were in resource poor territories. In addition, 2.9 million deaths occurred from tuberculosis worldwide (Kochi, 2001). With the advent of the HIV/AIDS epidemic and the appearance of multiple drug resistant tuberculosis the opportunity for the defeat of TB was lost. The introduction of DOTS, with new drug regimens and the reinstitution of tight public health measures, managed to halt the explosion in TB numbers and in the western resource rich countries brought about a reversal in the upward spiral of cases. Clearly, much work is required, and action is needed in the areas of finance, political commitment and medical and especially public health input.

Conclusion

Lives of great men all remind us
We can make our lives sublime
And, departing, leave behind us
Footprints in the sands of time

Henry Longfellow (1807-1882), Psalm of Life

The paper of Boire et al., (2013) was presented with the provocative title that TB has come from *an untreatable disease in antiquity to an untreatable disease in modern times.* In this

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[40] Wegner P.: History of Tuberculosis and its prevention in Newfoundland.
www.heritage.inf.ca/articles/society/tuberculosis-newfoundland.php

discourse I have, indeed, described the devastating effects of TB on humanity and mankind's long struggle to find an effective treatment for the disease. Once this was almost in his grasp the chance almost slipped away of arresting the disease following the upsurge in the 1980-90s. We now have the aid of new technology for the early diagnosis of TB, the development of potentially effective treatment for HIV infection and tuberculosis. There is renewed energy in the field of public health TB control with built in regular review and upgrades. I believe that as far as tuberculosis goes we have learned from history and the title of the paper should read *untreatable in the past but curable in the near future.*

The application of the words of Hippocrates from around 350 BC that 'extreme remedies are most appropriate for extreme diseases' holds true for today's situation[41]. Bernard Shaws' somewhat cynical statement that a cure is found in 'stimulating the phagocytes and drugs are a delusion' may contain a grain of truth[42]. This is based on the premise that immunology may hold the key to the conquest of TB. The discovery of an effective and safe vaccine may be the weapon to ultimately overcome the 'White Plague' and make the disease curable in the near future.

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[41] Hippocrates circa 460-357 BC *Aphorisms.*
[42] George Bernard Shaw (1856-1950) in *Doctor's Dilemma*.

References

Abubakar I., Story A., Lipman G. et al. (2010) Diagnostic accuracy of digital chest radiology for pulmonary tuberculosis in a UK urban population. *Euro Resp J* 35: 689-692.

Ahmed M., Aissat S., Djebli N. et al. (2012) Bees and Honey against Tuberculosis. *J Anc Dis Prev Rem* 1: e103+

Ahuja S., Knorr J., Proops D. et al. (2015) *Annual Summary*, Bureau of Tuberculosis, Department of Health and Mental Hygiene, Queens, New York.

Alling DW., Bosworth EB. (1960) The after-history of pulmonary tuberculosis. Vi. The first fifteen years following diagnosis. *Am Rev Respir Dis* 81: 839-49.

Baltussen R., Floyd K., Dye C. (2005) Cost effectiveness of strategies for tuberculosis control in developing countries. *BMJ* 331: 1364.

Barr RG., Diez-Roux AV., Knirsch CA., Pablos-Mendez A. (2001) Neighborhood poverty and the resurgence of tuberculosis in New York City, 1984-1992. *Am J Public Health* 91: 1487-1493.

Bastion H. (2006) Down and almost out in Scotland: George Orwell, tuberculosis and getting streptomycin in 1948. *JRSM* 99:95-98.

Bayer R., Wikinson D. (1995) Directly observed therapy for tuberculosis: history of an idea. *Lancet* 345: 1545-48.

Bilal S., Iqbal M., Murphy P., Power J. (2010) Human bovine tuberculosis – remains in the differential. *J Medical Microbiology* 59: 1379-1382.

Binkin NJ., Zuber PLF., Wells CD., Tipple MA., Castro KG. (1996) Overseas screening for tuberculosis in immigrants and refugees to the United States: current status. *Clin Infect Dis* 23: 1226-1232.

Bissielo, A., Lim, E., Heffernan, H. (2011) *Tuberculosis in New Zealand*: Annual Report 2010 2011, Institute of Environmental Science and Research Ltd (ESR): Wellington, NZ.

Blevins SM., Bronze MS. (2010) Robert Koch and the 'golden age' of bacteriology. *Int J Infect Dis* 14: e744-751.

Bohn HG., (1862) *Diary and correspondence of John Evelyn FRS*. www.books.google.uk accessed 20/07/2016.

Boire NA., Avery V., Riedel A. et al. (2013) Tuberculosis: from an untreatable disease in antiquity to an untreatable disease in modern times? *J Anc Dis Prev Rem* 1: 106

Bos K., Harkins KM., Herbiga A. et al. (2014) Pre-Columbian mycobacterial genomes reveal seals as a source of New World human tuberculosis. *Nature* 514: 494-497.

Bosch F., Rosich L. (2008) The contribution of Paul Ehrlich to chemotherapy: a tribute on the occasion of the centenary of his Nobel Prize. *Pharmacology* 82: 171-178.

Breen R., Smith C., Bettinson H. et al. (2004) Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infections. *Thorax* 59: 704-707.

Brewer TF. (2000) Preventing tuberculosis with Bacille Calmette-Guérin vaccine: a meta-analysis of the literature. *Clin Infect Dis* 31: S 64-S 67.

Brites D., Gagneux S. (2015) Co-evolution of Mycobacterium tuberculosis and Homo sapiens. *Immunological Reviews* 264:6-24.

Brookes-Pollock E., Roberts GO., Kealy MJ. (2014) A dynamic model of bovine tuberculosis spread and control. *Nature* 511: 228-231.

Brosch R., Gordon SV., Marmiesse M. et al (2002) A new evolutionary scenario for the *Mycobacterium tuberculosis* complex. *PNAS* 99: 3684-3689.

Bryder L. (1991) Tuberculosis in New Zealand. in *History of tuberculosis in Australia, New Zealand and Papua New Guinea,* Ed. A. J. Proust. Brolga Press, Canberra pp 81-87*.

Bynum H., (2015) *Spitting Blood*. Oxford University Press, Oxford.

Canadian Centres for Disease Control (2014) *Guidance for Tuberculosis Prevention and Control Programs in Canada*. HM the Queen in Royal Canada. HP 40-81/2013-pdf.

Centers for Disease Control and Prevention (2016) www.cdc.gov/travel/yellowbook/2016 accessed 23/9/2016.

Chalke HD., (1962) The impact of tuberculosis on history, literature and art. *Medical History* 6: 307-316.

Child J. (2008) *Miniature messages*. Duke University Press, Durham, USA. pp 13-24

Ibid page 4

Cohen T., Murray M. (2005) Incidence of tuberculosis among recent US immigrants and exogenous reinfection. *Emerg Infect Dis* 11: 725-728.

Cole ST., Brosch R., Parkhill J. et al. (1998) Deciphering the biology of *Mycobacterium tuberculosis* from the complex genome sequence. *Nature* 393: 537-544.

Comas I., Coscolla M., Luo T., et al. (2013) Out-of Africa migration and Neolithic co-expansion of Mycobacterium tuberculosis with modern humans. *Nature Genetics* 45: 1176-1182.

Cox GL. (1923) Sanatorium treatment contrasted with home treatment. After histories of 4,067 cases. *Br J Tuberc* 17: 27-30.

Crofton J., Mitchison DA. (1948) Streptomycin resistance in pulmonary tuberculosis *Br Med J* 2:1009-1015.

Daniel TM., (2000) The origins and precolonial epidemiology of tuberculosis in the Americas: can we figure them out? *Int J Tuberc Lung Dis* 4:395-400.

Daniel TM.,(2006) The history of tuberculosis. *Respiratory Medicine* 100: 1862-1870.

Daniel TM. (2011) Hermann Brehmer and the origins of tuberculosis sanatoria. *Int J Tuberc Lung Dis* 15; 161-162.

Das D., Baker M., Venugopal K., McAllister S. (2006) Why the tuberculosis incidence rate is not falling in New Zealand. *NZ Med J* 119:17-31.

Dasgupta K., Menzies D. (2005) Cost effectiveness of tuberculosis control strategies among immigrants and refugees. *Eur Resp J* 25: 1107-1116.

Davies PDO. (2006) Tuberculosis in humans and animals: are we a threat to each other? *J R Soc Med* 99: 539-540.

Division of Tuberculosis Elimination, National Center for HIV, STD and TB prevention. Centers for Disease Control (2003). *Surveillance Report 2002*: United States Department of Health and Human Services. Atlanta, Georgia.

Dlodlo RA., Fujuwara PI., Enarson DA. (2005) Control of HIV related tuberculosis requires control of HIV transmission. *Eur Resp J* 25: 751-757.

Dubos R., Dubos J. (1952) *The white plague*. Little, Brown. Boston

Dots-plus and the Green Light Committee
www.who.int/tb/publications/2000/en/index.html accessed 25/9/2016

Dunsford DA. (2008) *Seeking the prize of eradication.* PhD Thesis. University of Auckland

Editorial, (2003) Rise and decline of the tuberculosis sanatorium. *Am Rev Respir Dis* 98; 515.

Enarson DA. (1991) Principles of IUATLD collaborative tuberculosis programmes. *Bull Int Union Tuberc* 66: 195-200.

Falzon D., Jaramillo E., Schunemann HJ. et al. (2011) WHO guidelines for the programme management of drug-resistant tuberculosis: 2011 update. *Eur Resp J* 38: 516-528.

Faria NR., Rambaut A., Suchard MA. et al. (2014) The early spread and epidemic ignition of HIV-1 inhuman populations. *Science* 346: 56-61.

Francis RSR. (1956) Mate Kohi could be wiped out. www.teahou.natlib.govt.nz accessed 21/02/2017

Frieden TR., Fujiwara PI., Washko RM. Hamburg MA. (1995) Tuberculosis in New York City – turning the tide. *N Engl J Med* 333: 229-33.

Frith J. (2014) History of Tuberculosis. *J Mil Vets Health* 22: 29-35.

Glaziou P., Falzon D., Floyd K., Raviglione M. (2013) Global epidemiology of tuberculosis. *Semin Respir Crit Care Med* 34: 3-16.

Gutierrez MC., Brisse S., Brosch R., et al. (2005) Ancient origin and gene mosaicism of the progenitor of Mycobacterium tuberculosis*. PLoS Pathog* 1:e5.

Gagneux S. (2012) Host-pathogen co-evolution in human tuberculosis. *Philos Trans R Soc London Biol Sci* 367: 850-9.

Geffen N. (2011) Battling the white plague: a brief history of tuberculosis. *Global TB Advisory Board: TB on line* www.tbonline.info/posts/2011/6/29/battling-white-plague accessed 30/07/ 2016

Hajar R. (2012) The air of history (Part 11). Medicine in the Middle Ages. *Heart Views* 13:158-162.

Hardie RM., Watson JM. (1992) *Mycobacterium bovis* in England and Wales: past present and future. *Epidemiol Infect* 109: 23-33

Hayman J. (1984) *Mycobacterium ulcerans*: an infection from Jurassic time? *Lancet* 2:1015-6.

Helb D., Jones M., Story E. et al. (2010) Rapid detection of mycobacterium tuberculosis and rifampicin resistance. *J Clin Microbiol* 45: 229-237.

Hershkovitz I., Donoghe HD., Minnikin DE et al. (2008) Detection and molecular characterization of 9,000 year-old Mycobacterium tuberculosis from a Neolithic settlement in the Eastern Mediterranean. *PLoS One* 3:e3426

Hertzog H. (1998) History of Tuberculosis. *Respiration* 65: 5-15.

Hierholzer J., Hierholzer C., Hierholzer K. (1994) Johann Lukas Schönlein and his contribution to nephrology and medicine. *Am J Nephrol* 14: 467-74.

Hurt R. (2004) Tuberculosis sanatorium regimen in the 1940s: a patient's personal diary. *J Roy Soc Med* 97: 350-353.

Isaacs D. (2016) Power of visual images. *J Paediatr Child Health* 52: 859-860.

Iseman MD. (2002) Tuberculosis therapy: past, present and future. *Eur Respir J* 20: Suppl. 36: 87s-94s.

Julich S. (2016) Mass miniature radiography surveys for tuberculosis in Sweden, c. 1940-1970. *Media History* 22; 201-216.

Kaminski R., Chen Y., Fischer T. et al. (2016) T-lymphoid cells by CRISPR/Cas9 gene editing. *Sci Rep* 6: Art 22555.

Keers R Y., (1982) Richard Morton (1637-98) and his Phthisiologica. *Thorax* 37: 26-31.

Kearns RA., Collins DCA. (2000) New Zealand children's health camps: therapeutic landscapes meet the contract state. *Social Science and Medicine* 51: 1047-1059.

Kerley P. (2014) Techniques in Mass Miniature Radiography. *BJR* 15: 180.

Keshavjee S., Farmer PE. (2012) Tuberculosis, drug resistance and the history of modern medicine. *N Engl J Med* 367: 931-936.

Kingston W. (2004) Streptomycin: Schatz versus Waksman and the balance of credit for discovery. *J Hist Med Allied Sci* 59: 44-62.

Kleeberg HH. (1984) Human tuberculosis of bovine origin in relation to public health. *Rev Sci Off Int Epiz* 3: 11-32.

Kochi A. (2001) The global tuberculosis situation and the new control strategy of the World Health Organisation. *Bull WHO* 79: 71-75.

Lemlein RF. (1981) Influence of tuberculosis on the work of visual artists: several prominent examples. *Leonardo* 14: 114-117.

Lennox E. (1977) Heredity or acquired disease? Early nineteenth century debates on the cause of infantile scrofula and tuberculosis. *J Hist Med Allied Sci* 32:356-374.

Leung CC., Chan CK., Law WS. et al.(2015) Immigrants and tuberculosis in Hong Kong. *Hong Kong Med J* 4: 318-326.

Levitt I. (2003) TB, Glasgow and the mass radiography campaign in the nineteen fifties: a democratic health service in action. *Scottish Health History.* Colloquium, University of Glasgow.

Liu Y., Weinberg MS., Ortega LS et al. (2009) Overseas screening for US-bound immigrants and refugees. *N Engl J Med* 360: 2406-15.

McFarlane N. (1989) Hospitals, housing and tuberculosis in Glasgow, 1911-1951. *Social History of Medicine* 2: 59-85.

McKinney JD., Honer zu Betrupt KH., Munoz-Elias EJ. (2000) Persistance of *mycobacterium tuberculosis* in the macrophages of mice requires the glyoxylase shunt enzyme isocitrate lyase. *Nature* 406: 735-738.

McMillan JS. (1957) Examination of the association between housing conditions and pulmonary tuberculosis in Glasgow. *Br J Prev Soc Med* 11: 142-157.

Marais BJ., Graham SM. (2014) Childhood tuberculosis: a road map towards zero deaths. *J Paediatr Child Health* 52:258-261.

Messer T. (1987) *Edvard Munch*. Thames and Hudson. London p. 12

Metcalfe JZ., Everett CK., Steingant KR. et al. (2011) Interferon gamma release assays for active pulmonary tuberculosis diagnosis in adults in low- and middle – income countries: a systematic review and meta-analysis. *J Infect Dis* 204: S1120 Supplement 4.

Miglioni GB., Loddenkemper R., Blasi F., Raviglioni MC. (2007) 125 years after Robert Koch's discovery of the tubercle bacillus: the new XDR-TB threat. Is science enough to tackle the epidemic? *Eur Respir J* 29:423-427.

Mistiaen V. (2016) *Time the great healer*.
www.theguardian.com/education/2002/nov/02/ accessed 26/8/2016.

Ministry of Health (2010) Guidelines for tuberculosis control in New Zealand.
www.health.govt.nz/system/files/documents/publications/guidelines-tuberculosis-control-new-zealand_0.pdf accessed21/02/2017

Mitchell RS. (1951) Artificial pneumothorax: a statistical analysis of 557 cases initiated in 1930-1939 and followed in 1949. The influence of clinical findings before induction on early and late results. *Am Rev Tuberc* 64: 1-20.

Morens DM. (2002) At the deathbed of consumptive art. *Emerging Infectious Diseases*. 8: 1353-1558.

Murray JF., (2003) Bill Dock and the location of pulmonary tuberculosis; How bed rest might have helped consumption. *Am J Respir Crit Care Med* 168: 1029-1033.

Murray JF. (2004) A century of tuberculosis. *Am J Respir Crit Care Med* 169: 1181-1186.

Murray JF., Schraufnagel DE., Hopewell PC. (2015) Treatment of Tuberculosis. *Ann Am Thoracic Society* 12: 1749-1759.

Murray S. (2006) Challenges of tuberculosis control. *CMAJ* 174: 32-34.

Nuessel F. (1996) Postage stamps: a pedagogical tool in second language classroom. *Mosaic: a Journal for Teachers* 3.2: 12-17.

O'Toole RF., Freeman JT. (2013) Molecular epidemiology of human tuberculosis in New Zealand and potential insights for disease control. *NZ Med J* 126; 100-102.

Pai M., Bloom BR. (2016) *TB elimination: India can lead the way*. www.bmj.com/bmj/2016/06/08/tb-elimination-india-can-lead-the-way/ accessed 31/10/2016

Piatek AS., Van Cleef M., Alexander H. et al. (2013) GeneXpert for TB diagnosis: planned and purposeful implementation. *Glob Health Sci Pract* 1: 18-23.

Proust AJ. (1991) Tuberculosis in Australia. in *History of Tuberculosis in Australia, New Zealand and Papua New Guinea.* ed. AJ Proust, Brolga Press, Canberra p. 81

Raviglione MC., Narain JP., Koch A. (1992) HIV associated tuberculosis in developing countries; clinical features, diagnosis and treatment. *Bull World Health Organ* 70:515-526.

Registrar-General's Office (1900) *Statistics for the Colony of New Zealand 1899*, Wellington p.40

Rothschild BM., Martin LD., Lev G. et al. (2001) Mycobacterium tuberculosis complex DNA from an extinct bison date 17,000 years before the present. *Clin Infect Dis* 33:305-311.

Schwartz M., (2009) Tuberculosis a journey through time. *Hektoen International* www.hektoeninternational.org/index.php?option=content

Sakula A. (1983) Who were Calmette and Guérin? *Thorax* 38: 806-812.

Salo W., Aufderheede AC., Buikstra J. et al. (1994) Identification of Mycobacterium tuberculosis DNA in a pre-Columbian Peruvian mummy. *Proc Natl Acad Sci* USA 91; 2091-94.

Sanitize E., Shengelia R. (2015) First partnerships to fight tuberculosis. *Clinical Research and Bioethics* 6: 5-10.

Schechter M., Zajdenverg R., Falco G. et al. (2006) Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts. *Am J Respir Crit Care Med* 173: 922-926.

Shoja M., Rashid MR., Tubbs RS et al. (2011) Legacy of Avicenna and evidence–based medicine. *Int J Cardiol.* 150: 243-6.

Shampo MA., Rosenow EC. (2009) A history of tuberculosis on stamps. *Chest* 136: 578-582.

Smith H. (2004) The strange case of Mr. Keats' tuberculosis. *Clinical Infectious Diseases* 38: 991-993.

Sterling TR., Lehmann HP., Frieden TR. (2003) Impact of DOTS compared with DOTS-Plus on multidrug resistant tuberculosis deaths: decision analysis. *BMJ* 326: 574.

Stoetzer C. (1953) *Postage Stamps as Propaganda*. Washington Public Affairs Press. 1; 24-5

Stop TB Working Group (2003) A prioritised research agenda for DOTS-Plus for multiple drug resistant tuberculosis. *Int J Tuberc Lung Dis* 7: 410-444.

Stop TB Working Group (2006) *DOTS-Plus for MDR-TB*, Strategic Plan 2006-2015.

www.stoptb.org/assets/documents/global/plan/StopTB Working Group on DOTS Final.pdf

accessed 25/9/2016

Tbfreeenngland: www.tbfreeengland.co.uk   accessed 17/9/2016

TB prevalence in Great Britain and New Zealand cattle (2016). www.bovinetb.info accessed 21/02/2017

Tennant M. (1994) *Children's health, the nation's wealth: a history of camps children's* health. Bridget Williams Books, Historical Branch, Department of Internal Affairs. p 295.

The Economist (1995) *TB: join the DOTS*. May 20, p85.

Toms C., Stapledon R., Waring J., Douglas P. (2015) Notification rates for tuberculosis, Australia, 1960-2013 by year. *Commun Dis Intell Q Rep* 39; E217-E235.

Udwadia ZF., Amale RA., Ajbani KK., Rodrigues C. (2012) Totally drug-resistant tuberculosis in India. *Clin Infect Dis* 54: 423-427.

Vanham G., Edmonds K., Oing L. (1996) Generalized immune activation in pulmonary tuberculosis: co-activation with HIV infection. *Clin Exp Immunol* 103: 30-34.

Vatanoglu-Lutz EE., Ataman AD. (2016) Medicine in Philately: Rene T.H. Laennec, the father of the stethoscope. *Anatol J Cardiol* 16: 346-7.

Volmik J., Garner P. (2003) Directly observed therapy for treating tuberculosis. *Cochrane Database Systemic Review* CD003343 Issue 1, Oxford..

Waksman S. (1965) *The conquest of tuberculosis*. Robert Hale Ltd.

Weise C. (2015) Tuberculosis elimination in the post Millenium Development Goals era. *Int J Infect Dis* 32: 152-5.

Williams HE., Phelan PD. (1995) The epidemiology, mortality and morbidity of tuberculosis in Australia: 1850-94. *J Paediatr Child Health* 31; 495-498.

With T., Hildebrand F., Allix-Béguic C. et al. (2008) Origin, spread and demography of the Mycobacterium tuberculosis complex. *PLoS Pathogens* http//dx.doi.org/10.1371/journal.ppt/1000160

Working Alliance for TB Drug Development. (2000) *Int J Tuberc Lung Dis* 4: 489-490.

World Health Organisation (1993) Tuberculosis: a global emergency. *World Health* 4: 3.

www.who.int/mediacentre/facts sheet/who104/en/print.html accessed 23/9/2016

World Health Organisation (2011)
www.who.int/tb/publications/global_report/gtbr12_main.pdf accessed 8/9/2016

World Health Organisation (2013) *Published evidence and commentary on the Xpert MTB/RIF diagnostic test*.
www.stoptb.org/wg/gli/assets/documents/map/XpertPublications.pdf accessed 28/9/2016

www.hsp.harvard.edu/news/press-releases/antobodies-may (2016) *Study antibodies may offer protection against tuberculosis suggests*. accessed 8/10/2016

www.ndtv.com/health/researchers-may-have-found-a-possible -cure-for-HIV-report-1469420 accessed 9/10/2016

WHO (2015) Digital health for the end TB strategy: an agenda for action. http//apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf   accessed 21/02/2017

Wunderly HW. (1940) An investigation into the incidence of pulmonary tuberculosis in young women of Adelaide in the age group 15 to 30 years. *Med J Aust* 2: 229-32.

Yen S., Bower JE., Freeman JT., Basu I., O'Toole RF. (2013) Phylogenetic lineages of tuberculosis isolates in New Zealand and their association with patient demographics. *Int J Tuberc Lung Dis* 17: 892-7.

Yoshioka A. (1998) Use of randomisation in the Medical Research Council's clinical trial of streptomycin in pulmonary tuberculosis in the 1940s. *Br Med J* 317: 1220-1223.

Zignol M., Hosseini MS., Wright A. et al. (2006) Global incidence of multi-resistant tuberculosis. *J Infect Dis* 194: 479-485.

Zink AR., Sola C., Reisch U. et al. (2003) Characterization of MTB Complex DNAs from Egyptian mummies by spoligotyping. *J Clin Microbiol* 41: 359-367.